15th Annual Meeting of

The PsychoNeuroImmunology Research Society

PROGRAM

PNIRS 2008

Promoting Innovation in Psychoneuroimmunology:

From Cytokines to Society

May 28 - 31, 2008
Madison, Wisconsin
Monona Terrace

Co-sponsored by
The National Cancer Institute
National Institutes of Health
Department of Health and Human Services

TABLE OF CONTENTS

Donations Acknowledgement

We would like to express our sincere gratitude to the following companies that donated funds in support of the 15th annual meeting of the PNIRS.

Centocor, Inc. Horsham, PA

Forest Laboratories, Inc, New York, NY

Jannsen & Company, Waukesha, WI

Sepracor, Marlborough, MA

Funding for the 2008 meeting was made possible in part by a conference grant R13 CA134006 from the National Cancer Institute. We also gratefully appreciate the support of Elsevier Inc for sponsoring the Editorial Board luncheon and providing the complimentary copies of Brain, Behavior, and Immunity.

Special acknowledgments are also due Ms. Susan Solomon for all of her dedicated help in organizing the meeting, ensuring the fiscal soundness of our society, and her long-standing commitment to the field of PNI ever since its inception.

Norman Cousins Award Lecture

Norman Cousins was an articulate spokesman and advocate for psychoneuroimmunology whose support and generosity enabled many investigators to get a start in this interdisciplinary field of research. In an effort to recognize his contributions and, at the same time, to contribute to the advancement of knowledge in the field, Ellen Cousins, Norman's wife, the Norman Cousins Memorial Fund, and the California Wellness Foundation provided the endowment for an annual Norman Cousins Memorial Lecture to be delivered at the meetings of the PsychoNeuroImmunology Research Society. Thus, an international Lectureship that bears his name continues to honor Norman Cousins. Because the Lectureship is a vehicle for the presentation of new ideas, those of us who knew Norman Cousins believe he would have approved of this form of recognition. The *PsychoNeuroImmunology Research Society*, professionals and students, alike, are the grateful beneficiaries of this continuing Lectureship.

1991 – Robert Ader
1993 – George F. Solomon
1994 – Jean E. Merrill
1996 – Hugo O. Besedovsky
1997 – John F. Sheridan
1998 – Janice K. Kiecolt-Glaser
1999 – Cobi Heijnen
2000 – Robert Dantzer
2001 – Christopher Coe
2002 – Steven Maier
2003 – Keith Kelley
2004 – Ronald Glaser
2005 – Nicholas Cohen
2006 – Linda Watkins
2007 – Michael Irwin

Norman Cousins Award Lecture 2008

"Cytokines sing the blues: PNI at the translational interface"

Andrew Miller
Department of Psychiatry and Behavioral Sciences
Director, Mind-Body Program
Emory University School of Medicine

Robert Ader New Invesigator Award

The PNIRS also presents another award for outstanding contributions in basic and clinical research in PNI. This award provides a $500 honorarium from a generous gift by the Fund for Psychoneuroimmunology. The following scholars have been honored with the Ader award in the past.

2000 – Firdaus Dhabhar
2001 – Annemieke Kavelaars
2002 – Kurt Ackerman
2003 – Lucille Capuron
2004 – Susan Lutgendorf
2005 – Marian Kohut
2006 – Julienne Bower
2007 – Suzanne Segerstrom

GENERAL INFORMATION

DATES

The 2008 annual meeting of the Psychoneuroimmunology Research Society begins Wednesday, May 28, 2008, and adjourns Saturday, May 31, 2008. The PNIRS Scholars mentoring session takes place on the evening of Wednesday, May 28, 2008.

VENUE

Monona Terrace Convention Center and Madison Hilton Hotel
One John Nolen Drive, Madison, WI

REGISTRATION INFORMATION

Name badges and and meeting bags will be distributed at the registration desk of the Monona Terrace located on the first floor, near the main Lecture Hall. The registration desk will be open during the following hours:

Wednesday, May 28	noon - 8:30 pm
Thursday, May 29	8:00 am - 6:30 pm
Friday, May 30	8:00 am - 6:30 pm
Saturday, May 31	8:00 am - 6:30 am

ACCOMPANYING PERSONS

Individuals (guests) accompanying registrants are welcome to attend the Opening Reception and the Banquet as long as they inform us in advance. Guest tickets for both events can be purchased at the registration desk. Guests are not permitted in either the meeting rooms or poster halls.

MOBILE (CELLULAR) PHONES

As a courtesy to others, please switch off mobile phones during all sessions.

INSTRUCTIONS TO PRESENTERS

Chairs

Chairs of the sessions should be in the designated room 10 minutes before the session starts in order to assist the speakers.
In the event of a talk cancellation, the order and timing of the session should not be changed so that the meeting stays on schedule and to coordinate with other presentations when we are in double session. Any unanticipated long gap due to a cancellation or shorter-than-expected talk should be used for general discussion and/or a brief break.

Speakers

Speakers should go to the designated room 10 minutes before the session starts to meet the moderators andto upload talks onto the laptop computers.

Computer presentation guidelines

To minimize the need for connecting multiple computers to the projectors, a laptop is provided. Talks can be uploaded via a flashdrive or CD. Both pc and Mac laptops are available in the event that your presentation will work with only one type of software. Unless our computers do not work, please do not use your own personal laptops. It is assumed that all presentations will use Powerpoint software. Please contact the registration desk if you are using a different program.

Poster presentations

The Poster Sessions will be held in the rooms adjacent to the main lecture on the first floor. The 2 Poster Sessions are organized in alphabetical order by the first author's last name. Poster Session 1 (A-L) will be from 4:00 -6:30 on Friday, May, 30, and Poster Session 2 (M-Z) will be on Saturday, May 31, from 4:00-6:30. All posters can be mounted during the morning, andn prerferably no later than 3:00, one hour before the session. Pins for mounting the posters will be provided. Look for your poster number in this Program Book or on a list that will be posted in the rooms. Please remove your posters at the end of the session. The poster boards will be removed by 7:00 on Saturday; remaining posters may be discarded if they are not taken down by that time.

Data Blitz

For the first 30 minutes of each poster session, there will also be short oral presentations of a subset of posters on display. The Data Blitz talks will take place in the main Lecture Hall. Given their brevity, please upload all files in advance before the 30-min Blitz begins. After your presentations, please re-join everyone in the poster rooms.

PNIRS Senior Faculty-Trainee Colloquium

Supported by R13 CA134006 from the National Cancer Institute (NCI)

Wednesday, May 28, 2008 – 6:30 P.M.- 8:30 P.M.

Room K	Room L	Room M	Room O	Room P
Andrea Danese Kings College UK	**Jennifer Curry** Ohio State University USA	**Yael Goldfarb** Tel Aviv University Israel	**Marganit Benish** Tel Aviv University Israel	**Elinor Fondell** Karolinski Institute Sweden
Lisa Christian Ohio State University USA	**Kriste Grebe** National Institutes of Health USA	**Steven Kinsey** Virginia Commonwealth USA	**Issac Bernstein-Hanley** Univ. of Colorado USA	**Jessica Gill** National Institutes of Health USA
Andrea Liatis Emory University USA	**Chris Henry** Ohio State University USA	**Eoin McNamee** Trinity College Ireland	**Sarah Bull** King's College UK	**Brandy Lehman** University of San Francisco USA
Erica Sloan UCLA USA	**Hadas Melboom** Tel Aviv University Israel	**Karen Ryan** Trinity College Ireland	**Niamh Curtin** Trinity College Ireland	**Andrea Marques** National Institutes of Health USA
Sarah Short University of Wisconsin USA	**Yair Ben-Menachem** Hadassah-Hebrew University Hospital Israel	**Christina Sherry** University of Illinois USA	**Aofie O'Donovan** UCSF USA	**Michelle Okun** University of Pittsburgh USA
Jutta Wolf University of British Colombia Canada	**Bahareh Zyaei** University of Illinois USA	**Auriel Willette** University of Wisconsin USA	**Hao Zhang** Ohio State University USA	**Victoria Viera** University of Illinois USA
Adam Walker University of Newcastle Australia				

Congratulations to the 2008 Scholar Awardees!

Meeting Faculty

Faculty Mentors:
Special thanks to the following faculty who are participating in the NCI-sponsored mentoring session:
Julienne Bower, Robert Dantzer, Moni Fleshner, Cobi Heijnen, Rodney Johnson, Keith Kelley, Margaret Kemeny, Andrew Miller, Jan Moynihan, John Sheridan, Mark Laudenslager

We also appreciate the assistance of Michael Bailey, Stacey Bilbo, and Michelle Okun in leading the discussions in the Junior Faculty mentoring workshop.

SHORT COURSE FACULTY: New Molecular and Biological Approaches in PNI
Elissa Epel: Neuroendocrine and Cell Aging Measurement in PNI Research
Steve Cole: Genomic Approaches in PNI
Anil K. Sood: Impact of Microenvironment on Tumor Growth

PRESIDENTIAL SYMPOSIUM: Neural Mediation of the Effects of Stress and Psychological Factors on the Endocrine and Immune Systems

Richard Davidson Interactions between the brain and the periphery in the regulation and dysregulation of emotion
Naomi Eisenberger: Social pain: Neurocognitive, neuroendocrine, and immunological correlates.
Avgusta Shestyuk: Brain regulation of stress reactivity: higher cortical regulation of peripheral actviation in response to social threat.
Tor Wager: Neuroimaging of autonomic responses to social evaluative threat: Localizing cortical-subcortical-peripheral pathways.

PROGRAM COMMITTEE

Michael Antoni
Julienne Bower
Christopher Coe
Steve Cole
Mary Coussons-Read
Adrianna del Rey
Firdaus Dhabhar
Lisa Goehler
Cobi Heijnen
Rodney Johnson
Margaret Kemeny
Andrew Miller
Mark Opp
Manfred Schedlowski
Eric Smith
Rainer Straub
Raz Yirmiya

MEETING SCHEDULE

<table>
<tr><th>TIME</th><th>Wednesday,
May 28</th><th>Thursday, May 29</th><th>Friday,
May 30</th><th>Saturday, May 31</th></tr>
<tr><td>8:15 - 8:30</td><td></td><td>Welcoming Remarks</td><td></td><td></td></tr>
<tr><td>8:30 – 9:00</td><td rowspan="11"></td><td rowspan="3">Oral Session 1</td><td rowspan="3">Symposium: Impact of Inflammation on the Vulnerable Brain</td><td rowspan="3">Oral Session 5</td></tr>
<tr><td>9:00 – 9:30</td></tr>
<tr><td>9:30 – 10:00</td></tr>
<tr><td>10:00 – 10:30</td><td></td><td></td><td>Coffee Break</td></tr>
<tr><td>10:30 – 11:00</td><td>Coffee Break</td><td>Coffee Break</td><td rowspan="3">Symposium: Individual Responses to the Environment</td><td rowspan="3">NeuroAIDS Symposium</td></tr>
<tr><td>11:00 – 11:30</td><td rowspan="2">Cousins Lecture</td><td rowspan="2">Robert Ader Symposium: New Frontiers in PNI</td></tr>
<tr><td>11:30 – 12:00</td></tr>
<tr><td>12:00 – 12:30</td><td rowspan="2">BUFFET LUNCH
Round Table with NIH Staff</td><td rowspan="2">BUFFET LUNCH

BBI Edit Board Lunch (at Hilton Hotel)</td><td rowspan="2"></td></tr>
<tr><td>12:30 – 1:00</td><td rowspan="2">BUFFET LUNCH
Workshop Discussion</td></tr>
<tr><td>1:00 – 1:30</td><td rowspan="3">Presidential Symposium</td><td rowspan="3">Oral Session 3</td><td rowspan="3">Oral Session 4</td></tr>
<tr><td>1:30 – 2:00</td><td rowspan="3">Symposium: Dynamic Innervation of Lymphoid Tissue</td></tr>
<tr><td>2:00 – 2:30</td></tr>
<tr><td>2:30 – 3:00</td><td rowspan="12">SHORT COURSE</td><td rowspan="2"></td></tr>
<tr><td>3:00 – 3:30</td><td rowspan="2">Coffee Break</td><td rowspan="2">Coffee Break</td><td rowspan="2">Coffee Break</td></tr>
<tr><td>3:30 – 4:00</td></tr>
<tr><td>4:00 – 4:30</td><td rowspan="4">Oral Session 2</td><td>Poster Data Blitz</td><td>Poster Data Blitz</td></tr>
<tr><td>4:30 – 5:00</td><td rowspan="3">Poster Session 1</td><td rowspan="3">Poster Session 2</td></tr>
<tr><td>5:00 – 5:30</td></tr>
<tr><td>5:30 – 6:00</td></tr>
<tr><td>6:00 – 6:30</td><td>Break</td><td rowspan="3">Council Meeting (NOTE: Council will meet again if needed from 6-8 on Friday)</td><td rowspan="3">6:30-7:15
Past Trainee-Current Trainee Roundtable</td><td rowspan="3">Business Meeting</td></tr>
<tr><td>6:30 – 7:00</td><td rowspan="4">Senior Faculty/Trainee Colloquium (6:30-8:45)</td></tr>
<tr><td>7:00 – 7:30</td><td rowspan="3">BANQUET
(7:30 – 9:00
dance to 12:00)</td></tr>
<tr><td>7:30 – 8:00</td><td>OPENING RECEPTION</td><td>Trainee Dinner at Essen Haus (7:30-9:30)</td></tr>
<tr><td>8:00 –</td><td></td><td></td><td></td></tr>
</table>

Wednesday, May 28, 2008

12:00 - 3:00 REGISTRATION OPEN

3:00 – 6:00 SHORT COURSE: New Molecular and Biological Approaches in PNI
(Will take place in Hall of Ideas, Room J)

Elissa Epel: *Neuroendocrine and Cell Aging Measurement in PNI Research*
Steve Cole: *Genomic Approaches in PNI*
Anil K. Sood: *Impact of Microenvironment on Tumor Growth: Mechanisms and Targets*

6:30 – 8:30 SENIOR FACULTY/TRAINEE COLLOQUIUM
(The 5 groups will meet in Rooms K, L, M, O, P)

Thursday, May 29, 2008

7:30-8:30 CONTINENTAL BREAKFAST (on the Grand Terrace)

8:30 – 10:30 ORAL SESSION 1: Cytokine Effects on the Brain and Behavior: Animal Models
Chairs: Robert Dantzer and Keith Kelley

Switching transcription factor use preserves cytokine production after NF-kB inhibition in neonatal cerebral hypoxia-ischemia.
Cobi J. Heijnen, *Cora Nijboer, Floris Groenendaal, Frank van Bel, Annemieke Kavelaars*

IL-1 signaling in astrocytes is essential for hippocampal-dependent memory functioning.
Ofra Ben Menachem-Zidon, *Raz Yirmiya, Yair Ben Menahem, Inbal Goshen, Sys Kochavi, Omer Gaist, Tamir Ben Hur*

Interferon-α and its CNS action: from JAK/STAT signaling to behavioral impact.
Jianping Wang

How does immune activation influence motivated behavior? Autonomic and limbic inputs drive the rostral nucleus accumbens following lipopolysaccharide injection.
Lisa Goehler*, Gregory Thacker, Ron Gaykema*

Alterations in brain and behavioral development of offspring following prenatal flu infection in rhesus monkeys.
Sarah J. Short, *Christopher L. Coe, Gabriel Lubach, Martin Styner, John H. Gilmore*

Minocycline attenuates Lipopolysaccharide (LPS)-induced brain cytokine expression, social withdrawal, and anhedonia.
Christopher Henry*, Yan Huang, Angela Wynne, Justin Himler, Jonathan Godbout*

Prenatal exposure to endotoxin sensitizes rhesus monkeys to exogenous stress throughout infancy.
Auriel Willette*, Gabriele Lubach, Martin Styner, John Gilmore, Christopher Coe*

Role of p38 MAP kinase-GRK2 interactions in chronic inflammatory hyperalgesia.
Annemieke Kavelaars*, Niels Eijkelkamp, Ilona den Hartog, Cobi J. Heijnen*

10:30 - 11:00 COFFEE BREAK

11:00 – 12:00 2008 NORMAN COUSINS MEMORIAL LECTURE:
Cytokines sing the blues: PNI at the translational interface
Andrew Miller, Emory University

12:00 – 1:30 LUNCH BREAK: Roundtable Discussion of NIH Funding Opportunities (Hall of Ideas, H)
Buffet lunch for all registrants on the Grand Terrace
Presidential Luncheon (Hall of Ideas, I)

1:30 – 3:30 PRESIDENTIAL SYMPOSIUM: Neural Mediation of the Effects of Stress and Psychological Factors on the Endocrine and Immune Systems

Richard Davidson *Keynote Speaker: Interactions between the brain and the periphery in the regulation and dysregulation of emotion, University of Wisconsin, Madison, WI.*

Naomi Eisenberger: *Social pain: Neurocognitive, neuroendocrine, and immunological correlates. University of California Los Angeles, C.A*

Avgusta Shestyuk: *Brain regulation of stress reactivity: higher cortical regulation of peripheral activation in response to social threat. University of California, Berkeley, CA.*

Tor Wager: *Neuroimaging of autonomic responses to social evaluative threat: Localizing cortical-subcortical-peripheral pathways. Columbia University, NY.*

3:30 - 4:00 COFFEE BREAK

4:00 – 6:00 ORAL SESSION 2: Effects of Stress, Mood and Cognition on Inflammatory Processes
Chairs: Julie Bower & Janice Kiecolt-Glaser

Effects of an acute laboratory stressor on regulatory T cell (Treg) levels in normal human peripheral blood mononuclear cells (PBMC).
Gailen D. Marshall, *Kevin S. Del Ben*

Attachment avoidance predicts inflammatory response to marital conflict.
Jean-Philippe Gouin*, Ronald Glaser, William Malarkey, Timothy Loving, Janice Kiecolt-Glaser*

University examinations cause hyper-inflammation of mucosal tissues.
Christopher G. Engeland, *Zongjan Fang, Phillip T. Marucha*

Application of repeated social stress to pregnant gilts during early or late gestation diferentially affects HPA axis and immune system activity of the piglets.
David Couret*, Armelle Prunier, Isabelle Oswald, Francoise Thomas, Anne-Marie Mounier, Elodie Merlot*

The effects of the physical work environment on circadian variations in heart rate variability.
Andrea Marques*, Julian Thayer, Israel Christie, Anthony West, Carolyn Sterling, Darrell Abernethy, Giovanni Cizza, Terry Phillips, Judith Heerwagen, Keven Kampschroer, John Sollers, Marni Silverman, Esther Sternberg*

Inflammation as a response to bereavement is associated with increased subgenual anterior cingulate activity.
Mary-Frances O'Connor, *David Wellisch, Michael Irwin*

Hostility is related to clusters of T-cell cytokines and chemokines in healthy men.
Annemieke Kavelaars*, Paula Mommersteeg, Eric Vermetten, Elbert Geuze, Cobi J. Heijnen*

Telomere length and pessimistic attitudes in older women.
Aoife O'Donovan*, Jue Lin, Erin Clevenger, Alanie Lazaro, Jean M Tillie, Firdaus S Dhabhar, Owen Wolkowitz, Elizabeth Blackburn, Elissa Epel*

6:00 – 7:30 COUNCIL MEETING
(for members of Council, the meeting will take place in Hall of Ideas, H)

7:30 – 8:30 OPENING RECEPTION
(All registrants please join us on the Grand Terrace. Tickets for guest can be purchased at Registration Desk)

Friday, May 30, 2008

7:30 - 8:30 CONTINENTAL BREAKFAST (on the Grand Terrace)

8:30 – 10:30 SYMPOSIUM I: Impact of Inflammation on the Vulnerable Brain

Chair: Marina Lynch
Co-Chair: Rodney Johnson

Systemic inflammation and stroke
Stuart Allan, *Faculty of Life Sciences, Oxford Road, Manchester, UK*

Functional consequences of the systemic response to brain injury and disease
Daniel Anthony, *Department of Pharmacology, University of Oxford, Oxford, UK*

Neuroinflammation and cognitive and motor impairment in the aged: Evidence for a dysregulated linkage between the immune system and brain
Rodney Johnson*, University of Illinois at Urbana Champaign, Urbana, IL.*

Modulating microglial activation modulates age-related neuroinflammation
Marina Lynch, *Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland*

10:30 - 11:00 COFFEE BREAK

11:00 – 12:00 ROBERT ADER SYMPOSIUM: NEW FRONTIERS IN PNI

Chairs: Jan Moynihan & **Cobi Heijnen**

Behavioral regulation of immune response genes
Steve Cole, *UCLA School of Medicine*

The Future Lies in the Past
Keith W. Kelley, *University of Illinois, Urbana-Champaign*

Drug Conditioning and the Wisdom of the Body
Shepard Siegel, McMaster University, Hamilton, Ontario, Canada

12:00 – 1:30 Buffet lunch for all registrants on the Grand Terrace

BBI EDITORIAL BOARD MEMBERS LUNCH (back at the Hilton Hotel)
(Founders Room, back at Hilton Hotel, 2nd floor)

1:30 – 3:30 ORAL SESSIONS 3 and 4 are concurrent (SESSION 3 IN LECTURE HALL; SESSION 4 IN HALL OF IDEAS: J)

ORAL SESSION 3: Cytokines and Behavior: Bidirectional Relationships
Chairs: Mark Opp & Mark Laudenslager

Acute and chronic IL-1beta administrations differentially modulate learning and memory, acetylcholine efflux and neurotrophin expressions in the hippocampus: possible mechanisms involved in neuroprotection and neurodegeneration.
***Cai Song**, Pornnarin Teapavarapruk, Ye Zhang*

Young adult APOE e4 carriers show a stress-induced decline in "hot cognition" and sIL-6r, but not IL-6.
***Andrine Lemieux**, Douglas Walton, Jon Nelson*

Sleep, sleep deprivation and responses to lipopolysaccharide of interleukin-1b receptor 1 and tumor necrosis factor-a receptor 1 double knockout mice.
***Francesca Baracchi,** M. R. Opp*

Gender -specific associations between disturbed sleep and biomarkers of inflammation, coagulation and insulin resistance.
Edward C Suarez

Chronic stress reduces glucocorticoid and alpha-adrenergic receptor expression, and induces an inflammatory state characterized by increased IL-12 and IFN-gamma production.
***Niamh Curtin**, Kingston Mills, Thomas Connor*

Serum Interleukin (IL)-6 and sTNF-R1 are associated with development of multiple symptoms during first 30 days of allogeneic hematopoietic stem cell transplantation.
***Xin Shelley Wang**, Sergio Giralt, Qiuling Shi, Loretta Williams, Jemas Rueben, Charles Cleeland*

Rats infected early in life with bacteria exhibit exaggerated fever, sickness behavior, and lack of endotoxin tolerance in adulthood.
***Staci D. Bilbo**, Julie Wieseler, Ruth M. Barrientos, Linda R. Watkins, Steven F. Maier*

Interferon-γ receptors are required for upregulation of indoleamine 2,3-dioxygenase and depressive-like behavior induced by Bacillus Calmette-Guerin.
***Jason O'Connor**, Caroline Andre, Marcus Lawson, Sandra Szegedi, Jacques Lestage, Nathalie Castanon, Keith Kelley, Robert Dantzer*

ORAL SESSION 4: SNS Mediators, Glucocorticoid Mediators, Viral Outcomes
Chairs: John Sheridan & Manfred Schedlowski (in Hall OF IDEAS J)

Sympathetic nervous system (SNS) regulation of T-lymphocyte proliferation in aging F344 rats.
***Denise L. Bellinger**, Christine Molinaro, Brooke A. Millar, Sam Perez, Cheri Lubahn, Dianne Lorton*

Social temperament and lymph node innervation.
***Erica Sloan**, John Capitanio, Ross Tarara, Steve Cole*

Disease-induced changes in sympathetic to immune signaling in adjuvant-induced arthritis (AA).
***Dianne Lorton,** Cheri Lubahn, Tracy Osredkar, Jeff Carter, Terry Der, Denise Bellinger*

Glucocorticoid eeceptor expression in children shows opposite patterns of associations with anxiety and depression.
***Jutta M Wolf**, Edith Chen*

Dexamethasone activates Epstein Barr Virus lytic replication through immediate early BZLF1 gene expression.
***Seung-jae Kim,** Eric V. Yang, Min Chen, Jeanette I. Marketon, Marshall V. Williams, Ronald Glaser*

Optimism is associated with attenuated stressor-induced increases in inflammatory cytokines and negative mood states.
***Lena Brydon**, Cicely Walker, Andrew Wawrzyniak, Daisy Whitehead, Andrew Steptoe*

The association of poor sleep to immunogenicity following an avian flu vaccine in healthy older adults.
***Wilfred R. Pigeon,** John Treanor, Stefan Costescu, Jan Moynihan*

Effects of social disruption stress on CD4+ T cell activation, trafficking, and survival during influenza infection.
***LaTonia Stiner-Jones,** Mark Hanke, Nicole Powell, David Padgett, John Sheridan*

FRIDAY AFTERNOON PROGRAM (continued)

3:30 - 4:00 COFFEE BREAK

4:00 – 4:30 POSTER DATA BLITZ (selected presenters from A-L see below) (main Lecture Hall)
Chair: Suzanne Segerstrom
4:00 – 6:30 POSTER SESSION 1: First Author names beginning with letters A-L
("First Author" refers to author listed first on the submitted abstract) (in Meeting Rooms K-R)

6:30 – 7:15 PAST TRAINEE—CURRENT TRAINEE ROUNDTABLE (in Lecture Hall)

7:30 – TRAINEE RECEPTION DINNER (at Essen Haus, for escort, meet in front of Hilton at 7:20)

Saturday, May 31, 2008

7:30 - 8:30 CONTINENTAL BREAKFAST (on Grand Terrace)

8:30 – 10:00 ORAL SESSION 5: Psychoneuroimmunology and Cancer
Chairs: Ronald Glaser & Shamgar Ben-Eliyahu

Chronic stress promotes tumor growth through a Src-dependent mechanism in a mouse model of ovarian cancer.
Guillermo N. Armaiz-Pena*, Anil K. Sood, Lingegowda S. Mangala, Liz Y. Han, Yvonne G. Lin, Rosemarie Schmandt, Angela M. Sanguino, Gabriel Lopez-Berestein, Susan K. Lutgendorf, Steve W. Cole*

Stress attenuates the efficacy of IL-12 immunostimulation: An in vivo study of resistance to experimental metastasis.
Hadas Meiboom, *Shamgar Ben-Eliyahu, Ben Levi, Shaily Shemer*

Restraint stress increases breast tumor growth and angiogenesis.
Jennifer Curry, *Clay Marsh, Tim Eubank, Ryan Roberts, John Sheridan*

Exercise therapy for ovarian cancer: How does exercise counteract stress-induced tumor growth?
Rosemarie Schmandt*, Anil K. Sood, Susan K. Lutgendorf, Lingegowda S. Mangala, Guillermo Armaiz-Pena*

Marginating pulmonary leukocytes in C57BL/6 mice: Distinct characteristics and enhanced NK cytotoxicity against syngeneic tumor cells.
Marganit Benish, *Shamgar Ben-Eliyahu, Ariella Glasner, Yael Kalderon, Rivka Melamed*

Norepinephrine upregulates VEGF IL-6, and IL-8 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression.
Eric V. Yang, *Seung-jae Kim, Elise L. Donovan, Min Chen. Amy Beickelman, Brian J. Hutzen, Jiayuh Lin, Sanford H. Barsky, Ronald Glaser*

10:00 - 10:30 COFFEE BREAK

10:30 – 12:30 SYMPOSIA II AND III ARE CONCURRENT (Symposium II in Hall E; Symposium III in Lecture Hall)

SYMPOSIUM II: Individual Responses to the Environment: Immune and health correlates
Chairs: Sonia Cavigelli & John Capitanio (in Hall of Ideas E)

Role of acute vs. long-term depressive mood in systemic inflammatory activity
Nicolas Rohleder *and Greg E. Miller, University of British Columbia, Vancouver, BC Canada*

Caregiving, repetitive thought, and serum IL-6 in older adults
Suzanne C. Segerstrom*, Lindsey J. Schipper and Richard N. Greenberg, University of Kentucky, Lexington, KY*

Antagonistic characteristics are positively associated with inflammatory markers independently of trait negative emotionality.
Anna Marsland, *University of Pittsburgh, PA*

Female temperament, tumor development and life span: Relation to glucocorticoid and TNFα levels in rats
Sonia A. Cavigelli, *Jeanette M. Bennett, Kerry C. Michael and. Laura Cousino Klein, Penn State University, University Park, PA*

SYMPOSIUM III: NeuroAIDS Symposium: HIV and the Brain: Models and Treatment Approaches
Chairs: Keith Kelley and Robert Dantzer (in main Lecture Hall)

Stress, substance abuse and HIV interactions
Mary Jeanne Kreek, *Rockefeller University*

Role of innate immune responses in the neuropathogenesis induced by SIV in macaques
Janice E. Clements, *John Hopkins University School of Medicine*

Neural progenitors and HIV neuropathogenesis
Lynnae M. Schwartz, *University of Pennsylvania School of Medicine*

Genetic and epigenetic factors in neuroAIDS
Ian P. Everall, *University of California at San Diego*

Biomarkers, laboratory, and animal models for the design and development of adjunctive therapies for HIV-1 dementia and other neuroinflammatory disorders
Howard E. Gendelman, *University of Nebraska Medical Center*

12:30-1:30 LUNCH (Symposium Discussion over lunch) (Buffet Lunch on Grand Terrace)

1:30 – 3:30 SYMPOSIUM IV: Dynamic innervation of lymphoid tissue: Mechanisms and impact
Chair: Steve Cole

Neuroanatomy of lymphoid innervation: Recent advances and insights
Dwight M. Nance*, Department of Physical Medicine and Rehabilitation, UCI School of Medicine, Orange, CA*

Psychosocial and viral modulation of lymphoid innervation
Erica Sloan, *UCLA, Cousins Center for PNI, CA*

Injury and sprouting responses of sympathetic nerves in lymphoid organs: Impact on altered immunity in rheumatoid arthritis and potential therapeutic target
Dianne Lorton, *Hoover Arthritis Research Center, Sun Health Research Institute*

Sympathetic innervation across the lifespan: Implications for immune function
Denise Bellinger, *Loma Linda University, School of Medicine*

Dynamic innervation of lymphoid tissue: Themes and implications
Steve Cole*, UCLA School of Medicine and HopeLab*

3:30 – 4:00 COFFEE BREAK

4:00 – 4:30 POSTER DATA BLITZ (in main Lecture Hall, selected presenters from M-Z see below)
Chair: Mary Coussons-Read

4:00 – 6:00 POSTER SESSION 2: First Author names beginning with letters M-Z
("First Author" refers to author listed first on the submitted abstract)
(Posters located in Rooms K-R)

6:00 – 7:00 BUSINESS MEETING
(in main Lecture Hall)

7:30 – 12:00 BANQUET AND DANCE

(all registrants are invited to join us on the Grand Terrace; Guest Tickets can be purchased)

Poster Session 1, Authors A-L, Friday, May 30, 4:00 - 6:30

1. Central inhibition of IL-1β ameliorates lipopolysaccharide-induced sickness behavior in aged mice.
Jayne Abraham, & Rodney Johnson

2. Repeated social defeat-induced increases in microbicidal activity of splenic macrophages are diminished by inhibiting NO production
Rebecca Allen, David Padgett, John Sheridan, & Michael Bailey

3. Sex-specific relations between leptin and self-rated health
Anna Andréasson, Kerstin Brismar, Susanna Jernelö, Anna-Lena Undén, & Mats Lekander

4. A working week with restricted sleep: effects on self-rated health and immune responses to a mitogen challenge
John Axelsson, Torbjorn Akerstedt, Rolf Ekman, Caroline Olgart-Hoglund, & Mats Lekander

5. Repeated social defeat increases cytokine production by *Porphyromonas gingivalis* LPS-stimulated macrophages.
Michael Bailey, Steven Kinsey Rebecca, Allen David Padgett, & John Sheridan

6. Effects of spaceflight stress on anti-inflamatory response
FP Baqai, DS Gridley, EJM Bayeta, M Andres, X Luo-Owen, TA Jone, B Biansk, A Rizv, HQ Han, D Lacey, L Stodieck, V Ferguson, LM Green, GA Nelson, & MJ Pecaut

7. Practitioner empathy and duration of the common cold
Bruce Barret, Dave Rakel, Theresa Hoeft, Betty Chewning, Benjamin Craig, & Min Niu

8. Long-term impact of repeated strong hypothalamus pituitary adrenal axis activation on basal glucocorticoid sensitivity
Christiane Berndt, Jana Strahler, Clemens Kirschbaum, & Nicolas Rohleder

9. Gene expression profiling in the stressed spleen: Dissecting stress-induced suppression of the primary antibody response.
Isaac Bernstein-Hanley, Brian Helwig, Sarah Kennedy Thomas, Maslanik Kristen Speaker, & Monika Fleshner

10. LPS-induced suppression of defensive rage behavior: role of peripheral TNF-α; and hypothalamic 5-HT_{1A} receptors.
S Bhatt, R Bhatt, S Zalcman, & A Siegel

11. The INSPIRE study Stress-management psychotherapy improves disease specific quality of life in distressed patients with ulcerative colitis but not in distressed patients with Crohn's disease
Birgitte Boye, Knut E. A. Lundin Kjell. Mokleby Siv Leganger, Slawomir Wojniusz, Astri Dahlstrom, Arne Roseth Ingvard Wilhelmsen, Tone Tangen, Trygve Hausken, Ann-Christin Rivenes, Günter Jantschek, Ingrid Jantschek, Dieter Benninghoven, Svein Blomhof, Michael Sharpe, Ulrik F. Malt, & Jorgen Jahnsen

12. Functional Polymorphisms in the Interleukin-6 and IL-10 Genes and Psychopathological Symptoms in Patients with Chronic Fatigue Syndrome
Sarah Bull, Carmine Pariante, Pattricia Huezo-Diaz, Katherine Aitchison, & Anthony Cleare

13. Acute stress reduces the incidence and severity of self-reported adverse events following vaccination
John PA Campbell, Kate M Edwards, Victoria E Burns, Christopher Ring, Douglas Carroll, & Mark Drayso

14. **Inflammatory Activity of the Neutrophil is Elevated During Exam Stress**
Judith E. Carrol, Aric A. Prather, Anna L. Marsland, & Andrew Baum

15. Chronic But not Acute HIV-1 gp120 Induces Depressive-Like Behavior in Mice
Qing Chang, Xin Fu, Keith Kelley, & Robert Dantzer

16. **Prospective Association between C-Reactive Protein and Fatigue - The Coronary Artery Risk Development in Young Adults (CARDIA) Study**
Hyong Jin Cho, Teresa Seeman, Julienne Bower, Catarina Kiefe, & Michael Irwin

17. **DEPRESSIVE SYMPTOMS PREDICT INFLAMMATION DURING PREGNANCY**
Lisa Christian, Jay Iams, Ronald Glaser, Albert Franco, & Janice Kiecolt-Glaser

18. **Social disruption enhances lung inflammation.**
Jennifer Curry, Michael Bailey, Benjamin Bringardner, Melissa Hunter, John Sheridan, & Clay Marsh

19. **ELEVATED INFLAMMATION LEVELS IN DEPRESSED ADULTS WITH A HISTORY OF CHILDHOOD MALTREATMENT**
Andrea Danese, Terrie E. Moffitt, Carmine Pariante, Antony Ambler, Richie Poulton, & Avshalom Caspi

20. **Relationship between Regulatory T cells (Treg) and Posttraumatic Stress Disorder (PTSD)**
Kevin Del Ben, Alison McLeish, Kevin Connolly, & Gailen Marshall

21. **Exploration of a Novel Behavioral Phenotype in the Interleukin-18 Receptor Knockout Mouse**
A. F. Dorman, & V. J. Bolivar

22. **Serologically documented influenza B infection during pregnancy: Differential effects on birth weight among preschizophrenia infants compared to control infants**
Lauren M. Ellman, Robert H. Yolken, Stephen L. Buka, E. Fuller Torrey, & Tyrone D. Cannon

23. **The effect of Physical Activity and Chronic Stress on Self-reported Upper Respiratory Tract Infection**
Elinor Fondell, Anna L.V. Johansson. Ylva Trolle Lagerros, Carl Johan Sundberg, Mats Lekander, Olle Bälter, Kenneth J. Rothman, & Katarina Bälter

24. Perceived discrimination predicts elevated levels of fibrinogen in a national sample: data from the Survey of Midlife in the United States (MIDUS)
Elliot Friedman David Williams Burton Singer, & Carol Ryff

25. Lipopolysaccharide Induces the Enzyme Indoleamine 2,3-dioxygenase in Mouse Organotypic Hippocampal Slice Cultures
Xin Fu, Samantha Zunich, Robert Dantzer, & Keith W. Kelley

26. Naked Mole-Rat: A Model for Investigating Neuropeptides and Healing
P. Gajendrareddy, J.A. Ruttencutter, T.J. Park, C.E. Laurito, & P.T. Marucha

27. Difficulty waking up when sick: LPS-induced immune activation disengages central arousal network
Ronald Gaykema, & Lisa Goehler

28. Low Levels of Cortisol and sIgA, High levels of DHEA-S, and High Stimulated Levels of TNF-alpha and IL-6 in Women with PTSD
Jessica Gill, & Gayle Page

29. Combined administration of a β-adrenergic antagonist and a COX-2 inhibitor increases survival rates in a model of spontaneous post-operative metastasis in mice: Potential clinical ramifications and mediating mechanisms
Ariella Glasner. Marganit Benish, Shaily Shemer, Ella Rosenne, Christina Katanov, Shiri Weinberg, & Shamgar Ben-Eliyahu

30. The use of CpG-C ODN immunostimulation in the context of stress and surgery: differential modulation of NK cell cytotoxicity and distribution, and protection against NK suppression
Yael Goldfarb, Marganit Benish, Ella Rosenne, Tamar Geron, & Shamgar Ben-Eliyahu

31. The Sympathetic Nervous System Influences Anti-Influenza Immunity
Kristie Grebe, Heather Hickman, Jack Bennink, & Jonathan Yewdell

32. Biobehavioral Correlates of Overweight and Obesity in Postpartum Women
Maureen Groer

33. Beta-2 Adrenergic Blockade Decreases the Immunomodulatory Effects of Social Disruption Stress (SDR)
Mark Hanke, Michael Bailey, Nicole Powell, Latonia Stiner, & John Sheridan

34. RELATIONSHIP OF IL-4 AND SEROTONIN TRANSPORTER GENE POLYMORPHISMS ON HUMAN ACOUSTIC SENSORIMOTOR GATING RESPONSES AND EMOTION.
Joanne Hash, & Alexander Kusnecov

35. Cortisol may influence HIV progression via effects on T-cell activation and CCR5
Frederick Hecht, Elissa Epel, Patricia Moran, Michael Acree, Adam Carrico, Steven Deeks, Elizabeth Sinclair, Margaret Kemeny, & Susan Folkman

36. Fatigue in adolescent girls: a psychoneuroimmunological approach
Cobi J. Heijnen. Maike ter Wolbeek, Lorenz J.P. van Doornen, & Annemieke Kavelaars

37. Depression and Anxiety, Health locus of control and Quality of life among Gouty Arthritis Males.
Roger C.M. Ho, Jason Tan, Alicia Cheak, & Anselm Mak

38. A Potential Effect of Beta-blockers on Inflammatory Responses to a Psychological Stressor in Congestive Heart Failure Patients
Suzi Hong, Laura Redwine, Sarah Linke, Douglas DeJardin, Barry Greenberg, & Paul Mills

39. Repeated administration of cannabidiol enhances nonspecific, antiviral and antitumor immune response
B. Ignatowska-Jankowska, M. Jankowski, W Glac, & A. H. Swiergiel

40. Can consumption of omega-3 fatty acid (ω-3FA) attenuate laparotomy-induced NK suppression and metastasis progression in rats?
Yael Kalderon, Rivka Melamed Ben Levi, Marganit Benish, Ella Rosenne, Ariella Glasner, Hadas Meiboom, Shaily Shemer, & Shamgar Ben-Eliyahu

41. Modulation of Antibody Production by Stress in Interferon-γ Receptor Knockout Mice
Jonathan Karp, Jenny Stanwix, & Sujata Kumar

42. Written Emotional Disclosure: Sympathetic Habituation?
Kimberly Kelly, Damini Malhotra, Kenneth Sewell, & Daniel Tomczyk

43. Physical activity modulates stress effects on tetanus toxoid antibody responses.
Sarah Kennedy, Teresa Foley, Thomas Maslanik, Monika Fleshner, & Monika Fleshner

44. Modulation of RAW 264.7 Murine Macrophage Responses to Lipopolysaccharide by Larch Arabinogalactan
Shannon Kennedy, & David Freier

45. Hypermetabolic syndrome as a consequence of chronic psychological stress in mice
Cornelia Kiank, Maren Depke, Gerhard Fusch, Grazyna Domanska, Robert Geffers, Uwe Voelker, & Christine Schuett

46. Sympathetic neurotransmitter, epinephrine, regulates adaptive immunity through antigen presenting cells
Byung-Jin Kim, & Harlan Jones

47. Neuropathic pain is attenuated by a cannabinoid mechanism of action
Steven Kinsey, & Aron Lichtman

48. Increasing endogenous cannabinoids attenuates the neuropathic pain response to touch and cold.
S G Kinsey, A H Lichtman

49. Influence of prenatal stress on behavioral, endocrine, and cytokine responses to adulthood endotoxin exposure
Rachel Kohman, Andrew Tarr, Kristina McLind, & Gary Boehm

50. Toll-like receptor expression is altered by stress of intense physical conditioning
Marian Kohut, Cole Sanderson, Ishrat Sultana, Shan Yu, Young-Je Sim, Gina Flinn, & Jodi McKay

51. Anti-NMDA Receptor Antibodies and Cognition in nonNPSLE
Elizabeth Kozora, Steven Maier, Lening Zhang, David Arciniegas, Mark Brown, Christopher Filley, David Miller, Alex Grimm, Marie Devore, Christy Wingrove, & Sterling West

52. Cytokines, Antiphospholipids, and Cognition in NonNPSLE
Elizabeth Kozora, Steven Maier, Lening Zhang, David Arciniegas, Mark Brown, Christopher Filley, David Miller, Alex Grimm, Mark Devore, Christy Wingrove, & Sterling West

53. Addiction, personality traits, stress, and AIDS: Possible role of specific gene variants and epigenetic changes
Mary Jeanne Kreek

54. INFLAMMATORY LIPOPOLYSACCHARIDE INCREASES BEHAVIORAL DESPAIR IN THE C57BL6 MOUSE
Donald M. Lamkin, Susan K. Lutgendorf, & Alan Kim Johnson

55. Gender effects on diurnal rhythms in salivary cortisol among American Indians with and without posttraumatic stress disorder (PTSD)
Mark Laudenslager, Carolyn Noonan, Jack Goldberg, Dedra Buchwald, Douglas Bremner, Viola Vaccarino, Spero Manson

56. Diet-induced obesity causes depressive-like behavior in mice
Desiree Lavin, Christina Sherry, Jason O'Connor, Robert Dantzer, & Gregory Freund

57. Sleep, Depression, Stress and Immunity in Dementia Caregivers: A Seven Day Study
Brandy Lehman

58. Increased Stress-Induced Plasma IL-6 Responses in Male Depressed Patients with Increased Early Life Stress: Role of Catecholamines
Andrea I. Liatis, Andrew H. Miller, Tanja M. Mletzko, Chrsitine M. Heim, Robert Bonsall, & Thaddeus W. W. Pace

59. Is Bipolar Disorder an Autoimmune Disease?
Lin Lu

60. Behavioral, neurotransmitter and immunological comparison of three common MPTP mouse models of Parkinson's disease
Dirk Luchtman, Di Shao, & Cai Song

61. Mucosal Wound Healing: The Relationship With Human Sex Hormones
Bahareh Zyaei, Christopher G. Engeland, & Phillip T. Marucha

Trainees: Right after Poster Session 1, please remember to join us for the Junior Faculty/Trainee Worskhop in the Main Lecture Hall. From 6:30 – 7:15, three of our members will lead a discussion about building a research and academic career in PNI.

At 7:30 the Trainee Dinner begins at the Essen Haus. This is a very casual, german-style pub three blocks from the Hilton. You will be treated to a local polka band and a more traditional side of early Wisconsin. Please bring your dinner ticket that should have been in your packet; guests can be accommodated for $25 each.

For anyone wanting a guide to the Essen Haus, there will be someone at the main entrance of the Hilton at 7:20 to show the way.

Poster Session 2, Authors M-Z, Saturday, May 31, 4:00 -6:00

1. Effects of an Acute Laboratory Stressor on Regulatory T cell (Treg) Levels in Normal Human Peripheral Blood Mononuclear Cells (PBMC)
Gailen D. Marshall, & Kevin S. Del Ben

2. Fever and sickness behavior vary among related rodent species
Lynn Martin, Zachary Weil, & Randy Nelson

3. Gender, aging, stress, and salivary growth factors in mucosal wound healing
Phillip T. Marucha, Tricia R. Crosby, Jos A. Bosch, & Chistopher G. Engeland

4. Intense, acute stressor exposure impairs splenic killing/clearance of intravenously delivered Escherichia coli.
Thomas Maslanik, Isaac Bernstein-Hanley, Lida Le, & Monika Fleshner

5. Epigenetic patterns associated with psychosocial distress mediated immune dysregulation.
Herbert Mathews, & Linda Janusek

6. Pharmacological enhancement of central noradrenergic tone induces IL-10 production and signaling in rat brain: A role for β-adrenoceptor activation
Eoin N. McNamee, Rodrigo E. González-Reyes, Andrew Harkin, & Thomas J. Connor

7. Plasma Cytokine Levels in Astronauts Before and After Spaceflight
Satish Mehta, Barat B. Aggarwal, Alan H. Feiveson, Dianne K. Hammond, Victoria A. Castro, Raymond P. Stowe, & Duane L. Pierson

8. Predictors of depressed mood in heart failure (HF)
Paul J. Mills, Sarah Linke, Suzi Hong, Laura Redwine, Joel Dimsdale, Thomas Rutledge, & Barry Greenberg

9. Long-term alterations in neuroimmune and neuroendocrine responses following neonatal exposure to lipopolysaccharide in Wistar rats
Tamo Nakamura, Adam Walker, & Deborah Hodgson

10. Increased DNA methylation in the promoter region of the μ-opioid receptor gene (*ORPM1*) in lymphocytes of Caucasian methadone maintained former heroin addicts
David Nielsen, Vadim Yuferov, Sara Hamon, Colin Jackson, Jurg Ott, & Mary Jeanne Kreek

11. Induction of Depressive-like Behavior in Mice by *Bacillus Calmette-Guerin* is Dependent on Indoleamine 2,3-dioxygenase
Jason O'Connor, Marcus Lawson, Caroline Andre, Jacques Lestage, Nathalie Castanon, Robert Dantzer & Keith Kelley

12. The Relationship between Poor Sleep Quality and PPMD Recurrence is Not Mediated by IL-6
Michele Okun, Aric Prather, Martica Hall, Barbara Hanusa, Katherine Wisner

13. Variability in Cortisol among the Aging: Relationships to Chronic Stress and Good Sleep
Michele Okun, Charles Reynolds III, Timothy Monk, Martica Hall

14. The curcumin analog, UBS-109 decreases peripheral expression of LPS-induced inflammatory cytokines
Anlys Olivera, Fang Hu, Andrew P. Brown, Hyunsuk Shim, Dennis Liotta, Andrew Miller, & Thaddeus W. Pace

15. Effect of Compassion Meditation on Autonomic, Neuroendocrine and Inflammatory Pathway Reactivity to Psychosocial Stress
Thaddeus Pace, Lobsang Tenzin Negi, Daniel Adame, Steven Cole, Teresa Sivilli, Timothy Brown, Michael Issa, & Charles Raison

16. Blocking of beta-2 adrenergic receptor hastens recovery from hypoglycemia-associated social withdrawal
Min Jung Park, Christopher B. Guest, Meredith B. Barnes, Jonathan Martin, Uzma Ahmad, & Gregory G. Freund

17. Effects of breast cancer risk and psychological distress on immune responses in healthy women
Na-Jin Park, & Duck-Hee Kang

18. Acute Effects of Oral Administration of a Glycerol Extract of Echinacea purpurea on Peritoneal Exudate Cells in Female Swiss Mice
Tanha Patel, Audra Crouch, Kayla Dowless, & David Freier

19. Strain Differences in Basal Activity: Effects of Aging and Stimulation of Central Imidazoline-1 Receptors on Splenic Sympathetic Activity and β-AR-stimulated cAMP Production in Middle-aged F344 and Brown Norway Rats.
Sam D Perez, Brooke A Kozic, Christine Molinaro, Jeff Carter, Sharda Vyas, Srinivasan ThyagaRajan, & Denise L Bellinger

20. The relationship between rape survivor's levels of distress, health profile, ways of coping and measures of the immune system
Prishika Pillay

21. HIV-1-infected subjects with neuropsychological impairment have a unique gene expression profile
Lynn Pulliam, Bing Sun, Linda Abadjian, & Hans Rempel

22. Tumors induce depression and alter neuroimmne and neuroendocrine systems
Leah M. Pyter, Vanessa M. Pineros, Jerome A. Galang, Martha K. McClintock, & Brian J. Prendergast

23. The relationship between psychosocial and immune variables in American women with breast cancer.
Sarah M. Rausch, Nancy L. McCain, Stephen Auerbach, & Sandra Gramling

24. Increased lymphocyte glucocorticoid sensitivity to chronic stress in aging Fisher rats.
Laura Redwine, Amelia Chen, & Michael Irwin

25. Neuroinflammation and cognitive function in aged mice following minor surgery
Heidi Rosczyk, Nathan Sparkman, & Rodney Johnson

26. Increased parental stress correlates with poorer asthma control in children
Sitesh Roy, Jake Olivier, Kevin DelBen, & Gailen Marshall

27. Psychoneuroimmunology and Acculturation in Hispanic Pregnant Women
R. Jeanne Ruiz, & Sheryl Bishop

28. The glucocorticoid dexamethasone prevents inflammation-induced suppression of glial β_2-adrencoceptor expression: Implications for Multiple Sclerosis
Karen M. Ryan, Eoin N. McNamee, & Thomas J. Connor

29. Biobehavioral and Spiritual Responses of Women in a Labyrinth Walking Program
M. Kay Sandor

30. Relationships between Perfectionism and Self-Reported Short-Term Physical Illness Complaints
Debra Schroeder

31. Neural progenitors and neuroinflammation in the pathogenesis of pediatric neuroAIDS
Lynnae Schwartz, & Steven Douglas

32. Soluble fiber enhances recovery from LPS-induced social withdrawal in a manner dependent on IL-4
Christina Sherry, Stephanie Kim, Ryan Dilger, George Fahey, Kelly Tappenden, & Gregory Freund

33. Association of Promoter Polymorphisms in the α7 Nicotinic Acetylcholine Receptor with Cortisol Stress Response
Melissa L Sinkus, Marianne Z Wambold, Amanda Barton, Sherry Leonard, & Mark Laudenslager

34. Specificity in the Association of Comorbid Anxiety and Atopic Disorders in Adolescents
Marcia J. Slattery, & Marilyn J. Essex

35. The Association between Fatigue, Vital Exhaustion and Inflammatory Markers in Chronic Heart Failure
Otto R.F. Smith, Susanne S Pedersen, & Johan Denollet

36. Effects of relaxation training on physiological and psychological measures of distress and quality of life in HIV-seropositive subjects
Sharon Stout-Shaffer, & Gayle Page

37. The Effects of Personality and Stress on HSV-2 Shedding in Women Undergoing a Randomized, Placebo-Controlled, Crossover Trial of Acyclovir
Eric Strachan, Amalia Margaret, Dedra Buchwald, & Anna Wald

38. HCV infection induces monocyte secretion of proinflammatory cytokines that are neurotoxic
Bing Sun, Alexander Monto, Hans Rempel, & Lynn Pulliam

39. Significance of Glutamatergic Neurotransmission in Interleukin-1-Induced Hypophagia.
Artur H Swiergiel, & Adrian Dunn

40. No Apparent Role for Glutamatergic Neurotransmission in Interleukin-1-Induced Hypophagia
Artur H Swiergiel, & Adrian Dunn

41. The conditioned effects of heroin on nitric oxide are mediated by dopamine D1, not D2, receptors within the basolateral amygdala
Jennifer Szczytkowski, & Donald Lysle

42. DIFFERENTIAL EFFECTS OF DEPRESSED MOOD AND EXERCISE STRESS ON SOLUBLE ADHESION MOLECULE RESPONSES IN HEART FAILURE (HF)
Joseph Tafur, Suzi Hong, & Paul J Mills

43. LPS-Induced Memory Consolidation Impairment in Active Avoidance Conditioning: Effects of Age
Andrew Tarr, Kristina McLinden, Rachel Kohman, Gary Boehm

44. Type C Coping and Alexithymia are Associated Differentially with Specific Immune Mechanisms (Interleukin-6 and Beta-Chemokine Production) Linked to HIV Progression
Lydia Temoshok, Rebecca Wald, Stephen Synowski, Alfredo Garzino-Demo, & James Wiley

45. Stress, Anxiety, and Heat Shock Proteins in Women Undergoing Surgery for Suspected Endometrial Cancer
Sannes Tim, Sally Jensen, Stacy Dod, Lindsey Boegeheld, Linda Morgan, Ed Chan,& Deidre Pereira

46. Psychological Distress and Coping Predict the Healing of Chronic Wounds: The Case of Diabetic Foot Ulcers
Kavita Vedhara, Jeremy Miles, Mark Wetherell, Aidan Searle, Deborah Tallon, Karen Dawe, Nicky Cullum, Andrew Day, Colin Dayan, Nikki Drake, Patricia Price. John Tarlton, John Weinman, & Rona Campbell

47. Stress and Wound Healing: Effects of housing conditions and coping with a psychological stress.
Oscar Vegas, Joanne Vanbuskirk, Steven Richardso, David Parfitt, Dana Helmreich, Max Rempel, & Francisco Tausk

48. Fluorocitrate attenuates a lipopolysaccaride-induced spinal learning deficit
Elisabeth Vichaya, Kyle Baumbauer, James Grau, & Mary Meagher

49. Effects of Exercise Training on the Immune Response to Influenza Vaccination in Older Adults: A Randomized Controlled Trial
Victoria Vieira, K. Todd Keylock, Thomas Lowder, William Zelkovich, Sara Dumich, Kim Colantuano, Kristin Potter, Kurt Leifheit, Edward McAuley, & Jeffrey Woods

50. Effect of a Preoperative Warming Intervention on the Acute Phase Response of Surgical Stress
V. Doreen Wagner, & Maureen Groer

51. Neonatal lipopolysaccharide exposure alters neonatal and adulthood neuroendocrine functioning, sexual maturation and blood composition in the rodent
Adam K. Walker, Tamo Nakamura, Deborah M. Hodgson

52. The double-hit hypothesis of psychopathology: Neonatal lipopolysaccharide exposure predisposes male but not female rodents to anxiety-like behaviour following stress in adulthood
Adam K. Walker, Tamo Nakamura, Deborah M. Hodgson

53. Kynurenine Metabolism in Primary Murine Microglia Activated with Interferon-γ and LPS is Inhibited by Nitric Oxide
Yunxia Wang, Marcus Lawson, Jason O'Connor, Robert Dantzer, Keith Kelley

54. Mechanisms by which interleukin-1 affects behavior and the HPA axis in rats: the roles of cyclooxygenase, the vagus nerve and brain norepinephrine.
Marek Wieczorek, Adrian Dunn

55. With increasing body mass index (BMI) mental stress reduces the capacity of glucocorticoids to suppress inflammatory cytokine production in men
Petra H. Wirtz, Ulrike Ehlert, Luljeta Emini, Tobias Suter

56. Adiposity and IL-6 in Women Diagnosed with Breast Cancer
Linda Witek-Janusek, Herbert L. Mathews

57. Disruption of the joint- immune-brain communication during experimental arthritis in the rat
Christine Wolff, Anja Hahnel, Johannes Wildmann, Hugo O. Besedovsky, Rainer H. Straub, & Adriana del Rey

58. Interleukin-2 Potentiates Behavior Activating Effects Induced by a Dopamine D1 but not D3 Receptor Agonist
R T Woodruff, J, Magid, M.D. Bobbin, E. Kuzhikandathil, & S.S. Zalcman

59. IMPACT OF NEONATAL INFECTION ON ADULT HIPPOCAMPAL GLUCOCORTICOID RECEPTOR AND MINERALOCORTICOID RECEPTOR ABUNDANCE
Olivia Wynne, Jay Horvat, Roger Smith, Philip Hansbro, Vicki Clifton, & Deborah Hodgson

60. *In vitro* Stress Hormone Glucocorticoid (GC) Exposure Alters Gene Expression on both GC and Cytokine Receptors and Cytokine Production in Normal Human PBMC
Lianbin Xiang, & Gailen D. Marshall

61. Impact of chronic restraint stress during early Theiler's virus infection on CNS disease severity in SJL mice.
Erin Young, Amy Sieve, Elisabeth Vichaya, Luis Carcoba, Andrew Steelman, Colin Young, Ralph Storts, Tom Welsh, C. Jane Welsh, & Mary Meagher

62. Six different promoters control IL-1RI expression in human
Hao Zhang, Qiming Li Ying, An Qun, Chen, & Ning Quan

After Poster Session 2, please join us for the Business Meeting (which takes places from 6:00-7:00 in the Main Lecture Hall on Saturday).

And don't miss the Banquet that will take place out on the Grand Terrace.

Dinner and drinks start at 7:30. Do remember to bring your dancing shoes. The music begins at 8:30 and continues until midnight. Our society also has this important post-meeting festive tradition and reputation to maintain.

Abstracts for the Four Symposia

Symposium I: The impact of inflammation on the vulnerable brain
Chairpersons: Marina Lynch & Rodney Johnson

The link between neurodegeneration, neurodegenerative diseases and inflammation is now widely accepted and there is a growing awareness that inflammatory stress, even in early life may have a significant impact on the likelihood of developing neurodegenerative diseases in later life. Similarly, underlying inflammation (e.g., with systemic infections) can exacerbate symptoms and trigger rapid progression in some neurodegenerative diseases. The objective of this symposium is to explore the mechanisms by which underlying inflammatory changes impact on neuronal function, particularly following a stressful stimulus. The 4 speakers have contributed significantly to the literature in this area. Anthony and his team have analysed the interaction between the peripheral immune response and CNS function and have highlighted the importance of peripheral responses to acute brain injury. He will discuss the consequences of chronic IL-1β expression in brain on neuronal function and on peripheral, particularly hepatic, function. Johnson and his team have reported that aging is associated with an exaggerated sickness response following central innate immune activation and will discuss the underlying mechanisms responsible for this and for the associated disruption in cognitive function. Allen and his colleagues have highlighted the importance of IL-1β in mediating the exacerbated effect of systemic lipopolysaccharide in an animal model of stroke. Lynch and her group have found that aged rats, in which neuroinflammatory changes have been described, exhibit greater sensitivity to acute and chronic administration of amyloid-β. The presentations will include a discussion of the role of activated microglia in these models and will highlight the importance of specific chemokines in cell-cell interaction and recruitment of peripheral cells to the brain in the development of the inflammatory changes.

Symposium II: **Individual responses to the environment: Immune and health correlates**
Chairpersons: Sonia Cavigelli & John Capitanio

Individuals differ reliably in their responses to environmental conditions/demands. These stable response profiles (i.e., traits, personality) involve specific physiological correlates and recent evidence indicates these differences are associated with prominent differences in health trajectories. The proposed symposium will address the issue of how individual response differences – both behavioral and physiological - provide the nexus through which cytokines and societies interact, and can influence individual health outcomes. The symposium features an interdisciplinary panel of scientists to present recent findings on individual response differences and reliable associations with immune function and health outcomes. Specifically, speakers will focus on differential behavioral profiles as they relate to cytokine production and health outcomes. This symposium will highlight the 2008 PNIRS meeting theme: "Promoting innovation in PNI: From cytokines to society". Furthermore, the speakers will address an area of research – mechanisms underlying individual differences in health profiles – identified as a key issue for health research by the director of the National Institutes of Health.

Symposium III: HIV and the brain: Models and treatment approaches. A NIMH-sponsored symposium
Chairpersons: Keith Kelley & Robert Dantzer

The symposium entitled, *HIV and the Brain: Models and Treatment Approaches*, will further elaborate on the concept that HIV neuropathology and psychopathology share similar pathophyiological mechanisms (Kopniski et al., *Brain, Behavior, and Immunity, 2007, 21:428-441*). It will focus on basic neuroscience research that studies interactions between the central and peripheral nervous and immune systems in the context of HIV infection. The session speakers will provide a brief overview regarding neuroAIDS and mechanisms of neuropathogenesis, discuss rodent and SIV models to evaluate their interactions, show how

epigenetic modifications may alter inter-individual disease progression susceptibility and present CNS gene delivery and other drug developments that target potential immunomodulatory and neuroprotective mediators.

Symposium IV: Dynamic innervation of lymphoid tissue: Mechanisms and impact
Chair: Steve Cole

Direct innervation of lymphoid tissue has long been recognized as a potential regulatory influence on immune function. Recent studies have revealed a surprising degree of plasticity in the structure of lymphoid tissue innervation. Factors such as social stress, aging, and inflammation all appear to dynamically regulate the density of sympathetic innervation in lymphoid tissues. This symposium will examine some of the causes and consequences of those structural alterations. The Chair, Steve Cole (UCLA), will introduce the symposium with some brief remarks on the physiologic and historical context for the presented research. Dwight Nance (UC Irvine) will anchor the symposium with a survey of the neuroanatomy of lymphoid innervation, using recent work from his own laboratory to illustrate the consequences of innervation for immune function and CAM therapy. Erica Sloan (UCLA) will present data showing that social stress can enhance sympathetic innervation of lymph nodes in the SIV model of viral infection, resulting in altered cytokine production and enhanced viral replication. Dianne Lorton (Sun Health Research Institute) will present studies analyzing the molecular mechanisms and functional consequences of neural reorganization that occurs in lymphoid tissue during rheumatoid arthritis, including changes in cytokine profiles that impact disease outcome. Denise Bellinger (Loma Linda University) will present data on the relationship between aging and lymphoid innervation, analyzing the trophic factors that support neural fibers and assessing their impact on health and disease over the life span. The symposium chair will then integrate some of the emerging themes, and coordinate an audience-driven panel discussion on the dynamic nature of lymphoid innervation, and its implications for immune function and human health.

For early risers on Saturday morning, don't miss the Farmer's Market on the Capitol Square before the first sessions begin. The market should get started by 7:00 A.M. and will give you a nice exposure to the local people and cuisine. If you want to to try a unique Wisconsin snack, buy a bag of fresh cheese curds to munch on while you walk around the Square.

ABSTRACTS FOR ALL TALKS AND POSTERS LISTED ALPHABETICALLY BY FIRST AUTHOR

Central inhibition of IL-1β ameliorates lipopolysaccharide-induced sickness behavior in aged mice.

* Jayne Abraham[1] Rodney Johnson[1]
[1]Div. of Nutritional Sciences, Integrative Immunology and Behavior, University of Illinois, Urbana IL, USA
** Corresponding author: Jayne Abraham, (jabraham@uiuc.edu)*

Peripheral infection induces excessive production of interleukin-1 beta (IL-1β) in the brain of healthy aged mice. Although high levels of IL-1β in the brain have been implicated in infection-related behavioral pathologies in aged animals, this has not been directly tested. Therefore, the objective of this study was to determine if the sickness behavior elicited by peripheral infection is mediated through central IL-1β in aged animals. Adult and aged mice were injected intracerebroventricularly (ICV) with either vehicle or IL-1ra (4 μg) immediately prior to intraperitoneal (i.p) administration of vehicle or LPS (10 μg) and locomotor and social exploratory behaviors were assessed. While both adult and aged mice peripherally injected with LPS had reduced spontaneous locomotor and social behavior, IL-1ra pretreatment effectively ameliorated sickness behavior in aged but not adult mice. In addition, 24h after LPS, levels of IL-1β mRNA in the hippocampus in young mice did not differ from saline controls while hippocampal levels of IL-1β mRNA in aged animals were significantly elevated. This LPS-induced increase in IL-1β mRNA was inhibited by pretreatment with IL-1ra. These findings suggest that IL-1ra affects adult and aged mice differentially and that centrally mediated effects of IL-1β account for a significant part of LPS-induced sickness behavior in aged mice. Inhibiting the central actions of IL-1β may be useful for minimizing behavioral complications in older individuals with a peripheral infection. This research was supported by NIH grants AG16710, AG023580, and MH069148 to R. W. J.

Repeated social defeat-induced increases in microbicidal activity of splenic macrophages are diminished by inhibiting NO production

* Rebecca Allen[1] David Padgett[2] John Sheridan[2] Michael Bailey[2]
[1]Integrated Biomedical Sciences Graduate Program, College of Medicine, The Ohio State University, Columbus, OH [2]Section of Oral Biology, College of Dentistry; Institute for Behavioral Medicine Research, College of Medicine, The Ohio State Univ., Columbus, OH
** Corresponding author: Rebecca Allen, (rga_1473@yahoo.com)*

Repeated social defeat was previously shown to enhance the ability of splenic macrophages to kill bacteria both *in vitro* and *in vivo*. This increase was associated with enhanced gene expression of inducible nitric oxide synthase (iNOS), which results in the production of nitric oxide (NO). These experiments were designed to test the hypothesis that inhibiting the production of NO would abrogate the stress-induced increase in bactericidal activity. Male mice were repeatedly defeated using social disruption (SDR), which involves interactions between resident mice and an aggressive intruder. This occurred over a 2 hr period on 6 consecutive days. Following the final day of SDR, single cell suspensions were created from the spleen. To block the production of NO, adherent splenic macrophages were cultured *in vitro* and treated with L-N^G-monomethyl arginine citrate (a synthetic form of arginine that cannot be converted to produce NO). *Escherichia coli* were co-cultured with the macrophages, and the number of bacteria within the macrophages was enumerated at 20 and 90 min (to determine the number of bacteria phagocytosed and then killed, respectively). In the absence of the NO inhibitor, SDR increased the percentage of bacteria that were killed by the splenic macrophages ($p < .05$). Importantly, the percentage of bacteria that were killed by macrophages from SDR were similar to percentages killed by non-stress controls after blocking NO production. These data indicate that NO plays a central role in the stress-induced increase in bactericidal activity of splenic macrophages. Supported by NIH grant RO3AI069097 (MB).

Sex-specific relations between leptin and self-rated health

Anna Andréasson[1] Kerstin Brismar[2] Susanna Jernelöv[3] Anna-Lena Undén[1] * Mats Lekander[3, 4]
[1]Center for Family Medicine, Karolinska Institutet, Stockholm, Sweden [2]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockolm, Sweden [3]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden [4]Osher Center for Integrative Medicine, Karolinska Institutet, Stocholm, Sweden ** Corresponding author: Mats Lekander, (Mats.Lekander@ki.se)*

Poor self-rated health (SRH) is associated with overweight, as well as higher levels of IL-6 and TNF-alpha in women. IL-6 and TNF-alpha can be produced but also by adipocytes. To investigate the relation between adipose tissue, inflammation and SRH, leptin (a marker of adipose tissue amount) and haptoglobin were used. A random selection of the Stockholm County population with 90 men and 100 women, 20 to 75 years, attended a health control, provided blood samples and rated SRH. Two years later, they responded to questions about SRH and chronic disease. Cross-sectional and prospective relations between leptin, haptoglobin and SRH were analysed with ordinal logistic regressions. Dependent variables were SRH from the first or the second assessment. Independent variables were leptin, haptoglobin, BMI, presence of chronic disease and age. In men, high leptin was associated with poor SRH (p=0.01) while low leptin was associated with poor SRH in women (p=0.01). Prospectively, a relation was found in women between low leptin and poor SRH two years later (p=0.04). In men, chronic disease was associated with poor SRH at both time points (p=0.01 and p=0.006). In women, higher BMI was associated with poor SRH (p's <0.05). Haptoglobin and age were not related to SRH at either occassion. Surprisingly, the results suggest that high levels of leptin are associated with poor SRH in men and good SRH in women. The finding in women could possibly be explained by the fact that leptin not only marks cytokine-producing adipose tissue but also displays partly dissimilar features compared to TNF-alpha and IL-6.

Chronic stress promotes tumor growth through a Src-dependent mechanism in a mouse model of ovarian cancer

Guillermo N. Armaiz-Pena[1] Lingegowda S. Mangala[2] Liz Y. Han[2] Yvonne G. Lin[2] Rosemarie Schmandt[2] Angela M. Sanguino[3] Gabriel Lopez-Berestein[3] Susan K. Lutgendorf[4] Steve W. Cole[5] * Anil K. Sood[6]
[1]Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center; Program in Cancer Biology, University of Texas Graduate School of Biomedical Sciences at Houston [2]Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center [3]Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center [4]Department of Psychology, University of Iowa [5]Division of Hematology-Oncology, Department of Medicine, University of California at Los Angeles School of Medicine [6]Departments of Gynecologic Oncology and Cancer Biology, The University of Texas M. D. Anderson Cancer Center ** Corresponding author: Anil K. Sood, (asood@mdanderson.org)*

Clinical studies indicate that chronic stress, depression, and other psychological factors might influence cancer progression; however, the underlying mechanisms are not fully understood. Src, a non-receptor tyrosine kinase, is a central converging point for many cancer signaling pathways. In this study, we examined the effects of stress hormones on Src and downstream tumor growth. Norepinephrine rapidly activated Src at Y416 in β-adrenergic receptor (βAR)-positive ovarian cancer cell lines (HeyA8 and SKOV3ip1), but not in βAR null A2780 cells. Furthermore, confocal microscopy showed that Src was rapidly recruited to the cellular membrane after Norepinephrine exposure in βAR-positive ovarian cancer cells. Additionally, in two orthotopic mouse models of ovarian carcinoma (HeyA8 and SKOV3ip1), restraint stress significantly increased tumor weights (182 to 315% increase, $p < 0.05$). This increase in tumor growth was completely blocked by Src silencing with Src siRNA-DOPC. These data provide the first evidence regarding the critical role of Src activation in chronic stress mediated increase in ovarian cancer growth.

A working week with restricted sleep: effects on self-rated health and immune responses to a mitogen challenge

* John Axelsson[1, 2] Torbjorn Akerstedt[2] Rolf Ekman[3] Caroline Olgart-Hoglund[1] Mats Lekander[1]
[1]Karolinska Institutet, Stockholm, Sweden [2]Stockholm University, Stockholm, Sweden [3]Goteborgs University, Goteborg, Sweden
** Corresponding author: John Axelsson, (john.axesson@ki.se)*

There is little understanding of how the immune system reacts to continued sleep restriction. Our aims were to investigate how restricted sleep affect self-rated health (an important predictor of future mortality) and whether it disrupts the immune response to a mitogen challenge.

Nine subjects participated in a strict 6-week sleep protocol, including 12 days in the sleep laboratory, one habituation day (sleep 23-07h), two baseline days (23-07h), five days with restricted sleep (03-07h) and four recovery days (23-07h). For 9 of those days, blood was drawn every hour 23-08h and every 3rd hour 08-23h. Selected blood samples were stimulated in vitro with phytohemagglutinin (PHA) and were analysed with respect to cytokines.

Sleep restriction resulted in a gradual decrease of self-rated health ($p<.0001$) and three subsequent recovery days were needed before levels had returned to baseline. The immune responses to PHA were affected by 5 days of sleep restriction. TNFα and MCP-1 (monocyte chemoattractant protein-1) increased during late evening and early night hours as compared to baseline values (p's<.01). The IL-2/IL-4 ratio decreased significantly ($p<.01$), indicating an altered T helper (Th) 1/ Th2 response.

The switch from Th1 to Th2 cytokines suggests that repeated sleep restriction have similar effects as acute sleep restriction and stress. Moreover, the strong relationship between restricted sleep and self-rated health indicate a need for further studies on immune activation and reduced health in individuals with impaired sleep, as suggested by recent studies of non-stimulated cytokines.

Repeated social defeat increases cytokine production by *Porphyromonas gingivalis* LPS-stimulated macrophages.

* Michael Bailey[1] Steven Kinsey[2] Rebecca Allen[3] David Padgett[1] John Sheridan[1]
[1]Section of Oral Biology, College of Dentistry; Institute for Behavioral Medicine Research, College of Medicine, The Ohio State Univ, Columbus, OH [2]Department of Pharmacology and Toxicology, The Virginia Commonwealth Univ., Richmond, VA [3]Integrated Biomedical Sci Grad Program, College of Med, The Ohio State Univ., Columbus, OH
** Corresponding author: Michael Bailey, (bailey.494@osu.edu)*

Exposure to psychological stress is well known to suppress immune cell reactivity, and many of the health implications for such immunosuppression have been well described. There is mounting evidence that stress can also enhance the immune response, but the impact of this immune-enhancing activity on disease processes has not been as well studied. Stress is a known risk indicator for the development of oral inflammatory diseases like periodontitis. However, the causal mechanisms linking stress and this disease are not understood. The purpose of this study was to determine whether a social stressor would enhance macrophage reactivity to LPS from *Porphyromonas gingivalis*, a causative agent of periodontitis. Male mice were exposed to the social disruption (SDR) stressor, which involves repeated social defeat by an aggressive intruder mouse. This occurred over a 2 hr period on 6 consecutive days. After SDR, macrophages from the spleen were positively selected and stimulated with *P. gingivalis* LPS in culture. The levels of IL-1β and TNF-α were assessed in culture supernatants. Exposure to SDR prior to ex vivo LPS stimulation significantly increased the production of both IL-1β and TNF-α by total splenocytes ($p < .05$) and by splenic macrophages ($p < .05$). Because IL-1β and TNF-α play prominent roles in oral tissue destruction during periodontal disease, the data provide the rationale to develop animal models to study the mechanisms through which social stressors affect oral inflammatory diseases. Supported by OSU College of Dentistry Seed Grant (MB, BL).

Effects of spaceflight stress on anti-inflamatory response

* FP Baqai[1] DS Gridley[1, 2] EJM Bayeta[2] M Andres[2] X Luo-Owen[2] TA Jones[2] B Bianski[2] A Rizvi[1] HQ Han[3] D Lacey[3] L Stodieck[4] V Ferguson[4] LM Green[1, 2] GA Nelson[2] MJ Pecaut[1, 2]
[1]Loma Linda University Department of Microbiology and Biochemistry [2]Department of Radiation Medicine LLURM Molecular Radiation Biology Lab. [3]Amgen Research [4]BioServe Space Technologies, University of Colorado - Boulder.
* *Corresponding author: FP Baqai, (fpirayesh05b@llu.edu)*

Spaceflight conditions have a significant impact on a number of physiological functions. Preliminary studies indicate that many of the changes noted in immune parameters are due to spaceflight-induced oxidative stress. We hypothesize that exposure to the spaceflight environment causes an overall increase in ROS (reactive oxygen species) that, in turn, down-regulates inflammatory mechanisms. In August of 2007, female C57BL/6 mice were flown aboard the Space Shuttle Endeavor for 13 days using NASA's animal enclosure modules (AEMs). Ground controls were maintained under conditions similar to those experienced by flight mice on a 48 hour delay using telemetry from the shuttle. Within 3 hours of landing, the mice were euthanized and organs were harvested. After an initial assessment at Kennedy Space Center (KSC), tissues were sent to Loma Linda University via overnight courier for further processing. Splenocytes were counted via flow cytometry and automated hematology analyzer, plated at 1e6 cells/mL, and incubated with 0.017mg/mL lipopolysaccharide (LPS, 0111:B5) for 48 hours. We found spaceflight-induced decreases in spleen, liver, and thymus mass ($p<0.005$). There were also significant reductions in all major leukocyte populations ($p<0.05$). Similarly, overall T and B cell counts decreased ($p<0.01$). Although spontaneous blastogenesis increased, there were significant decreases in mitogen-induced blastogenesis ($p<0.001$). Finally, there were decreases in tumor necrosis factor-α (TNF-α, $p<0.001$) with corresponding increases in interleukins- 6 and 10 ($p<0.05$). These results suggest that exposure to the spaceflight environment leads to an anti-inflammatory response. These changes may cause a disturbance in the homeostasis maintained by the CNS and immune system.

Sleep, sleep deprivation and responses to lipopolysaccharide of interleukin-1b receptor 1 and tumor necrosis factor-a receptor 1 double knockout mice

Francesca Baracchi[1] * Mark Opp[1, 2, 3]
[1]Department of Anesthesiology University of Michigan, Ann Arbor, MI, USA [2]Molecular & Integrative Physiology, University of Michigan, Ann Arbor, MI, USA [3]Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI, USA
* *Corresponding author: Mark Opp, (mopp@umich.edu)*

IL-1b and TNFa are well characterized sleep regulatory substances. We used mice lacking both the IL-1β receptor 1 and TNFα receptor 1 (double KO) to further investigate roles for IL-1β and TNFα in sleep regulation and in responses to immune challenge.

Male double KO and B6129SFs/J control mice were surgically implanted with EEG electrodes and a thermistor to record brain temperature. After recovery, 48h undisturbed baseline recordings were obtained. Mice were then sleep deprived for 6h at the beginning of the light period. After several days, mice were injected intraperitoneally with vehicle and on a subsequent day with LPS.

Double KO mice spent less time in non-rapid eye movement sleep (NREMS) during the dark period and less time in rapid eye movement sleep (REMS) during the light period. After sleep deprivation, control mice exhibited prolonged increases in NREMS and REMS, whereas in double KO mice the duration of the NREMS increase was shorter and there was no increase in REMS. The LPS-induced increase in NREMS of double KO mice was less than that of control mice. LPS suppressed REMS of control mice for 12h, and of the double KO mice for 6h.

These data demonstrate that the lack of both IL-1R1 and TNFR1 alters baseline sleep, impairs compensatory responses to sleep deprivation, and reduces the effects of LPS on sleep-wake behavior when administered prior to light onset. These results further implicate IL-1 and TNF in the regulation of physiological sleep and in the alterations in sleep that occur after immune challenge.

Practitioner empathy and duration of the common cold

* Bruce Barrett[1] Dave Rakel[1] Theresa Hoeft[2] Betty Chewning[3] Benjamin Craig[1] Min Niu[4]
[1]Department of Family Medicine, School of Medicine and Public Health, University of Wisconsin-Madison [2]Department of Population Health, School of Medicine and Public Health, University of Wisconsin-Madison [3]School of Pharmacy, University of Wisconsin-Madison [4]Department of Statistics, Univ. of Wisconsin-Madiso
* *Corresponding author: Bruce Barrett, (bruce.barrett@fammed.wisc.edu)*

Background/Purpose: To assess the relationship of empathy in the medical consultation to subsequent cold outcomes.
Methods: 350 subjects, 12 years of age or older from southern Wisconsin received either a standard physician visit or an enhanced patient-oriented visit as part of an ongoing randomized controlled trial (RCT). The patient-scored Consultation and Relational Empathy (CARE) questionnaire assesses several aspects of the doctor-patient interaction with a focus on measuring empathic communication. CARE scores can range from 0-to-50, with 50 being a perfect score. Area-under-the-curve (AUC) cold severity is assessed from twice daily symptom reports using the Wisconsin Upper Respiratory Symptom Survey (WURSS-21). Cold duration is also monitored. The cytokine interleukin-8 (IL-8) was monitored at study intake and approximately 48 hours later.
Results: 84 individuals reported perfect CARE scores. These individuals differed in some demographics, tending to be older with less education, but reported similar health status, quality of life, and levels of optimism. In those with a perfect CARE score, cold duration was shorter (mean 7.10 days vs. 8.01 days, $p= 0.032$) and the mean WURSS-21 AUC measure was lower (mean 240.40 vs. 284.49,

p= 0.118). After accounting for possible confounding variables, cold severity and duration remained significantly lower in those reporting a perfect CARE score ($p < 0.05$). A perfect score also predicts a larger increase in IL-8 levels ($p < 0.05$).
Conclusions: Clinician empathy, as perceived by patients with the common cold, significantly predicts subsequent duration and severity of illness, and is associated with immune system changes.

SYMPATHETIC NERVOUS SYSTEM (SNS) REGULATION OF T-LYMPHOCYTE PROLIFERATION IN AGING F344 RAT

* Denise L. Bellinger[1] Christine Molinaro[1] Brooke A. Millar[1] Sam Perez[1] Cheri Lubahn[2] Dianne Lorton[2]
[1]Loma Linda University School of Medicine, Department of Pathology & Human Anatomy, Loma Linda, CA 92350 [2]Hoover Arthritis Research Center, Sun Health Research Institute, Sun City, AZ 85351
** Corresponding author: Denise L. Bellinger, (dbellinger@llu.edu)*

The SNS modulates T-lymphocyte proliferation, a crucial step in cell-mediated immunity. In aging, concanavalin-A (Con-A) and anti-CD3/anti-CD28-stimulated T-lymphocyte proliferation significantly decline concomitant with increased SNS activation. In this study, we investigated the role of SNS hyperactivity on reduced T lymphocyte proliferation in aging. Fifteen-month-old male F344 rats received twice-daily injections of rilmenidine (0, 0.5 or 1.5 μg/kg/day, i.p.) for 90 days. Rilmenidine is an antihypertensive agent and imidazoline receptor-1 agonist that selectively acts on presympathetic neurons in the rostral ventrolateral medulla (RVLM) to reduce SNS activity. Three- and 18-month-old rats served as young and old, age-matched controls, respectively. Con-A- and anti-CD3/anti-CD28-stimulated splenocyte proliferation were measured using [3H]-thymidine incorporation. Plasma and splenic NE levels, and splenic NE turnover studies were used to verify rilmenidine-induced sympathoinhibitory activity. Our data confirmed the age-related decline in T-cell proliferative responses, and the sympathoinhibitory action of rilmenidine in aging rats, with the lowest dose normalizing SNS activity toward young adult levels. Treatment with low-dose rilmenidine reversed the age-related decline in Con-A-stimulated proliferation, and there was a trend toward reversal of Con-A and CD3/CD28 co-stimulated proliferation with high-dose treatment. Vehicle treatment significantly increased and reduced Con-A- and CD3/CD28-induced proliferation, respectively, compared with all other treatment groups, indicating a stress response to chronic intermittent i.p. injection and handling. Collectively, these findings suggest that chronically lowering SNS activity beginning during middle age can reverse the age-related decline in mitogen- and antigen-stimulated T cell proliferation, and prevents the chronic, intermittent stress-induced changes in T-lymphocyte proliferative responses. (This research is funded by NIH Grant No. NS44302).

IL-1 signaling in astrocytes is essential for hippocampal-dependent memory functioning

Ofra Ben Menachem-Zidon[1, 2] Yair Ben Menahem[1] Inbal Goshen[1] Sys Kochavi[1] Omer Gaist[1] Tamir Ben Hur[2] * Raz Yirmiya[1]
[1]Department of Psychology, The Hebrew University of Jerusalem, Jerusalem, Israel [2]Department of Neurology, Hadassah-Hebrew University Hospital, Jerusalem, Israel ** Corresponding author: Raz Yirmiya, (razyirmiya@huji.ac.il)*

Recent evidence indicates that brain interleukin-1 (IL-1) is involved in the regulation of hippocampal-dependent memory not only following exposure to immune challenges or stressful stimuli, but also under normal physiological conditions. For example, IL-1β gene expression is induced in the hippocampus following a learning experience, and blockade of IL-1 signaling, by either exogenous administration of IL-1ra or genetic manipulations results in impaired memory functioning. To elucidate the cellular substrate of memory-related IL-1 signaling, we examined the ability of intrahippocampal transplantation of neural precursor cells (NPCs) to rescue the memory disturbances exhibited by mice with deletion of the IL-1 receptor type I (IL-1rKO). IL-1rKO and WT mice were transplanted with NPCs that were isolated from WT or IL-1rKO newborn mice. NPCs labeled with bromodeoxyuridine (BrdU) were transplanted into the hippocampus of adult hosts. Four weeks later, memory functioning was examined in the fear-conditioning and the Morris water maze paradigms. As expected, IL-1rKO mice transplanted with IL-1rKO cells or sham- operated only displayed severe memory impairments in both paradigms. In contrast, IL-1rKO mice transplanted with WT cells performed similarly to WT mice. Transplantation of either IL-1rKO or WT NPCs in WT mice had no effect on memory functioning. Histological examination revealed that the transplanted NPCs differentiated into astrocytes (expressing GFAP and BrdU). The NPCs derived from WT mice displayed co-localization of GFAP with the IL-1RI, whereas IL-1rKO-derived NPCs expressed GFAP, but no IL-1RI. These findings suggest that astrocytic IL-1 signaling is essential for hippocampal-dependent memory functioning.

Marginating pulmonary leukocytes in C57BL/6 mice: Distinct characteristics and enhanced NK cytotoxicity against syngeneic tumor cells

Marganit Benish[1] Ariella Glasner[1] Yael Kalderon[1] Rivka Melamed[1] * Shamgar Ben-Eliyahu[1]
[1]Neuroimmunology Research Unit, Dept of Psychology, Tel Aviv University,Tel Aviv, Israel
** Corresponding author: Shamgar Ben-Eliyahu, (shamgar@post.tau.ac.il)*

Background: In rats, we recently reported that marginating-pulmonary (MP) leukocytes exhibit greater NK cytotoxicity (NKC) than circulating leukocytes. This study in mice aims at corroborating these findings and characterizing the cellular and molecular determinants of MP-leukocytes in naïve and in immuno-stimulated mice.
Methods: Mice were injected three times (48hs apart) with either saline or murine rIL-12 (0.2 mg/kg). Twenty-four hours later, blood was withdrawn and MP-leukocytes were harvested by forced perfusion.
Results: Expression levels of NKG2D and IL-12 receptors on NK cells significantly correlated with NKC in circulating-leukocytes, but not in MP-leukocytes. IFNγ receptor, CD69, and CD11a showed different patterns of expression in leukocyte subtypes (including NK) of the circulation versus the MP compartment. Importantly, per NK cell, MP-leukocytes reached markedly greater NK cytotoxicity than circulating leukocytes when tested against the syngeneic B-16 melanoma line, but not the allogenic YAC-1 line. Furthermore, MP-

cytotoxicity against B-16 linearly increased with increasing E:T ratios (60%), while circulating-cytotoxicity reached a plateau (30%) and declined at the same E:T ratios, suggesting inhibition by cells or factors originating from circulating leukocytes. IL-12 treatment elevated cytotoxicity in both compartments.
Conclusions: A distinct population of leukocytes occupies the MP compartment, exhibiting greater NKC against a syngeneic tumor. Ongoing studies seek to identify specific underlying cellular and humoral mechanisms. PNI related effects may be uniquely observed in the MP compartment, where the vasculature network forces physical interactions with all aberrant circulating cells. Our previous studies suggest differential impacts of stress hormones on MP-leukocytes, which will be tested concurrently.

Long-term impact of repeated strong hypothalamus pituitary adrenal axis activation on basal glucocorticoid sensitivity
Christiane Berndt[1] Jana Strahler[1] Clemens Kirschbaum[1] * Nicolas Rohleder[1, 2]
[1]Department of Psychology, Dresden University of Technology, Dresden, Germany [2]Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada * *Corresponding author: Nicolas Rohleder, (nicolasrohleder@mac.com)*
Repeated activation of the hypothalamus pituitary adrenal (HPA) axis without habituation, as previously described in competitive ballroom dancing, has been suggested as an antecedent of long-term dysregulations of stress hormone systems, with potential pathophysiological consequences. Since beneficial and adverse effects of glucocorticoids (GCs) depend on target tissue sensitivity, we designed the present study to investigate GC sensitivity of inflammatory cytokine production in competitive ballroom dancers. We hypothesized that repeated HPA activation during tournaments would be associated with development of relative GC resistance.

We recruited 17 professional competitive modern and Latin ballroom dancers (7 men and 10 women, mean age: 20.24 years) and 17 age- and sex-matched controls. Blood was obtained between 17:00h and 20:00h, and GC sensitivity was assessed by in-vitro inhibition of lipopolysaccharide-stimulated production of interleukin-6 by different concentrations of dexamethasone.

No differences were found between dancers and controls in the amount of dexamethasone required for cytokine suppression, reflecting no GC sensitivity differences between groups ($F=0.02$; $p=.88$). However, analysis further revealed a significant gender effect ($F=6.21$; $p=.02$), and group by gender interaction ($F=6.81$, $p=.02$). Female dancers showed a trend towards lower GC sensitivity compared to controls, while GC sensitivity of male dancers appeared to be higher than that of controls.

These results lead us to conclude that while ballroom dancers of both genders are potentially affected by repeated HPA activation, development of relative GC resistance seems to occur predominantly in women. It remains to be investigated whether these patterns are associated with adverse health outcomes in female dancers.

Gene expression profiling in the stressed spleen: Dissecting stress-induced suppression of the primary antibody response.
Isaac Bernstein-Hanley[1] Brian Helwig[2] Sarah Kennedy[1] Thomas Maslanik[1] Kristen Speaker[1] * Monika Fleshner[1]
[1]Department of Integrative Physiology, University of Colorado, Boulder, CO 80309 [2]Department of Anatomy and Physiology, Kansas State University, Manhattan, KS 66506
* *Corresponding author: Monika Fleshner, (Monika.Fleshner@Colorado.EDU)*
Exposure to an acute, intense stressor (e.g. tailshock in rats) can suppress the antibody response to neo-antigenic proteins, an effect mediated by splenic norepinephrine (NE) depletion secondary to excessive sympathetic nervous system activation. Prevention of splenic NE depletion by tyrosine administration (Kennedy et al., 2005) or physical activity (Greenwood et al., 2003) is sufficient to prevent stress-induced antibody suppression. In addition, NE depletion in the absence of stress via splenic denervation or alpha methyl p-tyrosine treatment produces antibody suppression that mimics the effect of stressor exposure on the antibody response. The precise immunological mechanisms for these phenomena remain unclear. To better understand the molecular events that mediate suppression of the antibody response after stress, we explored the effect of tailshock on the expression of immunologically-relevant genes in the spleen. In our first experiment, adult, male, F344 rats were exposed to either tailshock or no stress, and were sacrificed immediately after stressor termination. Spleens were dissected and flash frozen for quantitative RT-PCR and NE content. We also performed a second experiment in which stressed rats were given tyrosine to maintain splenic NE content during tailshock. In our first experiment, we saw reliable changes in the expression of genes relevant to a variety of critical immunological processes, including pathogen recognition, cytokine and chemokine production, and signal transduction. Those expression changes that are prevented by tyrosine administration are currently under investigation. Exploring how stress influences gene expression in the spleen will contribute to our understanding of the mechanisms of tailshock-induced suppression of the antibody response. (Supported by RO1 AI057797.)

LPS-induced suppression of defensive rage behavior: role of peripheral TNF-α; and hypothalamic 5-HT$_{1A}$ receptors.
S Bhatt[1] R Bhatt[1] S Zalcman[1] * A Siegel[1]
[1]Depts. of Neurology, Neuroscience and Psychiatry, UMDNJ-NJ Medical School, Newark, NJ 07103
* *Corresponding author: A Siegel, (siegel@umdnj.edu)*
In the present study, we attempted to identify cytokine and neurotransmitter mechanisms underlying the effects of LPS challenge upon defensive rage behavior in cat. **Hypothesis**: Peripheral cytokine release following LPS challenge powerfully modulates defensive rage behavior and that such effects are mediated centrally through 5-HT$_{1A}$ receptors in the medial hypothalamus (MH). **Methods**: Experiment 1: Sites in MH and the PAG from which defensive rage can be elicited were identified. In addition, dual stimulation of MH facilitated defensive rage elicited from PAG ($p<.01$, $N=4$), indicating the functional linkage between these two regions; Experiment 2: Identification of peripheral mediators of effects of LPS on defensive rage elicited from PAG following administration of an anti-TNF or IL-1 antibody 5 min prior to LPS challenge; Experiment 3: Identification of the central neurotransmitter-receptors mediating LPS-suppression by microinjecting the 5-HT$_{1A}$ receptor antagonist (mPPI, 12 nmol. in 0.5 ml) into MH 5 min prior to LPS challenge. **Results**: (1) LPS challenge totally suppressed defensive rage from 60 - 240 min post-injection, with no detectable signs of sickness behavior at 60 min;

(2) Suppression of defensive rage was blocked following peripheral pre-treatment with the anti-TNF antibody ($F_{1,168}$ = 536.15, p<.001) but not with an anti-IL1 antibody ($F_{1,92}$ = 0.0002, p=.99); (3) Pretreatment with the 5-HT_{1A} receptor antagonist ($F_{2,192}$ = 318.91, p<.001) into MH completely blocked the suppressive effects of LPS challenge. **Conclusions**: LPS suppression of defensive rage is mediated peripherally through TNFα; and not through IL-1, and centrally through 5-HT_{1A} receptors in MH. [Supported by NIH grant NS 07941-36].

RATS INFECTED EARLY IN LIFE WITH BACTERIA EXHIBIT EXAGGERATED FEVER, SICKNESS BEHAVIOR, AND LACK OF ENDOTOXIN TOLERANCE IN ADULTHOOD

* Staci D. Bilbo[1] Julie Wieseler[2] Ruth M. Barrientos[2] Linda R. Watkins[2] Steven F. Maier[2]
[1]Department of Psychology and Neuroscience, Duke University, Durham, NC [2]Department of Psychology and Center for Neuroscience, University of Colorado, Boulder, CO
** Corresponding author: Staci D. Bilbo, (staci.bilbo@duke.edu)*

Fever is an organized, adaptive strategy critical to host survival, but can be dangerous if uncontrolled. Endotoxin tolerance, in which individuals receiving a low dose of endotoxin are protected from a subsequent high dose, is well documented, and is also likely adaptive. Here we assessed whether infection early in life influences the response to infection in adulthood, given evidence that events occurring during the perinatal period may "program" later physiology and behavior. In Exp.1, rats infected neonatally with E.coli exhibited a slight but significant increase in fever and sickness behavior following a low dose of lipopolysaccharide (LPS) in adulthood compared to controls. Eight days after the LPS injection, the same rats received a high dose of live E.coli. Neonatally-infected rats exhibited a markedly longer fever compared to controls. In Exp.2, fever to a single high dose of E.coli in adulthood did not differ as a consequence of early infection, suggesting that the difference in Exp. 1 was a lack of LPS tolerance in early-infected rats. In Exp.3, TNFα expression in peripheral macrophages was higher basally in early-infected rats, but tolerance was observed in both groups. In Exp.4, cyclooxygenase-2 expression, a rate-limiting enzyme in fever, and a microglial activation marker within the preoptic area of the hypothalamus were significantly higher in neonatally-infected rats challenged with LPS and subsequent E. coli in adulthood compared to all other groups. In sum, early-life infection appears to sensitize the brain to each subsequent challenge in adulthood.

The INSPIRE study Stress-management psychotherapy improves disease specific quality of life in distressed patients with ulcerative colitis but not in distressed patients with Crohn's disease

* Birgitte Boye[1, 2] Knut E. A. Lundin[3, 4] Kjell Mokleby[1] Siv Leganger[1] Slawomir Wojniusz[1] Astri Dahlstrom[1] Arne Roseth[5] Ingvard Wilhelmsen[6, 7] Tone Tangen[8] Trygve Hausken[9] Ann-Christin Rivenes[10] Günter Jantschek[11] Ingrid Jantschek[11] Dieter Benninghoven[11] Svein Blomhof[1] Michael Sharpe[12] Ulrik F. Malt[1, 2] Jorgen Jahnsen[5]
[1]Department of Neuropsychiatry and Psychosomatic Medicine, Division of Clinical Neurosciences, Rikshospitalet University Hospital, Oslo, Norway; [2]Institute of Psychiatry, University of Oslo, Norway [3]Department of Internal Medicine, Gastroenterology section, Medical Division, Rikshospitalet University Hospital, Oslo; Norway [4]Rikshospitalet Faculty group, University of Oslo, Norway [5]Department of Gastroenterology, Aker University Hospital, Oslo [6]Institute of Internal Medicine, University of Bergen, Norway [7]Haraldsplass Deaconal Hospital, Bergen, Norway [8]Institute of Clinical Medicine, Section of Psychiatry, Haukeland University Hospital, Unversity of Bergen, Norway [9]Department of Internal Medicine, Gastroenterology section, Haukeland Univerversity Hospital, Bergen, Norway [10]Department of Psychiatry, Haukeland University Hospital, Bergen, Norway [11]Department of Psychosomatic and Psychotherapy, University-clinic Schleswig-Holstein, Campus Lübeck, Germany [12]School of Molecular and Clinical Medicine, University of Edinburgh, United Kingdom
** Corresponding author: Birgitte Boye, (birgitte.boye@rikshospitalet.no)*

Introduction: Distressed patients with inflammatory bowel diseases, Ulcerative colitis (UC) and Crohn's disease (CD), are associated with higher relapse rate and reduced disease specific quality of life.
Hypothesis: A stress-management psychotherapeutic intervention will improve disease specific quality of life in distressed UC and CD patients.
Materials and methods: Fifty-nine patients with UC and 55 patients with CD were included, age ranging from 18-60 years, with a relapse/continuous disease activity previous 18 months, a simple (CD) or clinical (UC) disease activity>4, a Perceived Stress Questionnaire score (PSQ)>60 and without serious mental diseases or other serious medical conditions were randomised to treatment as usual (TAU) or TAU+ stress-management psychotherapy consisting of 3 group sessions (psycho-education, problem-solving, relaxation) and 6-9 individual sessions based on cognitive behaviour methods with 1to 3 booster sessions at 6 and 12 months follow-up. The patients completed the Inflammatory Bowel Disease Questionnaire (IBDQ) at baseline, 6, 12 and 18 months.
Results: 53 patients with CD and 57 patients with UC completed the IBDQ at baseline. Mixed linear models, separate analyses of UC and CD where the IBDQ was outcome measurements and the predictor variables were intervention-group, time, interaction between time and intervention-group and baseline IBDQ-score, revealed that there was an intervention effect in UC patients only; improving the IBDQ score. In CD patients there was no intervention effect.
Conclusion: Stress-management psychotherapeutic intervention improves disease specific quality of life in UC patients but not in CD patients suggesting different psychobiological interactions.

Optimism is associated with attenuated stressor-induced increases in inflammatory cytokines and negative mood states.

* Lena Brydon[1] Cicely Walker[1] Andrew Wawrzyniak[1] Daisy Whitehead[1] Andrew Steptoe[1]
[1]University College London
** Corresponding author: Lena Brydon, (l.brydon@ucl.ac.uk)*

Psychological stress and infection are commonly accompanied by negative mood states. One mechanism thought to contribute to this effect is a stressor-induced increase in inflammatory cytokines, molecules which communicate between the brain and immune system. Positive psychological traits such as optimism are thought to protect against the detrimental effects of stress. We predicted that optimism would modulate stressor-induced changes in cytokines and mood.

Sixty healthy men took part in a double-blind study. Trait optimism was assessed by the Life Orientation Test. Participants received typhoid vaccine or saline placebo. Thirty minutes post-injection, they either rested or completed two challenging tasks; colour/word and public speaking, at the end of which they rested for a further two hours. Ratings of mood were obtained using the Profile of Mood States at baseline, immediately after tasks and during recovery.

Tasks induced a significant increase in circulating levels of IL-6 and negative mood. The mood effect was significantly more marked in participants who had received typhoid vaccine versus placebo. The IL-6 response was also larger in the vaccine versus placebo group, although the effect was not significant. Optimists had significantly smaller IL-6 responses to stress, and smaller increases in anxiety and negative mood compared to less optimistic individuals. There were no significant changes in mood or cytokines in the non-stress control group.

Taken together, these results suggest that optimism may protect against negative mood responses to psychological and immune stressors, potentially through modulating inflammatory cytokines.

Functional Polymorphisms in the Interleukin-6 and IL-10 Genes and Psychopathological Symptoms in Patients with Chronic Fatigue Syndrome

* Sarah Bull[1] Carmine Pariante[1] Pattricia Huezo-Diaz[1] Katherine Aitchison[1] Anthony Cleare[1]
[1]Institute of Psychiatry, King's College London
** Corresponding author: Sarah Bull, (s.bull@iop.kcl.ac.uk)*

The inflammatory response system (in particular high concentrations of IL-6) has been implicated in the pathophysiology of a number of psychopathological symptoms and disorders. The role of the inflammatory response system in the aetiology of chronic fatigue syndrome (CFS) is yet to be elucidated. Two functional polymorphisms have been identified as participating in the regulation of the inflammatory system, (rs1800795 in the IL-6 gene and rs1800896 in the IL-10 gene) and were tested in CFS patients.

The IL-6 and IL-10 polymorphisms will be associated with differential fatigue and current mental health.

130 Caucasian subjects were recruited at the CFS Unit at the Institute of Psychiatry, King's College London. At their initial consultation with a psychiatrist subjects completed self report questionnaires to measure fatigue and their current mental health, using the Chalder Fatigue Questionnaire (CFQ) Chalder et al, 1993 and General Health Questionnaire (GHQ) Goldberg, 1972 respectively. Polymorphisms were determined using SNPlex, using DNA extracted from cheek swabs.

The IL-10 polymorphism was associated with significant differences in mean CFQ (AA=27.06, AG=24.32, GG=27.46: F=4.327, df=2, P=0.015) but not GHQ (AA=20.17, AG=18.57, GG=19.14: F=4.34, df=2, P=0.649). Post-hoc analysis revealed that heterozygous subjects were significantly less fatigued than homozygous GG (P=0.009) and AA (P=0.027) genotype subjects(high and low IL-10 expressers) . The IL-6 genotype was not associated with significant differences in either the mean CFQ (CC=25.45, GC=26.65, GG=26.74: F=0.479, df=2, P=0.620) or GHQ scores (CC=19.32, GC=18.00, GG=20.55: F=1.35, df=2, P=0.264).

The functional polymorphism (rs1800896) in the IL-10 gene is associated with differential fatigue in patients with CFS.

Acute stress reduces the incidence and severity of self-reported adverse events following vaccination

John PA Campbell[1] Kate M Edwards[1] * Victoria E Burns[1] Christopher Ring[1] Douglas Carroll[1] Mark Drayson[2]
[1]School of Sport and Exercise Sciences, University of Birmingham, UK. [2]Department of Immunology, School of Medicine, University of Birmingham, UK. ** Corresponding author: Victoria E Burns, (v.e.burns@bham.ac.uk)*

Antibody responses to vaccination can be enhanced by acute stress in humans. The effect of these interventions for self-reported adverse events post-vaccination has not previously been investigated.

Two vaccination studies (N=60 and N=78) were analysed separately. Prior to vaccination, participants completed either an acute stress condition (mental arithmetic or cycling in Study One; eccentric exercise in Study Two) or a no-stress control condition. In both studies, participants were asked to report whether they had experienced any adverse events following vaccination and, if yes, to describe the symptoms. These were coded in two ways: a measure of incidence (yes/no); and a severity rating, experimenter-coded as 0 (no event), 1 (mild local symptoms), 2 (severe local or mild systemic symptoms), or 3 (severe systemic symptoms). Results were analysed using Chi-square.

In Study One, the stress group (mental arithmetic or cycling exercise) were significantly less likely than the control group to report an adverse event (c;2=5.16, p=.02), and reported significantly less severe events (c;2=12.41, p=.05). There was no significant difference between the two stress groups for adverse event occurrence (c;2=.173, p=.68) or severity (c;2=3.83, p=.28). In Study Two, the exercise group were significantly less likely than the control group to report an adverse event (c;2=5.64, p=.02), and reported significantly less severe events (c;2=9.25, p=.03).

These studies indicate that exposure to acute stress prior to vaccination may reduce the incidence and severity of adverse reactions. This may have clinical implications as reduced adverse reactions may increase a patient's compliance with future vaccination programme recommendations.

Inflammatory Activity of the Neutrophil is Elevated During Exam Stress

* Judith E. Carroll[1] Aric A. Prather[1] Anna L. Marsland[1] Andrew Baum[2]
[1]Department of Psychology, University of Pittsburgh, Pittsburgh, PA [2]Department of Psychology, University of Texas, Arlington, TX
** Corresponding author: Judith E. Carroll, (jec51@pitt.edu)*

Although prior work has demonstrated a positive association between psychological stress and systemic markers of inflammation, research investigating cellular sources of increased circulating inflammatory mediators is lacking. Neutrophils play a primary role in acute inflammatory responses. Thus, the primary aim of the current study was to investigate whether naturalistic stress is associated with changes in neutrophil activity. In addition, we examined circulating levels of Interleukin(IL)-6, a pro-inflammatory cytokine. For this purpose, blood was drawn from 18 students (78% white, 67% female, mean age 28.4), one week before and 4-6 weeks after taking their board examinations. Neutrophil activity was assessed using the nitro-blue tetrazolium assay and circulating levels of IL-6 were determined by ELISA. As expected, students reported higher perceived stress (Perceived Stress Scale; $p<.005$) and anxiety (Speilberger State Trait Anxiety Inventory; $p<.005$) one week before than after the examinations. Stimulated neutrophil activity was significantly higher ($F(1,16) =5.15$, $p=.037$) pre- than post-examination (means = 19.8 and 15.1, respectively). Interestingly, exam specific stress was highly correlated with neutrophil activity ($r =.61$, $p<.01$) prior to examination. Contrary to expectations, there was no change in circulating IL-6 across the two occasions of measurement, nor were IL-6 levels associated with neutrophil activity, exam stress, perceived stress, or anxiety at either time point. Overall, our findings provide initial evidence that naturalistic stress is associated with an increase in neutrophil activity. These findings are consistent with a growing body of evidence that psychological stress is associated with activation of innate inflammatory pathways. Further investigation of the role of neutrophils in this pathway is warranted.

Chronic But not Acute HIV-1 gp120 Induces Depressive-Like Behavior in Mice

Qing Chang[1] Xin Fu[1] Keith Kelley[1, 2] * Robert Dantzer[1, 2]
[1]Integrative Immunology and Behavior Program, Department of Animal Sciences, College of ACES and [2]Department of Pathology, College of Medicine, University of Illinois at Urbana-Champaign ** Corresponding author: Robert Dantzer, (dantzer@uiuc.edu)*

The HIV envelope glycoprotein (gp) 120 has been proposed to play a key role in the brain manifestations of AIDS. The present experiments aimed at assessing the effects of acute and chronic intracerebroventricular administration of gp120 on murine behavior and brain cytokines. In two different experiments, mice were injected with artificial CSF (aCSF), gp120 (400 ng) or LPS (100 ng). Changes in body weight, food intake, locomotor activity and immobility in the tail suspension test (TST) were measured 6 or 24 hr post-treatment. Brains were collected immediately after TST. LPS decreased body weight, food intake and motor activity at both time points but increased duration of immobility in the TST only at 24 h post-treatment. This was associated with increased expression of IL-1beta, TNF-alpha and IL-6 mRNA at both time points and increased indoleamine 2,3 dioxygenase (IDO) expression only at 6 h post-treatment. Gp120 induced sickness only at 6 h post treatment which was associated with increased expression of IFNγ. In three different experiments, chronic gp120 (200 ng per day over 8 days) caused sickness symptoms varying with time and reflected as a reduction in body weight, food intake and locomotor activity. Gp120 increased duration of immobility in the TST 48 h after the last injection and increased expression of brain IL-1beta, TNF-alpha and IL-6 mRNAs. The increase in brain IFNγ and IDO mRNA was only marginally significant. Although still preliminary, these findings indicate a possible role for gp120 in the development of depressive disorders in HIV-infected patients.

Prospective Association between C-Reactive Protein and Fatigue - The Coronary Artery Risk Development in Young Adults (CARDIA) Study

* Hyong Jin Cho[1] Teresa Seeman[2] Julienne Bower[1] Catarina Kiefe[3] Michael Irwin[1]
[1]Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, UCLA [2]Division of Geriatrics, Geffen School of Medicine, UCLA [3]Division of Preventive Medicine, University of Alabama at Birmingham
** Corresponding author: Hyong Jin Cho, (hjcho@mednet.ucla.edu)*

Background: Fatigue is highly prevalent and causes serious disruption in quality of life. Whether fatigue is a stand-alone symptom or associated with other morbidity, the underlying biological mechanism is unclear. Basic research on neuroimmune interactions suggests that inflammatory processes may play a role in fatigue. We examined whether C-reactive protein (CRP), a biomarker of inflammatory processes, was prospectively associated with fatigue.
Methods: We studied 3015 African-American and white participants in the bi-racial, longitudinal, community-based CARDIA study, aged 33-45 years. Those with very high CRP concentration (>20mg/L) were not included. Multivariable linear regression tested whether CRP at baseline (CARDIA Year 15, 2000-2001) was associated with fatigue assessed five years later using the Vitality Subscale of the 12-item Short Form Health Survey (Did you have a lot of energy during the past 4 weeks?; higher score means less fatigue, range 0-100).
Results: Overall, mean fatigue score and median CRP concentration at baseline were 61.35 (standard deviation 23.08) and 1.93mg/L (interquartile range 0.85-2.22), respectively. After adjustment for potential risk factors and baseline fatigue score, CRP concentration at baseline was a significant predictor of fatigue five years later (adjusted regression coefficient -0.48; P=0.009). Female gender, white ethnicity, history of medical disorders, low physical activity, depressive symptoms, poor sleep quality and fatigue score at baseline were also independent predictors of fatigue at follow-up.
Conclusion: This is the first study to demonstrate a prospective association between an inflammatory marker and fatigue, consistent with the notion of an underlying inflammatory process as an etiological mechanism of fatigue.

DEPRESSIVE SYMPTOMS PREDICT INFLAMMATION DURING PREGNANCY

* Lisa Christian[1] Jay Iams[1] Ronald Glaser[1] Albert Franco[2] Janice Kiecolt-Glaser[1]
[1]The Ohio State University [2]Carolinas Medical Center
* *Corresponding author: Lisa Christian, (christian.109@osu.edu)*

Depressive symptoms are associated with increased risk of negative perinatal outcomes including preterm delivery and gestational hypertension. Inflammation is a key potential mechanism by which depressive symptoms may influence such outcomes. The current study examined associations among psychosocial factors and serum inflammatory markers in 60 pregnant women who were primarily from lower socioeconomic backgrounds. Participants were 25 years old (SD = 5) and at 15 weeks (SD = 7.5) gestation on average. The sample included 33 African-American and 19 Caucasian women. Sixty-five percent reported an annual family income of less than $15,000. The Center for Epidemiological Studies Depression Scale (CES-D) was used to measure depressive symptoms. Serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β were determined using high sensitivity immunoassays. Regression analyses demonstrated that after controlling for body mass index (BMI) prior to pregnancy, higher scores on the CES-D were predictive of higher levels of IL-6 (β = .23, p = .05). Similarly, a relationship between higher CES-D scores and higher TNF-α approached statistical significance (β = .24, p = .06). Correlational analyses demonstrated that among the women with detectable levels of IL-1β (n = 20), higher CES-D scores predicted higher IL-1β (r = .52, p = .02). In sum, the current results indicate that depressive symptoms predict greater inflammation during pregnancy. This may have implications for pregnancy related outcomes.

Application of repeated social stress to pregnant gilts during early or late gestation diferentially affects HPA axis and immune system activity of the piglets

* David Couret[1] Armelle Prunier[1] Isabelle Oswald[2] Françoise Thomas[1] Anne-Marie Mounier[1] Elodie Merlot[1]
[1]INRA, UMR1079, SENAH, 35590 Saint-Gilles, France [2]INRA, UR66, laboratoire de Pharmacologie Toxicologie, 31931 Toulouse, France
* *Corresponding author: David Couret, (david.couret@rennes.inra.fr)*

Events acting prenatally on the foetus are important risk determinants of adult disorders, including deregulation of the HPA axis and immune function. The aim of this study was to determine whether prenatal stress (PNS) affects piglet immune system and HPA axis activity and whether these effects depend on the gestational period when PNS occurs. Pregnant gilts were exposed to repeated social stress by housing females in pairs modified twice a week during 4 weeks during either early (E, between DG21 and DG52, n=8) or late (L, between DG77 to DG108, n=11) pregnancy. Control pairs (C, n=13) were left undisturbed. Piglets were immunized against ovalbumin (OVA) at D7 and D20. At birth, L piglets were lighter than C and L ones (P<0.005). Proliferative responses to ConA and PHA were weaker in E group (P<0.05 and P=0.08 respectively) from D3 to D28. Prenatal treatment decreased the OVA-specific proliferative response at D26 in L and E males(P< 0.01). After weaning, the proliferative response decreased (P<0.001) but the diminution was weaker in L group (ConA P<0.05). Cortisol release tended to be higher in L pigs in response to both castration and weaning (P=0.07 and P=0.08 respectively). Adrenal glands weight at D3 was lighter in E group (P<0.05). These results point out that PNS induces a deregulation of HPA and immune systems. Moreover, the immune system, which develops during the first third of gestation in pigs, seemed to be more sensitive to early PNS whereas HPA axis, for which the ontogeny is achieved during late pregnancy, was more sensitive to late PNS.

Social disruption enhances lung inflammation.

Jennifer Curry[1] Michael Bailey[2] Benjamin Bringardner[3] Melissa Hunter[1] John Sheridan[2] * Clay Marsh[1]
[1]Division of Pulmonary Medicine, The Ohio State University [2]Section of Oral Biology, College of Dentistry, The Ohio State UniversityThe Institute for Behavioral Medicine Research, The Ohio State University [3]Carolinas Medical Center, Charlotte, NC
* *Corresponding author: Clay Marsh, (Clay.Marsh@osumc.edu)*

Alterations in social environments affect the immune functions and behavior. In a model of social conflict, social disruption (SDR), cycles of attack and defeat are followed by increased anxiety-like behavior and enhanced secretion of proinflammatory cytokines from LPS-stimulated splenocytes. We hypothesize that SDR will cause in inflammatory response in the lung.

C57BL/6 mice were subjected to six, 2 hour sessions of SDR. SDR consists of introducing an aggressive intruder mouse to resident mice and leads to attack and defeat of the residents. Control mice are untouched in their home cages. Upon sacrifice, lungs were insulflated, and one lung was frozen protein analysis, performed with the Sircol™ collagen assay. The remaining lung was formalin-fixed and sectioned for IHC. A board-certified veterinary pathologist subjectively analyzed and scored H&E sections of lung tissue for the presence of lymphocyte and macrophage aggregates.

SDR mice had greater lung inflammatory scores compared to control mice. We observed an increased number in neutrophils but not change in the number of macrophages in the lungs of SDR mice compared with control. While the macrophage number remained unchanged, we observed an increased expression of inducible Nitric Oxide Sythase in the SDR mice while arginase expression was not affected. Additionally, lung collagen deposition was elevated 2-fold in SDR mice compared with control.

These data illustrate the proinflammatory environment in the lungs created by social disruption stress. This state could produce detrimental effects, such as tissue damage, or beneficial effects, such as microbial killing.

Restraint stress increases breast tumor growth and angiogenesis.

Jennifer Curry[1] Tim Eubank[1] Ryan Roberts[1] John Sheridan[2] * Clay Marsh[1]
[1]Division of Pulmonary Medicine, The Ohio State University [2]Section of Oral Biology, College of Dentistry, The Ohio State UniversityThe Institute for Behavioral Medicine Research, The Ohio State University
** Corresponding author: Clay Marsh, (Clay.Marsh@osumc.edu)*

In this study, we combine two well-defined animal models to examine the role that stress plays in carcinogenesis. We evaluate the affects of restraint stress effects in Polyoma middle T antigen (PyMT) mice, which spontaneously develop breast cancer and eventual pulmonary metastases. We hypothesize that stress will negatively affect the disease course in these mice.

PyMT mice were subjected to 6 hours of restraint stress per day from week 9-12 of age. Serum was taken pre- and post-stress to assess glucocorticoid levels. Breast tumors were examined for size by weight, angiogenesis by CD34 staining, and for macrophage, and NK cell presence by F4/80 staining and by assessing mRNA levels of NK1.1. Lungs were examined for pulmonary metastases by whole lung staining with Hematoxylin.

Mice subjected to restraint stress had higher levels of serum corticosterone and a two-fold increase in total tumor size. Restraint stress did not affect levels of pulmonary metastases. Restraint stress decreased the number of macrophages infiltrating the tumors; however, an increased number of NK cells were present within the tumors. Finally, stress increase angiogenesis within the breast tumors, as illustrated with an increased number of CD34-positive cells and a trend towards increased angiogenic factors and decreased anti-angiogenic factors present within the tumors.

These results demonstrate that restraint stress increased breast tumor growth but did not affect pulmonary metastases in the PyMT mouse model. Restraint stress appeared to be increasing breast tumor size through increasing levels of angiogenesis within the tumors.

Chronic stress reduces glucocorticoid and α-adrenergic receptor expression, and induces an inflammatory state characterised by increased IL-12 and IFN-γ production *

Niamh Curtin[1] Kingston Mills[2] Thomas Connor[1]
[1]Neuroimmunology Research Group, School of Medicine & Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland. [2]Immune Regulation Research Group, School of Biochemistry & Immunology, Trinity College Dublin, Ireland.
** Corresponding author: Niamh Curtin, (ncurtin@tcd.ie)*

We have previously shown that psychological stress suppresses the innate IFN-γ response in mice in the hours immediately following stressor termination. In contrast, other studies suggest that stress induces a pro-inflammatory state that becomes evident within 24hr of stressor termination. Consequently, here we compared the effect of chronic restraint stress on the innate IFN-γ response in mice immediately, or 24hr following stressor termination. Consistent with our previous findings we show that immediately following the last episode of stress, LPS-induced IL-12 and IFN-γ production from cultured splenocytes is suppressed. In contrast, 24hr following stressor termination increased IL-12 and IFN-γ production was observed from LPS-stimulated splenocytes. We hypothesised that this pro-inflammatory action of stress may occur due to down-regulation of glucocorticoid and/or α2-adrenergic receptors, which mediate the anti-inflammatory actions of endogenous glucocorticoids and catecholamines respectively. In line with this hypothesis, the ability of the glucocorticoid receptor agonist corticosterone and the α2-adrencegic agonist salbutamol to suppress LPS-induced IL-12 and IFN-γ production was impaired following stress. Also, we demonstrate that glucocorticoid and α2-adrenergic receptor mRNA and protein expression is reduced in spleen tissue harvested from stressed animals. These data demonstrate that the initial immunosuppressive actions of stress are followed by a pro-inflammatory state most likely resulting from glucocorticoid and/or α2-adrenergic receptor down-regulation.

ELEVATED INFLAMMATION LEVELS IN DEPRESSED ADULTS WITH A HISTORY OF CHILDHOOD MALTREATMENT

* Andrea Danese[1] Terrie E. Moffitt[2] Carmine Pariante[3] Antony Ambler[1] Richie Poulton[4] Avshalom Caspi[2]
[1]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom [2]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom and Departments of Psychology and Neuroscience, Psychiatry and Behavioral Sciences, and Institute for Genome Science [3]Department of Psychological Medicine, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom [4]Dunedin School of Medicine, University of Otago, Dunedin 9015, New Zealand
** Corresponding author: Andrea Danese, (a.danese@iop.kcl.ac.uk)*

INTRODUCTION: The association between depression and inflammation is inconsistent across research samples. HYPOTHESIS: This study tested the hypothesis that a history of childhood maltreatment could identify a subgroup of depressed individuals with elevated inflammation levels, thus helping to explain previous inconsistencies. METHODS: A representative birth cohort of 1,000 individuals was followed to adulthood as part of the Dunedin Multidisciplinary Health and Development Study. At age 32 years, study members were assessed for history of childhood maltreatment, current depression, and current inflammation. RESULTS: Although depression was associated with high hsCRP (RR=1.45; 95%CI=1.06;1.99), this association was significantly attenuated and no longer significant when the effect of childhood maltreatment was taken into account. Individuals with current depression and childhood maltreatment history

were more likely to show high hsCRP levels than controls (N=27; RR=2.07; 95%CI=1.23;3.47). In contrast, individuals with current depression-only showed a non-significant elevation in risk (N=109; RR=1.40; 95%CI=0.97;2.01). CONCLUSIONS: A history of childhood maltreatment contributes to the co-occurrence of depression and inflammation. Information about experiences of childhood maltreatment may help to identify depressed individuals with elevated inflammation levels and thus cardiovascular disease risk.

Relationship between Regulatory T cells (Treg) and Posttraumatic Stress Disorder (PTSD)

* Kevin Del Ben[1] Alison McLeish[2] Kevin Connolly[2] Gailen Marshall[1]
[1]Laboratory of Behavioral Immunology Research, Division of Clinical Immunology and Allergy, Department of Psychiatry and Human Behavior, University of Mississippi Medical Center [2]Department of Psychiatry and Human Behavior, University of Mississippi Medical Center ** Corresponding author: Kevin Del Ben, (kdelben@psychiatry.umsmed.edu)*

A consistent relationship between increased psychological stress and altered immune markers and function has been established, both in normal hosts and patients with inflammatory diseases. Yet few studies have investigated the relationship between immune markers (particularly immunoregulatory associated with inflammatory diseases) and specific symptoms of various clinical psychological maladies. Posttraumatic stress disorder (PTSD) is an often unrecognized anxiety disorder characterized by re-experiencing aspects of a previous traumatic event through flashbacks and intrusive thoughts which often causes the person intense psychological and physiological arousal. We investigated the relationships between PTSD symptoms and Treg (CD4+CD25high FoxP3+) levels. As part of a larger study, 21 participants completed the Posttraumatic Stress Diagnostic Scale (PDS) and provided a blood sample for Treg analysis by flow cytometry. The PDS assesses the number and type of traumatic events along with symptoms of Re-experiencing, Avoidance (of trauma related stimuli), and hyperarousal (i.e. hypervigilance). Scores for the 3 PTSD symptom clusters correlated with Treg level : Re-experiencing ($r = -.46$, $p<.05$), Avoidance ($r = -.58$, $p<.01$), and Hyperarousal ($r = -.61$, $p<.01$). Treg levels were also significantly lower in individuals with high levels of PTSD symptoms [$F(1,21) = 7.0$, $p=.02$). These data support the relationship between amplified symptoms of an increasingly recognized anxiety disorder (PTSD) that affects approximately 10% of the population and Treg levels, a key component of normal host immunoregulatory networks. This also suggests a possible mechanism to explain data indicating that PTSD patients have an increased prevalence of inflammatory diseases.

Exploration of a Novel Behavioral Phenotype in the Interleukin-18 Receptor Knockout Mouse

* A. F. Dorman[1] V. J. Bolivar[1]
[1]School of Public Health, Department of Biomedical Sciences, State University of New York at Albany, Albany, NY, USA.
** Corresponding author: A. F. Dorman, (aeisener@wadsworth.org)*

Recent studies indicate that some cytokines (e.g. IL-1α, IL-2, IL-6) influence various behaviors and cognitive processes, in addition to their known roles in inflammation and immunity. Interleukin-18 and its receptor, members of the IL-1 proinflammatory family of cytokines, induce Th1 response and NK cell-mediated cytotoxic activity. However, little is known regarding the effects, if any, of these cytokines on CNS functions, including behavior. Given the increasing evidence supporting a role for proinflammatory cytokines in depressive-like and anxiety-based behaviors, we hypothesized that IL-18 and IL-18r1 knockout mice (B6.129P2-*Il18*^{tm1Aki}/J and B6.129P2-*Il18r1*^{tm1Aki}/J) would exhibit abnormal behavioral patterns. We assessed the abilities of these strains in a battery of behavioral tests, including open field, elevated zero maze, and rotorod. Compared to IL18$^{-/-}$ and C57BL6/J (B6), IL18r1$^{-/-}$ mice exhibit increased intersession habituation, decreased baseline activity, and decreased time spent in the center of the open field. IL18r1$^{-/-}$ mice performed proficiently on the rotorod and spent less time in the open quadrants of the zero maze. Our data suggest a potential role for the IL-18 receptor in anxiety-based behavior. We anticipate that LPS-induced stress will exacerbate these behaviors, thus we are currently assessing the effects of intraperitoneal-administered LPS on exploratory activity in the open field.

Serologically documented influenza B infection during pregnancy: Differential effects on birth weight among preschizophrenia infants compared to control infants.

* Lauren M. Ellman[1] Robert H. Yolken[2] Stephen L. Buka[3] E. Fuller Torrey[4] Tyrone D. Cannon[5]
[1]Psychiatry Department, Columbia University [2]Stanley Division of Developmental Neurovirology, Johns Hopkins University School of Medicine [3]Dept. of Epidemiology, Human Development & Health, Harvard School of Public Health [4]Uniformed Services University of the Health Sciences, Stanley Medical Research Institute [5]University of California, Los Angeles, Dept. of Psychology, Dept. of Psychiatry and Biobehavioral Sciences
** Corresponding author: Lauren M. Ellman, (le2194@columbia.edu)*

Introduction: Studies have linked prenatal influenza exposure to increased risk of schizophrenia and there have been mixed results relating decreased birth weight (BW) and gestational age (GA) to schizophrenia. Prenatal infection has been associated with adverse birth outcomes; however no study has investigated whether prenatal exposure to influenza accounts for the discrepancy in GA and BW findings among cases. **Hypothesis:** Cases exposed to influenza will have decreased GA and BW compared to unexposed cases and controls. **Methods:** Participants were 111 cases diagnosed with psychoses (70 with schizophrenia and 41 with affective psychoses) and 333 nonpsychiatric controls who were monitored prospectively during gestation as part of the National Collaborative Perinatal Project. Psychiatric morbidity was determined in adulthood by medical records review and confirmed by validation study. Assays were conducted from archived maternal sera collected at birth. IgG antibodies to influenza B were measured by solid-phase enzyme immunoassay. Infection was positive if IgG titers were > 75th percentile. Analyses controlled for infant's sex, maternal race, and

maternal age, and for BW analyses, GA**.** **Results:** Results indicated that there were significant decreases in BW among cases who were exposed prenatally to influenza B compared to cases who were unexposed. There were no differences in BW among controls who were exposed to infection compared to those unexposed or among unexposed cases compared to unexposed controls. No differences in GA were found among comparison groups. **Conclusion:** Findings suggest that a genetic or an environmental factor associated with psychoses renders the fetus particularly vulnerable to the effects of influenza, leading to disruptions in fetal growth.

University Examinations Cause Hyper-Inflammation of Mucosal Tissues

* Christopher G. Engeland[1] Zongjuan Fang[1] Phillip T. Marucha[1, 2]
[1]Dept. of Periodontics, University of Illinois at Chicago, Chicago IL, USA [2]Institute of Behavioral Medicine Research, The Ohio State University, Columbus OH, USA ** Corresponding author: Christopher G. Engeland, (engeland@uic.edu)*

It is gradually becoming accepted that chronic stress can produce low-grade peripheral inflammation which may have negative consequences to health. The present study examined the effects of stress on inflammation and healing rates in mucosal wounds. Sixty five dental students received a 3.5 mm diameter circular wound and a 1x5 mm longitudinal wound on the hard oral palate at two time points: during examinations (stress) and during summer vacation (non-stress). The first wound was videographed daily to assess closure. From the second wound, a 2x5 mm biopsy was obtained at 6h or 24h post-wounding. Real-time PCR was performed on all biopsies. Overall, wound closure was delayed during examinations compared to summer vacation (P<.05). In unwounded tissue, higher gene expression of inflammatory mediators was seen during examinations. Gene expression for IL-6, MIP-1α, ICAM and e-selectin were significantly upregulated compared to the non-stress period. In wounded tissue, gene expression was also significantly higher during the stress period. All genes examined (IL-1β, IL-6, TNF-α, IL-8, MIP-1α, MCP-1, ICAM, e-selectin) were more highly expressed at 6h post-wounding during examinations than during vacation. By 24h post-wounding much of this inflammation was resolved, although gene expression for IL-6 and MIP-1α remained higher during the stress condition. In conclusion, stress during examinations was associated with a state of hyper-inflammation in normal unwounded tissue, with higher inflammatory responses upon wounding, and with slower healing. Importantly, stress has been shown to inhibit inflammation in dermal wounds. The present finding that stress causes higher tissue inflammation is novel and may be specific to mucosal tissues. (Support NIH/NIDCR RO1DE12792, UIC COD)

The effect of Physical Activity and Chronic Stress on Self-reported Upper Respiratory Tract Infection

* Elinor Fondell[1, 2] Anna L.V. Johansson[1] Ylva Trolle Lagerros[3] Carl Johan Sundberg[4] Mats Lekander[2, 5] Olle Bälter[6] Kenneth J. Rothman[7, 8] Katarina Bälter[1]
[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden [2]Osher Center for Integrative Medicine, Karolinska Institutet, Sweden [3]Department of Medicine, Clinical Epidemiology Unit, Karolinska Institutet, Sweden [4]Department of Physiology and Pharmacology, Karolinska Institutet, Sweden [5]Department of Clinical Neuroscience, Karolinska University Hospital, Sweden [6]School of Computer Science and Communication, Royal Institute of Technology, Sweden [7]RTI Health Solutions, Research Triangle Park, North Carolina, USA [8]Department of Epidemiology, Boston University School of Public Health, Boston, USA
** Corresponding author: Elinor Fondell, (elinor.fondell@ki.se)*

Objective: Upper respiratory tract infection, URTI, is the number one reason for temporary work absenteeism in the US. Still, little is known about strategies to reduce susceptibility. We investigated the potentially beneficial effects of physical activity on the risk of contracting URTI among the general population.

Methods: We studied a population-based cohort recruited via paper mail, using the Internet as a novel tool for data collection. We followed a cohort of 1509 men and women for four months, contacting them every three weeks via e-mail. Physical activity was assessed through a questionnaire, giving total MET-hours (multiples of resting metabolic rate) per day. Chronic stress was assessed by the Perceived Stress Scale. We also collected data on potential confounding factors, including age, sex, body mass index, smoking, diet, education, asthma, contact with children, use of public transportation, effect of season, among other factors.

ResultsL High levels of physical activity (53-114 MET-hours/day) were associated with a 27 % reduced risk (IRR 0.73, 95% CI: 0.61-0.88) of contracting URTI compared to low levels of physical activity (<38 MET-hours/day). The effect was present among men and women, and across all ages. The protective effect of high physical activity appears stronger among those reporting high levels of stress (above median) as compared to lower levels of stress (below median).

ConclusionL We found that high physical activity was associated with a lower risk of upper respiratory tract infection. Highly stressed people might benefit more from physical activity than those with lower stress levels.

Perceived discrimination predicts elevated levels of fibrinogen in a national sample: data from the Survey of Midlife in the United States (MIDUS)

* Elliot Friedman[1] David Williams[2] Burton Singer[1, 3] Carol Ryff[1, 4]
[1]Institute on Aging, University of Wisconsin, Madison, WI [2]Harvard University, Cambridge, MA [3]Office of Population Research, Princeton University, Princeton, NJ [4]Psychology Department, University of Wisconsin-Madison
** Corresponding author: Elliot Friedman, (friedman1@wisc.edu)*

Perceived discrimination is considered a profound stressor that has been linked to a range of adverse health outcomes, but the biological processes mediating these associations are poorly understood. Given prior research linking chronic discrimination to coronary artery calcification, this study tested the hypothesis that perceived discrimination would predict increased serum concentrations of fibrinogen in a national sample of middle-aged and older adults. We also hypothesized that associations would be patterned by age and gender. Data were from the second wave of the Survey of Midlife in the United States (MIDUS). Participants (N=507) completed questionnaires

focused on lifetime instances of unfair treatment in multiple life domains. Fasting blood samples were obtained during an overnight stay at a General Clinical Research Center (GCRC), and serum levels of fibrinogen were assessed using a semiautomated modification of the Clauss method. Almost half the sample (43%) reported at least one instance of perceived discrimination. Participants under 65 years old reported significantly more instances than those over 65, and women reported more instances than men (P<.01 for both). Analyses of variance (ANOVA) that included interaction terms for age and gender showed that perceived discrimination predicted higher serum levels of fibrinogen in young men (P<.05), but not in other groups. This association remained statistically significant after adjustment for potential demographic, socioeconomic, health, and health behavior confounds. These results suggest that circulating levels of fibrinogen may be sensitive to perceived discrimination and may play a role in its health consequences. They also suggest that young men may be particularly vulnerable to the adverse impact of perceived discrimination.

Lipopolysaccharide Induces the Enzyme Indoleamine 2,3-dioxygenase in Mouse Organotypic Hippocampal Slice Cultures

Xin Fu[1] Samantha Zunich[1] Robert Dantzer[1, 2] * Keith W. Kelley[1, 2]
[1]Integrative Immunology and Behavior Program, Department of Animal Sciences, [2]College of ACES and Department of Pathology, College of Medicine, University of Illinois at Urbana-Champaign
** Corresponding author: Keith W. Kelley, (kwkelley@ad.uiuc.edu)*

Organotypic brain slice cultures (OHSC) conserve neuroanatomical organization and functional properties of brain structures. Despite these advantages over cell culture, OHSC has rarely been used for investigating murine neuroimmune interactions. Here we investigated the use of OHSC derived from brains of newborn C57BL/6 mice for studying the mechanisms of inflammation-induced activation of indoleamine 2,3-dioxygenase (IDO), a pivotal enzyme in the pathophysiology of inflammation-induced depression. Brains from neonatal C57BL/6 mice were removed. Hippocampi were dissected and cut into 350 μm slices with a McIlwain tissue chopper. Slices were cultured in MEM, 25% HBSS, 25 mM D-glucose with 25% heat-inactivated horse serum on Millicell inserts in six-well culture plates at 37C, 5% CO2. The concentration of horse serum was reduced to 5% on the day of treatment. We first showed that OHSC expressed a temporary increase in TNFα, IL-6 and iNOS mRNA on day 1 that was not accompanied by any detectable cytokine release into the medium. After 10 days in culture, LPS (100 ng/ml) induced expression of TNFα and IL-6 at the mRNA and protein levels in a time course similar to that found in the brains of LPS-treated mice. These increases were associated with heightened expression of iNOS and IDO mRNA that peaked at 6 h post LPS. Although LPS did not induce IFNγ transcripts in OHSC, exogenous IFNγ synergized with LPS to augment mRNA expression of IL-6, iNOS and IDO. These results with proinflammatory cytokines and IDO indicate that murine OHSC represent a reliable model for investigating neuroimmune interactions. KWK (MH51569; AG029573); RD (MH079829; MH71349)

Naked Mole-Rat: A Model for Investigating Neuropeptides and Healing

P. Gajendrareddy[1] J.A. Ruttencutter[1] T.J. Park[1] C.E. Laurito[1] * P.T. Marucha[1]
[1]University of Illinois - Chicago, ** Corresponding author: P.T. Marucha, (marucha@uic.edu)*

Introduction: African naked mole-rats congenitally lack Substance P (SP) and Calcitonin Gene Related Peptide (CGRP) from their skin and respiratory tract. The peripheral release of these peptides at wound sites promotes healing by triggering neutrophil migration, plasma extravasation, local vasodilatation, and immune responses.

Hypothesis: We hypothesized that the lack of neuropeptides in naked mole-rat skin wound would impair healing.

Experimental Methods: Standardized wounds were made just behind the shoulder blades, one on either side of the midline with a 3.5 mm biopsy punch. Digital photographs were taken of the wounds each day thereafter to calculate wound area. The rate of wound closure was then compared for naked mole-rats and mice. Wound closure in conjunction with SP treatment was also studied in the mole-rats. During wounding, the left wounds received a topical application of SP, while the right wounds received saline. Subsequently, once every day, the right wound received 50ul of saline while the left wound received SP (100uM).

Results: The results show the rate of wound closure was significantly slower for naked mole-rats compared to mice. At day 5 post-wounding, the wounds on mice were 80% closed whereas those on the naked mole-rats were less than 20% closed. Also, by Day 5, the SP treated wounds were 23% smaller when compared to the untreated controls.

Conclusion: These preliminary results support a role for the neuropeptide SP in wound healing. The naked mole-rat is a potential new model to study the mechanisms by which neuropeptides regulate healing. NIH R29DC02850, UIC COD, The Matula Fund.

Difficulty waking up when sick: LPS-induced immune activation disengages central arousal network

* Ronald Gaykema[1] Lisa Goehler[1]
[1]Department of Psychology, University of Virginia, Charlottesville, VA
** Corresponding author: Ronald Gaykema, (gaykema@virginia.edu)*

Fatigue, lethargy, and somnolence form characteristic hallmarks of sickness behavior, that are brain mediated, but mechanisms involved are poorly understood. To identify arousal-supporting systems as targets, we assessed changes in brain activity patterns due to inflammatory challenge in rats during ongoing behavioral activity without interference in the rats' early portion of their nocturnal, active, period. Rats were injected intraperitoneally with lipopolysaccharide (LPS) 90 minutes prior to dark onset, their behavior assessed in their home cage during the first hour of the dark period. The animals were sacrificed 90 minutes after dark onset. Brains were processed for immunohistochemical detection of c-Fos and neurochemical markers to identify, e.g., hypothalamic orexin and histaminergic neurons.

Whereas saline-treated rats were behaviorally active, the LPS-treated ones were most of the time immobile. The behavioral difference was mirrored by prominent c-Fos expression in arousal-supporting orexin and histamine neurons of saline-treated rats, whereas c-Fos expression in these populations was greatly diminished in the LPS-treated rats. Arcuate neurons expressing cocaine-amphetamine-reated transcript (CART) also expressed prominent c-Fos in saline-treated rats, probably related to ingestion of food. Paradoxally, LPS treatment completely suppressed activity of these CART neurons in the arcuate nucleus, which are implicated in satiety-induced suppression of feeding (serving an anorexigenic role). These findings support our notion that arousal-supporting systems, including the orexin and histaminergic components, which project to large parts of the brain, are functionally disengaged during sickness. This lack of functional activation, critical for goal-directed behavior, may underlie the characteristic lack of behavioral arousal during illness. This study was supported by NIH grant MH068834.

Low Levels of Cortisol and sIgA, High levels of DHEA-S, and High Stimulated Levels of TNF-alpha and IL-6 in Women with PTSD

* Jessica Gill[1] Gayle Page[2]
[1]National Institutes of Health, National Institute of Nursing Research [2]Johns Hopkins Univeristy, School of Nursing
** Corresponding author: Jessica Gill, (gillj@mail.nih.gov)*

Introduction: Post-traumatic stress disorder (PTSD) can occur following a traumatic event, and has been associated with hypothalamic-pituitary-adrenal (HPA) axis and immune function alterations; however few studies have reported relationships between these two systems in subjects with PTSD.
Hypotheses: Immune and neuroendocrine alterations would be present in women with current PTSD compared to both traumatized and non-traumatized controls and these alterations would be linked.
Methods: Participants were recruited from a health care clinic. Following diagnostic interview for PTSD and MDD, participants collected their saliva at 10 PM and 8 AM, and returned to the clinic for a blood draw within 3 days. 29 participants with current PTSD were compared to 30 traumatized and 24 non-traumatized controls.
Results: Compared to both control groups, women with PTSD exhibited lower morning salivary levels of both cortisol and sIgA, higher morning salivary DHEA-S, and produced higher levels of pro-inflammatory cytokines TNF-alpha and IL-6 (whole blood with 50 μg/ml PHA plus LPS, 48 hour incubation). Low levels of cortisol and high levels of DHEA were correlated with high levels of TNF-alpha and IL-6. High intensity of PTSD symptoms was correlated with high TNF-alpha, and IL-6 production and high DHEA-S. Diagnosis of comorbid MDD was associated with greater IL-6 production and morning DHEA-S.
CONCLUSIONS: Taken together, these results extend previous findings of biologic alterations associated with PTSD and provide evidence that both high PSTD intensity and comorbid MDD are associated with greater IL-6 production capacity and salivary DHEA-S.

Combined administration of a β-adrenergic antagonist and a COX-2 inhibitor increases survival rates in a model of spontaneous post-operative metastasis in mice: Potential clinical ramifications and mediating mechanisms

Ariella Glasner[1] Marganit Benish[1] Shaily Shemer[1] Ella Rosenne[1] Christina Katanov[1] Shiri Weinberg[1] * Shamgar Ben-Eliyahu[1]
[1]Neuroimmunology Research Unit, Dept of Psychology, Tel Aviv University,Tel Aviv, Israel
** Corresponding author: Shamgar Ben-Eliyahu, (shamgar@post.tau.ac.il)*

Background: Several physiological consequences of tumor excision were suggested to promote metastasis, including catecholamine-induced VEGF secretion, and suppression of cell mediated immunity (CMI). We recently reported the involvement of catecholamines and prostaglandins in stress and injury-mediated suppression of NK cytotoxicity. In this study we addressed the potential clinical benefits of inhibiting perioperative release of these factors, and sought to determine potential mediating mechanisms.
Methods: C57BL/6J mice were s.c. inoculated with syngeneic B16F10.9-melanoma cells into the footpad. When developing tumors reached approximately 120μl, the footpad was amputated under anesthesia and some of the mice underwent laparotomy. The clinically used β-adrenergic antagonist, propranolol, and the COX-2 inhibitor, etodolac, were administered 1h before amputation, and recurrence-free survival was assessed for 80 days. In different studies, NK cytotoxicity and circulating leukocyte subtypes and their molecular markers were evaluated in the context of surgery and drugs administration.
Results: (i) Laparotomy reduced survival rates, (ii) the combination of propranolol and etodolac (PE), but neither drug alone, doubled survival rates following amputation, with or without laparotomy, (iii) NK cytotoxicity was markedly impaired by laparotomy or amputation, and all lymphocyte-subtypes numbers were reduced, as were expression levels of FASL and CD11a on NK cells. PE administration attenuated these effects.
Conclusions: Although PE administration has restored some immunological perturbations, other mechanisms could also account for improved survival. This regimen could be tested clinically in most cancer patients with minimal risks and low cost. The treatment could be initiated days before surgery to reduce release of prostaglandins by some tumors, and antagonize pre-operative stress-induced sympathetic discharge.

How does immune activation influence motivated behavior? Autonomic and limbic inputs drive the rostral nucleus accumbens following lipopolysaccharide injection

* Lisa Goehler[1] Gregory Thacker[1] Ron Gaykema[1]
[1]University of Virginia * *Corresponding author: Lisa Goehler, (goehler@virginia.edu)*

The nucleus accumbens (NAc) of the ventral striatum is a critical component of brain neurcircuits that mediate behavioral responses to reward and hedonic value of stimuli. We have previously reported that systemic LPS challenge strongly activates neurons in the shell and core of the rostral NAc, which, based on its inhibitory inputs to the lateral hypothalamus (arousal, feeding, reward) suggests this brain region as a potentially important mediator of the effects of immune activation on mood and behavior. LPS dramatically inhibits ingestion of palatable food (sweetened milk), and together with findings from other groups, these previous findings suggest that LPS-increased drive from the rostral NAc may serve as a "brake" on feeding in this paradigm. However, still unknown are the neural inputs to the NAc that drives this response to immune challenge. To address this issue we injected the retrograde tracer Fluorogold (to identify inputs) into the rostral NAc of rats trained to drink sweetened milk (or water), and later challenged the animals with intraperitoneal LPS or saline injection. Brain regions that may drive the NAc in the context of illness were identified by the dual labeling of Fluorogold and c-Fos protein, an activation marker. From this study we identified the basolateral amygdala (BLA), paraventricular thalamus (PVT), and ventral hippocampal CA1/subiculum as regions that provide the bulk of immune-responsive input to the rostral NAc. These regions have in common roles in both homeostasis and motivated behavior. These findings suggest that the PVT, ventral hippocampus and BLA may contribute to neurocircuitry mediating behavioral effects of sickness.

The use of CpG-C ODN immunostimulation in the context of stress and surgery: differential modulation of NK cell cytotoxicity and distribution, and protection against NK suppression

* Yael Goldfarb[1] Marganit Benish[1] Ella Rosenne[1] Tamar Geron[1] Shamgar Ben-Eliyahu[1]
[1]Tel-Aviv University * *Corresponding author: Yael Goldfarb, (yaelgold@post.tau.ac.il)*

Following tumor resection, surgery-induced immunosuppression compromises host resistance to minimal residual disease. Our studies herein employ CpG-C oligodeoxynucleotides, a new class of BRMs that activates TLR9 and enhances CMI. We recently showed that CpG-C increases resistance to experimental metastasis following exposure to the pharmacological stressor metaproterenol (β-adrenergic agonist) and following surgery. Our current work focuses on elucidating underlying mechanisms. F344 rats were treated with 330μg/kg CpG-C 24hrs prior administration with metaproterenol (1mg/kg) or undergoing laparotomy. In vivo studies evaluating lung tumor retention of the syngeneic MADB106 tumor in NK-depleted rats indicated that NK cells (NKCs) are predominantly responsible for the beneficial effects of CpG-C in non-stressed and in metaproterenol-treated animals; nevertheless, additional mechanisms contribute to the beneficial effects of CpG-C in animals undergoing surgery. Ex-vivo examination of NKC numbers and activity indicated the following: In the most relevant marginating-pulmonary (MP) immune compartment, CpG-C increased the numbers of MP-NKCs, and their individual cytotoxicity, in non-stressed animals. CpG-C did not prevent the decrease in MP-NKC numbers caused by metaproterenol, but did reduce suppression of cytotoxicity per MP-NK cell (YAC-1 and MADB106 target-lines). However, similar suppression by surgery was not attenuated. In the blood, where NKC numbers were unchanged, CpG-C abolished NKC suppression by metaproterenol, but again not by surgery. Taken together, cytotoxicity and redistribution of MP-NKCs are independently affected by CpG-C. Augmentation of NK cytotoxicity and protection from suppression rely on different CpG-C-related mechanisms. The use of CpG-C in the perioperative context should be supplemented with pharmacological blockade of immunosuppressive factors.

Attachment avoidance predicts inflammatory response to marital conflict

* Jean-Philippe Gouin[1, 2] Ronald Glaser[2, 3, 4] William Malarkey[2, 3, 4, 5] Timothy Loving[6] Janice Kiecolt-Glaser[1, 2, 5]
[1]Department of Psychology, The Ohio State University, USA [2]Institute for Behavioral Medicine Research, Ohio State University College of Medicine, USA [3]Department of Internal Medicine, Ohio State University College of Medicine, USA [4]Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University College of Medicine, USA [5]Department of Psychiatry, Ohio State University College of Medicine, USA [6]Department of Human Ecology, The University of Texas at Austin, USA
* *Corresponding author: Jean-Philippe Gouin, (gouin.1@osu.edu)*

Marital stress has been associated with immune dysregulation, including increased production of circulating proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis-α (TNF-α). Attachment style is an individual difference in one's expectation about the availability and responsiveness of others in intimate relationships. Attachment avoidance, one dimension of attachment style representing difficulties in relying on and opening up to others, has been related to increased physiological stress reactivity. We hypothesized that individuals who exhibited higher levels of attachment avoidance would show an exacerbated inflammatory response to a marital conflict, but not to a socially supportive marital interaction, compared to individuals with lower levels of attachment avoidance. During the first of two 24-hour admissions to a hospital research unit, 40 married couples had a structured social support interaction; during the second visit they discussed a marital disagreement. Results from blood samples drawn at baseline, 4, 7, and 22 hours showed that attachment avoidance was not related to serum IL-6 and TNF-α levels during the social support visit. In contrast, during the conflict visit, husbands' attachment avoidance predicted wives' IL-6 baseline levels and husbands' levels of IL-6 at baseline, 4, and 7 hours. Wives' attachment avoidance predicted husband's baseline IL-6 and TNF-α at baseline and 4 hours. During the conflict visit, the wives' attachment avoidance was associated with their own negative behaviors, while husband attachment avoidance was related to both spouses' negative behaviors, suggesting a mechanism by which attachment style influences inflammatory response to marital conflict.

The Sympathetic Nervous System Influences Anti-Influenza Immunity

* Kristie Grebe[1] Heather Hickman[1] Jack Bennink[1] Jonathan Yewdell[1]
[1]Viral Immunology and Cellular Biology Sections, Laboratory of Viral Diseases, NIAID, NIH, Bethesda, MD, USA, 20892
** Corresponding author: Kristie Grebe, (grebek@niaid.nih.gov)*

Influenza infection activates both the hypothalamic-pituitary axis and the sympathetic nervous system. Lymphoid organs are extensively innervated by adrenergic fibers that release neurotransmitters, including norepinephrine and neuropeptide Y, that can modify the function of immune cells via receptors such as the alpha and beta adrenergic receptors and neuropeptide Y receptors. We hypothesize that neurotransmitters released by the sympathetic nervous system (SNS) play an important immunomodulatory role during a primary influenza A virus (IAV) infection. Using 6-hyroxydopamine (6OHDA) treatment to chemically sympathectomize mice, we have demonstrated that SNS ablation increases CD4+ and CD8+ T cell responses to IAV antigens following infection. Critically, 6OHDA-treated mice demonstrate increased survival following a lethal intranasal IAV challenge (80% 6OHDA treated vs. 35% saline treated; p=0.02). The lungs of the IAV infected 6OHDA-treated mice have a greater cellular infiltrate but less damage to lung tissue and inflammatory cytokines compared to the saline-treated mice. Taken together these data strongly suggest that the SNS suppresses T cell responses to IAV in mice and enhances lung pathology following influenza infection.

Biobehavioral Correlates of Overweight and Obesity in Postpartum Women

* Maureen Groer
** Corresponding author: Maureen Groer, (mgroer@health.usf.edu)*

In a psychoneuroimmunological study of the postpartum, overweight and obesity were present in 57% of 200 mothers. Therefore, we asked whether BMI was associated with stress and immune variables that were measured. Mothers were measured in their homes at approximately 5 weeks postpartum, completing stress, mood, and health questionnaires and providing a blood sample. Participants were healthy, had no chronic illnesses, had a full-term uncomplicated delivery, and about half were exclusively breastfeeding. Higher BMI was associated with lower socioeconomic status and increased incidence of Caesarean section. There was a tendency for higher BMI to be associated with greater perceived stress, depression, and anxiety. Decreased serum Interferon-γ and IL-2 levels were associated with higher BMI, independently of stress. However inflammatory biomarkers IL-6, TNF-α and C-reactive protein did not differ by BMI. Overweight and obesity did not increase infections reports. There was an association of higher BMI with elevated Thyroid-Stimulating Hormone levels, suggesting postpartum hypothyroidism.

The data suggest that overweight or obesity is distressing to postpartum mothers, and may impact Th1/Th2 balance. This postpartal stage is normally associated with upregulated innate immunity and overweight or obesity did not seem to alter inflammation biomarkers. The postpartum may be a somewhat protected period, and additional weight is tolerated because of the metabolic demands of lactation, sleep deficits, and healing during this time of life. Further longitudinal work is needed to more carefully examine the risks associated with overweight and obesity during the postpartum period.

Beta-2 Adrenergic Blockade Decreases the Immunomodulatory Effects of Social Disruption Stress (SDR)

* Mark Hanke[1] Michael Bailey[2, 3] Nicole Powell[2] Latonia Stiner[2] John Sheridan[1, 2, 3, 4]
[1]The Ohio State University College of Medicine, Integrated Biomedical Science Program [2]College of Dentistry, Section of Oral Biology [3]Institute for Behavioral Medicine Research [4]College of Medicine, Department of Molecular Virology, Immunology and Medical Genetics, Columbus, Ohio, 43218 ** Corresponding author: Mark Hanke, (hanke.9@osu.edu)*

Introduction: Catecholamines produced by the sympathetic nervous system play a significant role in the regulation of the immune response. Under physiological stress, plasma catecholamine levels increase altering cytokine production by immune cells. Macrophages, a major source of pro-inflammatory cytokines, express high levels of the β2 adrenergic receptor (β2AR), which mediates the actions of epinephrine and norepinephrine. Previous studies have shown that the activation of β2ARs can increase pro-inflammatory cytokine production in a number of different cell types. Hypothesis: β2AR blockade via propranolol will decrease the immunomodulatory effects of SDR. Experimental Methods: CD-1 mice were injected subcutaneously with propranolol, or vehicle, 1 hour before SDR. During SDR an aggressive male mouse was placed into a cage of 5 resident mice for 2 hours at the beginning of the animal's active cycle, and repeated for 6 days. Animals were sacrificed 18 hours following the last cycle of SDR. Results: SDR propranolol treated mice demonstrated decreased plasma IL-6 compared to SDR mice. Further, SDR propranolol treated spleen cells, cultured for 18 hours with LPS, produced less IL-6 and IL-1beta than SDR splenocytes. Splenocytes from SDR propranolol-treated mice also show decreased glucocorticoid insensitivity compared to SDR mice. Conclusions: Previous studies from our laboratory have shown that splenocytes from SDR mice are glucocorticoid insensitive, demonstrate a primed phenotype and produce more cytokines after stimulation with LPS. This study demonstrates that the immunomodulatory effects of SDR are, at least in part, due to activation of the sympathetic nervous system.

RELATIONSHIP OF IL-4 AND SEROTONIN TRANSPORTER GENE POLYMORPHISMS ON HUMAN ACOUSTIC SENSORIMOTOR GATING RESPONSES AND EMOTION.

Joanne Hash MS[1] * Alexander W Kusnecov PhD.[1]
[1]Behavioral Neuroscience Program, Department of Psychology, Rutgers University, Piscataway, New Jersey 08855
** Corresponding author: Alexander W Kusnecov PhD., (kusnecov@rci.rutgers.edu)*

Anti-inflammatory cytokines, such as interleukin-4, have received relatively less attention with regard to their role in behavioral modulation. Indeed, IL-4 has been shown to modulate the serotonin transporter, 5-HTT, and has been found at elevated levels in the orbitofrontal cortex of female suicide victims. Therefore, the current study sought to demonstrate a relationship between variations in IL-4 and 5-HTT genes and behavioral markers (e.g., baseline acoustic startle, ASR, and prepulse inhibition of startle, PPI) that engage neural substrates of anxiety. We hypothesized that IL-4 VNTR B2 allele-bearers (associated with immunoprotective effects of IL-4) would show enhanced ASR and reduced PPI, particularly in concert with the 5-HTT-linked polymorphic region (5-HHTLPR) s-allele. Young male and female subjects underwent genetic analyses, psychometric evaluation of anxiety, and psychophysiological testing for ASR (N=94, 58 F, 36 M) and PPI (N=31, 28 F, 3 M) during exposure to images with neutral, positive and negative emotional valence. The IL-4 VNTR B1 allele was significantly associated with the 5-HTTLPR s-allele, χ^2=8.705, p=0.003. Genotype did not predict variations in baseline ASR, but the IL-4 VNTR B2/B2 genotype showed a trend toward enhanced PPI when participants were viewing neutral images (p=0.094). While 5-HTTLPR alleles showed no relationship to anxiety, IL-4 B2 allele-bearers had high trait anxiety, χ^2=4.044, p=0.044. The data provide preliminary evidence suggesting a relationship between the IL-4 VNTR B2 allele, emotion, and sensorimotor gating, and are consistent with the behavioral impact of immune-related genes. Supported by PHS grants MH60706, NIEHS P30 ES05022, and a Busch Biomedical Research Grant.

Cortisol may influence HIV progression via effects on T-cell activation and CCR5

* Frederick Hecht[1] Elissa Epel[2] Patricia Moran[1] Michael Acree[1] Adam Carrico[3] Steven Deeks[4] Elizabeth Sinclair[4] Margaret Kemeny[3] Susan Folkman[1]
[1]Osher Center for Integrative Medicine, University of California, San Francisco [2]Dept of Psychiatry, University of California San Francisco [3]Health Psychology, University of California San Francisco [4]Department of Medicine, University of California San Francisco
** Corresponding author: Frederick Hecht, (rhecht@php.ucsf.edu)*

Stress and elevated cortisol are associated with more rapid HIV progression, but the pathways responsible are unknown. High T-cell activation and expression of chemokine receptor CCR5 are linked to HIV progression. We hypothesized that T-cell activation and CCR5 expression are associated with HPA function. We used baseline data from 29 persons in an on-going RCT testing meditation in HIV. Participants had a CD4+ T-cell count > 250 cells/μl and were untreated. T-cell activation (CD38+HLADR+) and CCR5 were measured with flow cytometry; mean fluorescent intensity (MFI) was used to quantitate receptor density. Salivary cortisol was tested at waking, 30 minutes post-waking (used to calculate the 30min-rise from waking), and at bedtime for 3 days. GC sensitivity was measured using cortisol level 30 min after waking during dexamethasone suppression test (DST). Greater average 30min-rise (consistent with greater stress responses) was associated with CD38MFI on CD4+ cells (r=0.38, P=0.04); there were weaker, non-significant correlations between other cortisol measures (including DST) and CD38 measures. Waking cortisol was weakly correlated with CCR5 MFI on CD4+ T-cells (r=0.27, P=0.16), and more clearly correlated with CCR5 MFI on CD8+ cells (r=0.44, P=0.01). DST results were weakly correlated with CCR5 MFI on CD4+ T-cells (r= -0.30, P=0.1) and strongly correlated on CD8+ T-cells (r= 0.54, P=0.002). Results are consistent with an HPA role in regulation of T-cell activation and CCR5 expression, although we cannot exclude mediation through other stress responses. There may be different characteristics of cortisol patterns that most influence T-cell activation and CCR5 expression.

Switching transcription factor use preserves cytokine production after NF-κB inhibition in neonatal cerebral hypoxia-ischemia

* Cobi J. Heijnen[1] Cora Nijboer[1, 2] Floris Groenendaal[2] Frank van Bel[2] Annemieke Kavelaars[1]
[1]Laboratory of Psychoneuroimmunology, University Medical Center Utrecht, Lundlaan 6, Utrecht, the Netherlands [2]Department of Neonatology, University Medical Center Utrecht, The Netherlands
** Corresponding author: Cobi J. Heijnen, (c.heijnen@umcutrecht.nl)*

Both NF-κB and AP-1 can regulate inflammatory and apoptotic target gene transcription. Our recent findings in a model of neonatal hypoxic-ischemic (HI) brain damage showed that NF-κB inhibition strongly reduced HI-brain damage. Surprisingly, however, NF-κB inhibition did not prevent HI-induced cerebral TNF-α production. Here we further explore the role of NF-κB and AP-1 neonatal HI-induced cerebral cytokine production and damage.

Brain damage was induced in P7 rats by unilateral carotid artery occlusion and hypoxia. We inhibited NF-κB by TAT-NBD and the JNK/AP-1 pathway by TAT-JBD.

We confirm that NF-κB inhibition protects against HI-brain damage without inhibiting TNF-α production. NF-κB inhibition enhanced HI-induced activation of AP-1 activation and reduced expression of XIAP, an NF-κB target that inhibits AP-1. JNK/AP-1 inhibition resulted in significant neuroprotection albeit less pronounced than after NF-κB inhibition. Inhibition of both NF-κB and JNK/AP-1 completely abrogated HI-induced early TNF-α production, but reduced the neuroprotective effect of TAT-NBD alone. HI-induced upregulation of expression of death receptor TNF-R1 and protective TNF-R2 were differentially regulated by NF-κB inhibition.

We conclude that switching to the JNK/AP-1 pathway, possibly via reduced expression of XIAP, is responsible for preserving early cytokine expression after neonatal HI when NF-κB is inhibited. Early TNF-α production does not enhance HI brain injury and may even have protective effects by signalling via TNF-R2.

Fatigue in adolescent girls: a psychoneuroimmunological approach

* Cobi J. Heijnen[1] Maike ter Wolbeek[1, 2] Lorenz J.P. van Doornen[2] Annemieke Kavelaars[1]
[1]Laboratory of Psychoneuroimmunology, University Medical Center Utrecht, Lundlaan 6, Utrecht, the Netherlands [2]Department of Health Psychology, Utrecht University, Utrecht, The Netherlands
** Corresponding author: Cobi J. Heijnen, (c.heijnen@umcutrecht.nl)*

Severe fatigue was reported by 20.5% of adolescent girls in our sample of the normal population. These girls often complain of comorbid symptoms which are also observed in chronic fatigue syndrome (CFS) patients, including unrefreshing sleep, pain and cognitive and emotional problems. In a multidisciplinary longitudinal study we investigated whether severe fatigue is related to neuro-endocrine and immunological dysfunctions as previously observed in adolescent CFS patients. Groups of 67 severely fatigued and 61 non-fatigued otherwise healthy girls (age resp. 15.2±1.4 and 14.7±1.6) were selected and blood was collected to determine plasma cortisol levels, mitogen-induced cytokines and glucocorticoid receptor (GR) sensitivity of leukocytes on three occasions using repeated measures analysis.

The results showed that plasma cortisol was higher in fatigued than in non-fatigued participants ($p<.05$). The ratios interferon (IFN)-gamma/IL-4 and IFN-gamma/IL-10 and actual levels of CD2/CD28-induced interleukin (IL)-10 and were only deviant in those severely fatigued participants who also had high depression and/or anxiety scores ($p<.01$ and $p<.05$). The sensitivity of GR in T-lymphocytes of severely fatigued girls with symptoms for at least one year (persistently fatigued girls) showed similarities with GR sensitivity of cells of CFS patients ($p<.05$).

An important result of our longitudinal study was that cytokine production and GR sensitivity fluctuated across seasons but individual stability was high. We conclude that cortisol production is affected in severely fatigued adolescents and that immunological and GR sensitivity deviations occur in distinct subgroups of severely fatigued adolescents. We hypothesize that these latter groups have an increased risk to develop fatigue-related illness, such as CFS.

Minocycline attenuates Lipopolysaccharide (LPS)-induced brain cytokine expression, social withdrawal, and anhedonia

* Christopher Henry[1] Yan Huang[1] Angela Wynne[1] Justin Himler[1] Jonathan Godbout[1, 2]
[1]Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University, [2]Institute for Behavioral Medicine Research, The Ohio State University, Columbus, OH 43210. ** Corresponding author: Christopher Henry, (henry.86@osu.edu)*

Activation of the peripheral innate immune system stimulates the production of CNS cytokines that modulate the behavioral symptoms of sickness. Excessive or prolonged production of CNS cytokines by microglia, however, may cause long-lasting behavioral and cognitive complications. The purpose of this study was to determine if minocycline, a purported microglial inhibitor, attenuates LPS-induced neuroinflammation, sickness behavior, and anhedonia in mice. In an initial study we confirmed that minocycline blocked LPS-stimulated inflammatory cytokine production in the BV2 and N13 microglia-derived cell lines. In the next set of experiments we confirmed that intraperitoneal (i.p.) lipopolysaccharide (LPS) injection (0.33 mg/kg) induced a sickness response in BALB/c mice characterized by increased social withdrawal, body weight loss, and anorexia 24h post injection. These symptoms were attenuated by minocycline pretreatment (50 mg/kg/day for 3 days, i.p.). Moreover, LPS caused anhedonia in mice 24h post challenge, as determined by a marked reduction in preference for a 2% sucrose solution over drinking water. This LPS-induced anhedonia was inhibited in mice pretreated with minocycline. Furthermore, plasma IL-6 levels at 4h and 8h post LPS injection were reduced by minocycline pretreatment while plasma IL-1β levels were reduced at 8h but not at 4h. Finally, the minocycline enhanced recovery from LPS-induced sickness behavior was paralleled by reduced levels of IL-1β, IL-6, and indoleamine 2,3 dioxygenase in the cortex and hippocampus. Taken together, these data indicate that minocycline mitigates inflammatory cytokine production in the brain and modulates the cytokine-associated changes in behavior.

Depression and Anxiety, Health locus of control and Quality of life among Gouty Arthritis Males.

* Roger C.M. Ho[1] Jason Tan[2] Alicia Cheak[2] Anselm Mak[2]
[1]Department of Psychological Medicine, National University of Singapore [2]Department of Medicine, National University of Singapore
** Corresponding author: Roger C.M. Ho, (pcmrhcm@nus.edu.sg)*

Introduction: Gout is a immunological disorder which is caused by deposition of uric acid crystal in joints and surrounding tissues with inflammatory reaction and its psychiatric aspects have not been well studied.

Hypothesis: The aim of this study was to evaluate the psychiatric status, health locus of control and quality of life in gout patients. We hypothesized that gout patients with depression have poorer health related quality of life.

Methods: Thirty-five consecutive male patients who met the American College of Rheumatology (ACR) classification criteria for gout were recruited. Each patient underwent assessment using the Hospital Anxiety and Depression Scale, Multidimensional Health Locus of Control Scale Form C (C-MHLC-C) and Short Form - 12.

Results: Of the thirty-five male patients with gouty arthritis, 21 (60%) were ethnic Chinese, 12 (34%) were Malay and 2 (5.7%) were Indians. Their mean age was 57.1±13.6 years while the mean age of onset and duration of gout was respectively 50.0±16.3 and 7.1± 7.9 years. 7 (20.6%) were depressed and 3 (8.6%) suffered from anxiety. For the health locus of control, patients perceived that the main sources of control were from the doctors (94.3%) and themselves (74.3%). For health related quality of life, patients with depression have significantly poorer physical ($p<0.01$) and mental health ($p<0.01$).

Conclusions: Results from this pilot study will provide valuable information to suggest strategies which target an improvement of psychiatric status and quality of life in gout patients. These strategies should take into consideration of the patients' cultural and healthcare system contexts.

A Potential Effect of Beta-blockers on Inflammatory Responses to a Psychological Stressor in Congestive Heart Failure Patients

* Suzi Hong[1] Laura Redwine[2] Sarah Linke[1] Douglas DeJardin[1] Barry Greenberg[2] Paul Mills[1]
[1]Department of Psychiatry, University of California San Diego [2]Department of Medicine, University of California, San Diego
* *Corresponding author: Suzi Hong, (s1hong@ucsd.edu)*

Congestive heart failure (CHF) is characterized by cardiac tissue damage and remodeling. Increased levels of pro-inflammatory cytokines contribute to cardiac dysfunction and disease progression in CHF patients. Beta-blockers are widely used to counteract sympathetic activation and bolster cardiac performance and shown to reduce inflammation. However, their effects on inflammatory responses to stressors in CHF remain unclear. We examined plasma IL-6 levels before and after a psychological stressor (combination of 3-min speech and 5-min arithmetic tasks) in 35 CHF patients treated with beta-blockers (61.9±14.1 years old) compared to 34 non-CHF (n-CHF) control participants not on beta-blockers (52.8±11.8 years old). CHF patients were NYHA Class II-IV with ejection fractions <40% and under optimal clinical care. Blood was drawn pre, immediately post, 10-min post, and 30-min post stressor, and hemodynamic responses were measured. Although pre-stressor IL-6 levels were higher in CHF patients (3.79 vs. 2.19 pg/ml; $p < 0.05$), there was a significant interaction for IL-6 responses ($F = 6.18$, $p < 0.05$) such that an increase in IL-6 levels post stressor shown in n-CHF was absent in CHF patients, after controlling for age and depressive symptoms. SBP, DBP, and HR responses were not different, although CHF patients exhibited smaller SBP and DBP levels at all time points compared to n-CHF ($p's < 0.01$). CHF patients treated with beta-blockers showed a suppressed IL-6 response in spite of similar hemodynamic responses to a psychological stressor to those in healthy individuals. The clinical significance of beta-blockers in stress-induced inflammatory responses merits further investigation in heart diseases.

Repeated administration of cannabidiol enhances nonspecific, antiviral and antitumor immune response

* B. Ignatowska-Jankowska[1] M. Jankowski[1] W Glac[1] A. H. Swiergiel[1]
[1]Department of Animal Physiology, University of Gdansk, Poland * *Corresponding author: B Ignatowska-Jankowska, (bmjank@wp.pl)*

The major non-psychoactive constituent of cannabis plant, cannabidiol, produces various immunosuppressive, anti-inflammatory and anti-autoimmune effects. Recent studies have shown cannabidiol to be a potent therapeutic agent in many inflammatory - autoimmune and neurodegenerative diseases (such as rheumatoid arthritis or type 1 diabetes). In spite of its therapeutic potential, mechanisms of immunomodulatory action of cannabidiol remain unknown. Present study aimed to evaluate lymphocyte subset distribution in peripheral blood after repeated, systemic administration of cannabidiol. Rats receive intraperitoneal injections of cannabidiol for 14 consecutive days in doses of 2.5, 5 and 10 mg/kg/day. Blood samples were collected 1 hour after the last injection and distribution of lymphocyte subsets was determined by flow cytometry. Three-color immunofluorescent antibody staining procedure (CD3-FITC/CD45RA-PC7/CD161A-APC and CD3-FITC/CD4-PC7/CD8-APC) was used for determination of T, B, NK, NKT, Th and Tc lymphocytes. Total leukocyte number and percentage number of leukocyte subpopulations were assessed, too. Cannabidiol administration caused significant increase in NK and NKT cells number, in a dose dependent manner, with the lowest dose being the most effective. A dose of 5mg/kg decreased the total number of leukocytes - this immunosuppressive effect influenced all lymphocyte subsets except NKT cells, number of which remained significantly increased. Administration of cannabidol, especially at dose of 2.5mg/kg, increased the numbers of monocytes and eosinophils. The results indicate that repeated treatment with cannabidiol enhances nonspecific immune response, manifested mainly as increase of NK and NKT cells numbers, responsible for primary, antiviral and antitumor immunity, and suggested to be important in cancer patients survival.

Can consumption of omega-3 fatty acid (ω-3FA) attenuate laparotomy-induced NK suppression and metastasis progression in rats?

* Yael Kalderon[1] Rivka Melamed[1] Ben Levi[1] Marganit Benish[1] Ella Rosenne[1] Ariella Glasner[1] Hadas Meiboom[1] Shaily Shemer[1] Shamgar Ben-Eliyahu[1]
[1]Neuroimmunology Research Unit, Dept of Psychology, Tel Aviv University, Tel Aviv, Israel
* *Corresponding author: Yael Kalderon, (yaelkald@post.tau.ac.il)*

Background: NK cells participate in immuno-surveillance against metastases, and their suppression following oncological surgery may enhance cancer recurrence. ω-3FA was reported to prevent immuno-suppression of lymphocytes in hyper-inflammatory states, and to improve several immune functions. The current study assessed whether ω-3FA can prevent NK-suppression and progression of experimental metastasis in non-operated and operated rats.

Methods: F344 rats consumed a diet enriched with either ω-3FA or ω-6FA (control) for a month, and either underwent laparotomy or not. One hour after laparotomy, rats were intravenously inoculated with radiolabeled NK-sensitive syngeneic MADB106 tumor cells. Twelve hours later, blood was withdrawn, marginating-pulmonary (MP)-leukocytes were harvested by forced perfusion, and lungs removed for assessment of MADB106 lung tumor retention (LTR).

Results: Surgery markedly decreased circulating-NK and MP-NK cytotoxicity against YAC-1 and MADB106 target cells (respectively), and markedly increased MADB106 LTR. Interestingly, ω-3FA had large positive effects in both naïve and operated rats, increasing NK cytotoxicity in both immune compartments, and decreasing MADB106 LTR. Suppression of MP-NK cytotoxicity by surgery correlated with reduced numbers of large MP-NK cells, and its attenuation by ω-3FA occurred on a per large-NK cell basis. Expression of cellular determinants, including β-adrenoceptors, CD11a, and CD25, were affected by surgery but not by ω-3FA.

Conclusions: ω-3FA can potentiate NK cytotoxicity and improve in-vivo resistance to NK-sensitive tumors, in non-stressed rats and following surgery. Assessing the potential clinical significance of these effects, ongoing studies evaluate the impact of ω-3FA on long-term recurrence-free survival rates in mice undergoing surgical excision of a metastasizing primary tumor. Molecular mechanisms of ω-3FA impacts will be discussed.

Modulation of Antibody Production by Stress in Interferon-γ Receptor Knockout Mice

* Jonathan Karp[1] Jenny Stanwix[1] Sujata Kumar[1]
[1]Rider University * *Corresponding author: Jonathan Karp, (jkarp@rider.edu)*

Psychological stress can influence antibody production in some but not all strains of mice. For example, when BALB/c mice are immunized with a protein antigen several hours before stressor exposure, restraint stress augments circulating antibody production. The same procedures do not augment antibody production in C57BL/6 mice. To investigate these strain-specific susceptibilities to restraint stress, we evaluated the ability of restraint stress to influence antibody production in IFN-γ receptor knockout C57/BL/6 mice. IFN-γ receptor knockout C57BL/6 mice were immunized with keyhole limpet hemocyanin (KLH) eight hours before overnight restraint or food-water deprivation. The next morning these treatments ended and all mice received unrestricted access to food and water in their home cages. Sera samples were collected from the mice several times over the subsequent month and were assayed for anti-KLH IgM and IgG antibodies by ELISA. We observed IFN-γ receptor knockout C57/BL/6 mice were sensitive to antibody augmentation by restraint stress. When subsets of IFN-γ receptor knockout C57/BL/6 mice were administered a chemotherapeutic agent known to augment the sensitivity of BALB/c mice to the antibody enhancing effects of restraint stress, additive effects on antibody levels in the IFN-γ receptor knockout C57BL/6 mice were not observed. We conclude that the IFN-γ signaling pathway is important for stress-mediated augmentation of antibody production in mice and that non-IFN- γ signaling pathways may play a role in neuroimmunomodulation in immunocompromised hosts.

Role of p38 MAP kinase-GRK2 interactions in chronic inflammatory hyperalgesia

* Annemieke Kavelaars[1] Niels Eijkelkamp[1] Ilona den Hartog[1] Cobi J. Heijnen[1]
[1]Laboratory of Psychoneuroimmunology, University Medical Center Utrecht, Lundlaan 6, 3584 EA Utrecht, The Netherlands
* *Corresponding author: Annemieke Kavelaars, (a.kavelaars@umcutrecht.nl)*

Inflammatory mediators can cause an increase in pain sensitivity (hyperalgesia) by sensitizing nociceptors via G Protein coupled receptors (GPCR). GPCR-kinases (GRK) regulate the activity of GPCRs and low intracellular GRK levels result in increased receptor signaling. Moreover, GRK2, a widely studied member of this family, interacts with downstream signalling molecules including p38, thereby regulating signal propagation. We have shown previously that GRK2 expression in the dorsal horn of the spinal cord is reduced in animal models of neuropathic pain. Moreover, animals partially deficient in GRK2 ($GRK2^{+/-}$ animals) display increased acute inflammatory hyperalgesia, but at base line pain sensitivity is not altered. These data demonstrate that GRK2 plays an important role in regulating the consequences of inflammation for pain sensitivity.

Here we show that thermal hyperalgesia induced by intraplantar injection of the chemokine CCL3 or the cytokine IL-1β was markedly prolonged in $GRK2^{+/-}$ animals; thermal sensitivity normalized within 24 h in WT animals but was maintained up to 8 days in animals deficient for GRK2. Prolonged inflammatory thermal hyperalgesia could be prevented by intrathecal administration of a p38 inhibitor, but not a MEK inhibitor. Moreover, spinal cord chemokine-induced activation of p38 was increased in $GRK2^{+/-}$ animals while there was no effect of genotype on ERK1/2 activation. Finally, we demonstrate that in vitro LPS-induced cytokine production by $GRK2^{+/-}$ microglia cultures was increased via a p38 dependent pathway. Collectively these data suggest a central role for GRK2-p38-cytokine interactions in chronic inflammatory hyperalgesia.

Hostility is related to clusters of T-cell cytokines and chemokines in healthy men

* Annemieke Kavelaars[1] Paula Mommersteeg[1] Eric Vermetten[2] Elbert Geuze[2] Cobi J. Heijnen[1]
[1]Laboratory of Psychoneuroimmunology, University Medical Center Utrecht, Lundlaan 6, 3584 EA Utrecht, The Netherlands [2]Military Mental Health-Research Centre, Ministry of Defense, Utrecht, the Netherlands
* *Corresponding author: Annemieke Kavelaars, (A.kavelaars@umcutrecht.nl)*

Hostility is a risk factor for adverse health outcomes such as cardiovascular disease and post-traumatic stress disorder. Cytokines have been suggested to mediate this relationship. We investigated whether in healthy men a relation existed between hostility and T-cell mitogen-induced cytokines and chemokines. Male Dutch military personnel (n= 304) were included before deployment. Eleven cytokines and chemokines were measured in supernatants of T-cell mitogen-stimulated whole blood cultures by multiplex immunoassay. Factor analysis was used to identify clusters of cytokines and chemokines. Hostility was the dependent variable in the regression analysis, with the cytokine/chemokine clusters, and the potential risk factors age, BMI, smoking, drinking, previous deployment, early life trauma and depression as explanatory variables.

Factor analysis revealed four functional clusters; a pro-inflammatory factor (IL-2, TNFα, IFNγ), an anti-inflammatory factor (IL-4, IL-5, IL-10), IL-6/chemokine factor (IL-6, MCP-1, RANTES, IP-10), and MIF. Hostility was significantly related to decreased IL-6/chemokine secretion and increased pro- and anti-inflammatory cytokines. Younger people had higher hostility scores. Early life trauma and depression were positively and independently related to hostility as well.

This study represents a novel way of investigating the relation between cytokines and psychological characteristics. Cytokines/chemokines clustered into functional factors, which were related to hostility. Moreover this relation appeared to be independent of reported depression and early trauma. In view of the relation between functional cytokine clusters and hostility, this study suggests a mediating role for cytokines in the relation between hostility and adverse health outcomes such as post-traumatic stress disorder and cardiovascular disease.

Written Emotional Disclosure: Sympathetic Habituation?

* Kimberly Kelly, Ph.D.[1] Damini Malhotra[1] Kenneth Sewell, Ph.D.[1] Daniel Tomczyk[1]
[1]University of North Texas Denton, TX
** Corresponding author: Kimberly Kelly, Ph.D., (kellyk@unt.edu)*

The present study investigated one physiological mechanism underlying written disclosure. Thirty-two undergraduate students engaged in four weekly expressive writing sessions. The dependent variables were salivary cortisol, state anxiety, physical symptoms, number of doctor visits, sick days and activity-restriction due to illness. Results showed there was significant decline in cortisol immediately after writing and across the four weeks that participants engaged in expressive writing, but amounts returned to pre-writing levels at follow-up. There were no significant changes in any of the other variables. The results suggest that expressive writing leads to sympathetic habituation to stressful stimuli, although only in the short-term.

Physical activity modulates stress effects on tetanus toxoid antibody responses

* Sarah Kennedy[1] Teresa Foley[1] Thomas Maslanik[1] Monika Fleshner[1]
[1]University of Colorado-Boulder ** Corresponding author: Sarah Kennedy, (kennedys@colorado.edu)*

Intense or chronic stressor exposure in humans and rodents suppresses primary in vivo antibody responses to keyhole limpet hemocyanin (KLH). We have reported that rats exposed to tailshock prior to subcutaneous KLH have reduced anti-KLH IgG, IgG1, and IgG2a, but not IgM (Gazda et al. 2003). Six weeks of prior voluntary physical activity (wheel running) prevents the deleterious effects of stress on KLH antibody (Moraska et al., 2001). The current study tested the hypothesis that the impact of stressor exposure and the protective effect of exercise would generalize to a more human relevant soluble vaccination protein, tetanus toxoid (TTX). Adult, male, Fischer 344 rats were either allowed access to running wheels or remained sedentary. Following eight weeks of voluntary activity, animals were immunized subcutaneously with 12 LF TTX, then either exposed to 100, 5 second, 1.6 mA tailshocks or remained as home cage controls. Blood samples were taken from the tail vein on day zero and every seven days for the next six weeks. ELISA measurement of antibody showed that physical activity alone enhanced anti-TTX IgM and IgG2a response compared to sedentary animals after subcutaneous immunization. Exposure to tailshock suppressed production of anti-TTX IgG1 (63% reduction), but not IgG2a or IgM compared to sedentary non-stressed rats. Interestingly, anti-TTX IgG was unaffected by both stress and activity status. Physical activity prevented the stress-induced reduction in anti-TTX IgG1. Neither stress nor activity affected anti-TTX IgG. Physical activity status appears to alter the effect of stress on acquired immunity. Supported by RO1MH068283, RO1AI057797

Modulation of RAW 264.7 Murine Macrophage Responses to Lipopolysaccharide by Larch Arabinogalactan

Shannon Kennedy[1] * David Freier[1]
[1]Program In Biomedical Sciences, Lynchburg College, Lynchburg, VA 24501
** Corresponding author: David Freier, (freier@lynchburg.edu)*

Plant glycoproteins, have become commonly used agents of complementary medicine, though their effectiveness is not unclear. A principal form of these glycoproteins are arabinogalactans, found in both larch and Echinacea species extracts. We hypothesize that the presence of larch arabinogalactans in solution may have the potential to enhance macrophage responsiveness to bacterial lipopolysaccharide (LPS). RAW 264.7 murine macrophages are maintained in log growth phase, and are plated at 4×10^5 cells per well in 24-well culture plate's and allowed to adhere overnight. Cells are then washed, and larch arabinogalactan (FoodScience of Vermont) solubilized in complete RPMI 1640 is added at concentrations of 0, 0.005 g/ml, 0.01 g/ml, 0.02 g/ml and 0.04 g/ml in a 0.5 ml volume and cells are incubated for 24 hours. Wells are then washed three times to remove arabinogalactans, and stimulated with 50 ng/ml LPS for 24 hours. Samples of the prepared arabinogalactan solutions are reserved and frozen for evaluation of potential LPS contamination. At 24 hours after LPS stimulation supernatants are removed and a sample frozen for cytokine analysis, and nitric oxide (NO) production is determined. The baseline response to LPS is 15 μM, where the concentrations of 0.02 and 0.04 g/ml of larch arabinogalactan significantly potentiated NO production with responses of 30 μM or greater. This suggests that arabinogalactans may have the ability to enhance macrophage responses to bacterial components such as LPS. Whether or not this occurs *in vivo* within gut associated macrophages is yet to be determined.

Hypermetabolic syndrome as a consequence of chronic psychological stress in mice

* Cornelia Kiank[1] Maren Depke[2] Gerhard Fusch[3] Grazyna Domanska[1] Robert Geffers[4] Uwe Voelker[2] Christine Schuett[1]
[1]Department of Immunology, Ernst-Moritz-Arndt-University Greifswald, Germany [2]Interfaculty Institute of Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, Germany [3]Department of Neonatology and Pediatric Intensive Care Medicine, Ernst-Moritz-Arndt-University Greifswald, Germany [4]Department of Mucosal Immunity, Helmholtz-Centre for Infection Research, Braunschweig, Germany ** Corresponding author: Cornelia Kiank, (cornelia.kiank@uni-greifswald.de)*

Stress exposure alters the homeostatic regulation of the neuroendocrine system, of immunological functions and behavior. After 4.5 days of intermittent combined acoustic and restraint stress as a murine model of chronic psychological stress, female BALB/c mice suffered from systemic immunosuppression, depression-like symptoms, and neuroendocrine activation with a drastic loss of body mass. To elucidate stress-induced alterations of metabolic functions we performed mRNA profiling of liver homogenates. Evidence of dysfunctional metabolic processes from gene expression analyses was verified in vivo. Chronically stressed mice developed a hypermetabolic syndrome characterized by hyperglycemia, dyslipidemia, increased amino acid turn-over, and acidosis that very likely caused the severe loss of lean body mass. Hypercatabolic processes were associated with hypercortisolism, hyperleptinemia, insulin resistance, and hypothyroidism. In contrast, a single acute stress exposure changed expression of metabolic genes to a much lesser extent and predominantly confined to

gluconeogenesis. Acutely stressed animals showed increased release of glucocorticoids but did not suffer from physiological significant metabolic alterations.

This indicates that metabolic homeostasis already is disruped due to acute stress exposure. However, stress will only cause severe metabolic dysregulations when the stressful burden increases and stress becomes chronic. Then a drastic reduction of the individual's energy reserves may further reduce the ability to cope with new stressors such as infection or cancer.

Sympathetic neurotransmitter, epinephrine, regulates adaptive immunity through antigen presenting cells

Byung-Jin Kim[1] * Harlan Jones[1]
[1]Department of Molecular Biology and Immunology University of North Texas Health Science Center, Fort Worth, TX 76107
** Corresponding author: Harlan Jones, (hajones@hsc.unt.edu)*

Sympathetic neurotransmitter, epinephrine (Epi), regulates adaptive immunity through antigen presenting cells (APC). Questions still remain on the behavior of APC, which are pre-exposed to sympathetic neurotransmitter or pathogenic factor, on generating adaptive immunity.

Thus, we hypothesize that short-term pre-exposure of APC to Epi or lipopolysaccharide (LPS) would induce the modified profile or intensity of cytokine production and predict adaptive immune responses.

Intraperitoneal-derived macrophage (IPMQ) and bone marrow-derived dendritic cell (BMDC) were pretreated with Epi or LPS for 2 h followed by either subsequent treatment of LPS (EL) or Epi (LE). In addition, IPMQ and BMDC were cocultured with total splenocytes isolated from ovualbumin (OVA)-primed mice in EL or LE condition in the presence of OVA.

Real-time RT-PCR and ELISA showed that expression of IL-12 and CXCL10 (Th1) was significantly decreased by both EL and LE treatment and, in contrast, IL-10, CCL17 and IL-23 (Th2/Th17) showed no significant changes in EL and significant increase in LE condition in both IPMQ and BMDC. In particular, LE induced great enhancement of IL-1b and IL-6 mRNA expression but not TNF-a. In coculture, EL and LE increased the production of IL-10 and IL-13 with significantly decreased production of IFN-g.

These results demonstrated that Epi enhanced adaptive immunity through Th2/Th17 responses and, in particular, the subsequent exposure to Epi after pre-exposure to pathogenic factor with suppressing Th1 responses. Our future questions will be to define the role of APC on intensity of T cell differentiation and, consequently, producing immunoprotective or immunopathologic properties.

Dexamethasone activates Epstein Barr Virus lytic replication through immediate early BZLF1 gene expression.

* Seung-jae Kim[1] Eric V. Yang[1, 2] Min Chen[1] Jeanette I. Marketon[1, 3] Marshall V. Williams[2] Ronald Glaser[1, 2, 3, 4]
[1]Institute for Behavioral Medicine Research, The Ohio State University Medical Center, Columbus, OH 43210 [2]Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University Medical Center, Columbus, OH 43210 [3]Department of Internal Medicine, The Ohio State University Medical Center, Columbus, OH 43210 [4]Comprehensive Cancer Center, The Ohio State University Medical Center, Columbus, OH 43210 ** Corresponding author: Seung-jae Kim, (kim.1133@osu.edu)*

Epstein Barr virus (EBV), associated with several human malignancies, infects over 90% of people worldwide and persists for life in a latent form. It is known that the cellular immune regulation plays an important role in controlling virus reactivation. Psychological stress has been shown to activate EBV lytic replication in latently infected cells. Although several studies have shown that glucocorticoid hormone can directly induce reactivation, the mechanism of stress hormone involvement on EBV gene expression is not well understood. We and others have shown that the synthetic glucocorticoid hormone, dexamethasone (Dex), can modulate EBV gene expression related to lytic replication. In this study, we measured the effect of Dex on mRNA expression of an immediate early EBV gene (BZLF1, which encodes for the lytic transactivator protein ZEBRA) and an early gene (BLLF3, which encodes for EBV dUTPase) in various EBV genome positive Burkitt lymphoma (BL) cell lines, lymphoblastoid cell lines (LCL), and multiple myeloma (MM) cell lines. Dex induced BZLF1 and BLLF3 gene expression in the BL cell line Daudi, but not in other EBV positive cells. Daudi cells expressed greater glucocorticoid receptor (GR) expression, as determined by Western blotting, compared to other BL cell lines, suggesting that glucocorticoid mediated lytic reactivation may depend on GR expression in EBV latently infected cells. These results further suggest that glucocorticoid hormone mediated EBV reactivation may result from the direct induction of immediate early BZLF1 expression, in addition to the stress-related immune dysregulation. Support: The Gilbert and Kathryn Mitchell Endowment to RG and the Ohio State University Comprehensive Cancer Center CA16058(NCI).

Neuropathic pain is attenuated by a cannabinoid mechanism of action

* Steven Kinsey[1] Aron Lichtman[1]
[1]Department of Pharmacology and Toxicology. Virginia Commonwealth University. Richmond, VA, USA.
** Corresponding author: Steven Kinsey, (sgkinsey@vcu.edu)*

Neural injury causes a range of symptoms, including increased sensitivity to normally painful stimuli (hyperalgesia), as well as inappropriate sensations of pain in response to typically non-painful stimuli (allodynia). Cannabinoids have long been used as therapeutic analgesics, and recent work has focused on the endogenous cannabinoid system in modulating stress, inflammation, and pain. Direct administration of endocannabinoids is problematical, because these proteins are rapidly degraded in vivo. For example, fatty acid amide hydrolase (FAAH) is one such enzyme that degrades the endocannabinoid anandamide. The drug URB597, a relatively selective FAAH inhibitor, increases concentrations of endocannabinoids. In the present study, chronic constrictive injury of the sciatic nerve (CCI), a common model of nerve injury, was used to test the hypothesis that neuronal pain is modulated by endogenous cannabinoids. Male C57BL/6 mice were subjected to CCI and tested for pain sensitivity. The CCI treatment resulted in hyperalgesia and allodynia in the ipsilateral hind paw, with no effect on the contralateral paw. The FAAH inhibitor URB597 attenuated both mechanical allodynia and

acetone-induced cold allodynia in the ipsilateral paw of mice subjected to CCI. These effects were entirely blocked by co-administration of the cannabinoid (CB1) antagonist SR141716, suggesting that the observed analgesic effects were at least partially modulated by a CB1 cannabinoid receptor mechanism.

Increasing endogenous cannabinoids attenuates the neuropathic pain response to touch and cold

* S G Kinsey[1] A H Lichtman[1]
[1]Department of Pharmacology and Toxicology. Virginia Commonwealth University. Richmond, VA, USA.
** Corresponding author: S G Kinsey, (sgkinsey@vcu.edu)*

Neural injury causes a range of symptoms, including increased sensitivity to normally painful stimuli (hyperalgesia), as well as inappropriate sensations of pain in response to typically non-painful stimuli (allodynia). Cannabinoids have long been used as therapeutic analgesics, and recent work has focused on the endogenous cannabinoid system in modulating stress, inflammation, and pain. Direct administration of endocannabinoids is problematical, because these lipid signaling molecules are rapidly degraded in vivo. For example, fatty acid amide hydrolase (FAAH) is one such enzyme that degrades the endocannabinoid anandamide. The drug URB597, an irreversible FAAH inhibitor, increases concentrations of anandamide as well as a variety of other fatty acid amides that do not bind to cannabinoid receptors. In the present study, chronic constrictive injury of the sciatic nerve (CCI), a common model of nerve injury, was used to test the hypothesis that neuronal pain is modulated by endogenous cannabinoids. Male C57Bl/6 mice were subjected to CCI and tested for pain sensitivity. The CCI treatment resulted in hyperalgesia and allodynia in the ipsilateral hind paw, with no effect on the contralateral paw. The FAAH inhibitor URB597 attenuated both mechanical allodynia and acetone-induced cold allodynia in the ipsilateral paw of mice subjected to CCI. These effects were entirely blocked by pretreated with the cannabinoid (CB1) receptor antagonist rimonabant, indicating a CB1 receptor mechanism. These data will contribute to the development of novel cannabinoid drugs for the treatment of pain and inflammation.

Influence of prenatal stress on behavioral, endocrine, and cytokine responses to adulthood endotoxin exposure

* Rachel Kohman[1] Andrew Tarr[2] Kristina McLinden[2] Gary Boehm[2]
[1]Department of Pharmacy and Toxicology, Environmental & Occupational Health Science Institute, Rutgers University, Piscataway, NJ 08854 USA [2]Department of Psychology, Texas Christian University, Fort Worth, TX, 76129 USA
** Corresponding author: Rachel Kohman, (rakohman@rci.rutgers.edu)*

Exposure to stress early in development can have lifelong effects on an organism's physiological and psychological health. Prior research suggests that prenatal stress exposure, among other effects, can increase reactivity of the HPA axis and alter immune function in offspring. These stress-induced changes have been linked to a greater propensity to develop depression or an anxiety disorder. Furthermore, prenatally stressed offspring have been found to be more susceptible to certain diseases. The immune alterations induced by prenatal stress exposure may disrupt the normal communication between the immune system, endocrine system, and central nervous system. The present study investigated whether prenatal stress exposure would alter the behavioral, endocrine, and cytokine responses to endotoxin administration. Beginning at 90 days of age, prenatally stressed and non-stressed control male and female C57BL/6J mice were evaluated for alterations in anxiety levels, motor behavior, learning, fever response, and IL-1β production following a single or repeated i.p. injections of LPS (50 or 250μg/kg) or sterile saline. The results suggest that prenatal stress exposure increased LPS-induced anxiety-like behavior relative to non-stressed controls. While prenatal stress exposure or LPS administration independently impaired learning, the data failed to support the hypothesis that prenatally stressed subjects would show exaggerated cognitive deficits, engendered via enhanced peripheral and central IL-1b; production, following immune activation. Collectively, the data suggest that while prenatal stress exposure may lead to increases in anxiety-like behavior following endotoxin exposure it did not appear to increase susceptibility to LPS-induced cognitive decline or alterations in cytokine production.

Toll-like receptor expression is altered by stress of intense physical conditioning

* Marian Kohut[1] Cole Sanderson[1] Ishrat Sultana[1] Shan Yu[1] Young-Je Sim[1] Gina Flinn[2] Jodi McKay[1]
[1]Immunobiology / Kinesiology DeptIowa State University, Ames IA 50011 [2]Genetics, Iowa State University, Ames IA 50011
** Corresponding author: Marian Kohut, (mkohut@iastate.edu)*

Intense physical training and the psychological stress associated with training/competition may contribute to an increased incidence of infection among competitive athletes. The toll-like receptors (TLR) and associated pathways act as a first response to pathogens or "danger signals". The TLR pathways may be compromised by intense training stress. We hypothesized that gene expression of TLR pathways associated with viral defense would decrease in response to intense exercise training, and that change in gene expression would predict subsequent illness. Eight male collegiate wrestlers participated in one month of intense pre-season conditioning designed to challenge both physical and mental capabilities. Blood was collected pre-training, after one 90-minute session of intense exercise, and at the end of the pre-season training. TLR receptor pathway expression was assessed by microarray. The mental skills questionnaire developed for competitive athletes was administered. Illness was monitored by questionnaire throughout the competitive season. The results showed that intense exercise training decreased expression of antiviral genes (IFN-alpha, TLR3, PKRKA, SARM1), and decreased three inflammatory genes (TNFSRF, PTGS2, REL). Ninety minutes of intense exercise decreased two antiviral genes (IFN-gamma, IRF1), whereas expression of TLR pathways associated with anti-bacterial defense increased (TLR5, TIRAP, PGLYRP2, LY86). Although caution is warranted in predicting illness with n=8, regression analyses showed that severe/prolonged illness was predicted by poorer performance on mental skills test, a greater drop in IFN-gamma following acute exercise, and greater IFN-alpha. These findings suggested that the stress of intense conditioning was associated with decreased expression of TLR pathways important in antiviral defense.

Anti-NMDA Receptor Antibodies and Cognition in nonNPSLE

* Elizabeth Kozora[1] Steven Maier[2] Lening Zhang[1] David Arciniegas[3] Mark Brown[3] Christopher Filley[3] David Miller[3] Alex Grimm[3] Marie Devore[1] Christy Wingrove[1] Sterling West[3]
[1]National Jewish Medical and Research Center [2]University of Colorado at Boulder [3]University of Colorado School of Medicine
** Corresponding author: Elizabeth Kozora, (Kozorae@njc.org)*

Introduction: Elevated N-methyl-D-aspartate (NMDA) receptor antibodies (anti-NR2) have been reported in 35% of patients with systemic lupus erythematosus (SLE) and may be associated with cognitive and memory dysfunction. **Hypotheses:** Anti-NR2 will be elevated in SLE patients with no prior overt neurological or psychiatric symptoms (nonNPSLE) compared to healthy controls. Elevated anti-NR2 will be associated with cognitive and memory dysfunction. **Methods:** Subjects included 29 nonNPSLE patients and 19 healthy control subjects with similar demographic characteristics. Cognitive function was assessed by administration of the ACR-SLE neuropsychological battery. A global cognitive impairment index (CII) and a memory impairment index (MII) were calculated using impaired test scores from the battery. Serum samples were obtained from all the participants; analyses were performed using a standard ELISA for anti-NR2. **Results:** Elevations of anti-NR2 were found in 13.8% of the nonNPSLE and 5.3% of the controls (p=0.64). There was no relationship between elevated anti-NR2 status and higher CII or performance on the MII. **Conclusions:** The overall frequency of elevated anti-NR2 was low (13.8%) in our sample of SLE patients and not significantly different from controls. Mild SLE disease activity and exclusion of patients with neuropsychiatric features may have contributed to these findings. The lack of relationship between elevated anti-NR2 and cognitive or memory function suggests that NMDA may not be a significant contributor to the mechanism of cognitive or memory decline in nonNPSLE patients. Small sample size limits findings to date.

Cytokines, Antiphospholipids, and Cognition in NonNPSLE

* Elizabeth Kozora[1] Steven Maier[2] Lening Zhang[1] David Arciniegas[3] Mark Brown[3] Christopher Filley[3] David Miller[3] Alex Grimm[3] Mark Devore[1] Christy Wingrove[1] Sterling West[3]
[1]National Jewish Medical and Research Center [2]University of Colorado at Boulder [3]University of Colorado School of Medicine
** Corresponding author: Elizabeth Kozora, (Kozorae@njc.org)*

Introduction: Patients with systemic lupus erythematosus may have elevated levels of antiphospholipids (aPLs) and proinflammatory cytokines, but the relationship of these immune markers to cognitive function is unclear. **Hypotheses:** Measures of aPLs, anticardiolipin (aCL) and lupus anticoagulant (LAC), and cytokines (IL-1, IL-6, INF-alpha, INF-gamma) will be elevated in SLE patients with no prior overt neurological or psychiatric symptoms (nonNPSLE) compared to healthy controls. Elevated aPL and cytokine levels will be associated with cognitive dysfunction. **Methods:** Subjects included 39 nonNPSLE patients and 26 healthy controls with similar demographic characteristics. Cognitive function was assessed by administration of the ACR-SLE neuropsychological battery from which a global cognitive impairment index (CII) was calculated. Serum samples were obtained from all subjects and analyses were performed using standardized laboratory procedures. **Results:** NonNPSLE patients showed higher levels of IL-6 (p=0.04) and moderately higher levels of INF-alpha (p=0.07) compared to controls. No other cytokine levels differed between groups. Few nonNPSLE or controls had elevated aCL or LAC and no differences could be detected between groups. In nonNPSLE patients, higher IL-6 was not correlated with overall CII, but showed moderate associations with lower visual memory, and higher visuomotor speed, complex attention, and motor speed. **Conclusions:** IL-6 and INF-alpha appear to be elevated in nonNPSLE patients compared to controls but show no correlation with global cognitive impairment. Moderate associations between higher IL-6 and individual cognitive tests suggest a potential underlying association between IL-6 and cognition in SLE, a finding consistent with prior research. Small sample size limits findings to date.

Addiction, Personality Traits, Stress, and AIDS: Possible Role of Specific Gene Variants and Epigenetic Changes

* Mary Jeanne Kreek[1]
[1]Laboratory of the Biology of Addictive Diseases, The Rockefeller University
** Corresponding author: Mary Jeanne Kreek, (kreek@rockefeller.edu)*

Specific genetic factors, along with environmental factors, including atypical stress responsivity and direct drug-induced effects, interact to contribute to the vulnerability for the development of drug addiction. Genetic factors also have been shown to contribute to the personality traits of impulsivity and risk-taking, as well as to comorbid conditions, such as depression and anxiety. The second most common risk group for the development of HIV/AIDS are parenteral drug abusers. Specific variants of specific genes related to addictive diseases and specific personality traits may be related to HIV-1 infection and also to the progression of AIDS disease. Specific variants of specific genes in coding regions may change protein structure of pertinent receptors or peptides. Variants in other regions of genes may alter levels of gene expression. Recently, our group has found evidence of allele-specific gene expression of genes under study. Further, we have new evidence of epigenetic changes of another gene which also may contribute to gene expression. Future studies may show relationship of gene variants or epigenetic changes to progression of AIDS. P60-DA05130 (Kreek), R01-MH79880 (Kreek), R01-MH76537 (Crystal), K05-DA-00041 (Kreek).

INFLAMMATORY LIPOPOLYSACCHARIDE INCREASES BEHAVIORAL DESPAIR IN THE C57BL6 MOUSE

* Donald M. Lamkin[1] Susan K. Lutgendorf[1, 2] Alan Kim Johnson[1, 3]
[1]Department of Psychology, University of Iowa [2]Department of Obstetrics & Gynecology, Department of Urology, Holden Comprehensive Cancer Center, University of Iowa [3]Department of Integrative Physiology, Department of Pharmacology, University of Iowa
** Corresponding author: Donald M. Lamkin, (donald-lamkin@uiowa.edu)*

Peripheral inflammation causes a variety of behaviors in animals that are deemed depressive in nature. These include decreased locomotion, social exploration, feeding behavior, and a loss of body weight. However, few studies have examined the effect of peripheral inflammation on the classical animal measure of behavioral despair using the Tail Suspension Test (TST), a widely used test for screening pharmacological antidepressant efficacy in pre-clinical murine models of depression. Thus, we decided to utilize this measure of depression-like activity and test the hypothesis that a standard peripheral inflammatory stimulus would cause an increase in behavioral despair. Female C57BL6 mice (N = 11) were randomly assigned to receive an intraperitoneal injection of the inflammatory stimulus, lipopolysaccharide (LPS), or saline vehicle only. 120 minutes after injection, mice completed the TST. Behavioral despair in the TST is measured by hanging the mouse by its tail for a duration of 6 minutes and recording the amount of time the mouse is immobile (as opposed to struggling to free itself). Mice were prohibited from climbing their tail by the nature of their attachment to the TST apparatus. Results showed that LPS-injected mice exhibited significantly more behavioral despair than control mice ($p = .05$). Behavioral despair time in minutes for LPS-injected mice was $M = 4.50$, $SE = .12$ and for control mice was $M = 3.97$, $SE = .21$. These results contribute to the mounting evidence that peripheral inflammation causes depression-like behavior in mice and provide new indication of inflammation-induced behavioral despair in the C57BL6 strain.

Gender effects on diurnal rhythms in salivary cortisol among American Indians with and without posttraumatic stress disorder (PTSD)

* Mark L Laudenslager[1] Carolyn Noonan[2] Jack Goldberg[2] Dedra Buchwald[2] Douglas Bremner[3] Viola Vaccarino[3] Spero M Manson[1]
[1]University of Colorado Denver School of Medicine, Department of Psychiatry, Denver, CO [2]University of Washington, School of Public Health and Community Medicine, Department of Epidemiology, Seattle, WA [3]Emory University, Department of Psychiatry, Atlanta, GA
** Corresponding author: Mark L Laudenslager, (mark.laudenslager@uchsc.edu)*

Disruptions in hypothalamic-pituitary-adrenal regulation and immunity are associated with PTSD. We examined the association of PTSD with diurnal rhythms in salivary cortisol in a population-based sample of male and female American Indians. Subjects with (n=29) and without (n= 35) PTSD were identified from American Indians living on/near a Northern Plains reservation. This was part of a larger investigation of PTSD with cardiovascular disease. Over two days diurnal saliva samples were collected by staff at the Denver Clinical Research Center. Collection time included waking, 30 minutes later, before lunch and before dinner. Generalized estimating equations linear regression investigated the influence of PTSD on cortisol over time. Effects of PTSD on cortisol were assessed for age, time of day, and sex. Subject mean age was 44 and 72% were women. An interaction between PTSD, gender and time of collection on cortisol levels was noted (p=.03). When stratified by gender, women with a lifetime diagnosis of PTSD had significantly higher cortisol levels (p =.01); conversely, there was no association of PTSD with cortisol in men (p=.83). The cortisol awakening response (CAR) was blunted in women with PTSD (p=.05) but did not differ in men (p=.10). Thus, PTSD may influence both diurnal cortisol and CAR among American Indian women but not men. The unexpected elevation in cortisol in American Indian women with PTSD may reflect enhanced anxiety associated with experiencing a number of novel tests (cardiac PET scan, medical and dental exams, etc.). Supported by NIH grants R01AA01397 (MLL), R01MH37373 (MLL), and R01HL073824 (SMM).

Diet-induced Obesity Causes Depressive-like Behavior in Mice

* Desiree Lavin[1] Christina Sherry[1] Jason O'Connor[2] Robert Dantzer[1, 2, 3] Gregory Freund[1, 2, 3]
[1]Division of Nutritional Sciences, University of Illinois, Urbana, IL 61801, USA [2]Department of Animal Sciences, University of Illinois, Urbana, IL 61801, USA [3]Department of Pathology, University of Illinois, Urbana, IL 61801, USA
** Corresponding author: Desiree Lavin, (lavin@uiuc.edu)*

Worldwide it is estimated that over 300 million people are obese. Importantly, a link between obesity and depression has been intimated, but how obesity would cause depression is unknown. Anhedonia is a biobehavior associated with depression that manifests in mice as a loss of interest in consuming a highly palatable sucrose solution. Here we show that diet-induced obese (DIO) mice fail to exhibit an interest in sucrose. C57BL/6J mice were placed on a diet containing either 10% or 60% fat for 12 wks. DIO mice exhibited no preference between a 10% sucrose solution and water over 5 days (25.8 mL 10% SS vs 25.2 mL H20), of which they were given free choice and unlimited access, as compared to non-obese control mice (87.2 mL 10% SS vs 10 mL H20). Non-obese mice drank 3.4 -fold (5.45 mL/day vs 1.61 mL/day) more 10% SS solution/day as compared to DIO mice. To further examine DIO-associated adverse biobehaviors, tail suspension (TS) was conducted. TS tests demonstrated that base-line immobility between non-obese and DIO mice were similar. However, when DIO mice were challenged with intraperitoneal LPS and TS measured 4 h after LPS administration, DIO mice were 12.5% more immobile than non-obese mice. Taken together these results indicate that DIO mice exhibit anhedonia and prolonged post-LPS helplessness that in humans is associated with depression.

Sleep, Depression, Stress and Immunity in Dementia Caregivers: A Seven Day Study

* Brandy Lehman[1]
[1]University of South Florida College of Nursing Center for Psychoneuroimmunology
** Corresponding author: Brandy Lehman, (blehman@health.usf.edu)*

Caregivers of dementia patients report significant sleep disruption. This exploratory study examined relationships between subjective reports of sleep and actigraphy, stress, mood, and a panel of endocrine and immune markers in 30 caregivers. The participants were recruited from an Alzheimer's clinic and collected saliva 4 times/day for 2 days, and a venipuncture was done at a home visit. They wore actigraphy watches for 7 days and completed questionnaires about stress, mood and sleep. Saliva samples were analyzed (ELISA) for cortisol. Serum samples were multiplexed using a kit from Millipore for a cross section of 13 cytokines and analyzed by Luminex. Serum norepinephrine and CRP were analyzed by ELISA. Not all data have been analyzed, but several findings can be reported.

Mean age was 65.4 years (22 women, 8 men). Several cytokines (IL-10, IL-13, IL-4, TNF-α and IL-6) were high in comparison to reported age-adjusted norms. The CES-D mean was 33, indicating severe depression. Depression was correlated with lower awakening salivary cortisol levels. The Perceived Stress Mean was 40, indicating extreme stress. Ratings of sleep quality as poor were associated with higher CES-D scores, poorer general health and higher serum TNF-α level. Actigraphy data indicating reduced and interrupted sleep.

This study will provide new understandings of poor sleep and well-being in dementia caregivers and will serve as the basis for interventions to improve quality and quantity of sleep.

Young adult APOE ε4 carriers show a stress-induced decline in "hot cognition" and sIL-6r, but not IL-6 *

Andrine Lemieux[1] Douglas Walton[1] Jon Nelson[1]
[1]The College of St. Scholastica ** Corresponding author: Andrine Lemieux, (alemieu2@css.edu)*

The apolipoprotein E epsilon 4 gene (APOE ε4) has been extensively studied in the late life development of Alzheimer's Disease, but early investigators of this gene refer to it a "silent gene" in young adults. It's role as a stress-vulnerability gene in young adults has not been investigated. It was hypothesized here that APOE ε4+ young adults tested in a developmentally appropriate manner would show stress-related cognitive deficits and elevations in cortisol, IL-6 and sIL-6r. Fifty-eight young adults (18-39 years) were evaluated in an exam stress paradigm. Outcome measures included cognitive functions (reasoning, memory and attention), as well as plasma cortisol, IL-6 and sIL-6r. Twenty-six young adults were APOE ε4+ and 32 were APOE ε4-. No gene effects were seen for cortisol, but gene X stress interactions were significant for both cognitive testing ($p < .05$) and sIL-6r ($p < .05$). Unexpectedly APOE ε4+ subjects showed impaired emotion-based reasoning at both sessions, while APOE ε4- counterparts showed a stress-related decline in performance. Gene effects on memory were seen only under stress whereby APOE ε4+ subjects performed more poorly than their APOE ε4- peers. Regression showed that the best predictors of the change in sIL-6r were gene status and change in perceived stress. Our results are the first demonstration of a stress vulnerability effect of APOE ε4 in young adult carriers. Possession of one or more copies of the gene may confer a differential stress vulnerability for cognition and sIL-6r, but not IL-6 or glucocorticoids. Further work is needed.

Distress, Control, Health Behaviors and Immune Responses to Relaxation-Guided Imagery in Breast Cancer Patients

* Cecile A. Lengacher[1] Mary P. Bennett[2] Robyn Choe[1] Lois Gonzalez[1] Paul Jacobsen[3] Danielle Gilvary[3] Charles E. Cox[3] Chiu Yang[4] Melissa Molinari[1] Julie Djeu[3]
[1]University of South Florida, College of Nursing [2]Western Kentucky University, College of Health and Human Services [3]H. Lee Moffitt Cancer Center and Research Institute [4]National Taiwan University
** Corresponding author: Cecile A. Lengacher, (clengach@health.usf.edu)*

Introduction to the problem: Psychoneuroimmunology is an evolving science. Use of relaxation-guided imagery to explore effects on distressing symptoms, and improvement of immune function in breast cancer patients needs further validation.

Hypotheses: To determine if there were significant differences and relationships in immune function, distress, control, and health behaviors between patients randomly assigned to relaxation-guided imagery, or a standard care control group.

Methods: A pre-test, post-test design (28 patients, aged 25-75, stage I or stage II). Measurements: immune function (NK cell cytotoxicity and IL-2 activated NK cells); distress (Beck Depression Inventory, Stressful Life Experiences Survey, and the Women's Role Strain Inventory); control (Health Locus of Control Scale); and health behaviors (Health Promoting Lifestyles II). Data were gathered prior to surgery and four weeks post surgery.

Results: T-tests showed significant differences in immune function at 4 weeks post surgery with increased NK cytotoxicity for the guided imagery group at 100:1, 50:1, and 25:1 ($p< .01$ to $p<.05$), and activation for IL-2 at 100:1, 50:1, and 25:1, and 12.5:1 ($p< .01$ to $p<.05$). Mean scores decreased in depression, stressful experiences and role distress. Significant correlations were found in the guided imagery group between locus of control and IL-2, at 100:1, 50: 1, 25:1, 12.5:1($p<. .05, .001$), and between health behaviors, and NK 50:1 and IL-2, 25:1, ($p<. 05$).

Conclusions: Enhanced NK and IL-2 cytotoxicity was evident in patients receiving guided imagery group with significant correlations found between immune function, locus of control and health behaviors.

* Funded by the American Cancer Society

Increased Stress-Induced Plasma IL-6 Responses in Male Depressed Patients with Increased Early Life Stress: Role of Catecholamines

* Andrea I. Liatis[1] Andrew H. Miller[1] Tanja M. Mletzko[1] Chrsitine M. Heim[1] Robert Bonsall[1] Thaddeus W. W. Pace[1]
[1]Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, 30322
** Corresponding author: Andrea I. Liatis, (aliatis@emory.edu)*

Previous work in our lab has shown that male patients with major depression and increased early life stress (ELS) exhibit an exaggerated inflammatory response to stress compared to male controls. This exaggerated stress-induced inflammatory response may be mediated, in part, by increased stress-induced catecholamines in these patients. Therefore, we measured plasma norepinephrine (NE) and interleukin (IL)-6 before, during, and after challenge with the Trier Social Stress Test (a public speaking and mental arithmetic task) in male patients with major depression and increased ELS (n=14) and non-depressed male controls (n=13). Despite significantly greater stress-induced plasma IL-6 responses, patients with major depression and increased ELS displayed NE responses to stress that were similar to controls. Interestingly, however, when NE responses were divided into those above and below the median, depressed patients with NE responses below the median exhibited significantly greater stress-induced plasma IL-6 responses compared to controls with NE responses below the median. IL-6 responses in patients and controls with NE responses above the median were comparable, and not different than IL-6 responses in depressed patients with NE responses below the median. These preliminary data indicate an increased sensitivity to NE in male depressed patients with increased ELS. Because these depressed patients also exhibited higher baseline IL-6 concentrations (suggesting chronic inflammation), the increased sensitivity to NE may be mediated by upregulation of the alpha-1 adrenergic receptor. Alpha 1 adrenoreceptor upregulation has been found in patients with chronic inflammatory disorders, and has been associated with an increased inflammatory response to catecholamines.

DISEASE-INDUCED CHANGES IN SYMPATHETIC TO IMMUNE SIGNALING IN ADJUVANT-INDUCED ARTHRITIS (AA).

* Dianne Lorton[1] Cheri Lubahn[1] Tracy Osredkar[1] Jeff Carter[2] Terry Der[1] Denise Bellinger[2]
[1]Hoover Arthritis Research Center, Sun Health Research Institute, Sun City, AZ 85351 [2]Loma Linda University School of Medicine, Department of Pathology & Human Anatomy, Loma Linda, CA 92350.
** Corresponding author: Dianne Lorton, (dianne.lorton@sunhealth.org)*

In AA rats, sympathetic innervation is diminished in splenic white pulp, sites of sympathetic signaling to immunocytes. We hypothesized that diminished sympathetic innervation with disease progression alters sympathetic-immunocyte signaling via β_2-adrenergic receptors (AR). Total and protein kinase A (PKA)-phosphorylated β_2-AR expression and β-AR-stimulated cAMP production in splenocytes were assessed in adjuvant-induced arthritic rats to test this hypothesis.

Harvested splenocytes from controls and AA rats were treated with isoproterenol (ISO), a β-AR agonist, forskolin, a cAMP inducer that bypasses the receptor, or vehicle. cAMP production was assessed using an EIA. Splenocyte β_2-AR expression was assessed in tissue punches from white pulp of frozen spleen sections by western blot analysis using anti-β_2-AR and anti-phosphorylated (Ser 345-346) β_2-AR antibodies.

ISO and forskolin significantly increased cAMP production in splenocytes from nonarthritic rats. In arthritic rats, ISO did not alter cAMP production; however, forskolin increased cAMP levels, indicating that direct adenylate cyclase activation increased cAMP production. Expression of phosphorylated β_2-AR (Ser 345-346), but not total splenocyte β_2-AR expression, was significantly decreased in arthritic compared to non-arthritic rats. PKA-phosphorylation of Ser 345-346 of the β-AR is known to switch β-AR from G-protein activation to G-protein desensitization through beta-arrestin recruitment and receptor internalization. These findings suggest that desensitization of β_2-AR reduces sympathetic-immune signaling in rheumatoid arthritis.

Is Bipolar Disorder an Autoimmune Disease?

* Lin Lu[1]
[1]Chicago Medical School at Rosalind Franklin University, Department of psychiatry and behavioral science, North Chicago, IL 60064
** Corresponding author: Lin Lu, (linlu_xi@yahoo.com)*

Introduction: Features common to idiopathic bipolar disorder and autoimmune disease, such as adolescent onset, relapsing-remitting pattern, chronic course, suggest to some possible pathophysiological relationship. Moreover, stress has been observed to affect the onset and clinical exacerbation of both illnesses.

Case Presentation: I am presenting a case, which describes a patient with history of bipolar illness: who was stable until a stressor triggered a relapse of manic episode with psychosis. This very common scenario inspires me to think about the plausibility of a role for stress-induced immune dysfunction, autoimmune pathology, as well as their implication for bipolar affective disorder.

Discussion: The communication between the CNS and the immune system is bidirectional. Many investigators are now focusing on how the activation of inflammatory-cytokine networks might shape mood, cognition and behavior. The high prevalence of organ-specific autoimmunity in patient with bipolar disorder was found: e.g. presence of GAD-Ab, anti-heat shock protein (HSP). Not only humeral immunity is increased in bipolar patient, cell-mediated immune response is activated as well. The another fascinating evidence that supporting the correlation of bipolar disorder and autoimmunity, origins from the recent finding of the links between immune system and sleep regulation.

Conclusion: There is emerging data show increased autoimmunity in bipolar disorder. The further investigation in PNI field might shed light on finding diagnostic markers, or discover adjunct or novel immunomodulatory therapy for bipolar disorder patients.

Behavioral, neurotransmitter and immunological comparison of three common MPTP mouse models of Parkinson's disease

Dirk Luchtman[1] Di Shao[1] * Cai Song[1]
[1]Department of Biomedical Sciences, AVC, University of Prince Edward Island
** Corresponding author: Cai Song, (cai.song@nrc.gc.ca)*

Introduction: 1-methyl 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been commonly used to induce a Parkinson's disease (PD) animal model. However, there is large variation in behavioral, neurophysiological and immunological characteristics due to different MPTP treatments and laboratory conditions, which may cause confusions and difficulties for further understanding PD and developing effective treatments. To clarify the differences between models, we investigated three common dose regimens.

Methods: Male C57BL6 mice (10-12 week old) were treated with MPTP acutely (2 x 40mg/kg i.p.); sub-acutely (5 x 25mg/kg i.p.) and chronically (10 x 25mg/kg s.c. combined with probenecid 250mg/kg i.p.). Two days following injection, behavior was tested on the Rotarod, Open Field, Pole test and Grid test and five days after injection, they were sacrificed for neurotransmitter measurements with HPLC and cytokine analyses by Bio-Plex protein array system.

Results: Striatal dopamine was depleted in all three models: acute (69% of control); sub-acute (76.6%); chronic (93%). Despite the marginal difference in DA depletion between acute and sub-acute models, there were marked behavioral differences. The acute model displayed impaired rotarod performance and decreased grooming in the Open Field, whereas the sub-acute model showed improved rotarod performance and increased grooming. The chronic model was impaired on the rotarod and showed hyperactivity in the Open Field. In other brain regions, MPTP also induced different patterns in neurotransmitters and metabolites. Furthermore, MPTP-induced neurodegeneration is related to an increase in proinflammatory cytokines and an imbalance between pro- and anti-inflammatory cytokines.

Conclusion: This study shows correlations change between behavioral, neurotransmitter and immune aspects in different MPTP models, which should be carefully considered.

Effects of an Acute Laboratory Stressor on Regulatory T cell (Treg) Levels in Normal Human Peripheral Blood Mononuclear Cells (PBMC)

* Gailen D. Marshall[1, 2, 3] Kevin S. Del Ben[1, 3, 4]
[1]Laboratory of Behavioral Immunology ResearchDivision of Clinical Immunology and Allergy [2]Department of Medicine [3]The University of Mississippi Medical CenterJackson, MS [4]Department of Psychiatry and Human Behavior
** Corresponding author: Gailen D. Marshall, (gmarshall@medicine.umsmed.edu)*

The relationships between high stress levels and increased susceptibility to inflammatory diseases has been established but the mechanisms remain under active investigation. Eighteen normal adults participants participated in the Trier Social Stress Test (TSST) which included a 5 minute speech and 5 minute of serial subtraction, and provided samples of blood at 6 time points (Pre and 0,1, 2, 6, and 24 hours Post TSST, n=14) or a control task of magazine reading with temporally identical blood sampling (n=4). Blood samples were then analyzed by flow cytometry for Treg ($CD4+CD25^{HIGH}FoxP3+$) levels. Using a repeated measures analysis, an overall difference was found between the two groups [$F(1, 16) = 3.28$, $p = .08$] with a significant between group difference found immediately after the TSST $F(1, 16) = 4.17$, $p = .05$]. Additionally, the shape of the time curves for both group differed significantly. Treg levels in control subjects showed no differences between time points while TSST individuals demonstrated significant differences between baseline levels and levels at 2 hours [$t(1, 12) = 3.47$, $p < .01$] and 6 hours post TSST [$t(1, 12) = 3.49$, $p < .01$], and between 1 and 2 hours post TSST [$t(1, 12) = 4.73$, $p < .001$]. The differences between groups disappeared by 24 hours. These data demonstrate an effect of a brief laboratory stressor on Treg levels. This suggests a potential mechanism to explain previously observed immune dysregulation occurring with high stress and may further characterize the relationships between psychological stress and immune based diseases.

Fever and sickness behavior vary among related rodent species

* Lynn Martin[1] Zachary Weil[2] Randy Nelson[2]
[1]The University of South Florida, Division of Integrative Biology, Tampa FL USA [2]The Ohio State University, Department of Psychology, Columbus OH
** Corresponding author: Lynn Martin, (lmartin@cas.usf.edu)*

Fever and sickness behavior are immune defenses most organisms engage to control bacterial and viral infections. Although generally beneficial, these defenses can be energetically expensive and self-damaging, which may lead to variation within and among species. Here, we asked whether fever and sickness behavior differ among five species of mice in the genus, *Peromyscus*. This comparison was motivated by our previous discovery of extensive, but systematic, immunological variation among species. In the present study, we asked whether variation in fever and sickness behaviour mirrored the previously detected continuum of immunological variation. We characterized changes in body temperature, activity, food intake and hedonic behavior in response to lipopolysaccharide (LPS) from *E. coli* in five species of *Peromyscus*. Species that showed little sickness behavior post-LPS engaged fever; species that engaged sickness behavior, however, either did not mount fevers or became hypothermic post-LPS. Analyses of pro-inflammatory cytokine expression from spleens, livers and hypothalami are ongoing. Nevertheless, the results of the present study further indicate a continuum of immunological strategies among *Peromyscus*.

Gender, aging, stress, and salivary growth factors in mucosal wound healing

* Phillip T. Marucha[1, 2] Tricia R. Crosby[1] Jos A. Bosch[3] Chistopher G. Engeland[1]
[1]Department of Periodontics,University of Illinois at Chicago,Chicago, Illinois [2]Institute of Behavioral Medicine Research,The Ohio State University [3]School of Sport and Exercise Sciences,University of Birmingham,Birmingham, United Kingdom
** Corresponding author: Phillip T. Marucha, (marucha@uic.edu)*

Introduction: Increasing evidence has demonstrated that psychosocial stress and gender can adversely impact mucosal healing. Saliva is thought to contribute to rapid/scarless mucosal healing.
Hypothesis: Reduced salivary growth factors will predict the negative impact of stress and gender on mucosal healing.
Methods: 112 subjects (18-88 years; 61M, 51F) were recruited and administered psychosocial questionnaires including the Beck Depression Inventory (BDI). Just before wounding, unstimulated saliva was collected for determination of Epithelial and Vascular Endothelial Growth Factors (EGF, VEGF). 3.5mm diameter wounds were placed on the hard palate and measured daily by photoplanimetry.
Results: Higher salivary VEGF was 1) found in older adults; and 2) associated with slower healing through day 7. There was no association between VEGF and BDI scores. Higher salivary levels of EGF were also found in older adults, but post-hoc analysis demonstrated this was due to lower levels of EGF in young women only. A significant negative correlation (r_s=-.483, $p<.01$) was observed between BDI scores and EGF levels in young women. Higher scores in anxiety, perceived stress, anger in, venting of emotion, and fear of negative evaluation also related to lower EGF levels in young women. Young men with lower EGF healed more quickly, whereas young women with lower EGF healed more slowly.
Conclusion: Although lower VEGF levels predicted faster healing in both sexes, a sexual dichotomy existed for EGF. Psychosocial parameters (e.g., depression) appeared to impact EGF in women only, driving levels downwards. This might explain why lower EGF levels in women, but not in men, were predictive of slower healing.

Support: COD, RO1DE12792, P50DE13749, P01AG16321.

Intense, acute stressor exposure impairs splenic killing/clearance of intravenously delivered Escherichia coli.

Thomas Maslanik[1] Isaac Bernstein-Hanley[1] Lida Le[1] * Monika Fleshner[1]
[1]University of Colorado ** Corresponding author: Monika Fleshner, (fleshner@colorado.edu)*

Exposure to stress modulates host defense against a variety of pathogens. The impact that stress has on host immune responses varies depending on both the intensity of the stressor and the route of pathogen challenge. It has been reported, for example, that exposure to an intense acute stressor (tailshock) potentiates host antimicrobial responses following subcutaneous *Escherichia coli* challenge (Campisi et al., 2003). More recently, Bailey et al. (2007) reported that repeated exposure to social defeat potentiates host antimicrobial responses following intravenous *E. coli* challenge. The current study, therefore, tested whether exposure to tailshock would also improve host antimicrobial responses to intravenous *E. coli* challenge. Adult, male, F344 rats were exposed to either a single tailshock session or no stress and all rats subsequently received 2.0 x 10^7 CFUs of *E. coli* via tail vein injection. Animals were sacrificed 1.5 and 3.0 hours after injection and bacteria were counted from splenic homogenates. In non-stressed controls, bacterial load decreased by 50% in the spleen after 3.0 hours from levels measured at 1.5 hours. Surprisingly, rats exposed to tailshock had splenic bacterial loads that remained unchanged across time and that were equal to peak levels found in non-stressed controls. This observation is supported by a significant time x stress interaction ($p=0.01$). Thus, tailshock impairs host antimicrobial responses when bacteria are injected intravenously, suggesting that the nature of the stressor and the route of infection may both impact the effect of stress on the host response to bacterial challenge. (Supported by RO1 AI057797.)

Epigenetic patterns associated with psychosocial distress mediated immune dysregulation.

* Herbert Mathews[1] Linda Janusek[1]
[1]Loyola University of Chicago, Maywood, IL USA 60153
** Corresponding author: Herbert Mathews, (hmathew@lumc.edu)*

The purpose of this study was to identify epigenetic nuclear patterns of peripheral blood mononuclear cell (PBMC) subsets, which relate to the immune dysregulation that accompanies the psychosocial distress of breast cancer diagnosis. Immune function was measured as the PBMC production of cytokines and the measurement of natural killer cell activity (NKCA). Epigenetic patterns were assessed by flow cytometric measurement of histone phosphorylation (PO4) and acetylation (Ac) as judged by mean fluorescence intensity. Women diagnosed with early stage breast cancer exhibited perceived stress, anxiety and total mood disturbance, which were negatively correlated with PBMC production of IL-2, IL-4 and interferon gamma (IFN) as well as NKCA. PBMC subset analysis revealed relationships among epigenetic nuclear patterns that were distinctly different for each of the cytokines and for NKCA. IFN production was correlated to the PO4 of Histone (H)3 serine (S)10 for the CD4+, CD8+ and CD56+ lymphocyte subsets as well as to the Ac of H4 lysine (K)8 for the CD4+ lymphocyte subset. IL-4 production was correlated to PO4 of H3S10 for CD4+ and CD8+ lymphocytes as well as Ac of H4K8 for CD4+ and CD8+ lymphocytes and Ac of H4K12 for CD56+ lymphocytes. IL-2 production showed no correlation with these epigenetic markers. NKCA was solely correlated to PO4 of H3S10 for the CD56+ lymphocyte subset. No relationships were found among CD16+ or CD19+ lymphocyte subsets for any of the epigenetic markers. These exploratory analyses demonstrate unique associations among epigenetic nuclear patterns and the immune dysregulation that accompanies psychosocial-distress mediated immune-dysregulation.

Pharmacological enhancement of central noradrenergic tone induces IL-10 production and signalling in rat brain: A role for β-adrenoceptor activation

* Eoin N. McNamee[1], Rodrigo E. González-Reyes[1], Andrew Harkin[2], Thomas J. Connor[1]
[1]Neuroimmunology Research Group, Department of Physiology & Trinity College Institute of Neuroscience, Trinity College, Dublin
[2]Neuropsychopharmacology Research Group, School of Pharmacy and Pharmaceutical Sciences & Trinity College Institute
** Corresponding author: Eoin N. McNamee, (mcnameee@tcd.ie)*

Evidence indicates that the monoamine neurotransmitter noradrenaline elicits anti-inflammatory actions in the central nervous system (CNS), and consequently may play a neuroprotective role where inflammatory events contribute to CNS pathology. Here we examined the ability pharmacologically enhancing noradrenergic tone to induce expression of anti-inflammatory cytokines in the rat brain. The noradrenaline reuptake inhibitor reboxetine (15mg/kg; ip) and the α2-adrenoceptor antagonist idazoxan (1mg/kg; ip) were administered to rats either alone, or in combination, in order to increase central noradrenaline availability. Rats were sacrificed 4hr later and hippocampal and cortical tissue was harvested for analysis. Our results demonstrate that administration of reboxetine alone, and to a greater extent in combination with idazoxan, induced IL-10 mRNA expression in hippocampus and cortex. This increase in IL-10 mRNA was accompanied by an increase in IL-10 protein expression. In addition, these drug treatments induced IL-10 signalling indicated by increased STAT3 phosphorylation and SOCS-3 mRNA expression. In contrast, pharmacological enhancement of central noradrenergic tone failed to alter expression of the anti-inflammatory cytokines IL-4 or TGF-β in rat brain. The ability of the reboxetine+idazoxan drug combination to induce IL-10 expression and signaling was mediated by β-adrenoceptor activation, as all of the aforementioned effects were blocked by the β-adrenoceptor antagonist propranolol. Moreover, administration of the centrally acting β2-adrenoceptor agonist clenbuterol (0.5mg/kg; i.p.) induced central IL-10 production and signaling. In all, these data indicate that increasing central noradrenergic tone induces IL-10 production and signaling in the CNS, which may protect against neurodegeneration occurring secondary to inflammation.

Plasma Cytokine Levels in Astronauts Before and After Spaceflight

* Satish Mehta[1] Barat Aggarwal[2] Alan H. Feiveson[3] Dianne K. Hammond[1] Victoria A. Castro[1] Raymond P. Stowe[4] Duane L. Pierson[3]
[1]Enterprise Advisory Services, Incorporated, Houston, TX, USA [2]The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA [3]Microgen Laboratories, La Marque TX, USA [4]NASA Johnson Space Center, Houston, TX, USA
** Corresponding author: Satish Mehta, (satish.k.mehta@nasa.gov)*

Space flight is a unique experience and results in adverse effects on human physiology. Changes have been reported in various physiological systems, including musculoskeletal, neurovestibular, cardiovascular, endocrine, immunity and increased latent viral reactivation as well as others. The potential mechanisms behind these changes are not fully understood. Various cytokines such as IL-1, IL-6, TNF and chemokines have been linked to several of these changes, like muscle loss, bone loss, fatigue, sleep deprivation and viral reactivation. Eighteen astronauts from 8 spaceflights and 10 controls were included in the present study. A panel of 21 plasma cytokines was analyzed with the Luminex 100 to measure the cytokines in these subjects 10 days before the flight (L-10), 2-3 hour after landing (R+0), 3 days after landing (R+3), and at their annual medical exam (AME). IL-10, IL-1, IFN-a ;lpha, MCP-1 and IP-10 increased significantly at L−10 than their AME levels. IL-6 and IFN-alpha showed significant increases at R + 0 ($P < .05$) over their baseline levels. Cytokine levels at R+3 were not significantly different from R+0. IL-10 and IL-6 have been reported to increase in during viral reactivation. These data show that there was a shift from TH1 to TH2 cytokines L-10 and R+0. We also studied viral reactivation in 10 of the 18 subjects. VZV shedding correlated with the increased cytokine levels especially IL-10 and IL-6.

Overall, our data suggests that cytokines may play an important role in regulating adverse changes in astronauts, and further studies are needed to fully understand the mechanism

Stress attenuates the efficacy of IL-12 immunostimulation: An in vivo study of resistance to experimental metastasis

Hadas Meiboom[1] Ben Levi[1] Shaily Shemer[1] * Shamgar Ben-Eliyahu[1]
[1]Neuroimmunology Research Unit, Dept. Of Psychology, Tel Aviv University, Tel Aviv, Israel.
** Corresponding author: Shamgar Ben-Eliyahu, (shamgar@post.tau.ac.il)*

Background: Despite promising animal studies, immunostimulatory regimens, including IL-12, have yielded limited success in cancer patients. Notably, patients, but not animals, are commonly subjected to psychological stress while treated with BRMs. Thus we tested the impact of behavioral stress on the efficacy of IL-12 immunostimulation in rats, employing an in vivo model resistive to NK activity.

Methods: The bedding in the home cages of male and female F344 rats was replaced by two-cm of room-temperature water for 20 hours, with a two-hour mid-break (behavioral stress). Naive and stressed rats were injected with saline or IL-12 (0.18m;g/kg/male, 0.3m;g/kg/female) two hours after the initiation of stress. Six hours after the secession of stress, rats were inoculated i.v. with radioactive syngeneic MADB106 tumor cells. Twenty-four hours later, animals were sacrifice and MADB106 lung tumor retention (LTR) was assessed. Additionally, half the animals in each group were subjected to a pharmacological stressor (metaproterenol, 1mg/kg/male; 3mg/kg/female, s.c.) simultaneously with tumor inoculation.

Results: Both the behavioral and the pharmacological stressors increased LTR. In rats not subjected to behavioral stress, IL-12 reduced LTR by half, irrespective of the effects of the pharmacological stressor. However, rats subjected to the behavioral stress showed reduced (females) or no (males) beneficial effects of IL-12. Ongoing studies seek to elucidate cellular and molecular mechanisms of this interaction and evaluate its biological significance.

Conclusion: Stress may dampen the efficacy of IL-12 immunotherapy in cancer patients. Integrating PNI based interventions alongside immunostimulation may potentiate BRMs without exacerbating side effects. Supported by RO1CA125456 to S.B-E.

Predictors of depressed mood in heart failure (HF)

* Paul J. Mills[1] Sarah Linke[1] Suzi Hong[1] Laura Redwine[1] Joel Dimsdale[1] Thomas Rutledge[1] Barry Greenberg[1]
[1]University of California, San Diego ** Corresponding author: Paul J. Mills, (pmills@ucsd.edu)*

Introduction: Depressed mood is common in HF, typically increasing in prevalence with disease progression. Inflammatory markers are associated with cardiovascular disease and its progression, as well as with fatigue and depression. This pilot study prospectively examined medical and inflammatory predictors of depressed mood in HF patients.

Methods: Twenty optimally treated HF patients (NYHA Class II-IV) (mean age 58.1 years) completed the Beck Depression Inventory (BDI) and the Multidimensional Fatigue Symptom Inventory-short form (MFSI-sf) and had a blood sample drawn at rest. Six months later patients again completed the BDI and MFSI-sf. B-type natriuretic peptide (BNP), C-reactive protein (CRP), and Interleukin-6 (IL-6) levels were determined in plasma. Data were analyzed by multiple linear regression, with depressed mood at the 6 month follow-up as the dependent variable. =

Results: The regression model ($f=15.3$; $p<.001$; adjusted $R2=.752$) indicated that depressed mood at the 6 month follow-up was independently predicted by depressed mood at intake ($\beta = .747$; $p=.000$), fatigue at intake ($\beta = .411$ $p=.01$), CRP levels at intake ($\beta=.427$; $p=.006$) and fatigue at the 6 month follow-up ($\beta=.331$; $p=.030$). Neither age, BMI, left ventricular ejection fraction (LVEF), BNP levels, nor IL-6 levels were related to depressed mood.

Discussion: These preliminary findings suggest that in addition to prior and ongoing feelings of fatigue, future rates of depressed mood are related to CRP levels, a global indicator of inflammation in HF. In contrast, depressed mood is unrelated to specific indicators of HF disease severity, i.e., BNP levels or LVEF.

Long-term alterations in neuroimmune and neuroendocrine responses following neonatal exposure to lipopolysaccharide in Wistar rats

* Tamo Nakamura[1] Adam Walker[1] Deborah Hodgson[1]
[1]Laboratory of Neuroimmunology, School of Psychology, The University of Newcastle, NSW, Australia
** Corresponding author: Tamo Nakamura, (Tamo.Nakamura@newcastle.edu.au)*

Some aspects of the adult systemic inflammatory response have been suggested to be susceptible to modification by early-life infection, which may be mediated by alterations to the hypothalamic-pituitary-adrenal (HPA) axis. We are investigating whether neonatal immune exposure alters immune and endocrine responses to immune stress in adulthood. Wistar rats (n = 24) were administered *Salmonella enteritidis* lipopolysaccharide (LPS, 0.05 mg/kg, ip) or saline on days 3 and 5 of life. In adulthood, subjects were administered LPS (0.10 mg/kg, ip) or saline, and the febrile response and activity were monitored for 24 hours. From a different set of rats receiving identical neonatal and adult treatments (n = 15), blood was collected at 0, 30, 60, 90 and 180 minutes following adult LPS or saline administration. One out of seven animals with neonatal LPS exposure showed an attenuated febrile response after adult LPS administration. Males exposed to neonatal and adult LPS displayed a blunted corticosterone response whereas increased levels were observed for saline controls following adult LPS administration. In male rats, no differences were observed between neonatal treatment groups exposed to saline in adulthood. This indicates that early life infection can produce alterations in HPA axis responsivity in preparation for later life exposure. Hippocampal interleukin-1β levels, sickness behaviours and blood compositions are being analysed. The lack of an attenuated febrile response in animals with neonatal LPS exposure may be due to the third and fifth days in Wistar rats being outside the critical period for programming of the immune system given other studies have found differences using other strains.

Increased DNA methylation in the promoter region of the μ-opioid receptor gene (*ORPM1*) in lymphocytes of Caucasian methadone maintained former heroin addicts

* David Nielsen[1] Vadim Yuferov[1] Sara Hamon[2] Colin Jackson[1] Jurg Ott[2, 3] Mary Jeanne Kreek[1]
[1]Laboratory of the Biology of the Addictive Diseases, The Rockefeller University, New York, NY 10065, USA [2]Laboratory of Statistical Genetics, The Rockefeller University, New York, NY 10065, USA [3]Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing, China ** Corresponding author: David Nielsen, (nielsen@rockefeller.edu)*

Activation of the μ-opioid receptor, site of action of opioids and opiates, by morphine induces CCR5 expression. CpG dinucleotide methylation, an important regulatory mechanism, attenuates gene expression.

We hypothesize that in the *OPRM1* gene promoter region 1) specific levels of DNA methylation occur at each CpG dinucleotide *in vivo* and 2) that percent DNA methylation at specific CpG dinucleotides is increased in stabilized methadone maintained former severe heroin addicts compared to controls.

To quantify cytosine methylation at the *OPRM1* promoter region, a 229 base pair fragment was amplified. This fragment was bisulfite treated, sequenced, and quantified using ESME software. Analysis of methylation at sixteen CpG dinucleotides was analyzed in 194 cases and 136 controls, all of Caucasian ethnicity.

The extent of percent methylation at each CpG dinucleotide varied from 5 - 56%. The percent CpG methylation was significantly associated with heroin addiction at two sites; 25.9% in cases and 21.8% in controls ($P = 0.0035$, GEE; $P = 0.0077$, t-test; FDR = 0.048) at one site, and 7.5% in cases and 5.5% in controls ($P = 0.0095$, GEE; $P = 0.0067$, t-test; FDR = 0.080) at a second site. Both CpG sites are in putative Sp1 transcription factor-binding sites.

Increased CpG dinucleotide methylation in the *OPRM1* promoter region may reduce the expression of μ-opioid receptors and, thus, may reduce CCR5 expression. The finding of differences in percent DNA methylation between stabilized methadone maintained heroin addicts and controls might provide insights into the role of opiates in HIV infection.

Interferon-γ Receptors are Required for Upregulation of Indoleamine 2,3-Dioxygenase and Depressive-Like Behavior Induced by *Bacillus Calmette-Guerin*

* Jason C. O'Connor[1] Caroline Andre[1] Marcus A. Lawson[1] Sandra S. Szegedi[1] Jacques Lestage[2] Nathalie Castanon[2] Keith W. Kelley[1, 3] Robert Dantzer[1, 3]
[1]Integrative Immunology and Behavior Program, Department of Animal Sciences1, College of ACES, University of Illinois at Urbana-Champaign [2]INRA-CNRS-University Victor Segalen Bordeaux II, Bordeaux, Franc [3]Department of Pathology, College of Medicine, University of Illinois at Urbana-Champaign * *Corresponding author: Jason C. O'Connor, (jcoconno@uiuc.edu)*

Cytokine-induced activation of the tryptophan catabolizing enzyme indoleamine 2,3 dioxygenase (IDO) causes depressive-like behavior in mice following acute activation of the innate immune system by lipopolysaccharide. Here we show that chronic infection of mice with *Bacillus Calmette-Guerin* (BCG) also leads to development of depressive-like behavior. Inoculation with BCG induced an acute episode of sickness (3 days) that was followed by development of depressive-like behavior. There was an immediate and long lasting (up to 14 days) expression of IL-1b and TNFa in the lungs and brains of mice inoculated with BCG, whereas IFNg and IDO expression was observed only at 14 days. To determine whether this distinct temporal pattern of cytokine expression is responsible for the transition from sickness to depression, WT or IFNγ-receptor deficient mice were treated with BCG or saline after pretreatment with etanercept (TNF-binding protein) or saline. BCG induced an acute reduction in body weight in all mice. WT and IFNg-receptor deficient mice displayed an acute decrease in motor activity in response to BCG that was completely blocked by etanercept. BCG increased depressive-like behavior in WT mice that was inhibited by etanercept. The depressive-like response to BCG was maximally reduced in all IFNg-receptor deficient mice. Although proinflammatory cytokines were elevated in all mice, IDO upregulation did not occur in IFNg-receptor-deficient mice. Taken together, these data demonstrate that the IFNγ receptor is necessary for upregulation of IDO and induction of depressive-like behavior in mice following BCG-induced chronic inflammation. [Supported by NIH to RD (R01 MH 079829 and R01 MH 71349) and KWK (R01 MH 51569 and R01 AG 029573)]

Induction of Depressive-like Behavior in Mice by *Bacillus Calmette-Guerin* is Dependent on Indoleamine 2,3-dioxygenase

* Jason C. O'Connor[1] Marcus A. Lawson[1] Caroline Andre[1] Jacques Lestage[2] Nathalie Castanon[2] Robert Dantzer[1, 3] Keith W. Kelley[1, 3]
[1]Integrative Immunology and Behavior Program, Department of Animal Sciences1, College of ACES, University of Illinois at Urbana-Champaign [2]INRA-CNRS-University Victor Segalen Bordeaux II, Bordeaux, Franc [3]Department of Pathology, College of Medicine, University of Illinois at Urbana-Champaign
** Corresponding author: Jason C. O'Connor, (jcoconno@uiuc.edu)*

Indoleamine 2,3-dioxygenase (IDO) mediates the occurrence of depressive-like behavior following acute activation of the peripheral innate immune response. To determine if IDO plays a similar role during chronic immune activation, mice were inoculated with *Bacillus Calmette-Guerin* (BCG), which chronically infects pulmonary macrophages. As expected, BCG increased IL-1β, TNFα, IFNγ and IDO mRNA expression in the lung and the plasma kynurenine/tryptophan ratio 7 d post-inoculation. Pretreatment with the competitive IDO inhibitor, 1-methyltryptophan (1-MT), reduced the plasma kynurenine/tryptophan ratio but did not affect induction of proinflammatory cytokines or IDO mRNA. The IDO inhibitor had no effect on the BCG-induced transient reduction in body weight (BW) or locomotor activity (LMA). However, 1-MT fully blocked the BCG-induced increase in duration of immobility in both the forced swim and tail suspension tests 7 d after inoculation. To further extend these findings, we used IDO-deficient mice and their WT controls. After confirming that IDO mRNA transcripts were not expressed in IDO-deficient mice, both strains were treated with either BCG or saline. Consistent with our previous findings in 1-MT treated mice, IDO-deficient mice exhibited a BCG-induced reduction in BW and LMA, but they did not exhibit any depressive-like behavior. Collectively, these results prove that IDO is required for the development of depressive-like behavior that is caused by a classic intracellular pathogen. [Supported by NIH to KWK (R01 MH 51569 and R01 AG 029573) and RD (R01 MH 079829 and R01 MH 71349)]

Inflammation as a response to bereavement is associated with increased subgenual anterior cingulate activity

* Mary-Frances O'Connor[1] David Wellisch[2] Michael Irwin[1]
[1]UCLA Cousins Center for Psychoneuroimmunology [2]UCLA Department of Psychiatry
** Corresponding author: Mary-Frances O'Connor, (mfoconnor@mednet.ucla.edu)*

Inflammation has been documented as a response to chronic stressful life events, such as bereavement. Bereavement often comprises symptoms of social withdrawal, decreased appetite and poor concentration. These symptoms have been described as "sickness behaviors", and peripheral inflammation is known to lead to these mood-related symptoms. However, a better understanding of how the peripheral pro-inflammatory cytokines act on the brain to induce this change in mood symptoms is needed. The present study examined the association between regional brain activity in those individuals suffering bereavement and their levels of peripheral inflammation. Based on prior research, we hypothesized that activity in the anterior cingulate cortex (ACC) would be positively associated with pro-inflammatory markers. Twenty-one women who had experienced the death of a mother or sister (but were screened against major depression) participated. Saliva samples were collected before and after completing a grief-eliciting task in an imaging scanner. Interleukin-1 receptor agonist (IL-1ra) and tumor necrosis factor-receptor II (TNF-RII) were measured. As hypothesized, activity in the subgenual anterior cingulate cortex (sACC), an area associated with mood regulation, was positively correlated with IL-1RA ($z=3.76$, $p<.001$) and TNF-RII ($z=3.08$, $p<.001$). Converging evidence of the importance of the sACC region in sickness behavior should lead to longitudinal research examining reduction in regional activity in the period following stressful life events.

Telomere length and pessimistic attitudes in older women

* Aoife O'Donovan[1] Jue Lin[1] Erin Clevenger[1] Alanie Lazaro[1] Jean M Tillie[2] Firdaus S Dhabhar[2] Owen Wolkowitz[1] Elizabeth Blackburn[1] Elissa Epel[1]
[1]University of California, San Francisco [2]Stanford University
* *Corresponding author: Aoife O'Donovan, (aoife.odonovan@ucsf.edu)*

The stress-buffering effects of dispositional optimism may explain the association of optimism with enhanced physical health and longer life expectancy. Leukocyte telomere length (TL) is an indicator of cellular age that predicts mortality. Proinflammatory cytokines including interleukin-6 (IL-6) may contribute to telomere shortening. Psychological stress has been associated with increased IL-6 and shorter TL. We predicted that optimism would be negatively associated with IL-6, and positively associated with TL, and that the reverse pattern would be observed for pessimism. Healthy post-menopausal women (N = 35; M age = 61.08) donated fasting blood and completed psychometric tests at baseline and one year later. The Life Orientation Test-Revised (LOT-R; Scheier et al., 1994) was used to assess general tendencies towards optimism and pessimism. High sensitivity ELISA was used to examine IL-6, and TL was estimated using quantitative PCR. In a multivariate model including both optimism and pessimism as predictors, and controlling for age and ethnicity, pessimism was significantly associated with shorter TL (β = -.70, $p < .001$) and higher IL-6 (β = .50, $p < .03$) at baseline. Conversely, optimism was not uniquely associated with either variable. There was also a trend towards an association between pessimism and accelerated telomere shortening across one year (β = .51, $p = .08$). In summary, pessimism is associated with higher levels of IL-6, shorter TL, and possibly greater decreases in TL over one year.

The Relationship between Poor Sleep Quality and PPMD Recurrence is Not Mediated by IL-6

* Michele Okun[1] Aric Prather[2] Martica Hall[1] Barbara Hanusa[1] Katherine Wisner[1]
[1]University of Pittsburgh, Department of Psychiatry [2]University of Pittsburgh, Department of Psychology
* *Corresponding author: Michele Okun, (okunml@upmc.edu)*

Postpartum major depression (PPMD) is a health concern affecting 14.5% of women. We found that poor sleep quality was a better predictor of recurrence after 4 weeks postpartum than traditionally assessed risk factors. Inflammation may mediate this relationship, as evidence indicates that depression is linked to dysregulation of inflammatory cytokines. We evaluated the mediating role of IL-6 in the relationship between sleep quality in late pregnancy and PPMD recurrence.

Participants were pregnant women (N = 33, 31 ± 4 yrs) with histories of PPMD but not depressed at enrollment. The Pittsburgh Sleep Quality Index (PSQI) was completed at week 36 gestation and the 21-item Hamilton Rating Scale for Depression (HRSD-21) at week 4 postpartum. Circulating IL-6 levels were assayed from early postpartum. Recurrence was determined by HRSD scores > 15 and clinician interview.

Eleven (33.3%) women recurred within 6 months postpartum. No relationship was found between PSQI scores and IL-6 levels or between IL-6 levels and PPMD recurrence (p's > .20). Poor sleep quality in late pregnancy, but neither HRSD scores in late pregnancy nor IL-6 at week 4 postpartum, was related to a recurrence of PPMD.

The current relationship between poor sleep quality and PPMD recurrence is not mediated by IL-6. Although these findings support previous reports that poor sleep quality is a prodrome for recurrent depression, the biological mechanism mediating this relationship remains unclear. Further exploration of the degree to which cytokine dysregulation is involved in this relationship and the pathophysiology of PPMD is warranted.

Variability in Cortisol among the Aging: Relationships to Chronic Stress and Good Sleep

* Michele Okun[1] Charles Reynolds III[1] Timothy Monk[1] Martica Hall[1]
[1]University of Pittsburgh, Department of Psychiatry
* *Corresponding author: Michele Okun, (okunml@upmc.edu)*

Variability in cortisol concentrations has been observed among the aging. Inter-individual variability and age-related cortisol changes are difficult to distinguish from changes linked to stressful conditions. We evaluated the relationship among subjective sleep, indices of stress, and 24-hour salivary cortisol concentrations (AUC) in two groups of "stressed" individuals: bereaved (BR) (N = 27, 71.6 ± 6.4 yrs, 76% female) and spousal caregivers (CG) of patients with dementia (N = 42, 73.5 ± 7.1 yrs; 74% female), and in a group of elders (HC) without significant sleep complaints or medical comorbidity (N = 49, 79.4 ± 3.2 yrs; 47% female). Baseline data included sleep diaries, questionnaires (the Pittsburgh Sleep Quality Index, Hamilton Depression Scale, and Perceived Stress Scale), and five saliva samples. HC had higher cortisol levels than either the BR or the CG ($F(3,117) = 9.0$, $p < .001$). No association between depressive symptomatology or perceived stress and cortisol was observed (all groups p's > .05). Higher 24-hr cortisol values, only among the HC, were associated with shorter sleep latency ($r = -.34$, $p < .05$) and greater sleep efficiency ($r = .39$, $p < .05$), and fewer sleep complaints (PSQI) ($r = -.42$, $p < .01$). These data suggest that older adults under chronic stress have blunted 24-hr cortisol levels. Hypocortisolism may be causally related to disinhibition of inflammatory processes. These data also suggest that cortisol secretion across a 24-hr period may be facilitated by good sleep. These complex interactions may identify sub-populations at risk of medical morbidity.

The curcumin analog, UBS-109 decreases peripheral expression of LPS-induced inflammatory cytokines

* Anlys Olivera[1] Fang Hu[1] Andrew P. Brown[1] Hyunsuk Shim[1] Dennis C. Liotta[1] Andrew H. Miller[1] Thaddeus W. W. Pace[1]
[1]Emory University * *Corresponding author: Anlys Olivera, (aolive3@emory.edu)*

Prior studies suggest that the inflammatory signaling molecule, nuclear factor-kappa B (NF-kB), plays a key role in transmitting peripheral cytokine signals to the brain. Therefore, NF-kB represents an attractive therapeutic target for developing drugs to prevent cytokine induced behavioral changes. Current work in our laboratories is focused on the development of novel compounds structurally related to

curcumin, (an active ingredient in the Indian spice, tumeric), which has been shown to have anti-inflammatory and anti-depressant properties. Data demonstrate that a water soluble analog of curcumin, UBS-109, has potent inhibitory effects on NF-kB DNA-binding in vitro. In the current study, we tested the ability of UBS-109 to reduce lipopolysaccharide (LPS)-induced expression of pro-inflammatory cytokines that are regulated by NF-kB pathways in peripheral tissues including the spleen. Young adult C57/BL6 (~23g) male mice (n=3/group, N=24) were treated with UBS-109 (150 mg/kg) or vehicle (90% Methyl cellulose [.5%] + 10% PEG200) orally prior to LPS administration (30ug/mouse). Mice were then sacrificed 6 or 24 hrs after LPS treatment, and spleens were collected for cytokine expression analysis using real-time PCR. Treatment with LPS increased the expression of IL-1 alpha and beta, IL-6, TNF-alpha and IFN-gamma. Administration of UBS-109 prior to LPS injection significantly reduced mRNA expression of these cytokines at both 6 and 24hrs post injection. These data indicate that oral administration of UBS-109 effectively reduces the expression of pro-inflammatory cytokines that are regulated by activation of NF-kB pathways. This novel compound may therefore block behavioral abnormalities induced by activation of peripheral cytokine signaling pathways including major depression.

Effect of Compassion Meditation on Autonomic, Neuroendocrine and Inflammatory Pathway Reactivity to Psychosocial Stress

Thaddeus Pace[1, 2] Lobsang Tenzin Negi[3] Daniel Adame[4] Steven Cole[5] Teresa Sivilli[1] Timothy Brown[6] Michael Issa[1] * Charles Raison[1, 2]
[1]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine [2]Winship Cancer Institute, Emory University [3]Emory-Tibet Partnership, Department of Religion, Emory College [4]Department of Health, Physical Education & Dance, Emory College [5]Research Design Associates, Inc. [6]Rollins School of Public Health, Emory University
** Corresponding author: Charles Raison, (craison@emory.edu)*

The widespread use of meditation as an intervention for medical and psychiatric conditions related to psychosocial stress highlights the need to evaluate mechanisms through which the benefits of practice might be conferred. To evaluate the effect of meditation on autonomic, neuroendocrine and inflammatory responses to psychosocial stress, 61 freshmen college students were randomized to six weeks of training in compassion meditation or to an active control condition consisting of a health discussion group. Upon completion of interventions participants were evaluated with a standardized laboratory psychosocial stressor (the Trier Social Stress Test [TSST]). Students randomized to compassion meditation demonstrated reduced heart rate responses to the TSST, but did not differ from controls in either interleukin (IL)-6 or cortisol (CORT) reactivity. Within the meditation group, however, practice time was correlated with reduced IL-6 responses to the TSST. Consistent with this, when high practice time and low practice time meditators (defined by median split) were compared to each other and to controls, students in the high practice time group had reduced TSST-induced heart rate and IL-6 responses, whereas students in the low practice time and control groups did not differ from each other. Students in the high practice time group also had less distress during the TSST. In all participants, TSST-induced heart rate and IL-6 responses were correlated. These findings suggest that compassion meditation may be of potential benefit to stress-related emotional and physical disorders as a result of reducing autonomic and inflammatory pathway responses to psychosocial stress.

Blocking of beta-2 adrenergic receptor hastens recovery from hypoglycemia-associated social withdrawal

Min Jung Park[1] Christopher B. Guest[1] Meredith B. Barnes[1] Jonathan Martin[2] Uzma Ahmad[2] * Gregory G. Freund[1, 2]
[1]Division of Nutritional Sciences, University of Illinois, Urbana, IL 61801, USA [2]Department of Pathology, University of Illinois, Urbana, IL 61801, USA
** Corresponding author: Gregory G. Freund, (freun@uiuc.edu)*

Hypoglycemia, especially if sever enough to cause neuroglycopenia, is associated with a variety of adverse biobehaviors including fatigue, visual disturbances, drowsiness, confusion and social withdrawal. While these clinical symptoms are well characterized, the mechanisms underlying them are not fully understood. Here we investigated the mechanism underlying hypoglycemia-associated social withdrawal (SW). C57BL/6J mice were injected with 0.4, 0.8, or 1.2 units/kg of insulin (I.P.). Insulin induced significant hypoglycemia with a plasma blood glucose nadir of 64 ± 4 or 48 ± 5 mg/dl 45 min after 0.8 or 1.2 units/kg of insulin, respectively. Insulin (0.8 or 1.2 units/kg) caused near total SW at 45 min with full recovery not occurring until 4 h (0.8 units/kg) or 8 h (1.2 units/kg) post insulin injection. Insulin also caused a marked elevation in plasma catecholamines. Basal 12 h fasting epinephrine (EPI) and norepinephrine (NE) were 350 ± 47 pg/ml and 287 ± 38 pg/ml, respectively. 0.8 units/kg of insulin increased plasma EPI and NE to 2184 ± 833 pg/ml and 994 ± 73 pg/ml, respectively. Administration of exogenous EPI, NE or terbutaline caused SW. When mice were injected with NE (1.0, 1.5, or 2.0 mg/kg), social exploration was reduced by 37 ± 5 %, 62 ± 9 %, and 81 ± 3 %, respectively, 30 min after NE. Importantly, blocking of the β-2 adrenergic receptor with butoxamine ablated both insulin- and NE-induced social withdrawal. These data demonstrate that hypoglycemia-associated SW is dependent on catecholamines via a β-2 receptor-mediated pathway.

Effects of breast cancer risk and psychological distress on immune responses in healthy women

* Na-Jin Park[1] Duck-Hee Kang[1]
[1]School of Nursing, University of Alabama at Birmingham, Birmingham, AL 35226 USA
** Corresponding author: Na-Jin Park, (najinp@uab.edu)*

Breast cancer (BC) risk, whether assessed objectively or subjectively, may influence immune responses such as natural killer cell activity (NKCA) in healthy women. High subjective risk may lead to high psychological distress, which may, in turn, negatively affect immune responses. However, these potential influences are unknown, as research has been limited in this area.

Objectives of the study were to examine: (1) the main effects of objective and subjective BC risk on NKCA; and (2) the mediating role of psychological distress in the relationship between subjective BC risk and NKCA in healthy women at varying levels of BC risk.

For this cross-sectional study, 117 healthy women (mean age 36.5 years) completed questionnaires and gave a blood sample for NKCA

measurements. Objective BC risk was calculated based on the modified Gail model.

Regression analyses revealed a significant inverse association between objective risk and NKCA at the 12.5:1 effector-to-target ratio ($p = .013$), whereas subjective risk showed no effect on NKCA after controlling for current birth control pill use. Current birth control pill users had significantly lower NKCA at all four ratios than non users. Because of the lack of main effect of subjective BC risk on NKCA, the mediating role of psychological distress was not tested. There was, however, a direct association between subjective BC risk and psychological distress.

Objective and subjective BC risks have different contributions to psycho-immune profiles in healthy women. Given the importance of NKCA in early tumor defense, the impact of objective BC risk on NKCA needs to be further investigated.

Acute Effects of Oral Administration of a Glycerol Extract of Echinacea purpurea on Peritoneal Exudate Cells in Female Swiss Mice

Tanha Patel[1] Audra Crouch[1] Kayla Dowless[1] * David Freier[1]
[1]Program In Biomedical Sciences, Lynchburg CollegeLynchburg, VA 24501
** Corresponding author: David Freier, (freier@lynchburg.edu)*

Numerous reports have suggested that *Echinacea purpurea* has immunoenhancing properties. A consensus in this area has yet to be established. Reports using murine models have indicated *E. purpurea* administration can enhanceme some measures of innate immunity. We evaluated whether in vivo *E. purpurea* administration enhanced innate responses following immunization. Female Swiss mice were immunized with $1x10^8$ sheep erythrocytes intraperitoneally. One hour later, the first dose of a 3 day oral administration of 0.8 ml/kg/day of a glycerol extract of *E. purpurea* [Nature's Way; stem, root and leaf in 50% glycerol & water] was administered. *E. purpurea* treated mice were compared to glycerol vehicle treated controls and naïve subjects. Upon euthanasia, peritoneal exudate cells (PEC) were isolated in cold, Ca2+ Mg2+ free DPBS and a sample of the DPBS was reserved for cytokine analysis. PEC ($1x10^6$ cells/ml) were plated overnight, washed to remove non-adherent cells, and stimulated with 50 ng/ml of bacterial lipopolysaccharide (*E. coli* O55:B5) for 24 hours. Supernatant was assayed for nitric oxide production and a sample frozen for cytokine analysis. No significant difference in number of PEC was observed. In PEC from *E. purpurea* treated mice an elevated nitric oxide response to LPS was observed, with a 2 to 4 fold difference compared to controls in the PEC response to LPS. These results suggest that treatment with *E. purpurea* can enhance PEC responsiveness to a common stimulus, and may provide an avenue for investigation into the mechanisms by which these immunoenhancing effects occur.

Strain Differences in Basal Activity: Effects of Aging and Stimulation of Central Imidazoline-1 Receptors on Splenic Sympathetic Activity and β-AR-stimulated cAMP Production in Middle-aged F344 and Brown Norway Rats.

Sam D Perez[1] Brooke A Kozic[1] Christine Molinaro[1] Jeff Carter[1] Sharda Vyas[1] Srinivasan ThyagaRajan[1] * Denise L Bellinger[1]
[1]Department of Pathology and Human Anatomy, School of Medicine, Loma Linda University, Loma Linda, California.
** Corresponding author: Denise L Bellinger, (dbellinger@som.llu.edu)*

INTRODUCTION: Sympathetic innervation of spleens from old male Fischer (F344) and Brown Norway (BN) rats exhibit age-related differences compared with young adults, resulting in a strain specific sensitivity of immune cell signaling via β-adrenergic receptor (AR) stimulation. We investigated the effects of reducing elevated basal sympathetic activity with the antihypertensive, rilmenidine on these features.

HYPOTHESIS: We hypothesized that 90-day treatment with rilmenidine begun at 15 months of age will reverse the age-related shifts in β-AR-stimulated cAMP production by spleen cells in aging F344 and BN rats.

EXPERIMENTAL METHODS: Rats were intraperitoneally (i.p.) injected with vehicle or rilmenidine (250 or 750 μg/kg b.i.d.) for 90 days. A separate group of rats received 200 mg α-methyl-paratyrosine to assess sympathetic activity in the spleen. Plasma and splenic catecholamines concentrations were measured using high-performance liquid chromatography (HPLC). β-AR-stimulated cAMP production was evaluated by ELISA after splenocytes were incubated with isoproterenol (10-5 M) for 10 min.

RESULTS: Treatment with rilmenidine reduced plasma catecholamine content in F344 and BN rats (30% and 25%) compared with young and old control rats. Rilmenidine also reduced splenic norepinephrine (NE) turnover rate in both strains. Static splenic NE concentration was reduced and increased with low- and high dose respectively in the F344 rats but unchanged in the BN rats. Treatment with low- and high dose of rilmenidine increased β-AR-stimulated cAMP production in F344 and BN rats respectively.

CONCLUSION: These findings indicate that treatment with rilmenidine increases sympathetic signal transduction in old spleen cells form F344 and BN rats in a dose-dependent manner. This research is supported by NIH Grant NS44302. Special Thanks to Servier for supplying the rilmenidine used in this study.

The Association of Poor Sleep to Immunogenicity Following an Avian Flu Vaccine in Healthy Older Adults

* Wilfred R Pigeon[1] John Treanor[1] Stefan Costescu[1] Jan Moynihan[1]
[1]Sleep & Neurophysiology Research Laboratory, Department of Psychiatry, University of Rochester, NY 14642
** Corresponding author: Wilfred R Pigeon, (Wilfred_Pigeon@urmc.rochester.edu)*

Introduction: There is a long-standing and cross-cultural belief that poor sleep makes one vulnerable to illness. Empirical evidence, especially in innate cytokine networks, supports a relationship between sleep and immunity. The elderly have high prevalence rates of insomnia and other sleep disorders and are more vulnerable to various influenza strains than their younger counterparts. Few studies (and none in elders) address sleep and antigen-specific or adaptive immune function. **Hypothesis**: Among an elderly cohort, non-response to an influenza virus vaccine will be associated with poor sleep. **Methods**: The parent study was a randomized, double-blinded study of an investigational inactivated influenza A/H5N1 virus vaccine in healthy adults aged 65+. A companion study added the Pittsburgh Sleep

Quality Index (PSQI), a validated self-report instrument which provides a global score, 7 subscales, sleep duration, and sleep efficiency (SE). Subjects in the drug condition only (n=36) were divided into a responder (n=16) and non-responder (n=19) groups based on the presence of a four-fold increase in antibody titer from baseline to 1, 2, or 7 months post-vaccination. Independent samples t-tests were performed (two-tailed). **Results**: Non-responders had higher global PSQI scores than responders at 2 and 7 months post vaccine ($p<.05$). There were no group differences on subscales, though non-responders had shorter sleep duration and lower SE than responders at all post-vaccination time points (all $p<.05$). **Conclusion**: The results suggest that poor sleep is associated with poor immunogenicity following an avian flu vaccine. More specifically, sleep that is typical for insomnia was associated with non-response in this cohort of otherwise healthy elders.

The relationship between rape survivor's levels of distress, health profile, ways of coping and measures of the immune system

Prishika Pillay[1]
[1]Pietermaritzburg, Kwa-Zulu-Natal, South Africa ** Corresponding author: Prishika Pillay, (prishika@mweb.co.za)*

Rape is a traumatic event which has devastating consequences for the survivor. Rape can impose demands which exceed the individual's ability to cope thus eliciting a psychological stress response composed of negative cognitive and emotional states. It is these responses that are thought to influence immune function through their effects on behavior and coping. Most studies reveal little about the nature of stressors that put a person at risk for disease, timing of the stressor relative to exposure and disease onset; and psychological and biological characteristics that moderate these effects.

This research aims to investigate the relationship between rape survivors' levels of distress, coping style, health profile and immune system.

The results revealed significant relationships between levels of distress and immune parameters; health profile and immune parameters; ways of coping and immune parameters; and levels of distress and immune parameters. Significant differences were obtained for CD4 ($p = 0.039$) between time1 and time 2, as well as between time 2 and time 3. Rape survivors experience changes in the levels of distress, health profile, ways of coping and immune parameters over 35 days post rape period.

The knowledge gained from this research provides a foundation for further research in psychoneuroimmunology focussing particularly on natural acute traumatic stressors like rape. This knowledge provides theoretical and applied insight into the processes involved subsequent to a traumatic rape experience. The significant relationships between levels of distress, ways of coping, health profile and immune parameters contributes to the theoretical understanding of these processes and provides information about a rape survivors\' experiences and wellbeing.

HIV-1-infected subjects with neuropsychological impairment have a unique gene expression profile

* Lynn Pulliam[1] Bing Sun[2] Linda Abadjian[3] Hans Rempel[2]
[1]Departments of Laboratory Medicine and Medicine,Veterans Affairs Medical Center, San Francisco, CA and University of California, San Francisco, CA. [2]Departments of Laboratory Medicine, Veterans Affairs Medical Center, San Francisco, CA [3]Department of Radiology, Veterans Affairs Medical Center, San Francisco, CA
** Corresponding author: Lynn Pulliam, (lynn.pulliam@ucsf.edu)*

During normal immunosurveillance or in response to chemotactic signals, HIV-1-infected and activated monocytes transmigrate to the CNS triggering neuroinflammation and neuronal degeneration. These changes in monocytes may exacerbate HIV infectivity and neurotoxicity in the CNS.

Neuropsychological/neurocognitive tests and gene expression analyses were performed on healthy controls (n=10) and HIV-1 seropositive (+) subjects (n=35), all on antiretrovirals. The neuropsychological tests evaluated eight domains including gross/fine motor skills, psychomotor function, information processing speed and verbal memory. The HIV-1+ subjects were categorized as normal (N) and 8 were moderately impaired (MI, 2 SD below normal in two of the eight domains tested). CD14+ monocytes were concurrently isolated and gene expression microarrays (55k targets) performed. Significant genes had a minimum 1.5 fold differential expression, a Student's t-test of $p <0.05$ and the Benjamin-Hochberg false discovery filter.

In the HIV-1+ group, 8 subjects were judged to be MI. Six genes were found significantly differentially regulated in monocytes from these 8 subjects. Of the six genes, Furin, a proprotein convertase that cleaves HIV glycoprotein gp160 and gp140 into gp120/gp41, was up-regulated 1.7 fold. A second gene, HLA-DQA1, which was down regulated 4.8 fold, has a role in the monocytic antigen presentation complex which is a key factor in the immune response to pathogens. Moderate neuropsychological impairment did not correlate with HIV viral load or CD4 count.

Neuropsychologically impaired subjects had different gene expression profiles in circulating monocytes that may contribute to the neuropsychological impairment in HIV-infected subjects.

Tumors induce depression and alter neuroimmune and neuroendocrine systems

* Leah M. Pyter[1] Vanessa M. Pineros[1] Jerome A. Galang[1] Martha K. McClintock[1] Brian J. Prendergast[1]
[1]Department of Psychology, University of Chicago, Chicago, IL
** Corresponding author: Leah M. Pyter, (pyter@uchicago.edu)*

The relationship between peripheral health and mental health is reciprocal. A striking example of this interaction is the high incidence of depression and anxiety disorders in cancer patients. A number of factors may contribute to this comorbidity, however, the extent to which tumor-derived chemical messengers (i.e., cytokines) contribute to the central states of depression and anxiety has never been investigated.

We tested the hypothesis that tumors produce cytokines and dysregulate the HPA axis, which in turn, affect the brain and behavioral measures of affective state. Female Wistar rats received an injection of nitrosomethylurea (NMU, chemical carcinogen) to induce mammary tumors. Within 2 weeks of tumor palpation, depression and anxiety-like behaviors were examined in NMU-treated, tumor-bearing and saline-treated control rats. In a separate cohort of similarly treated rats, pro- and anti-inflammatory cytokines were measured in blood, tumors, and limbic brain regions. In a second study, the effects of tumors on the HPA axis were assessed by measuring corticosterone responses to a stressor and dexamethasone, and by quantifying glucocorticoid receptor expression in the brain. Preliminary findings suggest that tumors increase depressive-like behaviors and cytokine production and increase HPA negative feedback sensitivity. These results suggest that the mechanism by which cancer increases the prevalence of mood disorders may be due to neuroimmune consequences of the tumors themselves.

The relationship between psychosocial and immune variables in American women with breast cancer.

* Sarah M. Rausch[1] Nancy L. McCain[2] Stephen Auerbach[2] Sandra Gramling[2]
[1]Mayo Clinic [2]Virginia Commonwealth University * *Corresponding author: Sarah M. Rausch, (Rausch.Sarah@Mayo.Edu)*

Immune functioning has been linked to psychosocial variables in cancer patients, but the relationships between psychoneuroimmunological variables are neither simple nor clear. Therefore, we evaluated the relationship between psychosocial variables (anxiety, depression, coping, optimism, fatigue, QOL) and immune function (by proinflammatory cytokines) in women newly diagnosed with breast cancer. The current study consisted of a subsample of 40 women in the U.S. with early stage breast cancer enrolled in a larger NCI-funded trial. Of the 40 participants in the subsample (mean age=49 years), 73% were Caucasian, 22% African American, and 5% identified themselves as other racial designation. All participants completed data collection one week prior to beginning chemotherapy. Correlations between psychosocial variables and proinflammatory cytokines revealed that more positive mood states were associated with higher levels of cytokines, whereas negative mood states were associated with lower levels of cytokines. Specifically, higher levels of TNF-α were associated with lower levels of total anxiety, somatic anxiety, and fatigue. Higher levels of IL-2 were associated with higher levels of QOL. Higher levels of positive reappraisal coping were associated with higher levels of IFN-y, and higher levels of confrontive coping were associated with lower levels if IL-1B. Optimism was not only positively correlated with TNF-α, but using a hierarchical regression model, it served as a significant predictor of TNF-α levels, accounting for 93% of the variance above and beyond age and race. This information may ultimately be of great relevance to knowledge development in psychosocial oncology.

Increased lymphocyte glucocorticoid sensitivity to chronic stress in aging Fisher rats.

* Laura Redwine[1] Amelia Chen[1] Michael Irwin[2]
[1]University of California, Department of Medicine, San Diego, CA, USA [2]University of California, Cousins Center for Psychoneuroimmunology, Los Angeles, CA, USA * *Corresponding author: Laura Redwine, (laura.redwine@gmail.com)*

Chronic stress in older adults is associated with greater morbidity and mortality. However, the mechanisms are not fully understood. Endocrine-immune dysregulation associated with aging and/or chronic stress may impact on frequency and severity of infections. To test the hypothesis that aging and chronic stress alter glucocorticoid sensitivity for antigen stimulated cytokine secretion, Fisher rats (n = 24) were stratified by age (18 mo and 6 mo) and housing: double or single (isolation stress) for 28 days, rats were sacrificed, and trunk blood collected; in vitro, 3ng/ml lipopolysaccharide (LPS) stimulated IL-6 levels were measured following lymphocyte preincubation with 0, 10, 50 and 100 nM dexamethazone (DEX). A 2 (age) x 2 (housing) x 4 (concentrations of DEX) repeated measures analysis of variance (ANOVA) revealed age ($p = 0.001$) and age x DEX concentration ($p = 0.049$) effects for stimulated IL-6. Older rats appeared to have greater lymphocyte glucocorticoid (DEX) sensitivity with increased suppression of stimulated IL-6, which may indicate dampen immune responsiveness and increased susceptibility to infection. There was also an age x housing interaction ($p = .05$) with increased stimulated IL-6 only in younger single housed animals, possibly indicating chronic stress associated resistance to glucocorticoids. In conclusion, younger age may protect against infectious diseases during chronic stress by increasing resistance to glucocorticoids. Whereas, aging itself may increase susceptibility to infectious disease, and with age immune resistance to glucocorticoids may be diminished during chronic stress, thereby reducing protection against infection.

Neuroinflammation and cognitive function in aged mice following minor surgery

* Heidi Rosczyk[1, 2] Nathan Sparkman[2] Rodney Johnson[1, 2, 3]
[1]Neuroscience Program, University of Illinois, Urbana IL 61801, USA [2]Integrative Immunology and Behavior Program, University of Illinois, Urbana IL 61801, USA [3]Department of Animal Sciences, University of Illinois, Urbana IL 61801, USA
* Corresponding author: Heidi Rosczyk, (hrosczyk@uiuc.edu)

Following surgery, elderly patients often suffer from postoperative cognitive dysfunction (POCD) which can persist long after physical recovery. Effects of variables such as anesthesia, analgesics, age and inflammation remain unclear and the underlying mechanisms of POCD are poorly understood. It is known that surgery-induced tissue damage activates the peripheral innate immune system resulting in the release of inflammatory mediators. Compared to adults, aged animals demonstrate increased neuroinflammation and microglial priming that leads to an exaggerated proinflammatory cytokine response following activation of the peripheral immune system.

Therefore we sought to determine if the immune response to surgical trauma results in exacerbation of neuroinflammation in the aged brain and whether this can lead to cognitive impairment. In the present study, adult and aged mice underwent minor abdominal surgery and 24h later hippocampal cytokines were measured and spatial working memory was assessed in a reversal learning version of the Morris water maze. While adult mice showed no signs of neuroinflammation following surgery, aged mice had significantly increased levels of IL-1b mRNA in the hippocampus. Although elevation in IL-1b did not result in gross learning and memory deficits in the Morris water maze, aged mice that underwent surgery tended to perseverate in the incorrect quadrant suggesting subtle underlying cognitive

dysfunction. These results suggest that while surgery increases IL-1b production in the brain of aged animals, a more sensitive cognitive test may be needed to determine the neurobehavioral deficits due to surgery in the aged. This research was supported by NIH grants AG016710 and AG023580.

Increased parental stress correlates with poorer asthma control in children

* Sitesh Roy[1] Jake Olivier[1] Kevin DelBen[1] Gailen Marshall[1]
[1]University of Mississippi Medical Center, Jackson, MS ** Corresponding author: Sitesh Roy, (sroy@ped.umsmed.edu)*

Introduction: Parental stress has been known to influence the development of atopy and wheezing illness in young children. Validated questionnaires for assessment of asthma control are now considered a part of standard outpatient asthma assessment.
Hypothesis: We sought to determine the impact of parental stress on childhood asthma control in a largely minority population at a tertiary care Asthma and Allergy Clinic. We hypothesized that higher parental stress would correlate with poorer asthma control in children.
Methods: A retrospective IRB-approved chart review study was conducted of 157 patients attending a Pediatric Allergy and Immunology Clinic. Patients and/or their parents routinely complete a standardized self-assessed asthma control questionnaire (ACT-Asthma Control Test) and a Perceived Stress Scale 10 item questionnaire (PSS-10) at every visit. Statistical analysis was performed using SAS software to determine Pearson's correlation coefficients for the above-mentioned parameters.
Results: There were 157 subjects, 125 African American and 32 Caucasian patients in the study group of children aged 7-21 years. The mean ACT score for the group was 19.4 out of a maximum of 25 (an ACT score of 15-20 suggests partially controlled asthma). Mean parental PSS score was 15.5. There was a negative correlation between parental stress and asthma control test scores ($r = -0.27$; p-value 0.0008).
Conclusions: In this largely African American, mixed urban-rural population higher parental stress correlated with lower asthma control in children aged 7-21 years of age. Overall asthma control was slightly below the well-controlled range. These findings support the clinical observation of adverse effects of stress on asthma control.

Psychoneuroimmunology and Acculturation in Hispanic Pregnant Women

* R. Jeanne Ruiz[1] Sheryl Bishop[1]
[1]University of Texas Medical Branch ** Corresponding author: R. Jeanne Ruiz, (rojruiz@utmb.edu)*

Previous studies show a Hispanic Paradox in which relatively less acculturated Hispanics with intact social relationships exhibit better than expected health outcomes and lower risk factors, despite low socio- economic status. Acculturation is the process by which individuals adopt the attitudes, values, customs, beliefs and behaviors of another culture. The Hispanic Acculturation Paradox suggests that, with greater acculturation, risk factors and health outcomes become unfavorable. A number of psychosocial, endocrine and immune factors have been associated with negative health outcomes. The definition of acculturation becomes critical in accurately identifying risk factors. Traditional definitions of acculturation have used primarily language proficiency or country of birth. The current study used a more robust definition of acculturation based on a cluster analysis consisting of years in the US, country of birth, language proficiency, insurance, education, age and number of relatives living nearby. This resulted in two clusters, representing American and Hispanic acculturated groupings. The hypothesis is: the American acculturated group would have more negative psychosocial, endocrine and immune outcomes. Numerous psychosocial and physiological blood measures were assessed on 446 self-identified Hispanic women at 22-24 weeks of pregnancy. T-test analyses across all variables showed significantly higher depression, higher stress, higher anxiety, lower support, higher IL-1Ra, lower cortisol, lower corticotropin releasing hormone (CRH), lower progesterone and a lower progesterone-estriol ratio for the American acculturated group as compared to the Hispanic acculturated group. Our evidence confirms that greater acculturation yields worsening psychological and physiological outcomes. This partially accounts for the Acculturation Paradox.

The glucocorticoid dexamethasone prevents inflammation-induced suppression of glial β_2-adrencoceptor expression: Implications for Multiple Sclerosis

* Karen M. Ryan[1] Eoin N. McNamee[1] Thomas J. Connor[1]
[1]Neuroimmunology Research Group, School of Medicine and Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland. ** Corresponding author: Karen M. Ryan, (kryan7@tcd.ie)*

β_2-adrenoceptors on astrocytes and microglia mediate the anti-inflammatory and neurotrophic effects of noradrenaline in the central nervous system and thereby play an endogenous neuroprotective role. Clinical studies demonstrate that β_2-adrenoceptors are absent from astrocytes of patients with Multiple Sclerosis and loss of glial β_2-adrenoceptors is likely to contribute to chronic inflammation and oligodendrocyte and neuronal damage in this disorder. The biological basis of this loss of β_2-adrenoceptors in Multiple Sclerosis is not known, therefore here we investigated the possibility that exposure to an inflammatory stimulus (LPS+IFN-γ) could down-regulate glial β_2-adrenoceptor expression. We demonstrate that in vitro exposure of rat primary mixed glial cells to LPS+IFN-γ down-regulates β_2-adrenoceptor mRNA and cell surface expression (by approximately 50%). LPS+IFN-γ also decreased β_2-adrenoceptor responsiveness, indicated by reduced cAMP accumulation following stimulation with the β_2-adrenoceptor agonist salbutamol. In contrast, forskolin-induced cAMP accumulation was not altered by LPS+IFN-γ, indicating that reduced cAMP production in response to salbutamol did not occur due to direct inhibition of adenylate cyclase. When β_2-adrenoceptor expression was examined on isolated microglia and astrocytes we observed that LPS+IFN-γ reduced receptor expression on both cell types.

Pre-treatment with the glucocorticoid dexamethasone prevented the suppression of β_2-adrenoceptor expression induced by LPS+IFN-γ and this was paralleled by reduced production of the pro-inflammatory cytokines IL-1β and TNF-α. Interestingly, dexamethasone also

increased β_2-adrenoceptor expression in its own right in the absence of inflammation. Based on these data we suggest that the ability of dexamethasone to up-regulate β_2-adrenoceptor expression on glial cells may contribute to its therapeutic efficacy in Multiple Sclerosis.

Biobehavioral and spiritual responses of women in a labyrinth walking program

* M. Kay Sandor[1]
[1]University of Texas Medical Branch, School of Nursing * *Corresponding author: M. Kay Sandor, (ksandor@utmb.edu)*

Walking the labyrinth may have stress reduction health benefits similar to a sitting meditation practice. The purpose of this pilot study was to examine the biobehavioral and spiritual responses in women to a program of labyrinth walking compared to a program of track walking at a slow pace. Women were randomly assigned to the groups. Biobehavioral and spiritual responses were measured at baseline (prior to program initiation), midway (1 month) and at the end of the walking program (2 months). The hypothesis was: Women who participate in a labyrinth walking program will show decreased serum cortisol levels, decreased behavioral levels of stress (perceived stress, negative affect, anxiety, aggression, and depression), and increased positive affect and spiritual well-being when compared to women who participate in a track walking program. Twenty women ranging in age from 54-68 were enrolled. All participants reported work-related stress and/or caregiver stress at baseline. Women in the labyrinth walking group showed a significant decrease in state anxiety and verbal aggression compared to the track walking group. Both groups showed a significant decrease in serum cortisol levels, however there were no significant differences between groups. Absolute change scores showed a decrease in state anxiety, verbal aggression, and perceived stress, as well as an increase in spiritual well-being over time in the labyrinth group. Few complementary or alternative interventions incorporate body, mind and spirit in an integrative, holistic health practice. Walking the labyrinth incorporates all three. Based on these preliminary findings, labyrinth research will be expanded to study at-risk populations.

Exercise Therapy for Ovarian Cancer: How does exercise counteract stress-induced tumor growth?

* Rosemarie Schmandt[1] Anil K. Sood[2] Susan K. Lutgendorf[3] Lingegowda S. Mangala[1] Guillermo Armaiz-Pena[4]
[1]Department of Gynecologic Oncology, University of Texas, M.D. Anderson Cancer Center, Houston, TX [2]Departments of Gynecologic Oncology and Cancer Biology, University of Texas, M.D. Anderson Cancer Center, Houston, TX [3]Department of Psychology, University of Iowa, Iowa City, IA [4]Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center; Program in Cancer Biology, University of Texas Graduate School of Biomedical Sciences at Houston
** Corresponding author: Rosemarie Schmandt, (rschmand@mdanderson.org)*

Increased physical activity following the diagnosis of cancer has been demonstrated to significantly improve outcome, but the underlying mechanisms are not well understood. Because chronic stress contributes to aggressive tumor growth, we hypothesized that stress-reducing behavior, such as voluntary exercise, will counteract stress-mediated tumor growth. To test this hypothesis, we utilized an orthotopic mouse model of ovarian carcinoma. Thirty-six mice were divided into four groups: no treatment; free access to an exercise wheel; two hours of daily immobilization stress; two hours daily immobilization stress plus voluntary exercise. Mice were monitored daily for overall health and wheel use and were sacrificed and autopsied when the first mice became moribund. Exercise had no significant effect on the growth rate of tumors in unstressed animals. However, stressed mice with no access to exercise demonstrated accelerated SKOV3ip1 tumor growth as compared to the unstressed controls (0.45g vs. 0.2g; p=0.03). Stressed mice with voluntary exercise developed significantly smaller tumors than stressed mice housed without wheels (0.15g vs. 0.45g, p=0.02), which were similar in size to those observed in unstressed animals. Furthermore, we demonstrated similar therapeutic effects when mice were treated with a daily dose of 10 mg/kg of the antidepressant, fluoxetine. Exercise clearly reverses stress-induced tumor growth. The beneficial effects of exercise on tumor growth can be mimicked with antidepressants, suggesting that exercise and antidepressants utilize common signaling pathways to prevent cancer recurrence.

Relationships between Perfectionism and Self-Reported Short-Term Physical Illness Complaints

* Debra Schroeder[1]
[1]The College of St. Scholastica * *Corresponding author: Debra Schroeder, (dschroed@css.edu)*

Relationships between types of perfectionism (self-oriented-belief that oneself must be perfect, socially-prescribed-belief that others expect perfection, other-oriented-belief that others must be perfect) and mental illness have been well-established. Additionally, the search for moderators (indicate when relationships will occur) and mediators (explain the relationships) of those links has advanced far. However, little data exist on perfectionism-physical health relationships, and even less on moderators or mediators of the relationships. This study examined whether perfectionism predicts physical illness and whether daily hassles moderate and/or mediate the relationships. A total of 107 students, employees, and alumni of a small college responded to a questionnaire measuring perfectionism, daily hassles, and short-term physical illness complaints (Survey of Immunological and General Health). Data showed that self-oriented perfectionism (SOP) positively correlated with days with infectious symptoms and gastrointestinal complaints. Further, achievement and interpersonal hassles moderated the SOP-infectious symptoms relationship and an SOP-days of fatigue relationship; those high on SOP encountering hassles reported the most days ill. Socially-prescribed perfectionism (SPP) showed even stronger correlations with the same physical illness complaints, adding days of fatigue. While daily hassles did not moderate SPP-physical illness relationships, achievement hassles mediated relationships for days with infectious symptoms and fatigue. That is, high SPP increased perceptions of hassles, and these perceptions more closely correlated with illness. In sum, SPP related best to physical illness complaints, perhaps through perceptions of hassles in daily events, supporting interventions at the cognitive level. SOP seemed to create particular problems when hassles were encountered, implying situational interventions.

Neural progenitors and neuroinflammation in the pathogenesis of pediatric neuroAIDS

* Lynnae Schwartz[1] Steven Douglas[1]
[1]Joseph Stokes Jr. Research Institute,The Children's Hospital of Philadelphia,University of Pennsylvania School of Medicine
** Corresponding author: Lynnae Schwartz, (schwartzl1@email.chop.edu)*
The neuropathological and neurodevelopmental consequences of vertical (in utero or perinatal) HIV-1 infection and HIV-1 associated inflammation of the immature (CNS) are incompletely understood. An important specific area requiring inquiry is that of unique vulnerabilities of distinct neural cell populations in the immature human brain exposed to multiple inflammatory molecules in the setting of HIV-1 infection.

Progressive encephalopathy (PE) is the severe clinical manifestation of pediatric neuroAIDS in patients in whom viral proliferation and virus-associated inflammation cannot be controlled with treatment and/or innate immune responses. Hallmarks of PE include systemic immune collapse, severe developmental delays, poor brain growth, neurocognitive impairment and neuroinflammatory pain syndromes. Although spared from the devastation of PE, treatment-responsive children surviving into adolescence and young adulthood may be at increased risk for: 1) depression, and other neuropsychiatric conditions; 2) pain; and 3) HIV-related CNS compromise syndrome with language, memory and subtle neurocognitive defects, all of which have a potentially profound negative impact upon academics, life skills and capacity for independent living.

Multi-potential neural progenitors differentiate into neurons or astroglia depending upon their environmental context, and are critical for learning, cognition, neuropsychiatric functionality and brain development. This talk will review the relevant immunobiology of neural progenitor cells, as well as accumulating cell culture and human tissue evidence that progenitors may be HIV-1 infected. The potential consequences of progenitor infection will then be considered in the context of CNS inflammation. One example discussed will be the potential role of substance P (SP) and its preferred receptor, Neurokinin-1 (NK-1R) in HIV-1 associated neuroinflammation and neural progenitor cell proliferation.

Soluble fiber enhances recovery from LPS-induced social withdrawal in a manner dependent on IL-4

* Christina Sherry[1] Stephanie Kim[2] Ryan Dilger[3] George Fahey[1, 3] Kelly Tappenden[1, 4] Gregory Freund[1, 2, 3]
[1]Division of Nutritional Sciences, University of Illinois, Urbana, IL 61801, USA [2]Department of Pathology, University of Illinois, Urbana, IL 61801, USA [3]Department of Animal Science, University of Illinois, Urbana, IL 61801, USA [4]Department of Food Science and Human Nutrition, University of Illinois, Urbana, IL 61801, USA ** Corresponding author: Christina Sherry, (csherry@uiuc.edu)*
High fiber diets have been shown to lower gastrointestinal inflammation and decrease the risk of developing inflammatory bowel disease, but the anti-inflammatory mechanism by which dietary fiber works is not established. Interestingly, dietary fiber is also tied to anecdotal health claims that apparently impact a vast range of quality-of-life metrics. A potential link between modified gastrointestinal inflammation and "non intestinal" biobehaviors is via the innate immune system and proinflammatory cytokines. Here we show that a semi-purified (SP) diet supplement with 10% pectin (SP+P) is protective against LPS-induced social withdrawal and up-regulates anti-inflammatory cytokines. Mice fed a SP+P diet recover 50% faster from LPS-induced social withdrawal than mice fed a SP diet. Mice fed a SP+P diet had increased basal IL-4 message in the brain (3-fold), ileum (75-fold), cecum (30-fold), and colon (21-fold). Importantly, IL-4 is a potent up-regulator of IL-1RA, and 2 h after LPS, mice fed a SP+P diet had a 2.6-fold increase in brain IL-1RA message. Peritoneal macrophages from mice fed a SP+P diet had a 3.8-fold increase in basal and a 3.3-fold increase in LPS-induced IL-1RA protein as compared to mice fed a SP diet. To determine the importance of IL-4 on social withdrawal, IL-4 knockout (KO) mice were fed a SP or SP+P diet. SP+P fed IL-4KO mice recovered 50% faster than wild-type mice or SP fed IL-4KO mice. Taken together these data indicate that dietary fiber in the form of pectin impacts biobehavioral recovery from LPS-induced social withdrawal through augmentation of the anti-inflammatory cytokine IL-1RA by IL-4.

Alterations in Brain and Behavioral Development of Offspring Following Prenatal Flu Infection in Rhesus Monkeys

* Sarah J. Short[1] Christopher L. Coe[1] Gabriel Lubach[1] Martin Styner[2] John H. Gilmore[3]
[1]Department of Psychology, University of Wisconsin, Madison, WI [2]Department of Computer Sciences, University of North Carolina, Chapel Hill, NC [3]Department of Psychiatry, University of North Carolina, Chapel Hill, NC
** Corresponding author: Sarah J. Short, (sjshort@wisc.edu)*
Maternal flu infection during pregnancy may be a risk factor for altered fetal brain development. An association between influenza and neurodevelopmental disorders, such as schizophrenia, is hypothesized from both rodent and retrospective human studies. Since influenza does not typically cross the placenta, inflammatory responses in the maternal compartment may be responsible for mediating this association, especially if infection occurs during sensitive periods in fetal brain development. Twelve pregnant rhesus monkeys were infected with a human-derived influenza virus, A/Sydney/5/97 (H3N2), one month before term (equivalent to late 2nd trimester) and compared to 7 control pregnancies. Nasal swabs and blood samples confirmed viral infection and inflammatory responses in pregnant females. Infant measures included a behavioral assessment at 2 weeks of age, and mother-infant observations until 3 mos. of age. Structural MR imaging (3T) was preformed at 13 mos.(equivalent to late childhood). Flu infants scored higher on measures of distress and lower on measures of motor development ($p<.05$) at 2 weeks of age and initiated autonomy earlier ($p<.05$) despite signs of distress. MRI analyses revealed significant reductions in total brain volume and overall gray matter (GM) in flu animals ($p<.05$). Analyses of additional neurodevelopmental measures are underway and results from diffusion tensor imaging (DTI) will be presented at the conference. These findings demonstrate that a moderate viral infection during pregnancy can adversely affect behavioral and neural development. Evidence of behavioral dysfunction at birth continued through the early infancy period. Reductions in total brain volume and GM are consistent with human and rodent studies of schizophrenic patients and prenatal flu infections respectively.

Association of Promoter Polymorphisms in the α7 Nicotinic Acetylcholine Receptor with Cortisol Stress Response

* Melissa L Sinkus[1] Marianne Z Wamboldt[1] Amanda Barton[1] Sherry Leonard[1] Mark Laudenslager[1]
[1]University of Colorado Denver Health Science Center, Colorado, USA
** Corresponding author: Melissa L Sinkus, (Melissa.Sinkus@UCHSC.edu)*

Introduction: The nicotinic acetylcholine receptor α7 subunit (α7-nAChR) is an essential regulator of inflammation via its ability to suppress production of pro-inflammatory cytokines. The nervous system, through the vagus nerve, can inhibit the release of macrophage TNF, attenuating systemic inflammatory responses. Polymorphisms in the promoter of *CHRNA7*, the α7 subunit gene, decrease expression of α7-nAChR and may dampen this cholinergic response leading to an increase in inflammatory conditions including atopy.
Hypothesis: Adolescents with atopic illnesses also have an attenuated cortisol response to stress. This attenuated response may be associated with disregulation of the α7 nACh receptor.
Experimental Methods: Subjects underwent a physical examination, pulmonary function testing, skin- prick testing for allergies, and had their blood drawn. At set points during these interventions, saliva was collected for cortisol assay. Time points were chosen to reflect the stress of the procedure preceding the saliva collection.

DNA for genotyping was extracted from blood. Gene polymorphisms were amplified using PCR and sequenced with a 3100-Avant genetic analyzer using Sequencher software.

Association analysis was performed using the UNPHASED genetic analysis software developed by Frank Dudbridge. Bonferroni Adjustment was applied to nominal p values produced by UNPHASED to correct for multiple testing.
Results: Polymorphisms in the *CHRNA7* proximal promoter are associated with quantitative changes in cortisol level after a stress ($p=1.711x10-6$). Subjects carrying *CHRNA7* promoter polymorphisms had smaller mean increases in cortisol level after a stress.
Conclusion: Polymorphisms in the *CHRNA7* proximal promoter are associated with a decreased cortisol response to stress.

Specificity in the Association of Comorbid Anxiety and Atopic Disorders in Adolescents

* Marcia J. Slattery[1] Marilyn J. Essex[1]
[1]Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
** Corresponding author: Marcia J. Slattery, (mslattery@wisc.edu)*

Introduction: Considerable research has focused on the association between internalizing psychiatric (anxiety and depressive) symptoms and immune-mediated atopic disorders [asthma, allergic rhinitis, atopic dermatitis, and urticaria]. Findings, however, are inconsistent, suggesting potential subtypes of internalizing (e.g. anxiety) and atopic disorders for who the association is particularly strong. We hypothesize that type of atopic disorder (i.e. respiratory-based), but not type of anxiety, will influence the strength of this association.
Methods: Subjects were 358 adolescents who participated in a community, longitudinal study investigating risk factors for the development of psychiatric and physical health problems. Children's mental symptoms were assessed at 7, 9, 11, and 13 years of age. Internalizing symptoms included depression, and generalized and separation anxiety. Lifetime history of atopic disorders was assessed at age 13. Analysis of variance was used to investigate the specificity of the association, including types of anxiety symptoms and atopic disorders.
Results: Correlational analyses showed a positive association of number of allergies with internalizing symptoms ($r =.11$; $p=.03$) which became even stronger when externalizing symptoms were controlled ($r =.14$; $p=.01$). This association remained significant when controlling on other types of chronic medical conditions. Analysis of variance demonstrated specificity for symptoms of generalized anxiety, and respiratory types of atopic disorders (asthma and allergic rhinitis).
Conclusions: This study provides new insight into the specificity of the association between generalized anxiety and respiratory-based atopic disorders. Findings suggest possible overlapping psychological, respiratory, and immune mechanisms in the pathophysiology of both types of disorders.

Social temperament and lymph node innervation

* Erica Sloan[1] John Capitanio[2] Ross Tarara[3] Steve Cole[1, 4]
[1]Cousins Center for Psychoneuroimmunology at the Semel Institute of Neuroscience and Human Behavior, Department of Medicine, Division of Hematology-Oncology, UCLA School of Medicine,UCLA AIDS Institute [2]Department of Psychology, University of California Davis, and California National Primate Research Center [3]California National Primate Research Center [4] Jonsson Comprehensive Cancer Center and UCLA Molecular Biology Institute ** Corresponding author: Erica Sloan, (esloan@ucla.edu)* Socially inhibited individuals show increased vulnerability to viral infections, and this has been linked to increased activity of the sympathetic nervous system (SNS). To determine whether structural alterations in SNS innervation of lymphoid tissue might contribute to these effects, we assayed the density of catecholaminergic nerve fibers in 13 lymph nodes from 7 healthy adult rhesus macaques that showed stable individual differences in propensity to socially affiliate (Sociability). Tissues from Low Sociable animals showed a 2.8-fold greater density of catecholaminergic innervation relative to tissues from High Sociable animals, and this was associated with a 2.3-fold greater expression of nerve growth factor (NGF) mRNA, suggesting a molecular mechanism for observed differences. Low Sociable animals also showed alterations in lymph node expression of the immunoregulatory cytokine genes IFNG and IL4, and lower secondary IgG responses to tetanus vaccination. These findings suggest that individual differences in social temperament are linked to alterations in the structure of lymphoid tissue sympathetic innervation in ways that might ultimately contribute to differences in immune system biology.

The Association between Fatigue, Vital Exhaustion and Inflammatory Markers in Chronic Heart Failure

* Otto R.F. Smith[1] Susanne S Pedersen[1] Johan Denollet[1]
[1]Medical Psychology, Tilburg University, the Netherlands * *Corresponding author: Otto R.F. Smith, (r.o.smith@uvt.nl)*

The aim of this prospective study was to examine whether fatigue and vital exhaustion predict inflammation at 12-month follow-up in chronic heart failure (CHF). 127 patients completed a questionnaire including the FAS (general fatigue), the DEFS (exertion fatigue), and the MQ (vital exhaustion), at baseline. Serum levels of TNF-α, soluble TNF-α receptors 1 (sTNF-R1) and 2 (sTNF-R2), IL-1ra, and neopterin were measured by ELISA at 12 months. Exertion fatigue was associated with both sTNF-R1 (r=.26;*p*=.003) and sTNF-R2 (r=.26;*p*=.003), whereas vital exhaustion was only associated with sTNF-R1 (r=.27;*p*=.002). General fatigue was not associated with any of the biomarkers. After controlling for gender, age, etiology of CHF, and LVEF, the associations found in univariable analysis remained significant (exertion fatigue: $\beta_{sTNF\text{-}R1}$=.25, *p*=.008; $\beta_{sTNF\text{-}R2}$=.23, *p*=.01; vital exhaustion: $\beta_{sTNF\text{-}R1}$=.26, *p*=.003). PCA on the MQ resulted in three factors: general fatigue, depressive symptoms, and sleep difficulties. Depressive symptoms were significantly associated with sTNF-R1 (r=.32;*p*<.001) only. The other MQ subscales did not correlate with cytokine levels. Entering exertion fatigue and depressive symptoms simultaneously in a multivariable model revealed that depressive symptoms (β=.26, *p*=.006) were independently associated with sTNF-R1, and exertion fatigue (β=.21, *p*=.03) was independently associated with sTNF-R2. In conclusion, (1) exertion fatigue, but not general fatigue, was associated with increased inflammation in CHF, (2) exertion fatigue was primarily associated with sTNF-R2, and (3) the effect of vital exhaustion on sTNF-R1 could primarily be attributed to depressive symptoms. Future studies are warranted to investigate the complex interactions between fatigue, vital exhaustion, cytokines, and CHF prognosis.

Acute and chronic IL-1β administrations differentially modulate learning and memory, acetylcholine efflux and neurotrophin expressions in the hippocampus: possible mechanisms involved in neuroprotection and neurodegeneration

* Cai Song[1] Pornnarin Teapavarapruk[2] Ye Zhang[1]
[1]Department of Biomedical Sciences, AVC, University of Prince Edward Island [2]Department of Physiology, Faculty of Medical Sciences, Naresuan University, Phitsanulok, Thailand.
* *Corresponding author: Cai Song, (cai.song@nrc.gc.ca)*

Introduction: Neuroinflammation and excessive glucocorticoid production may contribute to neurodegeneration. Interleukin (IL)-1β ;can induce neurodegeneration but also have neuroprotective effects. We hypothesized that acute and chronic IL-1 administrations may differentially modulate the function of the cholinergic system and neurotrophins. In this study, the effects of acute and chronic IL-1 administration on the ACh efflux while rats engaged in memory test and on the expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) were studied.
Methods: Rats (Long-Evans) were stereotaxically implanted with two guide cannulae aimed at the dentate gyrus of the hippocampus for the microdialysis probes and at the cerebroventricle for IL-1β injection. Saline or IL-1β ;(15 ng) was injected daily for 2 or 8 days and microdialysis was conducted on day 1 and 7 during animals were trained and tested in the eight-arm radial maze. The dialysates from the hippocampus were collected and analyzed by HPLC. Neurotrophin expressions were measured by quantitative PCR.
Results: Acute IL-1β injection decreased ACh efflux by 25%, while chronic IL-1 induced a larger decrease (40%), which was partially blocked by IL-1 receptor antagonist or a glucocorticoid receptor antagonist. During learning and memory retrieve, the elevation of ACh efflux was much less in the group treated with chronic IL-1 administration, ;which was correlated to the memory deficit. Furthermore, acute IL-1β administration increased, while chronic IL-1β decreased BDNF and NGF mRNA expressions in the hippocampus.
Conclusion: These results demonstrated that 1) chronic IL-1β impaired memory through reducing ACh releases and neurotrophin expressions, and 2) acute IL-1β may protect the brain by up-regulating neurotrophin expressions.

Effects of Social Disruption Stress on CD4+ T cell Activation, Trafficking, and Survival During Influenza Infection

* LaTonia Stiner-Jones[1] Mark Hanke[2] Nicole Powell[1] David Padgett[3] John Sheridan[3]
[1]Section of Oral Biology, College of Dentistry, The Ohio State University, Columbus, OH 43218, USA [2]Integrated Biomedical Sciences Graduate Program, The Ohio State University, Columbus, OH 43218, USA [3]Section of Oral Biology, College of Dentistry, Department of Molecular Virology, Immunology, and Medical Genetics, College of Medicine, Institute of Behavioral Medicine Research, The Ohio State University, Columbus, OH 43218, USA
* *Corresponding author: LaTonia Stiner-Jones, (stiner.3@osu.edu)*

Social disruption (SDR) stress has been shown to enhance innate and adaptive immune responses to pathogenic microorganisms, observations uncommon to other stress models that are usually associated with immunological attenuation. To uncover the immunological components augmented by this stressor, CD4+ T cell activation and survival were investigated as a precursor to improved trafficking and viral clearance, during influenza A/PR8 viral infection. It is hypothesized that SDR facilitates enhancement of CD4+ T cell activation during A/PR8 infection. Following 6-cycles of SDR, 0.1 HAU A/PR8 virus was administered intranasally to control and SDR mice. Activation state of the CD4+ population was assessed using flow cytometry, during the course of infection, within the lung, mediastinal lymph nodes (MLN), and spleen. These results indicate heightened infiltration of T helper cells into the lung of stressed mice. Enhanced infiltration was accompanied by increased expression of CD25+ and CD44+, a pattern not observed in the lungs from control mice. Furthermore, as assessed by M1 viral gene expression, viral load was decreased in SDR mice throughout the course of infection. Splenocytes from SDR mice, cultured for 48 and 96 hours, exhibited enhanced survival when stimulated with Concanavalin-A in the presence of corticosterone. Together, the data suggest that SDR enhanced activation, trafficking, and cell survival during influenza

infection, which may have contributed to heightened viral clearance. Stress, believed to be immunosuppressive, can enhance parameters of the immune response and confer accelerated recovery.
Supported by NIH grants NIMH/RO1MH046801-15 and NIDCR/T32DE014320-6

Effects of relaxation training on physiological and psychological measures of distress and quality of life in HIV-seropositive subjects

* Sharon Stout-Shaffer[1] Gayle Page[2]
[1]The Ohio State University Predoctoral Fellowship Award - National Institute of Nursing Research, Grant #1-F31-NR07422-01,School of Nursing Capital University Columbus, Ohio, USA [2]Professor and Independence Foundation Chair, Director, Center for Nursing Research and Scholarship, School of Nursing, Johns Hopkins University, USA
** Corresponding author: sharon stout-shaffer, (sstoutsh@capital.edu)*
Immunosuppressed populations are at particular risk for health changes associated with the stress of chronic illness. To test the possibility that relaxation and guided imagery (RGI) mitigates the biobehavioral sequelae associated with HIV infection, we examined changes in psychophysiological indicators of stress in HIV+ adults who regularly practice RGI. Participants from a Midwestern AIDS Clinical Trial Unit were randomly assigned to either undergo a 12-week RGI protocol (n = 14) or serve as wait list controls (n = 11). RGI consisted of intensive instruction in general relaxation plus individualized active coping imagery exercises with weekly follow-up. Outcomes were assessed at baseline (week 2) plus weeks 6, 10, and 14. Whereas there was no significant change in viral load from baseline to week 14 among the RGI participants, among the wait list control participants, viral load increased significantly over the 12-week wait. That a statistically significant increase in CD4+ cells was also evident in the RGI group during this period suggests there was a biologic benefit of the intervention. Behaviorally, compared to wait-list controls, RGI participants exhibited significant improvements on the MOS-HIV Role Function and Health Transition subscales and overall health behavior (p=.05). There was also some suggestion of treatment related reduction in psychological distress evidenced by improvement trends on the POMS total and 6 POMS subscales. Anecdotally, RGI was found useful for 9 most frequently reported symptoms including pain and fatigue. These findings support the possibility that RGI interventions can improve biobehavioral HIV sequelae.

The Effects of Personality and Stress on HSV-2 Shedding in Women Undergoing a Randomized, Placebo-Controlled, Crossover Trial of Acyclovir

* Eric Strachan[1] Amalia Margaret[1] Dedra Buchwald[1] Anna Wald[1]
[1]University of Washington School of Medicine ** Corresponding author: Eric Strachan, (erstrach@u.washington.edu)*
The role of stress on HSV infection has been equivocal. Data support the hypothesis that persistent stressors exacerbate HSV-1 and HSV-2 infections but there is considerable heterogeneity in effect sizes and statistical/clinical significance. In addition, stress appraisals and personality factors have been suggested as important individual difference variables that impact HSV clinical severity. In this study, we explored whether personality variables (i.e. Neuroticism and Extroversion) or daily stress ratings predicted the presence of HSV-2 virus in daily swabs taken from 19 HSV-2 positive women over the course of a 26-week randomized, double-blind, placebo-controlled, crossover trial of acyclovir (ACV). Using PCR analysis offered an important benefit over previous outcomes variables (lesions or antibody titres) in that it is a direct measure of clinical severity and potential for disease transmission. Using mixed effects linear regression modeling with an autocorrelated (AR1) covariance structure, we found that neuroticism and extroversion had significant impacts on shedding rates depending on treatment condition but the effects were paradoxical. Specifically, those high in neuroticism shed less overall than those low in neuroticism and the effects of treatment were different based on neuroticism. Extroversion seemed to moderate the effects of high but not low neuroticism. Stress was not a significant predictor of shedding alone or in combination with personality except when data from the ACV condition were examined separately. In that case, greater stress was associated with greater shedding. These data support the notion that personality traits deserve additional consideration in psychoneuroimmunology studies and that such traits may influence treatment responses among those with persistent infections.

Gender -specific associations between disturbed sleep and biomarkers of inflammation, coagulation and insulin resistance

* Edward C Suarez[1]
[1]Duke University Medical Center, Dept. of Psychiatry and Behavioral Sciences, Durham, NC, USA 27705
** Corresponding author: Edward C Suarez, (suare001@mc.duke.edu)*
Poor sleep quality and symptoms of poor sleep have been linked to increased risk of coronary heart disease, Type 2 diabetes, and hypertension with recent evidence suggesting stronger associations in women. At this time, the mechanisms of action that underlie these gender-specific associations are incompletely defined. The current study examined whether gender moderates the relation of subjective sleep and sleep-related symptoms to indices of inflammation, coagulation and insulin resistance (IR), factors that are associated with an increased risk of cardiovascular and metabolic disorders. Subjects were 210 healthy , nonsmoking men (n = 115) and women (n = 95) without a diagnosis of sleep disorders. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and frequency of sleep symptoms. Dependent measures included C-reactive protein (CRP) and interleukin (IL)-6, fasting insulin and glucose, estimated IR, and fibrinogen. In multivariate-adjusted models, overall poor sleep quality, more frequent problems falling asleep (> 2 night/week) and longer periods of time to fall asleep (> 30 min) were associated with higher levels of fasting insulin, ($p < .001$), fibrinogen ($p < .01$) and inflammatory biomarkers ($p < .02$), but only for women. Thus, subjective ratings of poor sleep quality, greater frequency of sleep-related symptoms, and longer periods of time to fall asleep were associated with a mosaic of biobehavioral mechanisms implicated in both CHD and Type 2 diabetes and these associations were more prominent in women. These data are consistent with recent observations suggesting gender-specific differences in the association between symptoms of poor sleep and cardiovascular disease.

HCV infection induces monocyte secretion of proinflammatory cytokines that are neurotoxic

Bing Sun[1] Alexander Monto[2] Hans Rempel[1] * Lynn Pulliam[3]
[1]Departments of Laboratory Medicine, Veterans Affairs Medical Center, San Francisco, CA [2]Department of Medicine, Veterans Affairs Medical Center, San Francisco, CA and University of California, San Francisco, CA [3]Departments of Laboratory Medicine and Medicine,Veterans Affairs Medical Center, San Francisco, CA and University of California, San Francisco, CA.
* *Corresponding author: Lynn Pulliam, (lynn.pulliam@ucsf.edu)*

Hepatitis C virus (HCV) plays a deleterious role in neurocognitive outcomes in HIV/HCV coinfected subjects. Like HIV, HCV can infect monocyte/macrophages (M/Mφ), which are known to traffic into the brain. In the brain, both HIV and HCV have been seen in astrocytes and microglia. Unlike HIV, individuals with untreated HCV may live with chronic viremia and not develop dementia; however, there are numerous reports that HCV is associated with cognitive impairment.

Gene microarrays were performed on CD14+ monocytes from subjects in a well-established cohort with HCV infection (n = 4), HIV/HCV coinfection (n = 4), HIV infection (n = 17) and uninfected subjects (n = 8). No subjects were treated for HCV; co-infected subjects were all on HAART with undetectable HIV viral loads and high HCV viral loads.

Our preliminary results show that M/Mφ from HCV monoinfection had significant increases in gene expression of IL-1, IL-6, IL-8 and the MIP chemokines. HIV/HCV coinfected individuals had increased expression of genes associated with chemotaxis (CCL2, MIP genes) and inflammation (IL-6, IL-1, IL-8) with increased interferon-induced genes. Significant genes were verified by qRT-PCR. Conditioned media from cultured M/Mφ of individuals with HCV or HIV/HCV caused neural cell death and apoptosis in human brain cultures. IL-6 protein was significantly elevated in conditioned media compared to controls.

HCV infection stimulates monocyte chemotaxis genes; coinfection with HIV compromises beneficial effects of HAART. Soluble monokines in HCV and HIV/HCV infections cause neuroinflammation and neuropathological

Significance of Glutamatergic Neurotransmission in Interleukin-1-Induced Hypophagia.

Artur H Swiergiel[1] * Adrian Dunn[2]
[1]Dept. of Pharmacology, Toxicology and Neuroscience, LSUHSC, Shreveport, LA 71130 [2]Pacific Biosciences Research Center and Dept. of Psychology, University of Hawaii at Manoa
* *Corresponding author: Adrian Dunn, (ajdunn@hawaii.edu)*

Infections often lead to suppression of appetite as a component of "sickness behavior" and similar response can be produced by interleukin 1 (IL 1). Significance of glutamatergic neurotransmission in IL 1-induced hypophagia was studied in a model of ingestion in which satiated mice are fed sweetened milk. The animals were pretreated with ionotropic or metabotropic glutamate receptor antagonists, injected ip with 100 ng of IL-1beta, and 90 min later tested for milk drinking. The non-competitive ionotropic glutamate NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5,10-imine maleate (dizocilpine, MK-801) administered ip at the doses of 0.083 or 0.25 mg/kg, did not attenuate decreases in milk drinking produced by IL-1. Likewise, the AMPA/kainate receptors selective antagonist 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide (NBQX, 16.36 mg/kg, ip), the mGlu receptor type-I (subtype mGluR5) selective antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP, 3 and 11.3 mg/kg, ip) and the metabotropic receptor antagonist (+/-)-2-amino-3-phosphonopropionic acid (AP-3, 50 mg/kg, ip), had no effects. The data indicate that glutamatergic neurotransmission is not critical to the hypophagic response to IL 1. It is possible that either we failed pinpointing critical glutamate receptor(s) or IL 1 induced hypophagia is mediated by multiply redundant neural mechanisms. Modulating one neural system at a time may not be sufficient to reverse hypophagia because of the activation of redundant and/or compensatory mechanisms.

No Apparent Role for Glutamatergic Neurotransmission in Interleukin-1-Induced Hypophagia

* Artur H Swiergiel[1] Adrian Dunn[2]
[1]Dept. Pharmacology, Toxicology and Neuroscience, LSUHSC, Shreveport, LA 71130 [2]Dept. Psychology and Pacific Biosciences Research Center, University of Hawaii, Honolulu, HI 96822, USA
* *Corresponding author: Artur H Swiergiel, (ASwier@lsuhsc.edu)*

Administration of interleukin-1 (IL-1) mimics the suppression of appetite in "sickness behavior" induced by infections. The potential role of glutamatergic neurotransmission in IL-1-induced hypophagia was studied in a model in which satiated mice are fed sweetened milk. The animals were pretreated with ionotropic or metabotropic glutamate receptor antagonists, injected ip with 100 ng of IL-1β, and milk drinking assessed 90 min later. The non-competitive ionotropic glutamate NMDA-receptor antagonist, MK-801 (dizocilpine) administered ip (0.083 or 0.25 mg/kg), did not attenuate the decreases in milk drinking induced by IL-1. Likewise, the AMPA/kainate receptors selective antagonist, NBQX (16 mg/kg, ip), the mGlu receptor type-I (subtype mGluR5) selective antagonist, MPEP (3 and 11 mg/kg, ip), and the metabotropic receptor antagonist, AP-3 (50 mg/kg, ip), had no effects. The data indicate that glutamatergic neurotransmission is not critical for the hypophagic response to IL-1. It is possible either that we failed to pinpoint the critical glutamate receptor(s), or that IL-1-induced hypophagia is mediated by multiply redundant neural mechanisms. The present data add to those previously reported for antagonists of dopaminergic, noradrenergic (α and β), serotonergic (5-HT1A/B, 2 and 3), muscarinic, histaminergic (1,2,3), opiatergic, neurokinin, melanocortin4, NPY, cholecystokinin (A & B), CRF, as well as inhibitors of nitric oxide synthase, and the synthetic enzymes for norepinephrine, serotonin and histamine. Thus modulating only one neural system may not be sufficient to prevent the hypophagia because there are redundant mechanisms.

The conditioned effects of heroin on nitric oxide are mediated by dopamine D1, not D2, receptors within the basolateral amygdala

* Jennifer Szczytkowski[1] Donald Lysle[1]
[1]University of North Carolina at Chapel Hill
** Corresponding author: Jennifer Szczytkowski, (jennifer_thomson@med.unc.edu)*

Heroin induces alterations in a number of immunological parameters including alterations in nitric oxide production. We have shown that heroin induced suppression of inducible nitric oxide synthase (iNOS) can be conditioned to environmental stimuli associated with drug administration. iNOS is the enzyme responsible for the production of nitric oxide which is known to be involved in host defense. Recent studies in our laboratory have shown that the basolateral amygdala (BLA) plays a critical role in the conditioned effects of heroin on iNOS and the present study investigates the role of dopamine signaling with the BLA on these effects. Dopamine is known to be involved in the rewarding effects of opiates and other drugs of abuse and has also been shown to play a role in the conditioned effects of these drugs. Rats were given five conditioning trials in which they received an injection of heroin immediately upon placement into a conditioning chamber. Rats were then re-exposed to the conditioning chamber ten days later without further drug administration. Prior to re-exposure, rats received intra-BLA microinfusions of either the dopamine D1 antagonist, SCH23390 or the D2 antagonist, raclopride. Analyses using real-time RT PCR indicate that blockade of D1, but not D2, receptors in the BLA reverse the effect of heroin associated environmental stimuli on iNOS expression. This study is important because it is the first to demonstrate that the conditioned effects of heroin on iNOS are mediated through dopamine D1 receptors within the BLA.

DIFFERENTIAL EFFECTS OF DEPRESSED MOOD AND EXERCISE STRESS ON SOLUBLE ADHESION MOLECULE RESPONSES IN HEART FAILURE (HF)

* Joseph Tafur[1] Suzi Hong[1] Paul J Mills[1]
[1]University of California, San Diego
** Corresponding author: Joseph Tafur, (jrtafur@yahoo.com)*

Depression is associated with increased morbidity in HF, possibly through its effects on neuroimmune function. Few studies have examined the effects of acute stressors on cellular adhesion molecule responses among depressed and non-depressed HF patients.

Twenty-seven optimally treated HF patients (NYHA Class II-IV) (mean age 62 years) completed a 15-17 min moderate exercise challenge. Depressed mood was characterized by the Beck Depression Inventory (BDI). Patients scoring above the BDI clinical cutpoint of 10 were considered to have depressed mood. Blood was drawn prior to and 0, 10 and 30 min post exercise. Circulating sICAM-1 and sP-selectin levels were determined (ELISA). Data were analyzed by repeated measures ANCOVA.

Controlling for age, gender and BMI, exercise led to different responses in non-depressed versus depressed patients. In non-depressed patients, an increase in sICAM-1 ($p<.05$) was followed by a return to baseline levels at 30 min post exercise. In depressed patients, exercise led to a decrease in sICAM-1 levels ($p<.05$). Exercise led to a decrease in sP-selectin levels in non-depressed patients ($p<.01$) but no change in depressed patients. Borg's ratings of perceived exertion were not different between the groups.

The findings indicate that depressed and non-depressed HF patients mount different inflammatory responses to acute exercise stress. In depressed patients, the response to an acute exercise stress may be linked to dysfunction of neuroimmune activation. Also in depressed HF patients, decreased serotonin levels may be affecting platelet sP-selectin responses. Future studies should examine depression's effects on serotonin levels in HF as they relate to neuroimmune activation.

LPS-Induced Memory Consolidation Impairment in Active Avoidance Conditioning: Effects of Age

* Andrew Tarr[1] Kristina McLinden[1] Rachel Kohman[2] Gary Boehm[1]
[1]Dept of Psychology, Texas Christian University, Fort Worth, TX 76129 [2]Dept of Pharmacology & Toxicology, Rutgers University, Piscataway, NJ 08855
** Corresponding author: Andrew Tarr, (andrew.tarr@tcu.edu)*

Administration of lipopolysaccharide (LPS) has been shown to have detrimental effects on learning/memory in a variety of behavioral paradigms. These behavioral deficits often correlate with increased central cytokine expression and diminished neurotrophin expression. A number of factors are known to alter the nature of the endotoxin-induced behavioral and neural effects, including the age of the experimental subjects; older subjects generally show exacerbated behavioral deficits and altered elevations of central cytokines versus younger counterparts. Only a small number of studies have shown how age influences memory consolidation following peripheral immune activation. This study tested the hypothesis that aged animals would show a greater LPS-induced deficit in memory consolidation than younger animals given the same treatment, utilizing a two-way active avoidance paradigm. Young (4 month) and old (18 month) male C57BL/6J mice were given intraperitoneal injections with either LPS (250μg/kg) or sterile saline immediately after the first day of testing only. Animals were tested for five consecutive days, with 52 trials per day. Main effects of LPS administration and Age were found, with LPS-treated animals showing deficits in both number of avoidance responses and response efficiency, and older animals also showing general deficits on these measures. Further, an interaction effect was found for response efficiency, in which older animals treated with LPS showed particularly poor learning. These effects were unrelated to motor or motivational decrement. Evaluation of cytokine levels is currently under way. These findings support previous work indicating that advanced age enhances the risk of cognitive deficit following peripheral immune activation.

Type C Coping and Alexithymia are Associated Differentially with Specific Immune Mechanisms (Interleukin-6 and Beta-Chemokine Production) Linked to HIV Progression

* Lydia Temoshok[1] Rebecca Wald[1] Stephen Synowski[1] Alfredo Garzino-Demo[2] James Wiley[3]
[1]Institute of Human Virology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD. [2]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD. [3]Public Research Institute, San Francisco State University, San Francisco, CA. ** Corresponding author: Lydia Temoshok, (ltemoshok@ihv.umaryland.edu)*

We hypothesized that β-chemokines MIP-1α/β which inhibit HIV entry into CD4+ T lymphocytes via the CCR5 coreceptor, and/or proinflammatory cytokines, particularly IL-6, which activate HIV replication, may be mechanisms underlying our previously reported finding that higher Type C coping predicted 12-month HIV progression. The present study examines baseline relationships between Type C coping (which allows unrecognized, unexpressed emotions to remain as chronic stressors) and the adjacent personality construct of alexithymia (deficits in the cognitive processing and regulation of emotion) and these mechanisms linked in biological studies to HIV progression. Participants were 200 HIV+ outpatients (92% African-American, 53% male, mean age 45). Type C was assessed by the Vignette Similarity Rating Method; alexithymia by the Toronto Alexithymia Scale. *In vitro* production of IL-6 and MIP-1α/β was measured in response to Candida, PHA, and the HIV core protein p24. Supernatants were collected, and assays performed by ELISA. A Stimulation Index was defined as antigen-stimulated chemokine/ IL-6 production compared to unstimulated controls. In regression analyses with independent variables Type C and the total alexithymia score, controlled for age and CD4 count, higher Type C coping was associated with IL-6 production stimulated by Candida (β=.207, *p*<.01), PHA (β=.182, *p*<02), and p24 (β=.138, *p*=.075). Regression analysis with the same IVs revealed a significant negative association for MIP-1α and alexithymia (β = -.196, *p* =.008). Conceptually but not statistically related, higher Type C coping is associated differentially with higher IL-6 production to several antigens, which amplifies HIV replication, while higher alexithymia is associated with lower production of the anti-HIV chemokine MIP-1α.

THE EFFECTS OF THE PHYSICAL WORK ENVIRONMENT ON CIRCADIAN VARIATIONS IN HEART RATE VARIABILITY

Julian Thayer[1] Israel Christie[2] Anthony West[3] Carolyn Sterling[3] Darrell Abernethy[3] Giovanni Cizza[3] * Andrea Marques[3] Terry Phillips[3] Judith Heerwagen[4] Kevin Kampschroer[4] John Sollers[1] Marni Silverman[3] Esther Sternberg[3]
[1]Ohio State University [2]University of Pittsburgh Medical Center [3]National Institutes of Health [4]United States General Services Administration ** Corresponding author: Andrea Marques, (marquesa@mail.nih.gov)*

Decreased heart rate variability (HRV), indicative of reduced parasympathetic/vagal tone, is an independent risk factor for morbidity and mortality. A prominent circadian variation in HRV, with significant increases during the night, is observed in healthy individuals. Previous studies showed that this increase in nighttime HRV is blunted by acute stress as well as conditions such as chronic alcoholism. Other studies demonstrated elevated levels of plasma and sweat proinflammatory cytokines and sympathetic neuropeptides, and reduced parasympathetic neuropeptides, in patients with major depressive disorder. In the present study we investigated the effects of the physical work environment on HRV circadian variations, salivary cortisol circadian rhythm and plasma and sweat patch neuroimmune biomarker levels. 24-hour recordings of HRV were performed on 63 participants in either a traditional work-space (a mixture of individual offices with opaque doors and old cubicles; n=43) or a modern work-space (individualized cubicles with improved airflow and lighting, and increased natural light; n=20). Cortisol and neuroimmune biomarker levels are being analyzed by enzyme immunoassay and recycling immunoaffinity chromatography, respectively. Several indices of HRV were derived from spectral analysis and hourly summaries. Mixed effect models were used to estimate both inter- and intra-individual variability. A significant quadratic trend by office type interaction for indices of vagally-mediated HRV was observed [t(1384)=2.8, p=0.004]. Moreover, individuals in the traditional work-space exhibited flatter HRV slopes and thus less circadian variation compared to those in the modern work-space. These results suggest that physical features of the work environment may contribute to circadian variations in HRV, and hence, serve as risk factors on health.

Stress, Anxiety, and Heat Shock Proteins in Women Undergoing Surgery for Suspected Endometrial Cancer

* Sannes Tim[1] Sally Jensen[1] Stacy Dodd[1] Lindsey Boegeheld[1] Linda Morgan[2] Ed Chan[3] Deidre Pereira[1]
[1]The University of Florida Department of Clinical and Health Psychology [2]Shands Gynecologic Oncology Clinic [3]The University of Florida Department of Oral Biology ** Corresponding author: Sannes Tim, (tsannes@phhp.ufl.edu)*

Heat shock proteins (HSPs), a class of ubiquitously expressed chaperone proteins involved in intracellular processes, and are implicated in carcinogenesis through inhibition of apoptosis. Some research suggests that stress is associated with elevations in anti-HSP antibody levels. However, virtually no research has examined these relationships in cancer. HSP70 overexpression suggests a poor prognosis in endometrial cancer (ECa), the 4th most common female cancer. In this study, we predicted greater stress/anxiety would be associated with greater HSP70 among women undergoing surgery for ECa. Subjects (Ss) were women attending a Gynecologic Oncology clinic for evaluation of ECa. Ss underwent pre-surgical psychological assessment and blood draw. Impact of recent negative life events was measured using a modified Life Experiences Survey; anxiety was assessed using a modified Structured Interview Guide for the Hamilton Anxiety and Depression Scales; serum anti-HSP70 antibody concentrations were assessed using ELISA. Ss were 33 women (M age=62 yrs, SD age=11 yrs) with premalignant endometrial disease (7%) or ECa (Stage: I=68%, II=13%, III=13%). Controlling for biobehavioral confounds associated with HSP70 (age, body mass index), greater impact of negative life events was not associated with HSP70, β=.282, p=.099. However, a marginally significant association emerged between greater anxiety and greater HSP70, β=.322, p=.055. Although based on a small sample size, these findings suggest a moderate-large effect size correlation between anxiety and serum anti-HSP70 antibody concentration in women undergoing surgery for endometrial cancer. Future research should examine mood states and HSP expression, and the possible hormonal mediators of this relationship, via immunohistochemistry.

Psychological Distress and Coping Predict the Healing of Chronic Wounds: The Case of Diabetic Foot Ulcers

* Kavita Vedhara[1] Jeremy Miles[2] Mark Wetherell[3] Aidan Searle[1] Deborah Tallon[1] Karen Dawe[1] Nicky Cullum[4] Andrew Day[1] Colin Dayan[1] Nikki Drake[5] Patricia Price[6] John Tarlton[1] John Weinman[7] Rona Campbell[1]
[1]University of Bristol [2]Rand Institute [3]University of Northumbria [4]University of York [5]Southmead Hospital [6]Wound Healing Research Unit [7]Institute of Psychiatry ** Corresponding author: Kavita Vedhara, (k.vedhara@bris.ac.uk)*

Research with acute experimental wounds has shown that psychological distress significantly delays healing. The present study extended this research by exploring the effects of both distress and coping in the healing of chronic non-experimental wounds i.e., diabetic foot ulcers.

Diabetic patients with an active ulcer were recruited from secondary care podiatry clinics (n=116). Demographic and clinical factors, psychological characteristics and ulcer size and status were assessed at baseline. Ulcer assessments were repeated at weeks 6, 12 and 24 post-baseline. Analyses involved logistic regressions exploring, first, potential clinical/demographic determinants of healing; then psychological distress and coping were entered into the model and finally baseline ulcer size.

Results revealed that, with regard to clinical/demographic determinants, only the measure of ulcer infection approached significance. The inclusion of distress and coping into the model revealed that patients whose ulcers had not healed by 24 weeks exhibited both greater distress (OR 0.559, CI 0.318-0.983, p=0.043) and a propensity towards confrontation coping (OR 0.819, CI 0.729-0.921, p=0.001) at baseline. Finally, inclusion of initial ulcer size, attenuated the effect of distress but not coping.

Patients with larger ulcers, high levels of distress and a confrontation coping style at baseline were less likely to have a healed ulcer by 24 weeks. The effect of confrontation coping appeared to reflect an independent pathway, while the effect of distress appeared to be related to initial ulcer size, suggesting that distressed patients may delay seeking treatmen

Stress and Wound Healing: Effects of housing conditions and coping with a psychological stress.

* Oscar Vegas[1] Joanne Vanbuskirk[2] Steven Richardson[2] David Parfitt[3] Dana Helmreich[3] Max Rempel[2] Francisco Tausk[2]
[1]Department of Basic Psychological Processes and Their Development, Basque Country University, 20018, San Sebastián, Spain
[2]Department of Dermatology and Psychiatry.University of Rochester School of Medicine601 Elmwood Avenue -Box 697. Rochester,NY
[3]Department of Psychiatry. Rochester Center for Mind-Body Research. University of Rochester Medical Center. Rochester, NY 14642
** Corresponding author: Oscar Vegas, (o.vegas@ehu.es)*

The purpose of this study was to determine the effect of a model of natural stress on the healing of cutaneous wounds, its relation to levels of corticosterone and the possible impact of differential individual coping.

Six week-old female SKH1 mice were randomly allocated to two groups: either individually housed or in groups of 4 per cage for a period of 14 days. Subsequently, half of the mice in each group were assigned to either the stressed or the non-stressed control sub-groups.

In order to address many of the contradictions in the previous studies, we set out to examine the effect of combined physical and psychological stressors on the cutaneous wound healing of female mice that had been housed in groups or in isolation. After 12 days of exposure to stressors, all mice were anesthetized and two 3 mm round wounds were placed on the shoulder blades. The wounds were measured daily.

The model of multiple ethological stressors utilized in this study (ultrasounds, predator odor and restraint) significantly increased the levels of corticosterone, but failed to dramatically alter healing of skin wounds. The results of this study provide evidence of the importance of housing conditions which in agreement with other authors shows that the positive social interactions, improve wound healing.

These data enable us to conclude that positive social interactions, improve wound healing, reduce the level of anxiety and circulating corticosterone.

Furthermore, the level of anxiety as measured by reactive behavior of immobilility, as well as the basal levels of corticosterone, are valid predictors of the evolution of wound healing.

Fluorocitrate attenuates a lipopolysaccaride-induced spinal learning deficit

* Elisabeth Vichaya[1] Kyle Baumbauer[1] James Grau[1] Mary Meagher[1]
[1]Department of Psychology, Texas A&M University, USA
** Corresponding author: Elisabeth Vichaya, (elisabeth.vichaya@tamu.edu)*

Research has shown that the spinal cord is capable of instrumental learning. A spinally transected rat can exhibit an increase in hind limb flexion duration when limb extension is associated with shock. However, prior exposure to non-contingent shock or inflammatory stimuli causes a learning deficit to develop. Research has demonstrated that pretreatment with fluorocitrate, a glial inhibitor, can protect against the development of the shock-induced learning deficit. Given that glial cells modulate the shock-induced learning deficit, we sought to determine if they also modulate a deficit induced by inflammatory stimuli, such as lipopolysaccharide (LPS). It was previously shown that systemic LPS induces a learning deficit. To verify that the observed effect was centrally and not peripherally mediated, we administered LPS (1, 10, or 100 μg) or vehicle intrathecally to spinally transected rats and tested instrumental learning 2.5 h post injection. LPS dose-dependently disrupted spinal instrumental learning. Next, we verified that LPS, like non-contingent shock, induced a long lasting deficit. Therefore, spinally transected rats were administered LPS (100 μg) or vehicle and tested for instrumental learning 24 h post injection. Even 24 h after injection, LPS induced a learning deficit. Then we sought to determine the role of glia in the LPS-induced spinal learning deficit. Spinally transected rats were administered 0.5 nmol fluorocitrate 20 m prior to LPS administration and were instrumentally tested 24 h post injection. Pretreatment with fluorocitrate attenuated the LPS-induced deficit. This demonstrates that the LPS induced learning deficit is partially mediated by glial cells.

Effects of Exercise Training on the Immune Response to Influenza Vaccination in Older Adults: A Randomized Controlled Trial

Victoria Vieira[1, 2] K. Todd Keylock[1, 3] Thomas Lowder[1, 4] William Zelkovich[1] Sara Dumich[1] Kim Colantuano[1] Kristin Potter[1] Kurt Leifheit[1] Edward McAuley[1] * Jeffrey Woods[1]

[1]Department of Kinesiology and Community Health, University of Illinois, Urbana-Champaign, IL [2]Division of Nutritional Sciences, University of Illinois, Urbana-Champaign, IL [3]Kinesiology Division, Bowling Green State University, Bowling Green, OH [4]Department of Physiology and Biophysics, University of Alabama-Birmingham, Birmingham, AL

** Corresponding author: Jeffrey Woods, (woods1@uiuc.edu)*

Introduction. Influenza infection is a significant public health problem in older adults. Unfortunately, many studies have found that older adults fail to develop protective responses after vaccination.

Hypothesis. We hypothesized that 10 months of cardiovascular exercise in previously sedentary older adults, would improve the antibody response to influenza vaccination.

Experimental Methods. In this randomized clinical trial, 145 older adults (age 60-83 yrs) were randomized to a 10 month cardiovascular (Cardio, n=75) or a flexibility/balance (Flex, n=70) exercise intervention. Four months after the start of the intervention, subjects were vaccinated with Fluzone™ and continued in the intervention. Serum samples were obtained prior to and 3, 6 and 24 weeks post-vaccination, and analyzed for antibody titer via hemagluttination inhibition (HI) assay. Here, we report on responses to the H1N1 viral strain (New Caledonia/20/99).

Results. Intent-to-treat analysis revealed that both groups responded to the vaccination with a similar protective response at 3 and 6 weeks, but not 24 weeks post-vaccination. Because prior exposure history impacts subsequent vaccine responses, we analyzed separately subjects with detectable (n=115) vs. non-detectable (n=30) pre-vaccine HI titers. Interestingly, while there were similar group responses in those with non-detectable titers ($F=0.36$; $p=0.66$), we found a significant ($F=2.8$; $p=0.04$) treatment x time interaction in those with detectable pre titers such that Cardio exhibited significantly higher HI titers at the 24 week time point.

Conclusions. Our results indicate that cardiovascular exercise improves the duration of protection of influenza vaccination in older adults that have detectable pre anti-influenza HI titers.

Supported by NIH(RO1-AG18861) to JW. Gary Munk (H.U.M.C, CDC) assisted with antibody analysis.

Effect of a Preoperative Warming Intervention on the Acute Phase Response of Surgical Stress

* V. Doreen Wagner[1] Maureen Groer[2]

[1]Kennesaw State University, WellStar School of Nursing, Kennesaw, GA [2]University of South Florida, College of Nursing, Tampa, FL

** Corresponding author: V. Doreen Wagner, (doreen1799@aol.com)*

Uncontrolled surgical stress may cause a weaker immune response that may lead to delayed wound healing. The phenomenon of unplanned perioperative hypothermia is known to expose patients to additional uncontrolled surgical stress. The aim of this experimental study was to evaluate the effect of a prewarming intervention using a forced-air warming (FAW) device versus routine care (RC) using warmed cotton blankets on the development of unplanned hypothermia, cytokine production, and endocrine responses. It was hypothesized that 1) FAW participants would experience less unplanned hypothermia than RC participants; 2) FAW participants would experience lower catecholamine and cortisol levels than RC participants; and 3) FAW participants would experience higher proinflammatory cytokine and CRP production intra- and post-operatively than RC participants.

Tympanic temperatures and blood samples were taken at 4 time intervals from each of the 28 (n = 14 each group) randomized participants that underwent routine general anesthesia surgery. Serum concentrations of CRP, cortisol and IL-1b, IL-6, TNF-a, and IFN-g, and plasma concentrations of epinephrine and norepinephrine were measured. To test the hypotheses, a repeated measures ANOVA design was used.

Though FAW was not associated with a differential endocrine or inflammatory response in this preliminary study, further study of forced air warming as a preoperative nursing intervention is warranted. The finding of higher than expected IL-6 levels in the preoperative period suggests a potential role for anxiety, an important factor in psychoneuroimmunological pathways, that could affect recovery and healing. The relationship between surgical stress, anxiety, and preoperative IL-6 deserves further study.

Neonatal lipopolysaccharide exposure alters neonatal and adulthood neuroendocrine functioning, sexual maturation and blood composition in the rodent

* Adam K. Walker[1] Tamo Nakamura[1] Deborah M. Hodgson[1]

[1]Laboratory of Neuroimmunology, Department of Psychology, The University of Newcastle, NSW, Australia

** Corresponding author: Adam K. Walker, (adam.walker@newcastle.edu.au)*

Early life stress has been shown to produce long-term changes in the functioning of physiological systems such as the hypothalamic-pituitary-adrenal (HPA) axis. The impact of early life bacterial exposure however, has not fully been elucidated. We investigated the impact of neonatal immune activation on HPA axis and sexual development. Wistar rats were administered 0.05mg/kg lipopolysaccharide (LPS) or saline (equivolume) intraperitoneally on postnatal days 3 and 5 (birth = day 1). Trunk blood was collected on a subgroup of animals 4 hours following neonatal injection and hippocampal tissue was obtained for IL-1b analysis. A second subgroup was left until adulthood, at which time animals were allocated into either a 30 minutes restraint stress or no stress condition. Blood was collected at baseline, 30, 60, 90 and 180 minutes following either condition and hippocampal tissue was obtained for IL-1b analysis. Neonatal corticosterone responses were higher for animals exposed to LPS. However, in adulthood LPS-treated rats exhibited an initial hyposecretion of corticosterone from baseline to 30 and 60 minutes, whereas saline controls displayed a hypersecretion at these time

points. For both groups these trends were reversed from 60 to 90 and 180 minutes following restraint. LPS-treated males also showed lower levels of red blood cells, white blood cells and haemoglobin, as well as reduced testicular descent compared to saline controls. Neonatal LPS exposure appears to produce long-term alterations to the neuroendocrine response to stress, blood cell composition and sexual maturation. Neonatal and adult IL-1b hippocampal concentrations will be assessed along with age at menarche between treatment groups.

The double-hit hypothesis of psychopathology: Neonatal lipopolysaccharide exposure predisposes male but not female rodents to anxiety-like behaviour following stress in adulthood

* Adam K. Walker[1] Tamo Nakamura[1] Deborah M. Hodgson[1]
[1]Laboratory of Neuroimmunology, Department of Psychology, The University of Newcastle, NSW, Australia
** Corresponding author: Adam K. Walker, (adam.walker@newcastle.edu.au)*

Research has demonstrated neonatal stress to produce permanent alterations in behaviour when exposed to a secondary stressor in adulthood, known as the double-hit hypothesis. We investigated the effect of neonatal lipopolysaccharide (LPS) exposure on adulthood anxiety-like behaviours following stress or no stress. Wistar rats were administered either LPS (Salmonella enteritidis, 0.05mg/kg, i.p.) or saline (equivolume) on postnatal days 3 and 5. In adulthood, animals were allocated to either a 3-day chronic stress paradigm, consisting of 30 minutes restraint on the first and the second days and 30 minutes isolation housing on the third day, or no stress. Following either condition, animals completed either a Hidebox/Open Field, Elevated Plus Maze or Acoustic Startle Response behavioural test, and behaviour was recorded using a computer-automated behavioural system. LPS-treated animals spent significantly less time resisting restraint compared to controls, indicative of learned helplessness (depression). Furthermore, on all behavioural tests, LPS-treated males exposed to stress in adulthood displayed a significantly increased anxiogenic profile compared to all other treatment groups. No differences were observed between LPS-treated animals not exposed to adult stress nor between neonatal treatment groups in females. LPS-treated animals exposed to adult stress also exhibited a blunted corticosterone response, whereas hypersecretion of corticosterone was observed in saline-treated controls. These results suggest that neonatal bacterial exposure can produce permanent increases in anxiety-like behaviour for males but not females. Furthermore, it exposure to a secondary stressor in adulthood appears necessary for such anxiety-like behaviour to manifest. Similarly, the neuroendocrine response to stress is perturbed in these individuals.

Interferon-α and its CNS action: from JAK/STAT signaling to behavioral impact

* Jianping Wang[1]
[1]Department of Pharmacology, University of Missouri-Kansas City School of Pharmacy, Kansas City, MO 64108
** Corresponding author: Jianping Wang, (wangjp@umkc.edu)*

Chronic interferon-alpha (IFN-α) therapy causes severe neuropsychiatric complications in humans including depression and anxiety. Rodents are used in studying the pathophysiology of IFN-α-induced CNS disturbances in humans, ranging from behavioral deficits to cellular and molecular mechanisms. However, the results have been highly controversial. With a multifaceted approach, we have found that systemic administration of mouse IFN-α but not human IFN-α, induced a robust expression of several prototypic IFN-stimulated genes (ISGs). There was a similar temporal profile in the ISG expression including signal transducers and activators of transcription (STAT) 1 in both brain and peripheral organs. In situ hybridization studies revealed that STAT1 transcripts activated by IFN-α were localized in several brain parenchymal cells including neurons. Behavioral battery showed increased anxiety profile on elevated plus-maze test in IFN-α-treated mice. In contrast to previous studies, we found that IFN-α decreased immobile time on forced-swimming test by either acute or repeated intraperitoneal injections while general activity was not altered. In addition, repeated IFN-α treatment significantly decreased the body weight gain in mice. HPLC data showed that IFN-α treatment increased tryptophan level and serotonin turnover in different brain regions. With the foregoing, we concluded that systemic IFN-α treatment can (i) stimulate the expression of IFN-α target genes in the brain, (ii) alter cerebral serotonergic neurotransmission and (iii) induce diverse behavioral alterations in mice, thereby providing an animal model for studying the neurobiology of IFN-α-induced CNS disorders in humans.

Serum Interleukin (IL)-6 and sTNF-R1 are Associated with Development of Multiple Symptoms During First 30 days of Allogeneic Hematopoietic Stem Cell Transplantation

* Xin Shelley Wang[1] Sergio Giralt[2] Qiuling Shi[1] Loretta Williams[1] Jemas Rueben[3] Charles Cleeland[1]
[1]Department of Symptom Research, The University of Texas M. D. Anderson Cancer Center, [2]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas Anderson Cancer Center, [3]Department of Hematopathology, The University of Texas Anderson Cancer Center, Houston, Texas ** Corresponding author: Xin Shelley Wang, (xswang@mdanderson.org)*

Introduction: Cancer patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) experience multiple severe treatment-related symptoms in first few weeks posttransplantation that often necessitate hospitalization. Whether an underlying common inflammatory cytokine mechanism supports the development of multiple symptoms is unknown. This descriptive study examined serum profiles of inflammatory cytokines during the development of treatment-related symptoms and aimed to provide a rationale for further study to establish a causal relationship as an intervention target for treatment-related symptoms during allo-HSCT.

Methods: We evaluated 30 patients with acute myelogenous leukemia or myelodysplastic syndrome during first 30 days of allo-HSCT. Multiple symptoms were repeatedly assessed using the M. D. Anderson Symptom Inventory (MDASI). Inflammatory cytokines (IL-1RA, IL-1β, IL-6, IL-8, IL-10, IL-12p40p70, sTNF-R1) were repeatedly measured by Luminex. Mixed modeling was used to analyze the longitudinal data.

Results: In response to conditioning and stem-cell infusion, multiple symptoms rapidly worsened, led by fatigue, poor appetite, pain, drowsiness, dry mouth, and disturbed sleep. Symptom severity and serum IL-6 peaked at the point of lowest white blood cell count (nadir), and both were significantly associated with their increased values. From baseline to nadir, serum IL-6, IL-8, and sTNF-R1 increased significantly, whereas IL-1RA and IL 12p40p70 decreased significantly. During the first 30 days of allo-HSCT, both serum IL-6 and sTNF-R1 were positively associated with significant changes in the most severe symptoms.
Conclusion: The study evidenced an association between fluctuations in serum inflammatory cytokines and the promotion of multiple symptoms during the acute phase of an aggressive cancer therapy, allo-HSCT.

Kynurenine Metabolism in Primary Murine Microglia Activated with Interferon-γ and LPS is Inhibited by Nitric Oxide
Yunxia Wang[1] Marcus Lawson[1] Jason O'Connor[1] Robert Dantzer[1, 2] * Keith Kelley[1, 2]
[1]Integrative Immunology and Behavior Program, Department of Animal Sciences, University of Illinois at Urbana-Champaign, USA
[2]College of ACES and Department of Pathology, College of Medicine, University of Illinois at Urbana-Champaign, USA
** Corresponding author: Keith Kelley, (kwkelley@ad.uiuc.edu)*
Indoleamine 2,3-dioxygenase (IDO) is a key enzyme that links systemic inflammation and depression, metabolizing tryptophan along the kynurenine pathway. In murine macrophages, nitric oxide (NO) is a potent inhibitor of IDO activity, but murine microglial cell lines are resistant. Here we tested this hypothesis in primary cultures of microglia (>95% CD11b+) from neonatal C57BL/6 mice. While neither IFN-γ (1 ng/ml) nor LPS (10 ng/ml) affected kynurenine concentration in the medium, the combination of IFN-γ and LPS induced a time-dependent reduction in kynurenine. This reduction was greatest at 24 h and was completely blocked by the iNOS inhibitor, L-NIL hydrochloride (30μM). To explore the mechanism for the reduction in kynurenine, we found that IFN-γ and LPS synergized to induce expression of steady-state transcripts for IDO by >900-fold within eight hours, as assessed by real-time RT-PCR. Similarly, microglia that were primed by IFN-γ and triggered with LPS induced abundant expression of iNOS in an identical time-course as IDO. However, L-NIL did not affect expression of IDO mRNA, whereas it fully blocked the ability of IFN-γ and LPS to induce nitrite. These data extend the concept that IFN-γ and LPS synergize to induce both IDO and iNOS and establish that NO does not affect expression of IDO mRNA in activated microglia. Instead, NO blocks the degradation of kynurenine, probably by inhibiting enzymes that act downstream of IDO to generate bioactive kynurenine metabolites. We are now exploring this hypothesis since these metabolites may be responsible for induction of depressive-like behavior induced by inflammatory stimuli. Supported by grants to KWK (MH 51569; AG 029573) and RD (MH 079829; MH 71349

Mechanisms by which interleukin-1 affects behavior and the HPA axis in rats: the roles of cyclooxygenase, the vagus nerve and brain norepinephrine.
Marek Wieczorek[1] * Adrian Dunn[2]
[1]Dept of Neurophysiology, University of Lodz, Lodz, Poland [2]Pacific Biosciences Research Center and Dept. of Psychology, University of Hawaii at Manoa ** Corresponding author: Adrian Dunn, (ajdunn@hawaii.edu)*
It is established that peripheral administration of interleukin-1 to rodents alters their behavior, increases body temperature, and activates the HPA axis and brain norepinephrine. Cyclooxygenases are involved in the behavioral, febrile, HPA and noradrenergic responses. The vagus nerve is involved in the behavioral, noradrenergic and HPA responses. However, although cyclooxygenase inhibitors prevent the febrile response, they do not prevent the HPA, noradrenergic and behavioral responses. Lesions of the central noradrenergic system impair the HPA responses, but do not block them, and the behavioral and febrile responses are unimpaired, suggesting that there may be multiple mechanisms by which IL-1 signals the brain.

We employed a rat model in which body temperature is monitored telemetrically, HPA axis function measuring plasma ACTH and corticosterone, and brain noradrenergic function by in vivo microdialysis. The cyclooxygenase inhibitor, indomethacin, prevented the increases in temperature, but only attenuated the noradrenergic and HPA responses. Subdiaphragmatic vagotomy also impaired the noradrenergic response, but did not prevent it, nor the HPA activation.

However, the combination of subdiaphragmatic vagotomy and indomethacin treatment, completely blocked the brain noradrenergic and HPA responses, suggesting that there are two independent pathways by which IL-1 activates brain norepinephrine and the HPA axis.

Preliminary experiments in mice, indicate that whereas indomethacin treatment and subdiaphragmatic vagotomy each impaired the noradrenergic and HPA responses, combination treatment completely blocked them.

Thus in both rats and mice there are two independent mechanisms by which IL-1 can activate brain norepinephrine and the HPA axis. The completeness of the blocks suggests that these mechanisms are the only significant ones.

Prenatal Exposure to Endotoxin Sensitizes Rhesus Monkeys to Exogenous Stress Throughout Infancy
* Auriel Willette[1] Gabriele Lubach[1] Martin Styner[2] John Gilmore[2] Christopher Coe[1]
[1]University of Wisconsin [2]University of North Carolina - Chapel Hill ** Corresponding author: Auriel Willette, (Willette@wisc.edu)*
INTRODUCTION: Infection during pregnancy increases the risk of developing mood and psychotic disorders in offspring. Prenatal administration of endotoxin (Lipopolysaccharide, LPS) impacts neural development in rodents, as well as physiological and behavioral reactivity. These effects may be mediated by proinflammatory cytokines such as Interleukin-6 (IL-6). A primate model was developed to assess postnatal effects of low dose LPS on neural development, as well as physiological and behavioral reactivity in stressful and non-stressful contexts. **METHODS**: Nine of 18 pregnant females were administered 4ng/kg LPS intravenously on 2 consecutive days starting on Day 125 of a 169-day pregnancy, and compared to saline-treated or unhandled controls. Offspring were longitudinally assessed for: 1) growth and motor activity; 2) temperament; 3) stress reactivity; 4) cortisol and IL-6 secretion; 5) regional gray and white matter using

MRI. **RESULTS**: Growth and motoric activity were similar, and behavior did not differ in normative situations. However, before 6 months of age, LPS-exposed infants were more emotionally reactive to handling disturbances and evinced higher IL-6 following PHA stimulation of whole blood cultures. After weaning at 6 months, these infants were less reactive during a Human Intruder Paradigm and showed reduced acoustic startle, as well as cortisol dysregulation and less PHA-stimulated IL-6. Neural analyses indicated greater white and gray matter in areas of emotional regulation. Anxious temperament was also correlated with maternal IL-6 post-LPS.
CONCLUSIONS: Prenatal endotoxemia affects neural development and predisposes monkey offspring to be emotionally and physiologically reactive in stressful environments, with consistent effects across different challenges and development.

With increasing body mass index (BMI) mental stress reduces the capacity of glucocorticoids to suppress inflammatory cytokine production in men

* Petra H. Wirtz[1] Ulrike Ehlert[1] Luljeta Emini[1] Tobias Suter[2]
[1]Department of Clinical Psychology and Psychotherapy, University of Zurich, Switzerland [2]Clinical Immunology, Department of Internal Medicine, University Hospital Zurich ** Corresponding author: Petra H. Wirtz, (p.wirtz@psychologie.uzh.ch)* **Background**: Body-mass index (BMI) and mental stress seem to exert parts of their cardiovascular risk by eliciting inflammation. However, the adverse effects of stress on inflammatory activity with BMI are not fully understood. We investigated whether acute mental stress leads to changes in the ability of glucocorticoids to downregulate monocyte inflammatory activity with increasing BMI while controlling for age and blood pressure. We measured glucorticoid inhibition of lipopolysaccharide (LPS)-stimulated release of the proinflammatory cytokine tumor necrosis factor (TNF)-a.
Methods: Forty-two men (range 21-65 years; body mass index (BMI) range 21-34 kg/m2) underwent the Trier Social Stress Test (combination of mock job interview and mental arithmetic task). Whole blood samples were taken immediately before and after stress, and during recovery up to 60 min post-stress. Glucocorticoid sensitivity of LPS-stimulated TNF-a expression was assessed in vitro with and without coincubating increasing doses of dexamethasone. Moreover, salivary cortisol was measured during the experiment and on a normal day for assessment of baseline circadian cortisol.
Results: Higher BMI was associated with lower glucocorticoid sensitivity of monocyte TNF-a production after stress (main effect of BMI:$p<0.001$) and with more pronounced decreases of glucocorticoid sensitivity following stress (interaction of stress-by-BMI:$p=0.002$). Baseline glucocorticoid sensitivity was not associated with BMI. Similarly, BMI was not associated with salivary cortisol, neither in reaction to stress nor in circadian cortisol secretion.
Conclusions: Our data suggest that with increasing BMI, glucocorticoids are less able to inhibit TNF-a production following stress. This might suggest a new mechanism linking BMI with elevated risk for adverse cardiovascular outcomes following stress.

Adiposity and IL-6 in Women Diagnosed with Breast Cancer

* Linda Witek-Janusek[1] Herbert L. Mathews[2]
[1]Niehoff School of Nursing, Loyola University of Chicago [2]Stritch School of Medicine, Loyola University of Chicago
** Corresponding author: Linda Witek-Janusek, (LJanuse@luc.edu)*
Obesity is prevalent in women diagnosed with breast cancer and many women gain weight after cancer treatment. Adipose tissue releases proinflammatory cytokines, like IL-6, which can stimulate breast cancer cell proliferation. We previously showed elevated IL-6 production by peripheral blood mononuclear cells (PBMC) of women experiencing psychological stress and mood disturbance at breast cancer diagnosis, which persisted after treatment. The purpose of this study was to determine whether adiposity contributed to IL-6 elevations in women diagnosed with breast cancer. Early stage breast cancer patients were evaluated prior to treatment and compared to women without breast cancer. Plasma IL-6, PBMC production of IL-6, and body mass index (BMI) were measured. Fifty-one percent of women with breast cancer and 58% of women without breast cancer were overweight (BMI >25 kg/m2); while 23% of women with breast cancer versus 28% of women without breast cancer met obesity criteria (BMI > 30 kg/m2). Women with breast cancer had greater plasma IL-6 levels than women without breast cancer. When plasma IL-6 levels were stratified by BMI, both overweight and obese women with breast cancer had higher plasma IL-6 than women with breast cancer with lower BMI (<25 kg/m2). IL-6 production significantly correlated ($r=0.461$; $p<0.01$) with BMI in women with breast cancer but no correlation was found in women without breast cancer. Thus, adipose tissue likely contributes to IL-6 elevations in breast cancer patients. Given the potential of IL-6 to stimulate breast cancer cell proliferation, adipose-tissue-driven inflammatory pathways may negatively impact cancer prognosis.

Glucocorticoid Receptor Expression in Children Shows Opposite Patterns of Associations with Anxiety and Depression

* Jutta M Wolf[1] Edith Chen[1]
[1]University of British Columbia ** Corresponding author: Jutta M Wolf, (juttawolf@psych.ubc.ca)*
Depression and anxiety are overlapping construct and often difficult to separate. Both have been related to dysfunctions in the hypothalamus-pituitary-adrenal axis. The present prospective study tested in healthy children and children with asthma whether depression and anxiety might have different patterns of activation at the molecular level, i.e., in terms of glucocorticoid receptor (GR) expression, which is central to cortisol signaling.

36 healthy (19m; 14±2.3yrs) and 50 children with asthma (35m; 13±2.7yrs) were assessed at two time points six months apart. Gene expression of the functional GRalpha (GRa) and the non-functional GRbeta (GRb) isoform were measured by RT-PCR at baseline and follow-up. Child anxiety (RCMAS) and depression (CDI) were measured at baseline.

Using multiple regression, we found that only in healthy children, higher levels of anxiety were associated with greater decreases over time in children's GRa and GRb expression (beta=-.64, $p<.001$; beta=-.66, $p=.007$; resp.). Contrary, higher levels of depression were

associated with greater increases over time in healthy children's gene expression (beta=.56, p=.004; beta=.53, p=.036; resp.). Children with asthma did not show any anxiety- or depression-related changes in gene expression.

The present results suggest that depression and anxiety show distinctive features at the molecular level, with decreases in GR expression in response to anxiety and increases in GR expression in response to depression. Interestingly, comparable changes in GRalpha and GRbeta expression suggest counter-balancing processes. Children with asthma, however, may have an immune system that has less flexibility in responding dynamically to negative psychosocial states, at least in terms of alterations to molecular pathways involving GR.

Disruption of the joint- immune-brain communication during experimental arthritis in the rat

* Christine Wolff[1] Anja Hahnel[1] Johannes Wildmann[2] Hugo O. Besedovsky[2] Rainer H. Straub[1] Adriana del Rey[2]
[1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, Dept. of Internal Medicine I, University Hospital Regensburg, Germany [2]Department of Immunophysiology, Institute of Physiology, Medical Faculty, Philipps University, 35037 Marburg, Germany
** Corresponding author: Christine Wolff, (christine.wolff@klinik.uni-regensburg.de)*

INTRODUCTION: Uncoupling of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) has been demonstrated in rheumatoid arthritis patients. This is evident by an over activity of the SNS and a relative low activity of the HPA axis. However, the reasons for this phenomenon and the consequences for the inflammatory disease are not known.
PURPOSE: Therefore, the purpose of this study was to investigate the time course of hypothalamic norepinephrine (NE) content and cytokine expression during the course of collagen type II - induced arthritis in the rat and to manipulate arthritis by central sympathectomy.
MATERIAL AND METHODS: Arthritis was induced in rats by injection of collagen type II in incomplete Freund\\\\\\\'s adjuvant. Brain cytokine gene expression and neurotransmitters, and parameters indicative of the disease were evaluated during arthritis development. Noradrenergic neurons in the brain were depleted with 6-hydroxydopamine
RESULTS: Depletion of noradrenergic fibres in the affected joints was detected with the start of overt arthritis. Initially increased corticosterone levels were reduced to baseline levels, and adrenaline levels were increased during the induction phase of the pathology. Hypothalamic NE content was increased from the onset of the disease. IL-1 and IL-6 were over-expressed in the hypothalamus only during the induction phase of the disease. Sympathectomy of hypothalamic noradrenergic neurons did cause anti-inflammatory effects only when applied before immunization but not in the arthritis phase.
CONCLUSION: During experimental arthritis, the two main efferent anti-inflammatory pathways under brain control - the HPA axis and the sympathetic nervous system - are disrupted.

Interleukin-2 Potentiates Behavior Activating Effects Induced by a Dopamine D1 but not D3 Receptor Agonist

R T Woodruff[1] J Magid[1] M D Bobbin[1] E Kuzhikandathil[1] * S S Zalcman[1]
[1]UMDNJ-New Jersey Medical School, Department of Psychiatry, 183 South Orange Avenue, Newark, NJ 07103, USA
** Corresponding author: S S Zalcman, (zalcmass@umdnj.edu)*

IL-2 is implicated in psychiatric disorders that involve an increased expression of repetitive motor activity, and that are associated with alterations in dopamine receptor activity. However, very little is known about the relationship between IL-2 and dopamine receptors. **Hypothesis**: A single injection of IL-2 modulates the expression of repetitive motor activity and locomotion induced by dopamine receptor agonists. **Methods**: Experiment 1: Balb/c mice received SKF (0-2 mg/kg, IP), a partial D1 agonist that stimulates repetitive motor behavior, and immediately thereafter were individually placed into a test arena (TruScan system, Coulbourn) for a 2-hr test session. Experiment 2: Determination of the effects of IL-2 pretreatment (0.4 μg, IP) on increased expression of stereotypic behavior induced by a submaximal dose of SKF. Experiment 3: Mice received PD128907 (0-0.4 mg/kg), a preferential D3 agonist that induces a biphasic (hypo- and hyper-) locomotor response. Locomotion was measured for 2-hr. Experiment 4: Determination of the effects of IL-2 pretreatment on alterations in locomotion induced by a submaximal dose of PD128907. **Results**: (1) SKF induced dose-dependent increases in the incidence and intensity of repetitive motor behavior, a major feature of which was increased grooming. (2) Pretreatment with IL-2 further augmented the effects of SKF on repetitive behavior. (3) PD128907 induced dose-dependent effects on locomotion, characterized by an initial hypo-locomotion and a subsequent hyper-locomotion. (4) IL-2 did not affect the hyper-locomotor phase induced by PD128907. **Conclusions**: IL-2 potentiates the expression of repetitive motor behavior associated with D1 receptor stimulation but not hyperlocomotion induced by a D3 agonist. [Supported by NIH grant MH074689-01].

IMPACT OF NEONATAL INFECTION ON ADULT HIPPOCAMPAL GLUCOCORTICOID RECEPTOR AND MINERALOCORTICOID RECEPTOR ABUNDANCE

* Olivia Wynne[1, 2] Jay Horvat[3, 4] Roger Smith[2] Philip Hansbro[3, 4] Vicki Clifton[2] Deborah Hodgson[1, 2]
[1]Laboratory of Neuroimmunology, University of Newcastle, Newcastle, NSW, Australia. [2]Mothers and Babies Research Centre, Hunter Medical Research Institute, Newcastle, NSW, Australia [3]Discipline of Immunology and Microbiology, University of Newcastle, Newcastle, NSW,Australia [4]Vaccines, immunology, viruses and asthma group, Hunter Medical Research Institute,Newcastle, NSW, Australia ** Corresponding author: Olivia Wynne, (olivia.wynne@newcastle.edu.au)*

Perinatal stress has been shown to alter receptor abundance in the hippocampus and modify the adult neuroendocrine stress response in a number of animal models. As yet no studies have investigated the effect of neonatal stress in the form of live infection on the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) in the mouse. Previously, we have found neonatal infection alters GR and MR mRNA abundance in the adult hippocampus. The hypothesis of the current study is that neonatal infection alters adult hippocampal GR and MR protein abundance in the adult mouse. Balb/c mice were intranasally infected at birth with Chlamydia muridarum (400 ifu) or vehicle. At nine weeks of age animals were euthanized, brains removed and frozen. The hippocampus was

removed with protein extracted using a parallel RNA/DNA/protein extraction method. Blood was taken to measure circulating corticosterone by radioimmunoassay. GR and MR protein was assessed by western blot. Preliminary analysis of the protein shows neonatally infected females to have higher levels of GR and MR protein compared to controls, while the males show no difference in protein between the treatment groups. Basal corticosterone was increased in the male treatment group and decreased in the female treatment group compared to same-sex controls. The current study demonstrates evidence of hippocampal programming and subsequent alterations to corticosterone levels in adulthood after neonatal infection. The results show for the first time a sexually dimorphic effect of neonatal infection on GR and MR. Both sexes demonstrated a reciprocal relationship between receptor abundance and circulating corticosterone.

***In vitro* Stress Hormone Glucocorticoid (GC) Exposure Alters Gene Expression on both GC and Cytokine Receptors and Cytokine Production in Normal Human PBMC**

Lianbin Xiang[1] * Gailen D. Marshall[1]
[1]Laboratory of Behavioral Immunology ResearchDivision of Clinical Immunology and Allergy
* *Corresponding author: Gailen D. Marshall, (gmarshall@medicine.umsmed.edu)*

Stress can alter cytokine production which significantly influences immune function *in situ*. Previous studies by us and others have also shown altered TH1/TH2 cytokine balance with *in vitro* stress equivalent levels of Dexamethasone (DEX) and epinephrine (EPI) after 24hr incubation and in 11day tetanus-specific PBMC cultures. In order to further understand the mechanisms associated with these effects, we studied PBMC from 13 healthy adults with 10-8M DEX or EPI incubation for changes in gene expressions of GC receptor (GCR), beta 2 adrenergic receptor (β2AR) and IL-4 receptor (IL-4R) by real time RT-PCR (2-δddCt), TH1/TH2 cytokines (IFNγ, IL-4, IL-10) by ELISA (pg/ml), and regulatory T cell populations (Treg - CD4+CD25+FoxP3+) by flow cytometry (% total CD4+). Results showed downregulation of GCR mRNA (cont 1.4, DEX 0.8; p=.0008) and IL4R mRNA (cont 2.3; DEX 1.3, p=.0015), but not β2AR after 24 hr incubation with DEX but not EPI. In contrast, after 11 day incubation with DEX, GCR mRNA increased (cont 1.0; DEX 1.5, p=.042) as did IL-4R (control 1.5; DEX 3.0, p=.004). β2AR expression trended upward in the DEX cultures (cont 1.6; DEX 2.4, p=.14). EPI had no significant effects on receptor gene expression. IFNγ/IL-4 (cont 21.4+9.2; DEX 11.7+2.5, p=.048) and IFNγ/IL-10 (cont 10.5+2.5; DEX 1.0+0.2, p=.001) ratios decreased with DEX after 11 days. Treg expression at 24 hrs decreased significantly with DEX (cont 1.34+.24; DEX 1.04+.21, p=.01). These data indicate that immunomodulatory effects of GC involve increasing the sensitivity of lymphocytes to both stress hormones and cytokines through increased receptor expression

Norepinephrine upregulates VEGF, IL-6, and IL-8 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression

* Eric V. Yang[1, 2] Seung-jae Kim[2] Elise L. Donovan[2] Min Chen[2] Amy Beickelman[2] Brian J. Hutzen[3, 4] Jiayuh Lin[4, 5, 6] Sanford H. Barsky[5, 7] Ronald Glaser[1, 2, 5, 8]
[1]Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University Medical Center, [2]Institute for Behavioral Medicine Research, The Ohio State University Medical Center [3]Graduate Program in Molecular, Cellular and Developmental Biology, The Ohio State University, [4]Center for Childhood Cancer, The Research Institute at Nationwide Children's Hospital, Columbus, OH 43205 [5]Comprehensive Cancer Center, The Ohio State University Medical Center, [6]Department of Pediatrics, The Ohio State University Medical Center, [7]Department of Pathology, The Ohio State University Medical Center, [8]Department of Internal Medicine, The Ohio State University Medical Center, Columbus, OH 43210
* *Corresponding author: Eric V. Yang, (yang.3@osu.edu)*

Recent sudies suggest that stress can be a co-factor for the initiation and progression of cancer. The catecholamine stress hormone, norepinephrine (NE), may influence tumor progression by modulating the expression of factors implicated in metastasis and angiogenesis. We tested the hypothesis that NE, a key component of the sympathetic-adrenal medullary (SAM) axis, can stimulate the aggressive potential of melanoma tumor cells by inducing the production of VEGF, IL-6, and IL-8. We examined the influence of NE on the production of VEGF, interleukin (IL)-6, and IL-8 by human melanoma tumor cell lines, C8161, 1174MEL, and Me18105. NE treatment upregulated production of VEGF, IL-6, and IL-8 by C8161 cells and to a lesser extent 1174MEL and Me18105 cells. The upregulation of protein levels was associated with induced gene expression. The effect on C8161 cells was mediated by both β1- and β2-adrenergic receptors (ARs). Nine of 10 primary and 9 of 10 metastatic melanoma biopsies examined expressed β2-AR. The data suggest that stress-related activation of the SAM axis may have a role in human melanoma tumor progression. This line of research further suggests that interventions targeting components of the activated SAM axis, or the utilization of β-AR blocking agents, may represent new strategies for slowing-down the progression of some tumors and improving cancer patients' quality of life.

Support: NCI CA100243 and The Gilbert and Kathryn Mitchell Endowment to RG, NCI CA100243-01A2S1 to EVY, and The Ohio State University Comprehensive Cancer Center Core Grant CA16058 (NCI).

Impact of chronic restraint stress during early Theiler's virus infection on CNS disease severity in SJL mice

* Erin Young[1] Amy Sieve[1] Elisabeth Vichaya[1] Luis Carcoba[1] Andrew Steelman[2] Colin Young[2] Ralph Storts[2] Tom Welsh[2] C. Jane Welsh[2] Mary Meagher[1]
[1]Texas A&M University, Department of Psychology [2]Texas A&M University, Department of Veterinary Integrative Biosciences
** Corresponding author: Erin Young, (erin.young1@gmail.com)*

Theiler's murine encephalomyelitis virus (TMEV) infection, a model of multiple sclerosis, is characterized by an acute CNS inflammatory phase followed by a chronic demyelinating disease in genetically susceptible strains of mice. Susceptibility to the chronic phase of disease has been shown to depend on a combination of genetic and environmental factors, including strain, sex, and stress exposure. Previous research from our laboratory indicates that chronic restraint stress during the first 4 weeks of infection exacerbates behavioral signs of disease in both male and female SJL mice. The present study examined the impact of sex and restraint stress exposure on spinal cord inflammation, glial activation, demyelination, and axonal loss during chronic TMEV infection. Histological analyses indicated that male SJL mice showed increased CNS inflammation, demyelination and axonal loss in the chronic phase of infection. These findings of increased CNS disease severity are in agreement with previous research from our laboratory showing significant restraint-induced exacerbation of the behavioral syndrome and motor impairment associated with chronic TMEV infection (Sieve et al., 2004). The present study provides evidence that exposure to chronic stress during the acute phase of TMEV infection subsequently augments the development of chronic demyelinating disease and that the impact of stress on disease course may be partially dependent on genetic factors such as sex. These findings may shed light on clinical findings that stress exacerbates MS disease course (Mohr et al., 2004) and that men develop more severe clinical symptoms and deteriorate more rapidly than women (Cottrell et al., 1999).

Six different promoters control IL-1RI expression in human

Hao Zhang[1] Qiming Li[1] Ying An[1] Qun Chen[1] * Ning Quan[1]
[1]Ohio State University
** Corresponding author: Ning Quan, (Quan.14@osu.edu)*

Type I Interleukin-1 receptor (IL-1RI) is the functional receptor for IL-1. IL-1 exerts all of its known biological functions by binding to IL-1RI. Two and three different promoters for IL-1RI of mouse and human respectively have been reported. In a previous study, we found an additional promoter for mouse IL-1RI. In this study, we conducted a 5' RACE to analyze the transcription initiation sites in order to determine other putative promoters for IL-1RI. Full-length cDNAs derived from 24 different tissues and organs were used. Two adaptors were added to 5'end of these full-length cDNAs. Nested PCR was performed using the adaptor sequences as 5' primers and two specific primers generated from published hIL-1RI cDNA sequence as 3' primers. Six major hIL-1RI transcript types were found. Sequence analysis shows that these six potential transcription initiation sites align to the genomic locus of IL-1RI on human chromosome 2. Five hundred bp genomic DNA fragments immediately upstream of each transcription initiation site were cloned by PCR. Six constructs were established by inserting these putative promoter fragments into the luciferase reporter vector, pGL4.10, which is employed to analyze promoter activities. Luciferase assays were performed. The putative promoters can drive expression of luciferase. This result suggests that human IL-1RI transcription is controlled by at least six promoters.

Mucosal Wound Healing: The Relationship With Human Sex Hormones

* Bahareh Zyaei[1] Christopher G. Engeland[1] Phillip T. Marucha[1, 2]
[1]Dept. of Periodontics, University of Illinois at Chicago, Chicago, IL, USA [2]Institute of Behavioral Medicine Research, The Ohio State University, Columbus OH, USA
** Corresponding author: Bahareh Zyaei, (bzyaei@gmail.com)*

Most wound healing studies have examined dermal wounds and reported a female advantage in healing rates. Recently our laboratory demonstrated women heal mucosal wounds more slowly than men (Engeland et al., Arch Surg, 141:1193-7, 2006) and with greater inflammation (unpublished observations). We hypothesized sex hormones play a role in wound healing, possibly through their modulating effects on inflammation. This study involved 384 volunteers aged 18-43 (198 men, 186 women). A 3.5mm diameter wound was created on the hard oral palate and videographed daily until healed. Tissue biopsy samples were obtained from a second longitudinal wound at 6h or 24h post-wounding and pro-inflammatory mediators were measured by real-time PCR. Circulating testosterone, progesterone and estradiol levels were determined from blood at the time of wounding. Men with higher testosterone levels exhibited significantly delayed wound closure on days 5-7 compared to individuals with lower testosterone. Interestingly, a similar relationship between healing and testosterone was observed in naturally cycling women but not in women taking oral contraceptives. Higher progesterone levels, but not stage of the menstrual cycle, were also associated with delayed closure. Preliminary results indicate that higher testosterone levels related to significantly lower tissue inflammation (IL-1β, TNF-α, IL-8) in men, but possibly to higher tissue inflammation in women (non-significant). Further data on tissue inflammation are forthcoming. This study suggests that human healing rates are modulated by sex hormones, possibly accounting for the observed gender effects. Importantly, a sexual dichotomy in how these hormones impact upon inflammation may be a critical factor in healing. (Support: NIH P01AG16321, NIH RO1DE12792, NIH P50DE13749, UIC COD)

See you next year in Colorado!

16th Annual PNIRS meeting

June 3, 2009 – June 6, 2009

Beaver Run Resort (http://beaverrun.com), Breckenridge Colorado

President: Andrew Miller

Local hosts: Mary Coussons-Read and Moni Fleshner