7th Annual
Illinois - Brain Behavior and Immunity Meeting

January 9 (1-5 pm) and 10th (8am-7pm), 2015
Hughes Auditorium in the Robert H. Lurie Medical Research Center
Feinberg School of Medicine
Northwestern University
303 East Superior Street
Chicago, IL 60611
Welcome to the 7th Annual Illinois Brain, Behavior and Immunity Meeting! This meeting continues to promote collaboration among research laboratories in Illinois and nearby locations in the field of psychoneuroimmunology, while encouraging a greater visibility of the field’s trainees. Scientists of all levels will be on hand to share their expertise and research findings in this multidisciplinary field. This year, we have a diverse array of presentation topics ranging from cancer, depression, genetics and exercise, as well as specific components of immune-modulatory pathways.

We encourage senior investigators and trainees alike to reach out and network with others you may not know, all in an effort to increase one’s awareness of other research agendas and opportunities.

This year, Keynote presentations will be given by:
Dr. John F. Sheridan, Ph.D., Professor at the Ohio State University and Associate Director of the Institute for Behavioral Medicine Research
and
Dr. Mark R. Opp, Ph.D., Professor at University of Washington and President of the Psychoneuroimmunology Research Society (PNIRS).

Also featured will be two new Assistant Professors:
Dr. Andrew J. Steelman, Ph.D., from the University of Illinois at Urbana-Champaign
and
Dr. Derek A. Wainwright, PhD. at the Northwestern University Feinberg School of Medicine.

Back again this year is the reception planned immediately after the conclusion of the formal talks Saturday evening. We envision this to be a tremendous opportunity to network, as well as initiating new scientific relationships in an informal and relaxed manner. Thank you for your continued support and we hope that you enjoy this year’s meeting!

Robert McCusker & Derek Wainwright
Organizers

Location

Hughes Auditorium in the Robert H. Lurie, 303 East Superior Street, Chicago, IL 60611
Friday Afternoon Program

1:00 - 1:55  Registration
1:55 – 2:00  Welcome: Derek Wainwright

Oral Session 1  Chair: Danielle Rendina

2:00 - 2:20  Rand T Akasheh1, Jason M York1, Jingbo Pang1, Otto Kalliokoski2, Klas Abelson2 and Giamila Fantuzzi1
1University of Illinois at Chicago, 2University of Copenhagen
Annexin A1 Mediates Hormonal and Metabolic Effects of Glucocorticoids

2:20 - 2:40  Alex Kelly, Keith W Kelley and Bob McCusker
University of Illinois Urbana-Champaign
Glucocorticoids and Inflammatory Mediators Interact to Regulate Genes Associated with Sickness and Depression-like Behavior

2:40 – 3:00  Lindsey Garfield1, Carmen Giurgescu2, Rosemary White-Traut3, Sue Carter4, Diane Holditch-Davis5, Barbara McFarlin3, Dorie Schwertz3 and Julia Seng6
Loyola University Chicago1, Wayne State2, University of Illinois at Chicago3, University of North Carolina4, Duke University5, University of Michigan6
Urban African American Women at Risk for Prenatal Depressive Symptoms: Oxytocin and Birth Weight are related to this Health Disparity

3:00 - 3:20  Albert Towers, Jay Patel, Maci Oelschlager and Gregory Freund
University of Illinois at Urbana-Champaign
Role of Caspase-1 and Dopamine Metabolism in Cognition Following Acute Calorie Restriction

3:20 - 3:35  Break

Oral Session 2  Chair: Adrienne Antonson

3:35 - 4:15  Derek Wainwright, New Faculty
Northwestern University
Targeting Tryptophan Catabolism in Brain Tumors: A Game of Whac-A-Mole

4:15 - 5:00  John Sheridan, Keynote Speaker
Ohio State University
Repeated Social Defeat Stimulates Anxiety-like Behavior: Role of Bidirectional Communication between the Brain and Immune System

6:00  Reservation for group dinner at Volare for those interested,
http://www.volarerestaurant.com/, directions at end of program
Dinner is at attendees’ expense.
Saturday Program

8:00 - 8:55  Breakfast - bagels, pastries, fruit and coffee
8:55 - 9:00  Welcome

Oral Session 3  Chair: Carlos Dostal

9:00 - 9:20  Karen Kotz Fishe, Dina Tell, Herbert L Mathews and Linda Janusek
Loyola University Chicago
Moderation of the Impact of Maternal Childhood Adversity on the Psychological-Inflammatory Profile during Pregnancy

9:20 - 9:40  Yi Sun, Brandt Pence, Novin Pishevar, Marni Boppart and Jeffrey A Woods
University of Illinois at Urbana-Champaign
Acute Eccentric or Concentric Exercise Does Not Improve Antibody Responses to Ovalbumin Vaccination in Mice

9:40 - 10:00  Dina Tell, Herbert H Mathews and Linda Janusek
Loyola University Chicago
Childhood Adversity and Inflammation: Epigenetic Profile in Women with Breast Cancer

10:00 - 10:20  Kharah M Ross, Edith Chen and Gregory E Miller
Northwestern University
Harsh Early Family Climate, Low Childhood Socioeconomic Status, and Pro-Inflammatory Phenotype in Adults

10:20 - 10:40  Break

Oral Session 4  Chair: Lijie Zhai

10:40 - 11:00  Tom Anastasio
University of Illinois at Urbana-Champaign
Computational Model of the Behavior of Microglia in the Alzheimer-diseased Brain

11:00 - 11:20  Christopher Coe, Gabriele Lubach, James Connor, Raghavendra Rao, Michael Georgieff and Pamela Kling
University of Wisconsin-Madison
Ironclad Insights into Inflammatory and Stress Responses Relevant to Maternal and Child Health

University of Illinois at Urbana-Champaign
Voluntary Wheel Running and a Diet Containing EGCG and Beta-Alanine: Effects on Cognition and Muscle Function

11:40 - 12:00  Stephen Gainey, Julie Bray, Kristin Kwakwa, Melissa Pillote, Vincent Tir, Marcus Lawson and Gregory Freund
University of Illinois at Urbana-Champaign

The Impact of High-Fat Diet Feeding on Inducing Anxiety-Like Behaviors and Mild Cognitive Impairments in a Juvenile Mouse Model with Differing Roles for the Amygdala and Hippocampus

12:00 - 1:00 Lunch

**Oral Session 5**  Chair: Desire Christensen

1:00 - 1:20  Jacob M Allen, Matthew R Panasevich, Brandt D Pence, Yi Sun, Ryan N Dilger and Jeffrey A Wood  
University of Illinois at Urbana-Champaign  
Acute Exercise Increases Short Chain Fatty Acid Concentrations in the Mouse Cecum

1:20 - 1:40  Rekha C Balachandran*, Michael B Leventhal, Paul A Eubig and Megan M Mahoney  
University of Illinois at Urbana-Champaign  
Impact of Shift Work on Attention and Female Estrous Cycling: Initial Findings in a Rat Model

1:40 - 2:00  Michael Misale, Linda Janusek and Herbert Mathews  
Loyola University Chicago  
The Relationship of the Nuclear Landscape to the Production of Proinflammatory Cytokines

2:00 - 2:45  Andrew Steelman, New Faculty  
University of Illinois Urbana-Champaign  
Galectin-9 Modulates Neuroinflammation and Promotes Remyelination

2:45 - 3:00  Coffee Break

**Oral Session 6**  Chair: Brian Leyshon

3:00 - 3:20  Stephanie M Matt and Rodney W Johnson  
University of Illinois Urbana-Champaign  
The role of Epigenetic Regulators and DNA Methylation in Aging Senescent Microglia

3:20 - 3:40  Scott E Nixon¹, Dianelys González-Peña¹, Marcus A Lawson¹, Robert H McCusker¹, Jason C O’Connor², Robert Dantzer³, Keith W Kelley¹ and Sandra L Rodríguez-Zas¹  
¹University of Illinois at Urbana-Champaign, ²University of Texas Health Science Center at San Antonio, ³University of Texas M D Anderson Health Center  
Comparing the Murine Response to Bacillus Calmette-Guérin (BCG) in Microglia and Peritoneal Macrophages by Developing a Transcriptome Response Profile

3:40 - 4:00  Andrew P Robinson¹, Jane M Rodgers¹, Elen S Rosler², Karen Lariosa-Willingham², Rachael E Persons³, Jason C Dugas² and Stephen D Miller¹  
¹Northwestern University, ²Myelin Repair Foundation, ³Medical College of Wisconsin  
IL-17A Enhances Differentiation of Oligodendrocyte Progenitor Cells
4:00 - 4:15  Christopher Coe
Editor-in-Chief, *Brain, Behavior, and Immunity*
University of Illinois at Urbana-Champaign
BBI Update

4:15 - 5:00  Mark Opp, PNIRS Presidential Lecture
University of Washington
Sleep Disruption, Cytokines and Mechanical Hypersensitivity: Bi-directional Interactions between Sleep and Pain

5:00 - 5:05  Concluding Remarks: Bob McCusker

5:00 - 7:00  Onsite beer/wine social

Acknowledgements
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Paul Eubig
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Leah Pyter

Tom Anastasio

Marian Kohut

Kimberly Stubbs

Christopher Coe

Linda Janusek, Herb Mathews

Elsevier for *Brain, Behavior and Immunity*
Participant Association

University of Illinois at Chicago

Rand Akasheh  Kayla Chase

University of Illinois at Urbana-Champaign

Jacob Allen  Tom Anastasio  Adrienne Antonson
Rekha Balachandran  Bindu Balakrishnan  Don Bradley
Angela Bustamante  John Capozzo  Megan Caputo
Carlos Dostal  Paul Eubig  Greg Freund
Stephen Gainey  Rod Johnson  Keith Kelley
Alexandra Kelly  Grace Kim  Rachel Klaren
Michael Leventhal  Brian Leyshon  Stephanie Matt
Shannon Maxey  Robert McCusker  Nnamdi Nelson
Jackie Newman  Scott Nixon  Brandt Pence
Novin Pishevar  Jennifer Rytych  Andrew Steelman
Yi Sun  Albert Towers

Hektoen Institute

Ellen Almirol  Beverly Gonzalez  Nicola Lancki
Kathleen Weber

Iowa State University

Matt Jefferson  Marian Kohut

Northwestern University

Priscilla Ambrosi  Molly Hermiller  Javier Jara
Ann B. Ragan  Andrew Robinson  Kharah Ross
Konrad Sawicki  Deborah Sindewald  Derek Wainwright
Lijie Zhai

Phyllis Adams
Centro Federal de Educação Tecnológica, CEFET-RJ
Ursula Maruyama

University of Kentucky
Ian Boggero Suzanne Segerstrom

Loyola University Medical Center
Lindsey Garfield Linda Janusek Karen Kotz Fishe
Herb Mathews Michael Misale Dina Tell
Kimberly Stubbs

University of Wisconsin-Madison
Wellington Amaral Chris Coe Danielle Rendina

The Pennsylvania State University
Christopher Engeland

Medical College of Wisconsin
Emily S. Hansen Erin C. Koester XiaoQian Liu

Marquette University
Stephen Hou

The Ohio State University
Leah Pyter John Sheridan

Rush University
Joan Swiatek

University of Washington
Mark Opp

University of Iowa
Desire Christensen
Location of the Robert H. Lurie Medical Research Center

Robert H. Lurie Medical Research Center
Directions for dinner Friday at
*Volare Ristorante Italiano*
201 East Grand Ave.
0.4 mile, 9 minute walk
West (briefly) on Superior St., south on Fairbanks Ct., west on Grand Ave.
Abstracts

Rand T Akasheh1, Jason M York1, Jingbo Pang1, Otto Kalliokoski2, Klas Abelson2, Giamila Fantuzzi1

1University of Illinois at Chicago, 2University of Copenhagen, Denmark

Annexin A1 Mediates Hormonal and Metabolic Effects of Glucocorticoids

Annexin A1 (ANXA1) mediates some of the anti-inflammatory actions of glucocorticoids. However, it is unknown whether ANXA1 also mediates hormonal and metabolic effects of these hormones. Here we investigated whether ANXA1 is necessary for exogenous glucocorticoids to alter glucose metabolism and affect the endogenous corticosterone levels in the absence of induced inflammation. Male BALB/c WT and ANXA1 KO mice received dexamethasone (5 mg/Kg) in drinking water for two weeks or as a single ip injection. Blood glucose was measured using a glucometer and plasma insulin by ELISA. Fecal samples were collected in the morning and the evening before and after dexamethasone treatment and fecal corticosterone was measured by ELISA. Populations of thymocytes were characterized by flow cytometry. ANXA1 KO mice had higher fecal corticosterone levels compared to WT mice. Dexamethasone failed to suppress fecal corticosterone levels and to induce insulin resistance in ANXA1 KO mice, although there were no differences between WT and ANXA1 KO mice in the ability of dexamethasone to reduce cellularity of the thymus. Additionally, acute administration of dexamethasone suppressed plasma insulin levels in WT but not in ANXA1 KO mice, while dexamethasone induced hyperglycemia only in ANXA1 KO mice. In conclusion, ANXA1 is an important mediator of glucocorticoids function, with ANXA1 KO mice being resistant to various hormonal and metabolic effects of dexamethasone.

Alexandra Kelly, Keith W Kelley, and Robert H McCusker

University of Illinois Urbana-Champaign

Glucocorticoids and Inflammatory Mediators Interact to Regulate Genes Associated with Sickness and Depression-like Behavior

An association between an activated immune system, sickness behaviors, and major depressive disorder (MDD) has been established. Additionally, MDD is frequently associated with elevated glucocorticoids and an elevation in tryptophan metabolism towards the production of kynurenine, via tryptophan/indoleamine-2,3-dioxygenase's (DO's: Ido1, Ido2 and Tdo2). Preclinical models suggest that DO activity within the brain plays a critical role in depression-like behaviors caused by stress and inflammation, but the role of glucocorticoids in DO regulation within the brain is unknown. Thus, we investigated the interaction between a glucocorticoid receptor agonist and inflammatory signals within the brain. Organotypic hippocampal slice cultures were prepared from C57BL/6J mice and then treated with dexamethasone (Dex) with or without pro-inflammatory mediators (LPS, poly I:C, IFNα or IFNγ). When given alone, all four of the inflammatory mediators increased Ido1 and Ido2 expression; whereas, Dex had no effect. Remarkably, Dex synergized with inflammatory mediators to further increase expression of specific Ido1 transcripts. In contrast, inflammatory mediators increased expression of pro-inflammatory markers (TNFα and IL-6), but Dex decreased their induction. Dex alone increased Tdo2 expression, a response unaltered by inflammatory mediators. These results advance the emerging hypothesis that glucocorticoids play a dichotomous role in the brain. In one role, glucocorticoids act to augment expression of Ido1, Ido2 and Tdo2, which may play a critical role in depression-like responses, while in another role, glucocorticoids elicit anti-inflammatory events needed to recover from sickness. Further defining this interaction is needed to understand the molecular basis for new treatments of MDD. Supported by RO1 MH083767 and RO1 MH1011145 to RHM and R01 SUB UT 00000712 to KWK

Lindsey Garfield1, Carmen Giurgescu2, Rosemary White-Traut3, Sue Carter4, Diane Holditch-Davis5, Barbara McFarlin3, Dorie Schwertz2 and Julia Seng6

Loyola University Chicago1, Wayne State2, University of Illinois at Chicago3, University of North Carolina4, Duke University5, University of Michigan6

Urban African American Women at Risk for Prenatal Depressive Symptoms: Oxytocin and Birth Weight are Related to this Health Disparity

Low-income African American women (AAW) report elevated prenatal depressive symptoms more often (42%) than the national average (20%). In the USA in 2012, 13% of AAW had low-birth-weight infants (<2500 grams) compared to 7% of white women. Variation in the neuropeptide oxytocin is implicated in perinatal depression, maternal behavior, stress and inflammatory responses, and potentially associated with this health disparity. The purpose of this investigation was to examine factors associated with prenatal depressive symptoms including oxytocin and birth weight in urban AAW. Pregnant AAW (N=57) completed surveys, blood draws (second and third trimester), and birth data were collected. A large number of participants reported elevated prenatal depressive symptoms in the second (n=20,35%) and third (n=19,33%) trimester. Depressive symptoms were higher in multigravidas (t(51)=2.374,p=.02), women with higher anxiety (t(47)=.71,p=.001), earlier gestational births (t(51)=.285,p=.04), and those without support of the offspring’s father (F(4,48)=2.676,p=.04). Depressive symptoms were also higher in women with low oxytocin compared to women with high oxytocin (F(2,47)=3.3,p=.05). Additionally, women with low oxytocin tended to have infants with lower birth-weights (F(2,47)=2.9,p=.06). These results demonstrate that multigravid AAW with increased anxiety and lacking the father’s support were at higher risk for prenatal depressive symptoms. Moreover, prenatal depressive symptoms were associated with lower oxytocin and earlier gestational birth. Further research is needed to clarify pathways linking prenatal depressive symptoms to altered oxytocin levels and poor infant outcomes.
Role of Caspase-1 and Dopamine Metabolism in Cognition Following Acute Calorie Restriction

Alzheimer’s disease and mild cognitive impairment are a growing concern to society. While classical thinking on the pathology of these disorders focuses on the accumulation of protein aggregates within the brain, the role of inflammation within the central nervous system is now seen as a major hallmark of these disorders, and treatments to limit inflammation are of increasing interest. We investigated the role of acute fasting, an anti-inflammatory stimulus, on learning and memory in mice. Mice that had been fasted for 24 hours before training in a novel object recognition (NOR) test showed improved memory 24 hours following training, but not at 2 or 48 hours after training. However, fasted mice showed no changes in memory 2 hours following a 24 hour fast in a novel object recognition (NOR) test. Fasting also reduced the levels of active caspase-1 and IL-1β mRNA throughout the brain. However, there was no change due to fasting in genes related to the inflammasome, a complex required for caspase-1 activity. Finally, fasting altered levels of neurotransmitters related to the dopamine system in the hippocampus, amygdala, and hypothalamus. Taken together, these data suggest that the mechanism by which calorie restriction based therapies improve learning and memory is through its anti-inflammatory effects within the CNS.

Karen Kotz Fishe, Dina Tell, Herbert L. Mathews and Linda Janusek
Loyola University Chicago

Moderation of the Impact of Maternal Childhood Adversity on the Psychological-Inflammatory Profile during Pregnancy

Women exposed to childhood adversity have greater risk for prenatal depression and poor infant outcomes. Childhood adversity may prime stress response systems increasing risk for greater psychosocial stress and elevations of proinflammatory cytokines during pregnancy. We investigated the relationship among maternal childhood adversity, poverty, and the psychological-inflammatory profile during pregnancy. We report findings from a diverse sample of healthy low risk pregnant women aged 18-40 years old. Based on federal guidelines of income and family size, 23% of the sample was currently living in poverty. Findings revealed that women exposed to greater childhood adversity had increased perceived stress, anxiety, and depression during pregnancy. Although childhood adversity did not independently associate with proinflammatory cytokines, poverty was found to be a significant moderator of the association between childhood adversity and TNF alpha in mid pregnancy and late pregnancy. That is, women living in poverty who experienced greater childhood adversity exhibited greater levels of TNF-alpha during mid and late pregnancy. In contrast, women living above the poverty guideline had virtually no association between maternal childhood adversity and TNF alpha in mid pregnancy or late pregnancy. Further, women with higher TNF alpha in the later part of pregnancy had lower birth weight infants when controlling for maternal childhood adversity. These findings suggest that the impact of childhood adversity on TNF alpha levels during pregnancy emerge in the presence of maternal poverty, with potential to disrupt fetal growth leading to infant low birth weight.

Yi Sun, Brandt Pence, Novin Pishevar, Marni Boppart, Jeffrey A Woods
University of Illinois at Urbana-Champaign

Acute Eccentric or Concentric Exercise Does Not Improve Antibody Responses to Ovalbumin Vaccination in Mice

Several published reports suggest that acute eccentric exercise can improve vaccination responses in young and old adults, especially if they are sub-optimal (Pascoe et al. Brain Behav Imm, 2014). The mechanisms are unclear but hypothesized to occur due to an inflammation-induced adjuvant effect on the immune response. In order to understand the mechanisms responsible for this effect, verification of this potential beneficial effect needs to be replicated in an animal model. PURPOSE: To determine the effects of acute eccentric or concentric exercise on the antibody response to vaccination in mice. METHODS: Balb/c male mice, aged 6 weeks (n=20) were randomized into one of three groups: concentric exercise (CON, n=7), eccentric exercise (ECC, n=6) or sedentary (SED, n=7). Initially, for the CON group, mice were exercised at 17m/min speed at +5% grade for 60 minutes on a treadmill. No electrical shock was used. The ECC group exercised at the same speed and duration but at -20% grade. After 24 hours, another bout of exercise was repeated. We have shown that this ECC protocol induces muscle damage and local inflammation in mice (Boppart et al, Am J Physiol Cell Physiol, 2011). All mice were intramuscularly inoculated in the gastrocnemius with 25μg (suboptimal dose from prior titration) of ovalbumin (OVA) and 200 μg aluminum hydroxide as adjuvant in 50μl sterile saline immediately after the second bout of exercise. Blood was collected before (pre) and one, two and four weeks after vaccination from the retro-orbital vein. Plasma anti-ovalbumin IgG was determined using ELISA procedures. RESULTS: We found a significant time main effect (p<0.001) indicating a significant increase in anti-OVA IgG at 1, 2 and 4 weeks relative to pre-vaccination. Interestingly, we found a significant time x treatment interaction (p=0.04) and a trend towards a treatment main effect (p=0.08) indicating that ECC exercise responses were blunted when compared to CON and SED, especially at the 4 week time point. CONCLUSION: We conclude, given the parameters of our study, that acute ECC or CON exercise does not improve antibody responses to vaccination in young mice when administered immediately after exercise. Future experiments will address whether acute exercise can improve vaccine responses in animals exhibiting impaired immunity (e.g. aged).
Computational Model of the Behavior of Microglia in the Alzheimer-diseased Brain

Alzheimer Disease (AD) remains a leading killer with no adequate treatment. Research implicates the brain’s immune system as a critical contributor to AD, but the complexity of the immune contribution poses a barrier to understanding. Here I describe a computational approach, based on process-analytic techniques from computer science, which can provide new insights into the inflammatory component of AD and can generate therapeutically relevant predictions. The inflammatory component of AD involves the responses of microglia to the peptide amyloid-β (Aβ), which is an inflammatory stimulus and a likely causative AD agent. The computational model represents the known interactions among 100 biological entities including the cytokines, receptors, signaling molecules, and transcription factors that together determine the microglial response to Aβ. Model analysis provides explanations for the puzzling findings that Aβ induces an anti-inflammatory and well as a pro-inflammatory response, and that Aβ is phagocytized by microglia in young but not in old animals. To explain the first puzzle, the model suggests that interferon-γ acts as an “autocrine bridge” over which an Aβ-induced increase in pro-inflammatory cytokines leads to an increase in anti-inflammatory mediators also. To explain the second puzzle, the model identifies a potential instability in signaling via insulin-like growth factor 1 that could account for the failure of old microglia to phagocytize Aβ. Using the model for simulated screens over all possible combinations of 10 selected, approved, small-molecule drugs reveals several novel drug combinations that could be effective in moving microglia from a pro-inflammatory to a phagocytic phenotype.
Ironclad Insights into Inflammatory and Stress Responses Relevant to Maternal and Child Health

Both poor nutrition and infections can compromise fetal and infant development. Our research has been investigating the mediating role of pathways associated with iron biology. Iron homeostasis is compromised by inflammation and infection, which result in reduced iron absorption by the gut as well as a sequestration of iron in macrophages and tissue. Recently, we found that even just the proinflammatory state of maternal obesity during pregnancy, without infection, can interfere with the placental transfer of maternal iron to the fetus, and results in low iron in the human neonate at delivery. We also refined a nonhuman primate model of infantile anemia to determine the consequences of iron deficiency for brain development. Because iron deficiency affects both peripheral functioning as well as brain functioning, we are evaluating novel approaches to improve iron supplementation, which may accelerate iron transport to the brain. A secondary aim is also to prevent the free iron in most oral treatments, such as ferrous sulfate, from being available to pathogenic bacteria in the gut. Currently, we are testing the efficacy of yeast biotechnically modified to express human ferritin both for treating the peripheral anemia and correcting the iron deficiency within the central nervous system. Iron biology provides a unique perspective for evaluating how dietary factors and inflammation affect infant development.

Voluntary Wheel Running and a Diet Containing EGCG and Beta-Alanine: Effects on Cognition and Muscle Function

We investigated whether voluntary wheel running and a diet containing epigallocatechin gallate (EGCG) and beta-alanine (BA) could synergistically improve cognitive and muscle performance in aged (18 mo) Balb/cByJ mice. In the first study, mice were fed control diet or a diet containing 1.5 mg/g EGCG and 3.43 mg/g BA and were given ad libitum access to a running wheel (VWR) or remained sedentary for 40 days. After 28 days of feeding, mice underwent cognitive and muscle function tests over 11 days. Following a rest day, mice were euthanized and tissues collected for analysis of gene expression. VWR, but not EGCG+BA, improved grip strength, performance on a treadmill test, and number of platform crossings during acquisition and reversal in the Morris Water Maze. VWR also altered expression of a number of genes in the hippocampus and gastrocnemius and increased neurogenesis in the former, while EGCG+BA had little effect. However, EGCG+BA reduced 4-HNE in the cerebellum, indicating that the diet may reduce oxidative stress. In the second study, mice (12 mo) were fed the same diets as above for 6 months, then underwent similar tests. EGCG+BA did not alter performance in Y-maze or active avoidance, but did increase rotarod and decrease treadmill performance. Interestingly, EGCG+BA also decreased mortality compared to control. In conclusion, VWR but not EGCG+BA has extensive effects on cognitive and muscle performance in aged mice, although the dietary intervention may reduce oxidative stress in the brain when fed short-term and may decrease mortality when fed over a longer period.

The Impact of High-Fat Diet Feeding on Inducing Anxiety-Like Behaviors and Mild Cognitive Impairments in a Juvenile Mouse Model with Differing Roles for the Amygdala and Hippocampus

We investigated the role that increased dietary fat intake from a high-fat diet (HFD) feeding (60% kcals from fat) compared to a low-fat diet (LFD) feeding (10% kcals from fat) has on obesity and obesity-associated comorbidities such as cognitive and behavioral impairments. Mice were fed a LFD or HFD for six weeks starting at 3-4 weeks of age and tested on novel object location (NOL), a hippocampal-sensitive task, and novel object recognition (NOR), an amygdala-sensitive task as well as open-field task (OFT) and elevated zero maze (EZM) in order to assess anxiety-like behaviors. After one and three weeks of HFD, NOR was impaired but was able to recover after six weeks of feeding. However, HFD did not impair mice after one week but showed impairment after three and six weeks on diet. Both the OFT and EZM mice after three weeks of HFD feeding showed reduced open exploration which did not occur after either one or six weeks on diet. Also, a reduction in the GSH:GSSG ratio occurs after three weeks of HFD feeding in both the hippocampus and amygdala but not after one or six weeks on diet. After three weeks of HFD feeding, there was an increased NE:NME ratio in the prefrontal cortex and amygdala. These data suggest a complex relationship between HFD feeding on cognition and anxiety-like behaviors with a mechanism involving imbalances in oxidative stress and neurotransmitter activity that may leave the hippocampus susceptible to prolonged HFD but allow the amygdala to recover.
The results of this investigation demonstrate the epigenetic impact of glucocorticoids on the nuclear landscape and associate such effects with a reduction of this form of immune function. Natural killer cells are the predominant producers of IFNg by human peripheral blood natural killer cells and these data suggest that the impact of glucocorticoids on natural killer cell population is due to an effect on that natural killer cell population. For the CD56 Bright population of natural killer cells, a significant increase in H3K27me3 was detected, but no effect on IFNg production was observed. CD56 Dim population of natural killer cells was localized to the nuclear periphery (consistent with the nuclear lamina). For the CD56 Bright population of natural killer cells, a significant increase in H3K27me3 and significantly decreased localization of the repressive epigenetic mark H3K27me3 and the cytoplasmic production of the proinflammatory cytokine interferon gamma (IFNg). Glucocorticoid treatment significantly increased levels of H3K27me3 and significantly decreased the effects with a reduction of this form of immune function.

**Impact of Shift Work on Attention and Female Estrous Cycling: Initial Findings in a Rat Model**

Shift work involves working beyond a traditional “9 to 5” schedule, which perturbs daily (circadian) rhythms, and is associated with poorer cognition, particularly impaired attention. Female shift workers are at risk of reduced fertility and irregular menstruation. We modeled shiftwork by testing adult, Long-Evans rats on the 5-choice serial response time task, a test of sustained attention, during their daily light or dark period 4 hours after lights turned on or off. We hypothesized that rats of both sexes tested during the light phase would be less attentive due to misaligned behavioral rhythms, and that female rats tested during the light phase would have disrupted reproductive cycles. Animals were food restricted to 85% of body weight, and sucrose pellets were used as reinforcers during testing. Control animals were not tested but were given sucrose pellets. Circadian activity patterns were assessed by quantifying running wheel activity in the home cages. We found that all tested rats aligned their behavioral rhythms to the time of the task. Thus, light-phase rats exhibited diurnal activity patterns and showed better sustained attention, contrary to our hypothesis. Both light- and dark-tested groups coordinated their activity to the time of the task, suggesting an alternate mechanism than circadian rhythm disruption for the performance differences. Control animals aligned their activity to the time reward pellets were given, confirming that scheduled meals are a powerful modulator of activity. Finally, tested and control female light-phase rats spent more time in estrous and less in proestrus, in agreement with our hypothesis.

**The Relationship of the Nuclear Landscape to the Production of Proinflammatory Cytokines**

Emotional distress is a common response to psychological stress. Such distress activates the hypothalamic pituitary adrenal axis resulting in excessive glucocorticoid production, which profoundly impacts immune function. We have modeled this effect by in vitro treatment of human peripheral blood mononuclear cells with glucocorticoids to assess the relationships between immune function and epigenetic post translational modifications. This was accomplished by evaluation of the nuclear intensity and localization of the repressive epigenetic mark H3K27me3 and the cytoplasmic production of the proinflammatory cytokine interferon gamma (IFNg). Glucocorticoid treatment significantly increased levels of H3K27me3 and significantly decreased levels of IFNg in the CD56 Bright natural killer cell population, with the relationship trending toward significance. Intensity of H3K27me3 was localized to the nuclear periphery (consistent with the nuclear lamina). For the CD56 Dim population of natural killer cells, a significant increase in H3K27me3 was detected, but no effect on IFNg production was observed. CD56 Bright natural killer cells are the predominant producers of IFNg by human peripheral blood natural killer cells and these data suggest that the impact of glucocorticoids on natural killer cell production of IFNg is due to an effect on that natural killer cell population. The results of this investigation demonstrate the epigenetic impact of glucocorticoids on the nuclear landscape and associate such effects with a reduction of this form of immune function.
Andrew Steelman, New Faculty
University of Illinois Urbana-Champaign

Galectin-9 Modulates Neuroinflammation and Promotes Remyelination

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system that causes substantial morbidity. While the etiology MS has not yet been completely defined, targeting the immune response by various therapeutic interventions has proven efficacious in reducing disease. Galectins are carbohydrate binding proteins that have received a substantial amount of recognition for their ability to modulate immune responses. Galectin-9 is reportedly increased in the brains of MS patients, although its physiological contribution to the disease course is unknown. As such, we utilized galectin-9 null mice to investigate the contribution of galectin-9 during both inflammatory demyelination and remyelination processes. We found that galectin-9 is increased in the CNS during the pathogenesis of experimental autoimmune encephalomyelitis (EAE), as well as during cuprizone intoxication where it localizes to macrophages/microglia and astrocytes. Compared to control mice galectin-9 mutant mice displayed heightened EAE severity which was associated with increased CNS infiltration of MOG-specific Th17 cells and neuropathology. However, using cell culture techniques we found that glial-derived galectin-9 did not influence the effector function or viability of Th17 cells, indicating that galectin-9 functions in the periphery to alter EAE pathogenesis. Interestingly, the absence of galectin-9 expression in the CNS was associated with delayed remyelination in both the cuprizone and lysolecithin injection models. Immunohistochemical analysis of the lesions demonstrated that while galectin-9 mutant mice have similar numbers of total oligodendrocytes within the lesion, the number of mature (CC1+) cells were reduced compared with control mice. Finally, treatment of primary mixed glial cultures with recombinant galectin-9 promoted oligodendrocyte maturation. Together, our data indicate that in response to inflammation galectin-9 becomes upregulated within the CNS, where it promotes repair.

Stephanie M Matt1 and Rodney W Johnson1,2
1Neuroscience Program, 2Department of Animal Sciences, Integrative Immunology and Behavior Program, University of Illinois Urbana-Champaign

The role of Epigenetic Regulators and DNA Methylation in Aging Senescent Microglia

Epigenetic changes to DNA have emerged as an important mechanism linking gene-environment interactions throughout the lifespan. Specifically, DNA methylation controls maintenance of genomic integrity and gene expression that is balanced in adult cells, but is shifted toward trends such as global DNA hypomethylation in aged animals. During healthy aging, changes in DNA methylation may be a critical risk factor contributing to cognitive aging and to the development of chronic age-related diseases. Notably, epigenetic alterations in peripheral cells increase the pro-inflammatory gene Il1β, but whether similar changes occur in aging microglia remains to be elucidated. Here we sought to determine whether aging-induced microglial hyperactivation represented by exaggerated pro-inflammatory cytokine gene expression was associated with DNA hypomethylation in aged microglia. Novel findings indicated that old age alone or in the presence of lipopolysaccharide (LPS) decreased methylation of the Il1β gene promoter region in primary murine microglia, in agreement with increased Il1β mRNA expression. Aged and also LPS treated microglia produced decreases in gene expression of epigenetic regulators including DNA methyltransferases, histone deacetylases, and methyl-binding proteins. Taken together, these data support a role for Il1β promoter hypomethylation and altered genetic expression of epigenetic regulators in promoting heightened microglial activation in the aged brain. Supported by NIH R01AG016710

Scott E Nixon1, Dianelys González-Peña1, Marcus A Lawson1, Robert H McCusker1, Jason C O’Connor2, Robert Dantzer3, Keith W Kelley1, and Sandra L Rodriguez-Zas1
1University of Illinois at Urbana-Champaign, 2University of Texas Health Science Center at San Antonio, 3University of Texas M D Anderson Health Center

Comparing the Murine Response to Bacillus Calmette-Guérin (BCG) in Microglia and Peritoneal Macrophages by Developing a Transcriptome Response Profile

Mice infected with Bacillus Calmette-Guérin (BCG) undergo an acute innate immune response that transitions to an adaptive immune response, represented by cellular and humoral components known to induce sickness behaviors that culminates in depression-like behavior. Genetic markers associated with the transition can be identified using transcriptome response profiles. An experiment was conducted, characterizing the transcriptome response of peritoneal macrophages and microglia from adult male C57Bl/6J mice (n=12/group) injected with 10 mg BCG i.p. or saline (Ctrl). Microglia and peritoneal macrophages were isolated 7 days post-challenge for differential gene expression of BCG versus Ctrl groups using RNA-Seq. Functional analysis via Gene Set Enrichment Analysis used the gene expression results between groups to test Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and Reactome gene sets for enrichment by cell population (FDR-adjusted p-value < 0.05). Comparing enrichment patterns across cell populations, 60 gene sets were enriched in both with 27 enriched by opposing directions of expression indicating divergent regulation. The cell populations shared up-regulation of cell cycle, interferon, and cytokine signaling pathways. Gene sets related to ribosomal activity and protein synthesis were up-regulated in microglia and down-regulated in macrophages. Neurodegenerative gene sets related through ATP synthesis, as well as proteasome complex and mitotic cell-stage regulation, were up-regulated in macrophages and down-regulated in microglia. These results indicate shared but opposing control of metabolic and protein synthesis pathways, potentially core to differential response profiles in microglia and peritoneal macrophages during behavioral transition and could be linked to depression-like behavior phenotypes.
Andrew P Robinson1,2, Jane M Rodgers1,2, Elen S Rosler3, Karen Lariosa-Willingham3, Rachael E Persons4, Jason C Dugas3, and Stephen D Miller1,2
1Department of Microbiology-Immunology, 2Interdepartmental Immunobiology, Center, Feinberg School of Medicine, Northwestern University, 3Myelin Repair Foundation, Saratoga, CA, 4Medical College of Wisconsin, Milwaukee.

IL-17A Enhances Differentiation of Oligodendrocyte Progenitor Cells.
Inflammatory signals present in demyelinated multiple sclerosis lesions affect the reparative remyelination process conducted by oligodendrocyte progenitor cells (OPCs). Interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin (IL)26 have differing effects on the viability and growth of OPCs, however the effects of IL-17A are largely unknown. Primary mouse OPCs were stimulated with IL-17A and their viability, proliferation, and maturation were assessed in culture. IL-17A-stimulated OPCs exited the cell cycle and differentiated with no loss in viability. Expression of the myelin-specific protein, proteolipid protein, increased in a cerebellar slice culture assay in the presence of IL-17A. Downstream, IL-17A activated ERK1/2 within 15 min and induced chemokine expression in 2 days. These results demonstrate that IL-17A exposure stimulates OPCs to mature and participate in the inflammatory response.