Embargoed until Nov. 17, 11 a.m. EST
Press Room, Nov. 15-19: (202) 249-4130

Contacts: Emily Ortman, (202) 962-4090
Anne Nicholas, (202) 962-4060

Brain's Inflammatory Response in Overdrive May Contribute to Common Brain Disorders

Depression, fatigue, and Alzheimer's disease are among identified conditions

WASHINGTON, DC — When the brain's protective inflammatory response, activated by injury or disease, lasts for too long, it can contribute to debilitating mental and physical problems, according to research released today. These early findings advance knowledge about the link between brain inflammation and the progression of many common brain illnesses and disorders and suggest possible targets for future treatments. The findings were presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Inflammation is a protective reaction that aids in the quick repair and regeneration of damaged brain cells. If it continues for too long, however, inflammation does more harm than good, damaging neurons and contributing to brain disorders such as depression, traumatic brain injury, Alzheimer's disease, Parkinson's disease, and certain types of fatigue. Thus, understanding how to keep inflammation in check is a major goal of neuroscience research.

Today's new findings show that:

- Inflammation in pregnant women due to infection or stress correlates with weaker connections between certain brain regions in their infant children (Claudia Buss, PhD, abstract 584.02, see attached summary).
- Feeding mice an inflammation-causing high-fat diet during pregnancy increases depression-like behavior in the mothers and their offspring (Staci Bilbo, PhD, abstract 545.19, see attached summary).
- A new imaging "tracer" offers clinicians a tool for following the progression of inflammation-related changes in the brain associated with Alzheimer's disease, perhaps enhancing the ability to diagnose and monitor the disease (Cynthia Lemere, PhD, abstract 385.06, see attached summary).
- A new lab technique is helping scientists better understand how inflammation leads to fatigue (Mary Harrington, PhD, abstract 545.20, see attached summary).
- Estrogen-producing cells in the brains of songbirds help inhibit inflammation, perhaps limiting neural damage after a brain injury (Colin Saldanha, PhD, abstract 640.09, see attached summary).

"The findings from these studies are helping scientists develop a deeper understanding of the crucial role that neuroinflammation plays in the progression of degenerative brain diseases," said Margaret McCarthy, PhD, an expert in neuroendocrinology at the University of Maryland in Baltimore. "It's an exciting and rapidly developing field of study, and one that promises to lead to new therapies for treatment and prevention."

This research was supported by national funding agencies such as the National Institutes of Health as well as other private and philanthropic organizations. Find out more about inflammation and its role in brain diseases at *BrainFacts.org*.

Related Neuroscience 2014 Presentation:
Symposium: Infiltration of Innate Immune Cells Into the Injured, Infected, or Inflamed Brain
Wednesday, Nov. 19, 8:30–11 a.m. Ballroom B, WCC

###

Abstract 584.02 Summary

Lead Author: Claudia Buss, PhD +49 30 450 529 224
Charité – University Medicine Berlin claudia.buss@charite.de
Berlin

Increased Inflammation in Mothers During Pregnancy Linked to Decreased Maturity in Baby's Brain Wiring

Weakened neural connections similar to those associated with psychiatric problems in adults

Increased inflammation in pregnant women, which can be triggered, for example, by exposure to stress or infection, may shape the development of their child's brain, according to a study released today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Previous research has suggested that many of the alterations in brain structure and connectivity associated with neuropsychiatric disorders can be traced back to conditions in the womb," said lead author Claudia Buss, PhD, of Charité – University Medicine Berlin. "Our research demonstrates that a specific elevated immune response experienced by some women during pregnancy may affect key aspects of the child's brain development."

Buss and her colleagues analyzed blood samples collected from 58 mothers in early, mid-, and late pregnancy to determine their levels of the cytokine interleukin-6 (IL-6), a protein that stimulates the body's immune response to infections and stress. Then, using functional magnetic resonance imaging (fMRI) technology, the researchers acquired brain scans of the women's newborns during natural sleep to detect and measure brain activity patterns.

An analysis of the data revealed that IL-6 concentrations during pregnancy, particularly during early pregnancy, predicted weaker connections between specific regions of the newborns' brains. These weaker connections were similar to those that have been previously associated with psychiatric problems in adults. The study's findings may one day lead to the development of diagnostic and treatment approaches to detect, prevent, and reduce the likelihood of mental health problems in at-risk individuals.

Research was supported with funds from the National Institute of Mental Health and National Institute of Child Health and Human Development.

Scientific Presentation: Tuesday, Nov. 18, 1–3:45 p.m., Room 147B

584.02. Maternal interleukin-6 concentrations during pregnancy and newborn functional brain connectivity
C. BUSS[1], A. M. GRAHAM[2], M. D. RUDOLPH[2], J. RASMUSSEN[3], S. ENTRINGER[1], P. D. WADHWA[3], D. A. FAIR[2]; [1]Charité Univ. Med. Berlin, Berlin, Germany; [2]Oregon Hlth. & Sci. Univ., Portland, Ore.; [3]UC Irvine, Irvine, Calif.

TECHNICAL ABSTRACT: Maternal gestational psychosocial and immune stress increases offspring risk for psychiatric disorders. Inflammatory cytokines represent a likely mediator for effects of maternal prenatal stress and inflammation on the developing fetal brain with implications for subsequent mental health. Maternal interleukin-6 (IL-6) is of particular interest due to evidence for increased concentrations in response to psychosocial stress and infection and its capacity to both cross the placenta and stimulate placental cytokine production. However, effects of maternal IL-6 during pregnancy on the fetal brain have not been reported in humans. We examined maternal IL-6, measured in each trimester of pregnancy, as a predictor of functional brain network strength in neonates (N=58, M=26.3 days, SD=13.2 days). We focused on the default mode network (DMN), as it appears to be influenced by events prior to term gestational age (e.g., preterm birth), and is associated with mental health status in children and adults. Higher average gestational maternal IL-6 was associated with weaker DMN connectivity involving the posterior cingulate cortex (PCC), dorsal and subgenual medial prefrontal cortex (MPFC), and bilateral lateral parietal cortex. Especially during the first trimester of pregnancy, higher maternal IL-6 was associated with weaker newborn PCC to MPFC connectivity. This research provides support for the role of maternal gestational immune activation in offspring risk for psychiatric disease via effects on functional brain organization, particularly during the first trimester of pregnancy.

Abstract 545.19 Summary

Senior Author: Staci Bilbo, PhD (919) 681-7005
Duke University staci.bilbo@duke.edu
Durham, N.C.

Maternal Diet During Pregnancy Connected to Weight and Behavior of Offspring

Animal studies also identified an increased depression-like behavior in mothers that consumed high-fat diets

The offspring of mothers that consumed inflammation-causing high-fat diets during pregnancy and breastfeeding weighed more and showed increased depression-like behaviors as adults, according to new animal research presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Maternal obesity during pregnancy can 'program' children for increased obesity themselves, thus setting in motion a vicious cycle of ongoing health problems," said senior author Staci Bilbo, PhD, of Duke University in Durham, N.C. "Our research suggests that these health problems include anxiety and depression, for both mothers and their children, and hyperactivity for male offspring."

Obesity has reached epidemic proportions in many areas of the world, with more than 1 billion people overweight or obese, including more than 40 million children, according to the World Health Organization. In the United States, 69 percent of adults are overweight and 35 percent are obese.

Previous animal research by Bilbo and her colleagues has suggested that the depression, anxiety, and other negative behavioral effects associated with diets high in fat and supplemented with branched-chain amino acids (BCAAs) — proteins that are found in high quantities in meat, dairy products, and other protein-rich foods — may be related to increased inflammation of brain cells. In their new study, Bilbo and her colleagues put groups of pregnant mice on different diets, including one that was both high in saturated fat and supplemented with BCAA.

The researchers found that the pregnant mice on the BCAA-supplemented, high-fat diet displayed depressive-like behavior one week after giving birth. In addition, the offspring of the animals on a high-fat diet showed increased depression- and anxiety-like behavior when they reached adulthood — even if they were put on a low-fat diet immediately after weaning or if their mothers' high-fat diet had not been supplemented with BCAAs. Hyperactivity was also observed in male, but not female, offspring, suggesting that the long-term effects of a mother's diet during pregnancy and breastfeeding may affect female and male offspring differently.

Research was supported with funds from the Duke University School of Nursing and a Duke University Brain and Society Bass Connections Fellowship.

Scientific Presentation: Tuesday, Nov. 18, 10–11 a.m., Halls A-C

545.19, Developmental programming of body weight, neuroinflammation, and behavior by Western diets
M. G. WILEY[1], J. L. BOLTON[2], L. A. SIMMONS[3], B. RYAN[2], S. TRUONG[2], **S. D. BILBO[2]**; [2]Psychology and Neurosci., [1]Duke Univ., Durham, N.C.; [3]Duke Univ. Sch. of Nursing, Durham, N.C.

TECHNICAL ABSTRACT: Obesity is now a multigenerational epidemic. Alarmingly, maternal obesity during gestation/lactation can "program" offspring long-term for increased obesity themselves, along with increased vulnerability to mood disorders. Emerging evidence suggests that this programming by perinatal diet is propagated via inflammatory mechanisms specifically linked to two components that are enriched in a "Western" diet: saturated fatty acids and branched-chain amino acids (BCAAs). We have previously shown that maternal high-fat diet (HFD) can "prime" microglia, the primary immune cells of the brain, and result in elevated levels of proinflammatory cytokines within the hippocampus of adult offspring, in conjunction with increased anxiety. BCAAs are known to compete with tryptophan transport across the blood-brain barrier, thus resulting in decreased serotonin production and increased anxiety. In the current study, we tested the hypothesis that the HFD and BCAA dietary components would synergize to result in exacerbated brain and behavioral consequences in offspring. We placed female mice on one of four diets: 1) high-fat diet (HFD), 2) low-fat diet (LFD), 3) HFD supplemented with BCAA (HFD+BCAA), or 4) LFD supplemented with BCAA (LFD+BCAA) for six weeks prior to breeding, resulting in the following weight pattern: HFD+BCAA > HFD = LFD+BCAA > LFD. HFD+BCAA dams had pups with significantly lower birth weights, and qPCR analysis of offspring brains at postnatal day (P)1 revealed that HFD and HFD+BCAA pups had

decreased expression of microglial markers (e.g., Iba-1, CD11b), suggesting that microglial colonization and maturation may be delayed or altered in these groups. At weaning (P28), HFD pups weighed more than LFD pups, whereas both BCAA groups weighed significantly less. Despite placement on a LFD at weaning, HFD and HFD+BCAA offspring showed signs of increased anxiety- and depressive-like behavior as adults. Analyses are currently ongoing to determine whether microglia are primed long term by these perinatal diets, as well as whether peripheral infiltrating macrophages play a role in the neuroinflammation of the adult offspring (as has been observed in other models), and what, if any, are the consequences for the serotonergic system. In sum, perinatal diet, particularly HFD, can program body weight, microglial development and behavior of offspring into adulthood.

Abstract 385.06 Summary

Senior Author: Cynthia A. Lemere, PhD (617) 525-5214
Brigham and Women's Hospital; Harvard Medical School clemere@partners.org
Boston

New Imaging 'Tracer' Shows Progression of Brain Inflammation

Technology may offer tool for monitoring Alzheimer's disease development and progression

Scientists report they have developed a new radioactive "tracer" to observe inflammation-related changes in the brain. They used the tool to monitor changes in Alzheimer's disease model mice, suggesting it might one day be useful in diagnosing and monitoring the disease. This research was presented at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

When brain cells become inflamed — as they do in patients with Alzheimer's disease — immune cells called microglia increase the expression of a protein, known as TSPO. The researchers developed a "tracer" molecule called [18F]-GE180 that binds to TSPO and can be imaged with positron emission tomography (PET) technology.

In this new study, scientists injected the TSPO tracer into the bloodstream of mice and then performed a PET scan for each animal. They found that the tracer showed much more activity in the brains of Alzheimer's-like mice than in the brains of non-diseased mice, specifically in the cortex and hippocampus, brain regions deeply involved with memory. This suggests that the new TSPO tracer may one day be a useful tool for following progression of this disease and others affected by neuroinflammation.

"One of the advantages of this new tracer is that it has high uptake and very specific binding in the brain," said senior author Cynthia Lemere, PhD, of Brigham and Women's Hospital and Harvard Medical School in Boston. "That makes it particularly helpful, for it means we're actually observing the tracer's signals during the PET scan and not signals from other molecules unrelated to inflammation."

Research was supported with funds from General Electric Healthcare.

Scientific Presentation: Monday, Nov. 17, 1–3 p.m., Room 152B

385.06, Imaging neuroinflammation in mice using the 18F-GE180 TSPO PET tracer
B. LIU[1], K.X. LE[1], M.-A. PARK[2], S. WANG[2], A.P. BELANGER[2], S. DUBEY[2], P. HOLTON[2], V. REISER[3], P. JONES[3], W. TRIGG[3], M.F. DI CARLI[2], **C.A. LEMERE**[1]; [1]Dept. of Neurol., Ctr. for Neurologic Diseases, Brigham & Women's Hosp. and Harvard Med. Sch., Boston, Mass.; [2]Radiology, Dept. of Radiology, Brigham & Women's Hosp. and Harvard Med. Sch., Boston, Mass.; [3]GE Healthcare, Amersham, United Kingdom

TECHNICAL ABSTRACT: Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Neuroinflammation is thought to play an early and important role in AD pathogenesis. The ability to detect microglial activation *in vivo* in patients may allow for selective monitoring of the progression of neuroinflammation as well as to assess efficacy in therapeutic trials. The 18 KDa translocator protein (TSPO), a marker for activated microglia, has been used as a positron emission tomography (PET) tracer target to reflect cerebral inflammation *in vivo* in human and transgenic (Tg) mouse models. In this study, we utilized the ^{18}F-labeled GE180 PET tracer, a new TSPO ligand, to investigate the differences in neuroinflammation between young wildtype (Wt, 4 mo-old, n=4), old Wt (26 mo-old, n=4), and old AD Tg mice (26 mo-old, n=4). *In vivo* PET imaging revealed an overt age-dependent elevation in whole brain uptake of ^{18}F-GE180 (peak-uptake and retention) in Wt mice from 4 months to 26 months of age and a significant increase in whole brain uptake of ^{18}F-GE180 in old APP/PS1 mice compared to either old or young Wt mice. A similar result was observed in hippocampal-specific uptake of ^{18}F-GE180 (old Tg > old Wt > young Wt) using co-registration of PET images with mouse brain MRI, suggesting that both aging and AD pathogenesis result in an increase in neuroinflammation. Quantitative analysis of ^{18}F-GE180 binding in cortex and hippocampus in 1 mm mouse brain slices by *ex vivo* PET and autoradiography (AR) further confirmed the *in vivo* PET results. The $SUV_{75\%}$ was determined to define the specificity of ^{18}F-GE180 uptake in the cortex and hippocampus, and revealed that old Wt mice had significantly enhanced uptake and specific binding of ^{18}F-GE180 compared to young Wt mice and that old APP/PS1 Tg mice had an even higher uptake and binding compared to all Wt mice. The specificity of ^{18}F-GE180 uptake in the brain was further confirmed by our *in vivo* cold tracer competition study, in which ^{18}F-GE180 labeling was dramatically reduced by pre-injection with unlabeled ("cold") GE180. In addition, we examined GE180 metabolites in 4-month-old Wt mice and found that even though total radioactivity declined over 2 hours, of the remaining radioactivity, ~90% was parent GE180. Taken together, our studies indicate that GE180 has potential as a novel PET tracer for neuroinflammation and may be useful for diagnosis, disease progression and monitoring treatment effects in human neurodegenerative diseases and animal models.

Abstract 545.20 Summary

Senior Author: Mary Harrington, PhD (413) 585-3925
Smith College mharring@smith.edu
Northampton, Mass.

Lab Technique May Lead to Better Understanding of the Fatigued Brain

Animal study shows fatigue from brain inflammation found to worsen with age

A procedure that induces fatigue in mice by activating the immune system has produced new insights into the underlying neural mechanisms that trigger fatigue, a common and often disabling symptom, according to research presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"It's important to have a method to induce fatigue in mice so that we can develop better clinical treatments," said senior author Mary Harrington, PhD, of Smith College in Northampton, Mass. "With this new procedure, we can now identify the brain cells that generate fatigue in mice and are beginning to map the brain pathways by which inflammation in the brain leads to that fatigue."

It's estimated that more than one-third of the workforce in the United States has experienced fatigue lasting longer than two weeks, costing employers more than $100 billion every year. Chronic fatigue is also common in people with neurological disorders. Up to 40 percent of people with Parkinson's disease and multiple sclerosis, for example, cite fatigue as being the most disabling symptom of their disease.

The procedure developed by Harrington and her colleagues uses the cytokine IL-1 to initiate fatigue in mice without other symptoms, thus allowing researchers to explore the brain pathways related specifically to fatigue. With the procedure, Harrington and her team have recently discovered that the fatigue associated with inflammation within the mouse brain gets worse with age and that it does not require, as was previously suspected, a reduction in the activity of orexin neurons, which play a big role in keeping the brain alert and awake.

Research was supported with funds from the National Institute of Nursing Research.

Scientific Presentation: Tuesday, Nov. 18, 11 a.m.–noon, Room 147B

545.20, Inflammation-induced fatigue: exploring neurobiological mechanisms and potential treatments
D. BONSALL[1], H. KIM[1], A. M. PETRONZIO[1], P. C. MOLYNEUX[1], T. E. SCAMMELL[2], **M. E. HARRINGTON[1]**; [1]Smith Col., Northampton, Mass.; [2]Beth Israel Deaconess Med. Ctr., Boston, Mass.

TECHNICAL ABSTRACT: The induction of fatigue is a common response of an animal to systemic challenge by pathogens. This response is in part mediated through action of the pro-inflammatory cytokine interleukin-1 beta (IL-1). We have characterized a dose of peripherally-administered IL-1 that can reduce wheel-running and general locomotor activity in middle-aged (6-12 mo) C57Bl/6 mice, without induction of other signs of sickness, such as fever, muscle ache or anhedonia (as measured with abdominal temperature probes, pre-treatment with the analgesic buprenorphine and through sucrose preference respectively). Here we report our studies of the effects of IL-1 on two possible candidate pathways implicated in fatigue, the orexin-containing neurons of the lateral hypothalamus and the circadian rhythmic neurons in the suprachiasmatic nucleus (SCN), as well as the impact of several possible pharmacological treatments. Prior research has shown that lipopolysaccharide (LPS)- and chemotherapy-induced reductions in general locomotor activity were associated with fewer Fos-positive orexin neurons and could be reversed by the intracerebroventricular (i.c.v.) administration of orexin (1,2). Here we first replicate prior work showing reduced wheel use in orexin-/- mice. We further demonstrate reduced wheel-running activity (normalized to baseline) following intraperitoneal (IP) administration of 400ng IL-1 in middle-aged male and female orexin-/- mice, equivalent to the response seen in wild-type controls. This suggests that orexin is not necessary for IL-1-induced reductions in wheel running. Given that patients with fatigue show dampened daily cortisol rhythms and disruptions in sleep-wake cycles, we hypothesized that fatigue may be associated with deficits in circadian output from the SCN. We used mPer2luc/+ mice (3) to show altered SCN responses to shifted light-dark cycles following chronic administration of IL-1. Our results suggest that following IL-1 administration, the SCN's ability to drive coordinated output rhythms may be impaired. Given that the availability and success of therapeutic treatments for fatigue is currently limited, we examine the effectiveness of three potential clinical treatments in our animal model of fatigue. These include the stimulants modafinil and methylphenidate, as well as the histamine H3 inverse agonist/antagonist pitolisant. We demonstrate the varying success of different potential treatments in restoring locomotor activity following IL-1 administration. These studies will allow us to determine possible neural pathways through which IL-1 induces fatigue. 1. Grossberg et al., J Nsci (2011) 31:11376-86. 2. Weymann et al., Brain Behav Immun (2014) 37:84-94. 3. Yoo et al. PNAS (2004) 101:5339-5346.

Abstract 640.09 Summary

Co-Author: Colin Saldanha, PhD (202) 885-2156
American University saldanha@american.edu
Washington

Specialized Brain Cells Produce Estrogen That Protects Neurons After Injury

Process inhibits cell-damaging inflammation in brains of songbirds

Researchers have uncovered new information on how certain estrogen-producing cells in the brains of songbirds reduce inflammation that leads to neural damage after a brain injury, according to a study released today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"We've known for a while that the brain can protect its neurons from the chronic consequences of a brain injury by synthesizing estrogen in glial cells," said co-author Colin Saldanha, PhD, of American University in Washington, DC. "But until now, how this protective process works hasn't been well understood."

As previous research has shown, when neurons become damaged from either injury or disease, the brain secretes small proteins called cytokines, which trigger an inflammatory response. The response is beneficial at first because it activates the immune system, but chronic inflammation can damage neurons and lead to memory, mood, and movement problems. Stopping that inflammation is therefore a key focus of neuroscience research.

Through a series of experiments, Saldanha and his colleagues found that certain glial cells in the songbird brain respond to an injury by rapidly and dramatically producing a protein (aromatase) that is vital for estrogen production. The estrogen appears to lower cytokines to normal levels, thus preventing chronic inflammation. Interestingly, the particular inflammatory cytokine most affected by the estrogen was different in the male and female brain, which suggests the hormone's anti-inflammatory role may work in sex-specific ways.

Research was supported with funds from the National Institute of Neurological Disorders and Stroke.

Scientific Presentation: Tuesday, Nov. 18, 1–2 p.m., Halls A-C

640.09, Estradiol, synthesized by reactive glia, is a potent anti-inflammatory in the injured vertebrate brain
A.L. PEDERSEN, L.H. NELSON, **C.J. SALDANHA**; Biology, Psychology, & Ctr. for Behavioral Neurosci., American Univ., Washington, D.C.

TECHNICAL ABSTRACT: Neuroinflammation following traumatic brain injury (TBI) may have detrimental and beneficial effects that likely differ between the acute and chronic periods post-trauma. In birds and mammals, traumatic brain injury increases the expression of cytokines in microglia and aromatase (estrogen synthase) in astroglia. In the songbird, TBI-induced synthesis of estrogens by glial aromatization is neuroprotective as aromatase inhibition and replacement with estradiol (E2) exacerbates and mitigates the extent of damage and apoptosis, respectively. The effect of glial estrogens on inflammation, however, remains unstudied. We hypothesized that induced astrocytic aromatization may affect neuroinflammation following TBI via the synthesis of neural E2 around the site of damage. In three separate experiments on adult zebra finches (Taeniopygia guttata) of both sexes we tested the influence of (a) mechanical TBI, (b) inhibition of induced aromatase expression, and (c) inhibition of induced aromatase with central E2 replacement on the expression of the pro-inflammatory cytokines TNFα, IL-1β, and IL-6, and aromatase. At 2hr post-injury, in both sexes, TBI increased ($p<0.05$), and tended to elevate, TNFα and IL-1β, respectively. At 24hr post-injury, also in both sexes, cytokines appeared to have returned to baseline, but aromatase was robustly elevated in the lobe that sustained TBI ($p<0.01$). Pharmacological inhibition of induced aromatization resulted in persistent neuroinflammation, as administration of fadrozole increased IL-1β (in females ($p=0.0007$)) and TNFα (in males ($p=0.0003$)) 24hr following TBI. This prolonged neuroinflammation following aromatase inhibition appears to be due to a failure to synthesize E2 locally, since E2 replacement lowered TNFα and IL-1β relative to fadrozole alone ($p<0.01$). IL-6 was not affected by TBI, aromatase inhibition or E2 replacement in either sex. These data suggest that astrocytic E2 synthesis following TBI is a potent and inducible anti-inflammatory signal, with specific modulation of discrete cytokine signaling. Induced neural provision of E2 following damage and compromise of central pathways may protect the brain from the deleterious effects of prolonged neuroinflammation.