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Studies Show How Diet and Obesity Alter Brain and Behavior

Scientists reveal exciting insights related to Parkinson's, depression, and other brain disorders

WASHINGTON, DC — Research released today on the effects of diet on different areas of the brain offers important insights into neurodegenerative disorders, including Parkinson's disease and depression. The research also sheds new light on how nutrition during pregnancy may alter children's brains in ways that promote obesity. 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.

The emotional and financial burden of neurodegenerative diseases and obesity on individuals, families, and societies around the world is significant. Health officials estimate that 6.3 million people have Parkinson's disease and 350 million people have depression. In addition, obesity has been declared a growing global epidemic by the World Health Organization. More than 1 billion people are currently overweight or obese, including more than 40 million children. Obesity is a major risk factor for a variety of illnesses, including some that affect the brain, such as stroke and dementia.

Today's new findings show that:

- Being overweight or obese is associated with shrinkage of an area of the brain involved in long-term memory in cognitively healthy older adults (Nicolas Cherbuin, PhD, abstract 19.04, see attached summary).
- Prenatal exposure to a high-fat diet results in altered brain wiring in young monkeys, a finding that suggests exposure to a high-fat diet in the womb may alter children's eating habits later in life (Heidi Rivera, abstract 290.04, see attached summary).
- The consumption of a high-fructose diet in adolescent rats exacerbates depressive- and anxiety-like behavior and affects the brain's response to stress, a finding with implications for adolescent nutrition and development (Constance Harrell, abstract 80.11, see attached summary).
- The "hunger hormone" ghrelin plays a pivotal role in helping a calorie-restrictive diet reduce brain-cell damage associated with Parkinson's disease in rats, a finding that suggests a possible new approach to treating the disease (Jacqueline Bayliss, abstract 138.08, see attached summary).

"The findings from today's studies demonstrate the complex effects that diet and obesity have on brain health, mental function, and behavior," said Ralph DiLeone, PhD, of Yale University, an expert in the neurobiological mechanisms associated with diet and obesity. "By deepening our understanding of those relationships, today's discoveries may eventually lead to better treatments for many neurological disorders."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find out more about diet, obesity, and the brain at *BrainFacts.org*.

Related Neuroscience 2014 Presentation:
Minisymposium: Is There a Neurological Basis for Food Addiction?
Wednesday, Nov. 19, 8:30–11 a.m., 146AB, WCC

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Abstract 19.04 Summary

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Findings Suggest Possible Link Between Obesity and Cognitive Decline

Obesity associated with smaller hippocampus in older adults

Being overweight or obese is associated with brain shrinkage in cognitively healthy older adults, according to research 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.

"Our study's findings provide important evidence indicating that being overweight or obese is associated with poorer brain health in older adults," said lead author Nicolas Cherbuin, PhD, of the Australian National University in Canberra. "The results further underscore the importance of reducing the rate of obesity through education, population health interventions, and policy."

Shrinkage of the hippocampus — an area of the brain that plays a critical role in long-term memory — is a hallmark of cognitive decline. One possible mechanism for that shrinkage is chronic inflammation, which animal studies have shown rises and falls with the increase or decrease of fat tissue.

To investigate whether being overweight or obese is associated with shrinkage of the hippocampus, Cherbuin and his colleagues followed 420 cognitively healthy adults aged 60-64 years who were participating in a large prospective study on aging. At the start of the study and twice more — at years four and eight — the participants had their body-mass index assessed. They also underwent a brain scan to measure the size of their hippocampus.

The researchers found that having a higher BMI was associated with a smaller hippocampus at the study's first assessment. In addition, greater shrinkage of the hippocampus was observed over the follow-up period among those participants with higher BMIs at the start of the trial, even after controlling for such factors as age, gender, education, diabetes, hypertension, smoking, and depression. These findings suggest that obesity may play a role in brain-structure changes linked to cognitive decline and dementia.

Research was supported with funds from the Australian National Health and Medical Research Council, the Australian Research Council, the Dementia Collaborative Research Centre – Early Detection and Prevention, and the Australian National Computing Infrastructure.

Scientific Presentation: Saturday, Nov. 15, 1–3 p.m., Room 150B

19.04, Obesity and being overweight is associated with hippocampal atrophy: the path through life study
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TECHNICAL ABSTRACT: Objectives: Investigate whether being overweight/obese or having an increasing body weight is associated with hippocampal atrophy. Methods: Participants were 420 unimpaired (MMSE>26) individuals aged 60-64 years, living in the community and taking part in a large prospective study of aging over an 8-year follow-up period. Body mass index (BMI) was computed with self-reported measure of height and weight with the formula weight (kg)/height x height (m2). High-resolution T1-weighted MRI scans were acquired on a 1.5T scanner at each assessment. Left and right hippocampi were manually traced by expert neuroscientists according to an established and published protocol. Multi-level analyses assessing the relationship between BMI and hippocampal atrophy over 8 years were conducted. Hippocampal volumes were adjusted for intra-cranial volume differences. Covariates, including sex, education, diabetes, physical activity, plasma cholesterol, hypertension, depression symptomatology and medication, and smoking, were controlled for in the analyses. Results: At baseline BMI was negatively associated with left (estimate per each unit above 25: -10.65mm3; SE 4.81; p=0.027) and right (estimate: -8.18mm3; SE 4.91; p=0.097) hippocampal volume. Over the follow-up period, those with a higher BMI experienced greater hippocampal atrophy in the left (p=0.001) but not right (p=0.058) hippocampus. Each 2-point increment on the BMI measure at baseline was associated with a 7.2% decrease in left hippocampal volume (0.9%/year) over the follow-up period. Individual change in BMI was not found to be significantly associated with hippocampal atrophy. Conclusions: After controlling for age, gender, education, diabetes, hypertension, depressive symptomatology and medication, plasma cholesterol, and smoking, being overweight/obese was found to be associated with smaller hippocampal volumes at baseline and greater hippocampal atrophy over 8 years in cognitively intact individuals.

Abstract 290.04 Summary

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High-Fat Diet During Pregnancy May Affect Offspring's Eating Habits

Prenatal exposure to high-fat diet alters dopamine system in young monkeys

New animal research offers important evidence that exposure to a high-fat diet while in the womb can alter the brain in ways that might affect food consumption later in life, 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. When pregnant monkeys consume a high-fat diet, their offspring have fewer dopamine fibers and receptors in the prefrontal cortex, an area of the brain that plays a major role in determining responses to appetizing food, according to the study.

"Our findings add to a growing body of research that suggests we may be able to reduce the epidemic of childhood obesity by targeting poor nutrition before children are even born," said lead author Heidi Rivera, PhD, of the Oregon National Primate Research Center in Beaverton. "Focusing on diet during pregnancy could have a life-long impact on health."

In earlier research involving non-human primates, Rivera and her colleagues found that maternal consumption of a high-fat diet increases weight gain and fat tissue in offspring. They also reported that offspring appear to prefer consuming flavorful, high-calorie diets.

The new research analyzed brain-tissue samples collected from 13-month-old monkeys (equivalent to toddlers in humans) whose mothers were fed either a high-fat (30 percent fat) or low-fat (12 percent fat) diet during gestation and lactation. They found that the monkeys exposed to the high-fat diet in the womb had fewer dopamine fibers and receptors in the prefrontal cortex, even if they had been fed a low-fat diet after weaning. Because the dopamine system is widely known to regulate the brain's food-reward pathway in humans as well as in monkeys, these findings suggest a possible link between the consumption of a high-fat diet by mothers during pregnancy and their offspring's eating habits later in life.

Research was supported with funds from the National Institute of Diabetes and Digestive and Kidney Diseases.

Scientific Presentation: Monday, Nov. 17, 8–11:15 a.m., Room 147B

290.04, Maternal high-fat diet consumption decreases dopamine signaling in prefrontal cortex of non-human primate (NHP) juvenile offspring
H. M. RIVERA, E. L. SULLIVAN, P. KIEVIT, M. A. KIRIGITI, L. BAUMAN, S. R. LINDSLEY, K. BAQUERO, P. BLUNDELL, T. A. DEAN, M. S. SMITH, K. L. GROVE; Division of Diabetes, Obesity, and Metabolism, Oregon National Primate Research Center, Beaverton, Ore.

TECHNICAL ABSTRACT: Using a non-human primate (NHP) model, our laboratory has shown that maternal high-fat diet (HFD) consumption during gestation and lactation is associated with metabolic-related complications in offspring. More recently, we have shown that HFD offspring have an increased preference for a diet high in fat and sugar. These animals appear to have reduced food-reward signals and compensate by overeating highly palatable diets. The dopamine (DA) system is widely known to regulate food reward; therefore, we hypothesized that maternal HFD consumption decreases central DA signaling in offspring. In the present study, we targeted the prefrontal cortex (PFC) due to the involvement of this region in higher-order executive functions, such as food reward. Our studies show that maternal HFD consumption causes a decrease in DA fiber innervation, specifically in the superficial layer of the PFC, as indicated by a decrease in the number of fibers expressing tyrosine hydroxylase. Furthermore, there was a decrease in the dopamine receptor 2 mRNA levels in the pyramidal cell layer of the PFC. Together, our findings reveal that maternal HFD consumption decreases DA signaling in the PFC, indicating a likely disruption in the food-reward pathway.

Abstract 80.11 Summary

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Consuming a High-Fructose Diet in Adolescence May Exacerbate Depressive-Like Behavior

Animal study shows diet alters brain's response to stress

The consumption of a diet high in fructose throughout adolescence may increase depressive- and anxiety-like behavior and alter how the brain responds to stress, 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.

"Our results offer new insights into the ways in which diet can alter brain health and may lead to important implications for adolescent nutrition and development," said lead author Constance Harrell of Emory University in Atlanta.

Fructose, a sugar found naturally in fruits and vegetables but also added to many processed foods and beverages, is known to promote insulin resistance, high blood pressure, and unhealthy cholesterol levels. It also stimulates neural pathways that affect how the brain responds to stress, which can have important behavioral effects, including the development of symptoms related to depression and anxiety. Such effects are of particular concern during the teen years, which is a critical time for the development of the brain's stress response.

To determine whether fructose consumption has the potential to create long-term changes in metabolism and behavior during adolescence, Harrell and her colleagues gave rats that had just been weaned either a standard or a high-fructose diet. After 10 weeks, the rats on the high-fructose diet had a different hormonal response to a stressor, which was consistent with their depressed-like behavior. A genetic pathway in the brain that plays a key role in regulating the way the brain responds to stress was also altered. These findings suggest that consuming a diet high in fructose throughout adolescence may exacerbate depressive behaviors and affect the way the body and the brain respond to stress.

Research was supported with funds from the National Institute of Mental Health.

Scientific Presentation: Saturday, Nov. 15, 3–4 p.m., Halls A-C

80.11, Developmental high-fructose diet consumption increases depressive-like and anxiety-like behavior and remodels the hypothalamic transcriptome
C. S. HARRELL, J. BURGADO, S. D. KELLY, Z. P. JOHNSON, G. N. NEIGH; Emory University, Atlanta, Ga.

TECHNICAL ABSTRACT: Fructose consumption, which promotes insulin resistance, hypertension and dyslipidemia, has increased by over 25 percent since the 1970s. In addition to metabolic dysregulation, fructose ingestion stimulates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated glucocorticoid production. Adolescents are the greatest consumers of fructose, and adolescence is a critical period for maturation of the HPA axis. Repeated consumption of high levels of fructose during adolescence has the potential to promote long-term dysregulation of the stress response. Therefore, we determined the extent to which consumption of a diet high in fructose affected behavior, serum corticosterone, and hypothalamic gene expression using a whole-transcriptomics approach. In addition, we examined the potential of a high-fructose diet to interact with exposure to chronic adolescent stress in male Wistar rats. Rats fed the peri-adolescent high-fructose diet showed increased anxiety-like behavior in the elevated plus maze test and depressive-like behavior in the forced swim test in adulthood, irrespective of stress history. They also showed elevated basal corticosterone, but a blunted response to forced swim. These behavioral and hormonal responses to the high-fructose diet did not occur in rats fed fructose during adulthood only. Finally, rats fed the high-fructose diet throughout development underwent marked hypothalamic transcript expression remodeling, with 966 genes (5.6%) significantly altered and a pronounced enrichment of altered transcripts in the proopiomelanocortin (POMC) pathway. Collectively, the data presented herein indicate that diet, specifically one high in fructose, has the potential to alter behavior, HPA axis function, and the hypothalamic transcriptome.

Abstract 138.08 Summary

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Animal Study Explores Role of 'Hunger Hormone' in Reducing Brain-Cell Loss From Parkinson's Disease

Hormone may offer direction on path to future treatments

New animal research released today suggests that the hormone ghrelin plays a pivotal role in helping a calorie-restricted diet reduce brain-cell damage associated with Parkinson's disease in rats, a finding that has implications for potential treatments for the disease. The study demonstrates for the first time that the protective effects previously associated with a calorie-restricted diet may be achieved by administering the hormone ghrelin, without the need for reducing what we eat. The 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.

Globally, an estimated 6.3 million people have Parkinson's disease, and that number is expected to double by 2030. Parkinson's disease occurs when brain cells that produce the chemical dopamine, which helps control physical movement, become damaged or die. Previous research has suggested that caloric restriction — consuming fewer calories than normal but not to the point of malnourishment — may protect against the loss of dopamine cells. Studies have also suggested that the hormone ghrelin, which sends a "hunger" message to the brain when the gut is empty, plays a role in that protection.

"Understanding the role of ghrelin, or the 'hunger hormone,' could allow us to develop new treatments that produce the benefits of a calorie-restricted diet without the necessity of drastically reducing an individual's caloric intake, which can be hard to maintain," said lead author Jacqueline Bayliss of Monash University in Melbourne, Australia.

To better understand the relationship between a calorie-restricted diet, ghrelin, and the preservation of dopamine cells, Bayliss and her colleagues put Parkinson's model mice that were genetically engineered to not produce ghrelin on a calorie-restricted diet. No beneficial effects from calorie restriction were observed in these mice, providing evidence that ghrelin is a key player in the protective benefits of calorie restriction. Some of the mice were later injected with ghrelin. Various analyses revealed that when the mice were given ghrelin, they experienced changes in the brain associated with a slowing down of cell loss from Parkinson's disease.

Research was supported with funds from Australia Research Council Future Fellowship and Monash University.

Scientific Presentation: Sunday, Nov. 16, 11 a.m.–noon, Halls A-C.

138.08, Ghrelin mediates the neuroprotective effects of calorie restriction in Parkinson's disease
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TECHNICAL ABSTRACT: Calorie restriction (CR) protects against neurodegeneration in Parkinson's disease; however, the mechanisms behind this neuroprotection remain unknown. Ghrelin is a gut hormone with neuroprotective effects in Parkinson's disease, and CR increases plasma ghrelin concentrations. Hence, we hypothesized that elevated endogenous ghrelin during CR prevents nigrostriatal neurodegeneration in the MPTP mouse model of Parkinson's disease. We placed ghrelin wildtype (WT) and knockout (KO) mice on a CR or ad libitum diet followed by treatment with either MPTP or saline. As a measure of nigrostriatal degeneration we used stereology to examine tyrosine hydroxylase (TH) number and volume by immunohistochemistry and striatal dopamine/metabolites by high-performance liquid chromatography (HPLC). MPTP treatment in WT mice reduced TH neuronal number and volume in the SNpc in both ad lib and CR mice with a significantly greater loss in ad lib animals, indicating the neuroprotective effect of CR. However, CR did not attenuate TH cell or volume loss after MPTP in KO mice, suggesting increased ghrelin mediates the neuroprotective effect of CR. In WT mice, CR prevented the increase in astrocyte number observed in ad libitum WT mice after MPTP treatment. However, KO mice still exhibited a significant increase in astrocytes after MPTP treatment, which may reflect a greater need to remove degenerating TH neurons in KO mice relative to WT mice. In order to understand the cellular mechanisms through which ghrelin acts to reduce neurodegeneration, we injected C57/Bl6 mice with ghrelin. We measured AMPK phosphorylation in these mice, as AMPK is a known downstream signaling target for ghrelin in the hypothalamus. There was a significant elevation in pAMPK and TH levels in the substantia nigra and striatum, which was ghrelin-dependent. Together, our data reveals that endogenous ghrelin mediates the neuroprotective effects of CR on the nigrostriatal dopamine system.