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THINK WHAT YOU EAT:
STUDIES POINT TO CELLULAR FACTORS LINKING DIET AND BEHAVIOR

Research highlights brain's vulnerability to obesity

CHICAGO — New research released today is affirming a long-held maxim: you are what you eat — and, more to the point, what you eat has a profound influence on the brain. The findings offer insight into the neurobiological factors behind the obesity epidemic in the United States and other developed countries. The findings exposed changes in brain chemistry due to diet and weight gain, and were reported at Neuroscience 2009, the Society for Neuroscience's annual meeting and the world's largest source of emerging news about brain science and health.

Obesity has been linked to rises in diabetes, stroke, and heart attacks, among other disorders. In the past decade alone, medical spending for obesity is estimated to have increased 87 percent in the United States — reaching $147 billion in 2008 — according to a study funded by the Centers for Disease Control and Prevention. The new research adds another dimension to understanding how obesity rates have more than doubled in the past 30 years.

The new findings show that:

- Disruptions in the sleep/wake cycle lead to weight gain, impulsivity, slower thinking, and other physiological and behavioral changes. These findings may be particularly important for people who do shift work (Ilia Karatsoreos, PhD, abstract 471.1, see attached summary).
- Pregnant mice fed a high-fat diet produced pups that were longer, weighed more, and had reduced insulin sensitivity — factors that indicate a predisposition toward obesity and diabetes. In addition, despite no further exposure to a high-fat diet, these pups passed on those same traits to their offspring (Tracy Bale, PhD, abstract 666.21, see attached summary).
- Feeding high-fat food to pregnant mice can affect the brain development of their offspring, causing the pups to be more vulnerable to obesity and to engaging in addictive-like behaviors in adulthood (Teresa Reyes, PhD, abstract 87.1, see attached summary).
- Brain pleasure centers became progressively less responsive in rats fed a diet of high-fat, high-calorie food — changes previously seen in rats as they became addicted to cocaine or heroin. Furthermore, the animals became less likely to eat a well-balanced, nutritious diet even when the less-palatable healthy food was all that was available. The finding may have implications for humans, as the diets were similar to those in developed countries (Paul J. Kenny, PhD, abstract 550.1, see attached summary).

Other research findings being discussed at the meeting show:

- There is considerable evidence that body weight and fat mass are highly heritable traits and have strong genetic determinants. This offers the potential to identify specific brain-derived factors contributing to obesity, eating behavior, and responses to food (Sadaf Farooqi, PhD, see attached speaker's summary).

"The brain is the foundation of all behavior, including eating," said press conference moderator Ralph DiLeone, PhD, of Yale University School of Medicine, an expert on the neural mechanisms of food intake and behavior. "With the growing rates of obesity in industrialized nations, brain research is important to understanding the underlying neurobiological responses to high-fat diet."

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

– more –

Related Presentation:

Lecture: **Genetic, Molecular and Physiological Mechanisms Involved in Human Obesity**
Wednesday, Oct. 21, 8:30–9:40 a.m., Hall B1
# # #

Abstract 471.1 Summary

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Mouse Study Finds Disruption of Circadian Rhythms Affects Both Brain and Body

Disruptions lead to weight gain, impulsivity, slower thinking

A new study has found that chronic disruption of one of the most basic circadian (daily) rhythms — the day/night cycle — leads to weight gain, impulsivity, slower thinking, and other physiological and behavioral changes in mice, similar to those observed in people who experience shift work or jet lag. The research, presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health, is helping scientists better understand the neurobiological mechanisms behind circadian disruptions.

"Our findings have implications for humans," said lead author Ilia Karatsoreos, PhD, of Rockefeller University. "In our modern industrialized society, the disruption of our individual circadian rhythms has become commonplace, from shift work and jet lag to the constant presence of electric lighting. These disruptions are not only a nuisance, they can also lead to serious health and safety problems," he said.

Karatsoreos and his colleagues housed the animals in a day/night cycle of 20 hours (10 hours of light and 10 hours of dark), rather than the roughly 24-hour cycle to which the animals' internal brain and body clocks are normally set. After six to eight weeks, the mice exhibited numerous physiological changes not seen in a control group. These included greater weight gain, changes in body temperature rhythms, and alterations in metabolic hormones such as insulin and leptin (a key regulator of appetite). The mice with the disrupted rhythms also demonstrated behavioral changes — specifically, increased impulsivity and decreased cognitive flexibility (the ability to adapt new strategies to new situations).

"We also found that the animals' brains displayed neural changes in the medial prefrontal cortex, an area important for regulating impulsivity and cognitive flexibility," Karatsoreos said. "Those changes may help explain some of the behavioral effects of circadian disruptions."

Research was supported by Canadian Institutes of Health Research, the National Institute of Mental Health, and Sepracor.

Scientific Presentation: Monday, Oct. 19, 1–2 p.m., South Hall A

471.1, Effects of circadian dysregulation on metabolism, cognition, and emotionality
I. N. KARATSOREOS, S. M. BHAGAT, B. M. MCEWEN; Neuroendocrinol, Rockefeller Univ., New York, NY

TECHNICAL ABSTRACT: Circadian (daily) rhythms in physiology and behavior are generated by the master circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. This brain clock communicates with myriad "peripheral" clocks in many different brain regions, and almost all body tissues. The mechanisms by which these clocks are synchronized by the SCN, and how they maintain their coherence are beginning to be revealed. Disruption of an individual's circadian rhythms have become commonplace in our modern industrial society, from shift-work and jetlag, to the constant presence of electric lighting. How circadian disorganization affects brain and body clocks is an important area of inquiry. We examined how being housed in a light-dark (LD) cycle with a period incongruent with an animals' own endogenous circadian clock affects the physiology and behavior of male mice. Our findings show that chronic circadian disorganization leads to weight gain, changes in body temperature rhythms, and alterations in metabolic hormones (such as leptin and insulin). We further show that behaviorally, animals housed in an incongruent LD demonstrate decreased cognitive flexibility - though relatively intact spatial learning - as measured by a modified Morris watermaze task. Finally, circadian shifted animals also demonstrate increased "impulsivity" as measured by the time spent in the center of an open field, as well as the time taken to emerge into the light in a dark-light transition test, while not showing any increases in general activity. Together, these results suggest that disrupting circadian rhythms by housing animals in an environmental LD cycle with a period different than their own endogenous period can result in behavioral and physiological decrements that may have important implications for human cognitive and metabolic functioning.

Abstract 666.21 Summary

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Maternal Mice Fed High-Fat Diet Produce Larger Pups

Diet during pregnancy may impact generations of offspring

Could a woman's food choices during pregnancy affect not only the size and health of her children, but of her grandchildren? Yes, suggests a new study in mice presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

University of Pennsylvania researchers found that pregnant mice fed a high-fat diet produce pups that are longer, weigh more, and have reduced insulin sensitivity — factors that indicate a risk for obesity and diabetes. Interestingly, despite the lack of further high-fat diet exposure, the traits of increased body length and insulin insensitivity persisted into the second generation.

Subsequent investigation found that the changes in gene expression responsible for alterations in body length and insulin insensitivity were sex-dependent. Only female offspring exhibited evidence of altered programming of the growth hormone axis, a gene pathway that controls overall growth and metabolism.

This work adds to the growing body of research in epigenetics, the study of heritable alterations in gene expression that act independently of changes in DNA sequence. Until very recently, scientists believed that our genes were the sole carrier of hereditary information. However, in addition to inheriting genes from our parents, we can also inherit their epigenetic "switches" that turn our genes on or off. These switches can be flipped by our environments and experiences to help us adapt to challenges put before us, and can be passed from generation to generation.

"Much research has focused on identifying genes (our developmental 'hardware') as predisposing factors for obesity. However, it turns out that epigenetics (our developmental 'software') likely makes a much larger contribution by dictating how our genes are actually utilized," said Tracy Bale, PhD, the study's senior author. "We found compelling evidence that the evolutionarily critical trait of body size can be modulated by maternal diet across at least two generations. In the end, you may not only be what you eat, but what your grandmother ate."

Research was supported by the National Institute of Diabetes and Digestive and Kidney Diseases.

Scientific Presentation: Tuesday, Oct.20, 1–2 p.m., South Hall A

666.21, Maternal high fat diet epigenetically programs offspring height in a sex dependent manner
G. A. DUNN, **T. L. BALE**; Univ. Pennsylvania, Philadelphia, PA

TECHNICAL ABSTRACT: Changes in available nutritional quality and quantity contribute to shaping somatic growth, and links between the nature and extent of caloric intake with body size are well recognized. Furthermore, intrauterine exposure to a maternal diet high in fat has been shown to impact adult offspring body size and insulin sensitivity, though few studies have examined the heritability of these features in the second generation. An epigenetic mechanism that controls body size inheritance over generations provides an evolutionarily advantageous mechanism by which maternal diet can influence the competitiveness of the bloodline. We hypothesized that maternal high fat diet exposure modulates body size and insulin sensitivity intergenerationally via epigenetic changes at the level of gene expression and DNA methylation. We previously reported that maternal exposure to a high fat diet in mice results in both significant body length increases and reduced insulin sensitivity that persist across at least two generations. This phenotype is not attributable to altered intrauterine conditions or maternal feeding behavior as both maternal and paternal lineages were able to pass on the effect to the second generation, supporting a germline-based epigenetic manner of inheritance. We report the novel finding that elevated plasma insulin-like growth factor-1 (IGF-1) in first and second generation females suggests a sex-specific epigenetic contribution of the growth hormone (GH) pathway. Gene expression patterns in these mice further demonstrate that only female offspring augment their body length through a molecular cascade originating at the ghrelin receptor (GHSR) gene. These findings extend to reduced expression of a GHSR-associated transcriptional repressor (AF5q31), suggesting a female specific reprogramming of the GH/IGF-1 axis that may lead to increased GH secretion. Alterations in methylation patterns at the GHSR locus in first and second generation mice represent a potential epigenetic basis for our observations. These data provide compelling evidence that the heritability of the evolutionarily critical trait of body size is modulated by maternal diet across multiple generations and is governed by sex-specific mechanisms, thus providing a strategy where height can increase rapidly in concert with high fat diet availability.

Abstract 87.1 Summary

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Mouse Study Finds Maternal High-Fat Diet Has Serious Implications for Brain Development of Offspring

Research may explain vulnerability to obesity and addictive-like behaviors

Feeding high-fat food to pregnant mice can affect their pups' brain development in ways that may cause them to be more vulnerable to obesity and to engage in addictive-like behaviors in adulthood, a new study has found. The research was presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"We discovered that pups born to mothers fed a high-fat diet during pregnancy and lactation had significant changes in their brain chemistry, with dramatic differences in dopamine- and opioid-related molecules," said lead author Teresa Reyes, PhD, of the University of Pennsylvania.

These changes may partially explain the differences in behavior observed in these pups compared with ones from normal pregnancies, Reyes added. The pups born to mothers fed a high-fat diet showed a greater preference for a sugar solution and a greater physical response to cocaine than did pups born to mothers fed a standard diet.

The study's findings may have implications for humans. Almost two-thirds of Americans are overweight and one in three is obese, according to government health surveys. Women who are obese currently account for between 20 and 35 percent of all pregnancies in the United States. "The potential long-term effects of maternal obesity on the brains and behavior of offspring are just beginning to be understood," Reyes said.

Research was supported by the National Institutes of Health.

Scientific Presentation: Saturday, Oct.17, 1–2 p.m., South Hall A

87.1, Behavioral and gene expression adaptations in mesocorticolimbic reward circuitry after prenatal exposure to high fat diet
T. M. REYES, Z. VUCETIC, K. TOTOKI, J. KIMMEL; Pharmacol., Univ. Pennsylvania, Philadelphia, PA

TECHNICAL ABSTRACT: Maternal obesity currently affects 20-35% of all pregnancies and nearly doubles the risk for a large-for-gestational age infant (LGA). LGA increases the risk for development of obesity and metabolic syndrome, and may also lead to adverse neurobehavioral outcomes. Central nervous system development can be affected by environmental stimuli and perinatal manipulations, including nutrition, maternal care, exposure to toxic chemicals and infectious agents. Midbrain dopamine and opioid circuitry are neural substrates associated with mediating reward and hedonic behaviors, and appear to be vulnerable to adverse prenatal conditions. Using a mouse model of maternal high fat diet, we have investigated the long-term effects of maternal high fat diet on reward-related behavior and gene expression within the mesocorticolimbic reward circuitry.
We assessed behavioral responses to naturally rewarding stimuli (sucrose) and psychostimulant drugs (cocaine), and gene expression and epigenetic changes in reward-associated brain regions of adult mice exposed to 60% high fat diet in utero and during lactation. Mice exposed to maternal HF diet showed an increased preference for sucrose solution and an augmented locomotor response to acute cocaine injection. This increased behavioral sensitivity to reward was associated in prenatal HF mice with significant upregulation of dopamine reuptake transporter (DAT) in ventral tegmental area (VTA), nucleus accumbens (NAC) and prefrontal cortex (PFC), and downregulation of dopamine receptor D1 and dopamine-related phosphoprotein DARP-32 in NAC and PFC. Furthermore, we detected an increase in expression of both mu-opioid receptor and endogenous opioid pro-enkephalin (PENK) in NAC, PFC and hypothalamus of prenatal HF mice. Epigenetic mechanisms have been associated with long term programming of gene expression and underlying phenotypic differences after various in utero insults. Similarly, we observed global DNA hypomethylation and upregulation of DNA-methyl transferase, Dnmt1 and methyl-CpG-binding protein, MeCP2 in reward-associated brain regions of prenatal HF animals.
Taken together, our data support the importance of early-life events, and specifically maternal high fat diet, in programming molecular targets and adult behavior via epigenetic mechanisms. Long-term changes in dopamine and opioid components of brain reward circuitry after prenatal exposure to high fat diet may lead to altered processing of natural and pharmacological rewarding stimuli (e.g. palatable food, drugs of abuse) and confer vulnerability for engaging in addictive-like behaviors in adulthood.

Abstract 550.1 Summary

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Junk Food Diet Causes Rats' Brain Pleasure Centers to Become Progressively Less Responsive

Study suggests explanation for compulsive overeating

Brain pleasure centers became progressively less responsive in rats fed a diet of high-fat, high-calorie food, a new study has found. As the changes occurred, the rats developed compulsive overeating habits — and became obese. The overeating continued even when it meant the rats had to endure an unpleasant consequence (a mild foot shock) in order to consume the food. The findings were presented at Neuroscience 2009, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The researchers also found that as the activity of the brain's pleasure centers decreased, the rats became less likely to eat a well-balanced, nutritious diet — even when the less palatable healthy food was the only food available to them.

"Not only did we find that the animals' brain reward circuits became less responsive as they continued to overeat and become obese," said senior author Paul J. Kenny, PhD, of the Scripps Research Institute in Jupiter, Fla., "but that decrease in responsiveness was similar to what our laboratory has seen previously in rats as they become addicted to cocaine or heroin. The data suggest that obesity and addiction may result from common neuroadaptations," he said.

The finding may have implications for humans, as the diets fed the rats (unlimited access to such high-caloric foods as bacon, sausage, cheesecake, and chocolate) were similar to those of millions of people who live in developed countries. Such diets are considered a major contributing factor to the current obesity epidemic in the United States.

Research was supported by Bank of America, the National Institute on Drug Abuse, and The Landenberger Foundation.

Scientific Presentation: Tuesday, Oct. 20, 8–9 a.m., South Hall A

550.1, Motivational drives in obesity: Evidence for addiction-like compulsive responding for palatable food
P. M. JOHNSON[1], **P. J. KENNY[2]**; [2]Mol. Therapeut., [1]The Scripps Res. Inst., Jupiter, FL

TECHNICAL ABSTRACT: In recent years it has been speculated that the powerful hedonic aspects of palatable food are mediated through similar neurobiological substrates as drugs of abuse and may therefore confer addictive properties. However, empirical evidence supporting this notion has been lacking. In rats, extended access to addictive drugs can result in the transition from casual to compulsive use, an effect that time-locked with reduced activity in brain reward circuits, reflected in elevated intracranial self-stimulation (ICSS) thresholds. This state of negative reward is hypothesized to increase the motivation to consume palatable food. Thus, brain reward deficits are thought to be a hallmark of addiction. Here we show that animals permitted extended (>18 h), but not restricted (1 h), daily access to a "cafeteria-style" diet consisting of high-fat palatable food readily available for human consumption exhibited rapid weight gain and a shift in dietary preference for the palatable food. Importantly, the development of obesity was time-locked to profound reductions in brain reward function, as measured by elevated ICSS thresholds. Diet-induced reward dysfunction lasted for at least two weeks during abstinence from the palatable diet. Furthermore, extended access to the cafeteria diet resulted in enhanced motivation to consume the diet, reflected in persistent consumption of palatable food in obese animals even under conditions of punishment (foot-shock). These findings suggest that extended access to a cafeteria diet manifest addiction-like deficits in brain reward function that may enhance the motivation to consume palatable foods, thus promoting the development and maintenance of obesity. These findings parallel those previously observed with extensive access to drugs of abuse, supporting the notion that obesity and addiction may result from common neuroadaptations.

Speaker's Summary

Speaker: Sadaf Farooqi, PhD (44-12) 2333-6792
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Lecture: **Genetic, Molecular and Physiological Mechanisms Involved in Human Obesity**
Wednesday, Oct. 21, 8:30–9:40 a.m., Hall B1

Whilst the recent rise in the prevalence of obesity has been driven in part by environmental factors, there is considerable evidence from twin and adoption studies that body weight and fat mass are highly heritable traits and differences in susceptibility to obesity have strong genetic determinants. The identification of patients with mutations in the gene encoding the adipocyte-derived hormone leptin, and their successful treatment with recombinant human leptin, have provided insights into the role of leptin responsive pathways in the regulation of eating behaviour, intermediary metabolism, the onset of puberty and T-cell mediated immunity. Leptin acts by regulating a complex network of brain responses that can be studied using functional imaging, to co-ordinate changes in nutritional state with changes in food intake and the "liking" of food. A downstream target of leptin action, the melanocortin 4 receptor (MC4R), plays a key role in modulating sympathetic nervous system mediated changes in blood pressure. Genetic disruption of brain-derived neurotrophic factor (BDNF) and its receptor cause a complex neurobehavioral phenotype including hyperactivity and memory loss, as well as severe obesity. BDNF is involved in neuronal development and synaptic plasticity, processes that are increasingly recognized as playing an important role in the coupling of nutrient availability to brain responses and ultimately behaviour.