

Abstracts

Plenary Lecturer

■PL-1

Leptin and the Homeostatic System Regulating Body Weight

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The discovery of leptin has led to the elucidation of a robust physiologic system that maintains fat stores at a relatively constant level. This hormone is made by adipocytes and acts on the hypothalamus to regulate food intake and energy expenditure. When fat mass falls, plasma leptin levels fall stimulating appetite and suppressing energy expenditure until fat mass is restored. When fat mass increases, leptin levels increase, suppressing appetite until weight is lost. By such a mechanism total energy stores are stably maintained within a relatively narrow range.

Mutations in the leptin gene are associated with massive obesity in mice humans and treatment of mutant animals with recombinant leptin markedly reduces food intake and body weight. The low leptin levels in patients with leptin mutations are associated with multiple abnormalities including infertility, diabetes and immune abnormalities all of which are corrected by leptin treatment. These findings establish a physiologic link between energy stores and many other physiologic systems . These findings also led to the use of leptin as a treatment for a number of other human conditions including a subset of obesity, some forms of diabetes including lipodystrophy and hypothalamic amenorrhea, the cessation of menstruation seen in extremely thin women. The identification of leptin has also provided a framework for studying the pathophysiology of obesity.

Recent studies have explored the relationship between leptin and the reward value of food. A novel optogenetic assay for quantifying the reward value of nutrient was used to show that leptin reduces food intake by diminishing the reward value of nutrient. The reward value of nutrient is associated with a post-ingestive effect that allows animals to sense the caloric content of independent of taste. We also found that MCH neurons, which are known to regulate food intake and body weight, are required for sucrose to elicit its post-ingestive effect.

Feeding is a complex motivational behavior controlled by many inputs including smell, taste, hormonal state, cognitive inputs, etc. However it is not known how or even where these multiple inputs are processed to formulate a “binary” decision i.e.; eat or don’t eat. To begin to address the question of how this complex behavior is regulated, we have used existing and newly developed methods for a) identifying novel populations of nerve cells that are linked to feeding and b) testing their function.

Two new methods named phospho-trap and retrotrap were developed to identify new neural populations regulating feeding. Phospho-Trap enables transcription profiling of genes from neurons that have been activated or inhibited by a specific stimulus. Retro-Trap enables transcription profiling of genes from neurons based on their pattern of projections. These methods are now being used to identify neural populations in higher order centers that respond to stimuli that are known to regulate food intake or project to reward centers. The putative function of these neurons to control feeding will be assessed by assaying the behavioral effects of optogenetic activation of these neurons as well as a novel non-invasive nanoparticle based method for activating neural function.

Session 1

S1-1

AMP-activated protein kinase in CRH neurons in the PVH controls food selection behavior

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Increased preference for high fat diet (HFD) under choosing multiple palatable diets is the prevalence in the modern society and causes accelerating rates of obesity, type 2 diabetes and cardiovascular disease. The paraventricular hypothalamus (PVH) is implicated in the control of food selection behavior while the regulatory mechanism remains elusive. AMP-activated protein kinase (AMPK) is a metabolic sensor and regulates feeding behavior, responding to hormones, neurotransmitters and nutrients. Here, we report that AMPK in the PVH regulates food selection behavior for high fat (HFD) and carbohydrate-rich (HCD) diets in mice. Overnight fasting or NPY injection into the PVH, which activated AMPK in the PVH, increased selection of HCD but decreased that of HFD in C57Bl/6J mice. Expression of shRNA for AMPK in the PVH by lentivirus blunted the fasting-induced change in food selection behavior. In contrast, expression of constitutively active AMPK in PVH neurons mimicked the effect of overnight fasting. We investigated the principle neuron that regulates food selection behavior. Microinjection of CRH into the PVH increased selection of HCD but decreased that of HFD in mice. Activation of CRH neurons in the PVH by DREADD also increased selection of HCD. Immunohistochemical analysis revealed the activation of AMPK in a subset of CRH neurons in the PVH in response to overnight fasting. In contrast, suppression of AMPK activity in CRH neurons or inhibition of CRH expression in the PVH by lentivirus decreased the fasting-induced change in food selection behavior. We examined the role of AMPK in the PVH in food selection behavior in obese mice. Diet-induced or KK-Ay obese mice increased selection of HFD that was associated with down-regulation of AMPK activity and CRH expression in the PVH. These results implicate that AMPK in CRH neurons in the PVH plays an important role in the control of food selection behavior for HFD and HCD.

CCHamide-2 controls the synthesis and secretion of Insulin-like peptides in *Drosophila melanogaster*

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Organisms have to coordinate growth with nutritional status for their better survival. In multicellular animals, nutritional information is mostly received by peripheral organs. It is subsequently relayed to the central nervous system which modulates physiological responses. Endocrine systems ensure such organ-to-organ communication via hormonal signals secreted from specialized glandular cells.

Here, we show that CCHamide-2 (CCHa2) is a novel Insulin regulator predominantly expressed in *Drosophila* adipose tissues. CCHa2 had been biochemically purified from adult flies as a bioactive peptide which activates a G protein-coupled receptor encoded by CG14593 (hereafter referred to as *CCHa2R*)¹. It is known that *Bombesin receptor subtype-3* (*BRS-3*), a member of the Bombesin-like peptide receptor family, is the closest mammalian homologue of *CCHa2R*². Interestingly, *BRS-3*-deficient mice develop obesity associated with reduced metabolic rate and elevated feeding activity³. However, neither its ligand nor the molecular mechanism by which *BRS-3* functions has been revealed. Our results show that *Drosophila CCHa2R* is specifically expressed in the brain and that mutations of *CCHa2R* affect the transcription of *drosophila insulin-like peptide 5* (*dilp5*) and secretion of *Drosophila* insulin-like peptide 2 (*Dilp2*) in Insulin producing-cells in the brain, leading to systemic growth retardation and developmental delay. Our additional results exhibit that expression of *CCHa2* mRNA is altered in response to nutrition levels, suggesting that CCHa2/CCHa2R is a novel adipose tissue-brain signaling which coordinates systemic growth with nutritional availability.

References

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Session 2

S2-1

Adipose tissue inflammation and ectopic lipid accumulation

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Obesity may be viewed as a chronic low-grade inflammatory disease as well as a metabolic disease. Indeed, macrophages infiltrate into obese adipose tissue to induce inflammatory pathways, thereby inducing adipose tissue dysfunction. In response to nutritional conditions, lipid metabolism in adipose tissue is tightly regulated by insulin and the sympathetic nervous system. Adipocytes increase their size (hypertrophy) and number (hyperplasia) during the course of obesity to store triglyceride effectively in adipose tissue. When adipose tissue cannot meet the demand of storing excessive energy, triglyceride is accumulated in non-adipose tissues as ectopic lipid, which may lead to insulin resistance in the liver and skeletal muscle and insufficient insulin secretion in the pancreas (lipotoxicity). Notably, chronic inflammation is capable of inducing insulin resistance, lipolysis, and interstitial fibrosis in adipose tissue, all of which may reduce its lipid-storage function.

Recently, we have reported that melanocortin-4 receptor-deficient (MC4R-KO) mice on a high-fat diet develop nonalcoholic steatohepatitis (NASH)-like liver phenotypes, associated with obesity, insulin resistance, and dyslipidemia. Histological analysis revealed inflammatory cell infiltration, hepatocyte ballooning, and pericellular fibrosis in the liver of MC4R-KO mice. Interestingly, they also exhibited accelerated adipose tissue inflammation. In this regard, we have found that Macrophage-inducible C-type lectin (Mincle), a pathogen sensor for *Mycobacterium tuberculosis* and pathogenic fungi, is crucial for adipose tissue fibrosis, thereby regulating ectopic lipid accumulation in the liver. Mincle expression was localized to the macrophages forming a unique histological structure, “crown-like structure (CLS)”, where they scavenged the residual lipid droplets of dead adipocytes. On the other hand, we observed a histological structure similar to adipose tissue CLS in the liver of MC4R-KO mice termed “hepatic CLS (hCLS)”. Our data suggest that hCLS is an important source of inflammatory and fibrogenic mediators during the development of NASH in MC4R-KO mice. Moreover, we observed increased number of hCLS in human NASH.

In this symposium, we would like to discuss the role of adipose tissue inflammation in ectopic lipid accumulation in the metabolic syndrome.

Transcriptional Coregulator CITED2 Stimulates Adipogenesis by Enhancing Preadipocyte Proliferation and PPAR γ Expression through Rb Inactivation

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An increase in the size of individual adipocytes (hypertrophy) and in the number of adipocytes (hyperplasia) is critical for adipose tissue expansion in obesity caused by overnutrition. Adipocyte hyperplasia is caused by enhanced proliferation and differentiation of preadipocytes. Adipocyte differentiation in 3T3-L1 cells, a widely accepted adipogenesis model, is critically regulated by the coordination of transient reentry into the cell cycle (mitotic clonal expansion: MCE) and activation of the adipogenic transcriptional program encompassing CCAAT/enhancer binding proteins (C/EBPs) and peroxisome proliferator-activated receptor (PPAR) γ as well as histone acetyltransferases, such as CREB binding protein (CBP), and general control of amino-acid synthesis 5-like 2 (GCN5). MCE is thought to be a prerequisite step for induction of PPAR γ . The transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2), which binds to the transcriptional coregulators, CBP and p300, interacts with many of these molecules. However, the role of this protein in the regulation of adipogenesis remains unclear. Therefore, we investigated the role of CITED2 in adipogenesis in both 3T3-L1 cells and mouse adipocytes *in vivo*.

Short-hairpin RNA-mediated CITED2 knockdown in 3T3-L1 preadipocytes impaired lipid accumulation and decreased the induction of the expression of PPAR γ and C/EBP α , but not of C/EBP β/δ , suggesting impaired adipogenesis. Defective adipogenesis induced by CITED2 knockdown was rescued, at least in part, by treatment with the PPAR γ -agonist, rosiglitazone, indicating that CITED2 promotes adipogenesis by PPAR γ induction. CITED2 knockdown also impaired transient cell proliferation 48 h after adipogenic induction, with a concomitant decrease in the phosphorylation of the retinoblastoma tumor-suppressor protein (Rb) and induction of cyclin A, thus indicating impaired MCE. Co-immunoprecipitation analysis revealed that CITED2 interacted with Rb, cyclin D1, and CDK4, and enhanced the phosphorylation of Rb by cyclin D1-CDK4 complex, resulting in Rb inactivation and promotion of MCE. We also investigated the effect of CITED2 loss-of-function in adipose tissue expansion in obesity using mice that were heterozygous for a null allele of the CITED2 gene and were fed on a high-fat diet (hetKO mice). The adipose tissue from hetKO mice exhibited a decrease in preadipocyte number along with a reduced expression of genes involved in cell cycle progression (e.g., *Ccnd1*, *Ccne1*, *Ccna2*, *Cdk2*). Thus, the hetKO mice were protected from diet-induced obesity.

Thus, we concluded that CITED2 loss-of-function impairs adipogenesis by inhibiting preadipocyte proliferation *in vitro* and *in vivo*, suggesting that CITED2 contributes to diet-induced adipose tissue expansion. Manipulation of CITED2 function may be a potential therapeutic target for the treatment of obesity and related metabolic disorders.

Session 3

■ S3-1

Molecular mechanisms underlying amino acid control of lipid metabolism

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We recently discovered an unexpected metabolic consequence of depriving mice of an essential amino acid. These mice mobilize fat stores from abdominal adipose tissue very quickly. We found that leucine deprivation decreases abdominal fat mass largely by increasing energy expenditure, as demonstrated by increased lipolysis in white adipose tissue (WAT) and uncoupling protein 1 (UCP1) expression in brown adipose tissue (BAT). It is well established that the central nervous system (CNS), especially the hypothalamus, plays an important role in regulating energy homeostasis and lipid metabolism. The involvement of CNS in this regulation, however, is not understood. While exploring molecular mechanisms, we found that intraventricular (icv) administration of leucine significantly attenuates abdominal fat loss and blocks activation of hormone sensitive lipase in WAT and induction of UCP1 in BAT in leucine-deprived mice. Furthermore, we provide evidence that leucine deprivation stimulates fat loss by increasing expression of corticotropin-releasing hormone (CRH) in the hypothalamus and activation of the sympathetic nervous system. In addition, We used intracerebroventricular injection of adenoviral vectors to identify a novel role for hypothalamic p70 S6 kinase (S6K)1, a major downstream effector of the kinase mammalian target of rapamycin, in leucine deprivation-stimulation of energy expenditure. Moreover, we show that the effect of hypothalamic S6K1 is mediated by modulation of CRH expression in a melanocortin-4 receptor-dependent manner. Interestingly, we found that leucine deprivation promotes leptin signaling in mice maintained on an otherwise normal diet and restores leptin responses in mice maintained on a high-fat diet, a regimen known to induce leptin resistance. In addition, using db/db mice homozygous for a mutation in leptin receptor and a knock-in mice line Y3F with abrogation of leptin receptor tyrosine1138-mediated Signal Transducer and Activator Transcripts (STAT)3 signaling, we identified an essential role for leptin signaling in the stimulation of energy expenditure and fat loss under leucine deprivation. Taken together, our studies provide a new perspective for understanding the regulation of energy expenditure by the CNS and the importance of crosstalk between nutritional control and regulation of endocrine signals. Our studies also describe a novel link between hypothalamic leptin signaling and stimulation of energy expenditure under leucine deprivation.

**CNS-Mediated Control of Energy and Mental Homeostasis;
Crosstalk between SF-1 and FoxO1 in the Ventromedial Hypothalamus**

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Obesity, diabetes, and metabolic complications are growing concerns for public health and could lead to detrimental life-threatening conditions. Accumulating evidence suggests that incidences of metabolic syndrome are closely associated with mental disorders such as anxiety and depression, and they share common pathways in the brain. Neurons whose activities are required for energy and psychiatric homeostasis are found in a number of hypothalamic nuclei. The ventral medial nucleus of the hypothalamus (VMH), among several hypothalamic nuclei, emerged recently as an important site for mediating body weight homeostasis and psychiatric behaviors. This lecture will be focused on the emerging homeostatic roles of the VMH, particularly highlighting the control of energy metabolism and psychiatric behaviors in the SF-1 neurons of the VMH. Furthermore, I will illustrate functional roles of transcription factors including SF-1 and FoxO1 and circulating factors such as insulin and leptin in the VMH. Finally, I will discuss the underlying molecular mechanisms responsible for the regulation of energy homeostasis and psychiatric behaviors in the VMH.

Role of Specific Phosphatidylinositol-3 Kinase Subunits in Ventromedial Hypothalamic Nucleus

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The steroidogenic factor-1 (SF-1) neurons located within in the ventromedial nucleus of hypothalamus (VMH) regulate energy and glucose homeostasis. Recently, leptin receptors and insulin receptors expressed by SF-1 neurons have been reported to play distinct role in regulating energy and glucose homeostasis. However, the cellular mechanisms involved in the regulation of these neurons by leptin and insulin have not been determined. In the present study, we found that leptin either activates or inhibits SF-1 neurons while insulin consistently inhibits SF-1 neurons. Of note, the leptin-activated cells were mainly located in the dorsomedial subdivision of VMH while leptin-inhibited cells were scattered throughout the VMH. Insulin-inhibited cells were found in the ventromedial part of VMH which is adjacent to the arcuate nucleus of hypothalamus (ARH). We also found that the putative transient receptor potential C (TRPC) channels mediate the activation of SF-1 neurons by leptin, while the ATP-sensitive K⁺ (KATP) channels mediate the inhibition of these neurons by leptin and insulin. Interestingly, we found that p110 β subunits of phosphatidylinositol-3-kinases (PI3Ks) are specifically required for the acute activation of SF-1 neurons by leptin: leptin- and insulin-inhibitions were not affected by p110 β deletion. It was noted that p110 α subunits are not required for the acute effects of leptin and insulin. In summary, we identified the specific ion channels and PI3K subunits that underlie the acute effects of leptin and insulin on VMH SF-1 neurons.

Session 4

■S4-1

Genome-wide Profiling of Brown Fat-Specific Open Regulatory Regions Identifies NFIA as a Transcriptional Regulator of Brown Fat Differentiation

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Role of novel isoforms of PGC-1 α in energy metabolism

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Peroxisome proliferator-activated receptor γ (PPAR γ) coactivator-1 α (PGC-1 α) is a transcriptional coactivator that regulates various metabolic processes, including mitochondrial biogenesis and thermogenesis. Given that mitochondrial dysfunction and impaired thermogenesis are often observed in individuals with insulin resistance and obesity, and that the abundance of PGC-1 α is reduced in skeletal muscle of such affected animals and humans, PGC-1 α has been implicated in the pathogenesis of these global health problems. The phenotype of mice with PGC-1 α deficiency has not clarified the contribution of this protein to these conditions, however. We and others have recently identified two variants of PGC-1 α generated by transcription from an alternative promoter and designated the variants as PGC-1 α b and PGC-1 α c, and the canonical form as PGC-1 α a. Whereas PGC-1 α a is relatively widely expressed in various tissues, the expression of PGC-1 α b and PGC-1 α c is detected only in skeletal muscle, brown adipose tissue, and heart. The mRNA abundance of PGC-1 α a was ~10 times greater than that of PGC-1 α b or PGC-1 α c in skeletal muscle under static conditions. The amounts of PGC-1 α b and PGC-1 α c mRNAs were however markedly increased in response to acute exercise, with their abundance surpassing that of PGC-1 α a after exercise. Forced expression of PGC-1 α b or PGC-1 α c in C2C12 myotubes with the use of adenovirus vectors resulted in increased expression of genes related mitochondrial function as well as lipid or glucose metabolism known to be induced by PGC-1 α a to an extent similar to that triggered by PGC-1 α a. These results suggest that, although PGC-1 α b and PGC-1 α c differ from PGC-1 α a in tissue distribution and mode of induction, their molecular functions are similar. We have generated mice lacking PGC-1 α b and PGC-1 α c by the deletion of the novel exon 1, from which these two isoforms were transcribed. The mutant mice manifested age-dependent obesity and insulin resistance. The number of mitochondria, fiber-type composition, and abundance of total PGC-1 α in skeletal muscle were unaltered in the mutant mice, likely because the canonical form of PGC-1 α is predominant under static conditions. However, increases in total PGC-1 α abundance and energy expenditure in response to acute exercise were attenuated in the mutant mice. Whereas motor performance during a heavy exercise load was impaired, remodeling of skeletal muscle induced by chronic exercise was not affected in these mice. Our data indicate that the acute induction of PGC-1 α in response to exercise, for which the new variants are largely responsible, plays an important role in the control of fat mass and insulin sensitivity through regulation of energy expenditure during exercise. Exercise mimetics are potential pharmacological treatments for obesity and type 2 diabetes mellitus and the new variants of PGC-1 α are promising targets for the development of such drugs.

Molecular Analysis of Fat Accumulation from the Aspect of Aging Signals

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Cellular senescence is a state of irreversible cell growth arrest induced by excessive replication or various stresses, including oncogenic stimuli. It is thought to be a defensive mechanism against malignant transformation. This response is controlled by negative regulators of the cell cycle like the p53 tumor suppressor protein. Accumulating evidence has suggested a role of p53 activation in various age-associated conditions, including vascular senescence, heart failure, and diabetes. It has also been reported that diabetes promotes vascular senescence and accelerates the development of cardiovascular complications. However, it remains unclear whether the senescence of vascular cells per se contributes to metabolic abnormalities and obesity in diabetic patients. We here identified a crucial role of endothelial p53 activation in the regulation of glucose homeostasis and obesity. Endothelial expression of p53 was markedly up-regulated when mice were fed a high-calorie diet. Disruption of endothelial p53 activation improved dietary inactivation of endothelial nitric oxide synthase that up-regulated the expression of peroxisome proliferator-activated receptor- γ coactivator-1 α in skeletal muscle, thereby increasing mitochondrial biogenesis and oxygen consumption. Inhibition of endothelial p53 also improved dietary impairment of glucose transport into skeletal muscle by up-regulating endothelial expression of glucose transporter 1. Mice with endothelial cell-specific p53 deficiency fed a high-calorie diet showed improvement of insulin sensitivity and less fat accumulation compared with control littermates. Conversely, up-regulation of endothelial p53 caused metabolic abnormalities and increased fat accumulation. These results indicate that inhibition of endothelial p53 could be a novel therapeutic target to block the vicious cycle of cardiovascular and metabolic abnormalities occurring in diabetic patients.

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