Thursday November 8, 2018
Olympic Museum - Quai d'Ouchy 1, 1006 Lausanne

LIMNA Symposium: Central Regulation of Metabolism and Feeding

Organizing Committee: Prof. Bart Deplancke, Prof. Béatrice Desvergne, Prof. Lluis Fajas, Prof. Nelly Pitteloud, Prof. Bernard Thorens, Prof. Kei Sakamoto, Prof. Kristina Schoonjans and Dr. Laurence Descamps.

Sponsored by

Invited Speakers

- **Daniela Cota, INSERM Neurocentre Magendie, Bordeaux University, France**
- **Sabrina Diano, Yale University School of Medicine, USA**
- **Ted Dinan, University College Cork, Ireland**
- **Ana I. Domingos, University of Oxford, UK**
- **Miguel Lopez, CiMUS, University of Santiago de Compostela, Spain**
- **Serge Luquet, University Paris Diderot, France**
- **Martin G. Myers, University of Michigan Medical school, Ann Arbor, USA**
- **Sophie Steculorum, Max Planck Institute for Metabolism Research, Cologne, Germany**

Sponsored by

Agenda

8h30-9h00 Welcome and distribution of badges

Opening

9h00 **Bernard Thorens**
Welcome

Morning session

Chairman: TBD

9h10 **Martin G. Myers**
"The CNS control of blood glucose-roles for VMN subpopulations"

9h45 **Sabrina Diano**
"Central mitochondria dynamics and metabolism"

10h20 Coffee Break

Chairman: TBD

10h40 **Miguel Lopez**
"Targeting hypothalamic AMPK for the treatment of obesity"

11h15 **Daniela Cota**
"Bile acid signaling as novel mechanism in the central control of energy balance"

11h50 **Selected speaker 1 based on abstract submission**

12h05 **Selected speaker 2 based on abstract submission**

12h20 Lunch

Sponsored by

Afternoon session

Chairman: TBD

13h05 Poster session

14h05 **Ted Dinan**
"Gut microbe to brain communication: implications for psychopharmacology"

14h40 **Ana I. Domingos**
"Sympathetic Neuroimmunity in Obesity"

15h15 **Selected speaker 3 based on abstract submission**

15h30 Coffee Break

15h50 **Selected speaker 4 based on abstract submission**

16h05 **Sophie Steculorum**
"Novel regulators of the central control of feeding and systemic insulin sensitivity"

16h40 **Serge Luquet**
"Triglyceride sensing in the mesolimbic system and the control of food reward"

17h15 Concluding remarks and poster prize distribution

ABSTRACTS

The CNS control of blood glucose-roles for VMN subpopulations

Martin G. Myers
University of Michigan Medical school, Ann Arbor, USA

While the ventromedial hypothalamic nucleus (VMN) plays an essential role in the control of glucose homeostasis, including by mediating the counter-regulatory response (CRR) to hypoglycemia, the VMN contains multiple subpopulations of neurons that play distinct roles in the control of hypoglycemia, and the neurons that control hepatic glucose output, including during the CRR have not previously been molecularly defined. Since we previously showed that cholecystokinin (CCK) neurotransmission plays an important role in the VMN-mediated CRR, we generated CCK receptor b (*Cckbr*)-cre mice to study the potential role of VMN^{Cckbr} neurons in the control of blood glucose. $Cckbr^{Cre}$ reporter mice identified a substantial population of VMN^{Cckbr} neurons in the dorsomedial VMN. The optogenetic activation of VMN^{Cckbr} neurons increased blood glucose, consistent with a role in the control of glucose production. Furthermore, while tetanus toxin-mediated silencing of the entire VMN (using $SF1^{cre}$) promoted obesity and hyperglycemia, silencing VMN^{Cckbr} neurons did not alter body weight, but reduced blood glucose at baseline and impaired the CRR (as well as the hyperglycemic response to other stimuli). Thus, VMN^{Cckbr} neurons play a crucial role in the control of glucose production, including during the CRR.

Central mitochondria dynamics and metabolism

Sabrina Diano1,2,3,4,5
1Program of Integrative Cell Signaling and Neurobiology of Metabolism, 2Departments of Obstetrics, Gynecology, and Reproductive Sciences, 3of Neuroscience and 4of Comparative Medicine, Yale University School of Medicine and Graduate School, New Haven, Connecticut, 06520 USA; Dept. Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy.

Our research has been focusing on deciphering intracellular mechanisms that enable cells in the Central Nervous System (CNS) to sense and respond to changes in circulating nutrient and hormone levels in the control of systemic energy and glucose metabolism. Our recent findings have unmasked CNS mitochondria as critical intracellular organelle in detecting changes in peripheral metabolism. By altering their size, shape and function, mitochondria enable cells to adjust their activity, which in turn alter behavior and peripheral tissue functions to fine tune systemic metabolism. This presentation will highlight these cellular biological process in the CNS regulation of energy and glucose homeostasis.

Targeting hypothalamic AMPK for the treatment of obesity

Miguel López. *E-mail: m.lopez@us.es*
NeurObesity Group, Department of Physiology, CIMUS, University of Santiago de Compostela-Instituto de Investigación Sanitaria, Santiago de Compostela, 15782, Spain

Besides the classical neuropeptide and neurotransmitter-based theory for feeding and energy expenditure regulation, recent data demonstrate that AMP-activated protein kinase (AMPK) plays a major role in the modulation of energy balance. At central level, the AMPK pathway is a canonical route regulating energy homeostasis, by integrating peripheral signals, such as hormones and metabolites with neuronal networks. Current evidence has linked hypothalamic AMPK with feeding brown adipose tissue (BAT) thermogenesis and browning of white adipose tissue (WAT), both through modulation of the sympathetic nervous system, as well as muscle metabolism, hepatic function and glucose homeostasis a process in with hindbrain AMPK has been also involved. The relevance of these data is interesting from a therapeutic point of view since several agents with potential anti-obesity and/or antidiabetic effects, currently being clinically used, such as nicotine, metformin and liraglutide are known to act through AMPK, at peripheral or central level. Furthermore, the orexigenic and weight-gain effect of worldwide used antipsychotic drugs, like olanzapine, are also mediated by hypothalamic AMPK. Overall, this evidence makes hypothalamic AMPK signaling an interesting target for drug development. This talk will summarize the role of hypothalamic AMPK on whole body energy metabolism and its potential as target for obesity treatment.

Novel regulators of the central control of feeding and systemic insulin sensitivity

Sophie M. Steculorum
Max Planck Institute for Metabolism Research

Over the last decades, our understanding of the fundamental processes governing energy balance and glucose homeostasis has largely evolved and pinpointed a pivotal role of the central nervous system and more particularly of the arcuate nucleus of the hypothalamus (ARH). Notably, activation of orexigenic AgRP-expressing neurons located in the ARH potently promotes feeding. We demonstrate that in addition to its orexigenic effects, chronically altering AgRP-neurons activity also affects peripheral glucose homeostasis. Acute activation of AgRP-neurons causes insulin resistance through impairment of insulin-stimulated glucose uptake into brown adipose tissue (BAT) and decreased sympathetic nerve activity. Optogenetic circuitry mapping reveals that feeding and insulin sensitivity are controlled by both distinct and overlapping AgRP-projections. We notably find that activation of AgRP⟶aBNSTvl (ventro lateral part of the anterior bed nucleus of the stria terminalis) projections mediates the effect of AgRP-neuron activation on insulin sensitivity and BAT gene expression. Our results thus reveal a mechanism by which these neurons rapidly coordinate hunger states with glucose homeostasis. Along this line, we discovered a novel AgRP-neurons' stimulatory pathway able to modulate both feeding and insulin sensitivity. We show that AgRP-neurons express the purinergic receptor 6 (P2Y6) and that activation of P2Y6 by its endogenous ligand uridine-diphosphate increases AgRP-neuron's action potential firing and promotes feeding. Further, selectively abrogating P2Y6-signaling in AgRP-neurons alleviates obesity-associated adiposity, hyperphagia, and insulin resistance. Our work therefore reveals that modulating AgRP-neurons by targeting P2Y6-signaling improves obesity-associated metabolic outcomes.

Gut microbe to brain signalling: implications for psychopharmacology

Ted Dinan MD, PhD
Department of Psychiatry and APC Microbiome Institute, University College Cork, Ireland

Evidence is accumulating to suggest that gut microbes may be involved in neural development and function, both peripherally in the enteric nervous system and centrally in the brain. There is an increasing and intense current interest in the role that gut bacteria play in maintaining the health of the host. Altogether the mass of intestinal bacteria represents a virtual inner organ with 100 times the total genetic material contained in all the cells in the human body. However, a disordered balance amongst gut microbes is now thought to be an associated or even causal factor for many chronic medical conditions as varied as obesity and inflammatory bowel diseases. While evidence is still limited in psychiatric illnesses, there are rapidly coalescing clusters of evidence which point to the possibility that variations in the composition of gut microbes may be associated with changes in the normal functioning of the nervous system. Studies in germ-free animals indicate aberrant development of the brain monoaminergic system together with memory deficits and autistic patterns of behaviour. These deficits can be partially normalised if there is early gut colonisation.
Recent pre-clinical studies suggest that certain *Bifidobacteria* may have anxiolytic or antidepressant activity while *Bifidobacterium infantis* has been found effective in treating patients with irritable bowel syndrome.
Metchnikoff was the first to observe the fact that those living in a region of Bulgaria who consumed fermented food in their diet tended to live longer. He first published his observations in 1908 and this gave rise to the concept of a probiotic or bacteria with a health benefit. That bacteria might have a positive mental health benefit is now becoming clear. Such bacteria may influence the capacity to deal with stress, reducing anxiety, perhaps positively impacting on mood and are now called psychobiotics. Whether, they are capable of acting like and in some circumstances replacing antidepressants remains to be seen. At a time when antidepressant prescribing has reached exceedingly high levels, the emergence of effective natural alternatives with less side-effects would be welcome. Recent studies also implicate the microbiota in the side effects of antipsychotic medications, especially the emergence of weight gain and metabolic syndrome.
The mechanisms of psychobiotic action are gradually being unravelled. It has been show that *Lacobacillus rhamnosus* has potent anti-anxiety effects in animals and does so by producing major changes in the expression of GABA receptors in the brain. GABA is the most important inhibitory transmitter in the human brain and these are the receptors through which benzodiazepines such as diazepam and various anaesthetic agents act. The changes in these receptors are mediated by the vagus nerve which connects the brain and gut. When this nerve is severed no effect on anxiety or on GABA receptors is seen following psychobiotic treatment. An impact on obsessive compulsive disorder type symptoms has also been reported with a similar strain of psychobiotic. Interestingly, *Lacobacillus rhamnosus* not only alters GABA receptors in the brain but has been shown to synthesise and release GABA. There is also evidence to support the view that gut bacteria may influence the brain in routes other than the vagus nerve, for example by immune modulation and by the manufacture of short chain fatty acids.

Communication between the brain and gut is bidirectional and complex. Increased understanding of this axis and the role of the gut microbiota may aid the development of therapies not just for functional bowel disorders but for mood disorders also.

Triglyceride sensing in the mesolimbic system and the control of food reward

Chloé Berland[1,2], Celine Cansell[1], Yuko Nakamura Y[3,4], Giuseppe Gangarossa[1], Mohammad Ali Shenasa[5], Julien Castel[1], Martine Cador[6.7] , Stephanie Caille[6.7], Stefania Tolu[8], Fabio Marti[8], Philippe Faure[8], Jacob Hecksher-Sørensen[9.10] ,Casper Bo Jensen[9,10] ,C. Mary Burke[3.4], Xue Sun[3,4], Matthias H. Tschöp[2,11,12] , Thomas S. Hnasko[5], Dana M Small[3.4], and Serge Luquet[1]

[1]*Univ Paris Diderot, Sorbonne Paris Cité, Unité de Biologie Fonctionnelle et Adaptative, CNRS UMR 8251, F-75205 Paris, France.*
[2]*Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health, München/Neuherberg,Germany.*
[3]*The John B Pierce Laboratory, 290 Congress Ave, New Haven CT, USA*
[4]*Yale University, 333 Cedar, New Haven CT, USA*
[5]*Department of Neurosciences, University of California, San Diego, La Jolla CA, USA.*

[6]*Univ. Bordeaux, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, UMR5287, 33076 Bordeaux, France*
[7]*CNRS, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, UMR5287, 33076 Bordeaux, France*
[8] *Neuroscience Paris-Seine – IBPS - UPMC UM CR18 – CNRS UMR 8246 – INSERM U1130. Equipe Neurophysiologie et Comportement (NPC), Universite P. et M. Curie, Paris, FRANCE*
[8]*Global Research, Novo Nordisk A/S, Måløv, Denmark;*
[9]*Image Analysis & Computer Graphics, Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kgs. Lyngby, Denmark;*
[10]*Gubra ApS, Hørsholm Kongevej 11B, 2970 Hørsholm, Denmark*

[11]*Division of Metabolic Diseases, TUM, Munich, Germany;*
[12]*Institute for Advanced Study, TUM, Munich, Germany*

Circulating triglycerides (TGs) normally increase after a meal but are altered in pathophysiological conditions, such as obesity in both human and rodent. TG-hydrolyzing enzymes are expressed in the mesolimbic dopaminergic system suggesting that central TG-sensing might regulate dopamine neurons activity and ultimately reward-driven behaviour.
Using brain-specific TG delivery (BTGD), we show nutritional TG access mesocorticolimbic (MCL) structures where they modulate dopamine (DA) neurons activity and signalling. Central TG sensing is mediated, at least in part, by the lipoprotein lipase (LPL) whose transcript is specifically found onto DA and medium Spiny Neuron (MSN) neurons. TG detected centrally create positive reinforcement in a conditioned place preference paradigm (liking) but lead to reduced motivation to work for reward (wanting) as assessed by both operant conditioning and self-administration. Finally, we find that TG action on reward seeking behaviour primarily rely on the indirect Dopamine receptor DRD2 pathway.
Using functional magnetic resonance (fMRI) we found that in human, post-prandial TG excursions modulate brain response to food versus non-food cues. The response of the ventromedial prefrontal cortex (vmPFC) was specific to TG and independent of other energy-related signals. Finally, the action of TG onto brain response was driven by the genetic

polymorphism TaqAI, a mutation known to affect D2DR signaling and susceptibility to addiction.

Collectively, these findings reveal new mechanisms by which dietary TG alter mesolimbic circuit function and reward seeking behaviour, and provide a novel hypothesis by which energy-rich diet might lead to dopamine circuitry adaptation and ultimately addictive behaviour.

Sponsors

Sponsored by