UNIL | Université de Lausanne
Faculté de biologie et de médecine

Cardiovascular and Metabolism PhD Program

Mini-Symposium

"Communication between peripheral tissues and the brain: key to keep a normal bodyweight and glycemia"

Organizer: Virginie Mansuy-Aubert, Department of Biomedical Sciences, University of Lausanne (DSB-UNIL)

When: 09 December 2022 from 9:00 – 13:00
Where: CHUV Lausanne, main building BH08, Auditorium MAYOR

Remote participation: ***https://chuv.webex.com/chuv/j.php?MTID=m75f743d1d5272dbafdc9d4bd11559249***

8:30 – 9:00	Welcome coffee
9:00 - 9:15	**Welcome** Virginie Mansuy-Aubert, Department of Biomedical Sciences, University of Lausanne
9:15 - 10:00	**Targeting the enteric nervous system with enterosynes to treat type 2 diabetes** Claude Knauf, INSERM U1220, Institut de Recherche en Santé Digestive (IRSD), Université Paul Sabatier, Toulouse, France.
10:00 - 10:45	**Tanycyte layer as a blood-hypothalamic interface regulating energy balance** Fanny Langlet, Department of Biomedical Sciences, University of Lausanne.
10:45 – 11:00	**Coffee break**
11.00 - 11:45	**Impact of pre-natal stress in offspring metabolic disorders onset** Lionel Carneiro, IRSD, Université de Toulouse, INSERM, INRA, ENVT, UPS, Toulouse, France.
11.45 - 12.30	**Molecular Mechanism Underlying a Gut/Brain Communication in Obesity** Virginie Mansuy-Aubert, Department of Biomedical Sciences, University of Lausanne.
14:00 – 16:00	**Afternoon workshops for PhD students with symposium speakers**

The meeting is free of charge, but for organization purposes please register by filling the form https://forms.gle/pVQQEMJtSDfdSwAr6 prior to December 1, 2022. The UNIL-FBM doctoral school attributes 1.0 ECTS to PhD students who present a signed participation form for the mini-symposium (0.25 ECTS morning session, 0.75 ECTS afternoon session). For additional information, please contact Dr. Ulrike Toepel (Ulrike.toepel@unil.ch).

Co-organized by UNIL | Université de Lausanne Faculté de biologie et de médecine CHUV

Talk abstracts

Targeting the enteric nervous system with enterosynes to treat type 2 diabetes

Claude Knauf, INSERM U1220, Institut de Recherche en Santé Digestive (IRSD), Université Paul Sabatier, Toulouse, France.

The gut-brain axis is of crucial importance for controlling glucose homeostasis. Alteration of this axis promotes the type 2 diabetes (T2D) phenotype (hyperglycaemia, insulin resistance). Recently, a new concept has emerged to demonstrate the crucial role of the enteric nervous system in the control of glycaemia via the hypothalamus. In diabetic patients and mice, modification of enteric neurons activity in the proximal part of the intestine generates a duodenal hyper-contractility that generates an aberrant message from the gut to the brain. In turn, the hypothalamus sends an aberrant efferent message that provokes a state of insulin resistance, which is characteristic of a T2D state. Targeting the enteric nervous system of the duodenum is now recognized as an innovative strategy for treatment of diabetes. By acting in the intestine, bioactive gut molecules that we called “enterosynes” can modulate the function of a specific type of neurons of the enteric nervous system to decrease the contraction of intestinal smooth muscle cells. Here, we focus on the origins of enterosynes (hormones, neurotransmitters, nutrients, microbiota, and immune factors), which could be considered therapeutic factors, and we describe their modes of action on enteric neurons. This unsuspected action of enterosynes is proposed for the treatment of T2D, but it could be applied for other therapeutic solutions that implicate communication between the gut and brain.

Tanycyte layer as a blood-hypothalamic interface regulating energy balance

Fanny Langlet, Department of Biomedical Sciences, University of Lausanne.

Energy balance is tightly controlled by complex neural circuits that sense metabolic signals and adjust food intake and energy expenditure in line with physiological needs. Within neural networks maintaining energy balance, tanycytes are peculiar ependymoglial cells that are nowadays recognized as multifunctional players in the metabolic hypothalamus. Indeed, their strategic position at the blood-brain interface and specific properties convey them diverse functions ranging from blood/brain traffic controllers, neuronal modulators, and neural stem/progenitor cells. In this talk, I will present a decade of findings revealing how tanycytes sense peripheral information while integrated into hypothalamic neural networks regulating energy balance.

Impact of pre-natal stress in offspring metabolic disorders onset

Lionel Carneiro, Loïc Pouvillon, Sarah Maurel, Eve Wemelle, Gaelle Payros, Nicolas Cénac, Claude Knauf
IRSD, Université de Toulouse, INSERM, INRA, ENVT, UPS, Toulouse, France.

Type 2 diabetes (T2D) is characterized by hyperglycemia, hyperinsulinemia and insulin resistance. Among risk factors for T2D, maternal stress during pregnancy has been described to participate to the onset of the disease during adulthood. A pre-natal stress triggers a hypothalamic-pituitary-adrenal gland axis activation. Such axis activity induces a cortisol release that acts on various metabolic processes including insulin sensitivity and glucose homeostasis. However, so far, the mechanisms at play linking pre-natal stress and metabolic disorders in offspring are not fully understood. Recently, an overexpression of the transcription factor FKBP51 in the central nervous system of stressed dam and their offspring has been shown. It is worth to note that FKBP51 negatively regulates the glucocorticoid receptor and therefore impacts the stress response loop. Furthermore, a recent study also reported a role for FKBP51 in glucose homeostasis.

Hence, here we aimed to study the mechanisms involved in metabolic disorders observed in adulthood of mice born from pre-natal stressed mothers. In addition, we studied the gut brain axis involved in the metabolic control and stress response regulations. To develop this project, pregnant mice were stressed during the 3rd week of pregnancy. After birth, offspring were tested for glucose homeostasis at 8 and 22 weeks of age. In addition, gene regulation of liver and brain were analyzed and gut function determined. Our results show the development of metabolic unbalance at the early age of 8 weeks that is followed by an intolerance to glucose at 22 weeks and a fasted hyperglycemia as observed in T2D. Finally, we observed differential gene regulations in mice from pre-natal stressed dam indicating the involvement of a gene reprogramming involved in the adulthood metabolic disorder onset.

These results support epigenetic alterations linking pre-natal stress and glucose homeostasis in adulthood that may contribute to the development of metabolic disorders.

Molecular Mechanism Underlying a Gut/Brain Communication in Obesity

Virginie Mansuy-Aubert, Department of Biomedical Sciences, University of Lausanne.

Obesity is accompanied with changes in the gut microbiome, we confirmed these data in Western-Diet fed models that received fecal transplantation from lean mice (reviewed in Gut Microbes, 2022). This resulted in changes in blood glucose levels and nerve regeneration (PNAS, 2020). Fermentation of soluble fiber by gut bacteria produces short-chain fatty acids (SCFAs), which provide various known metabolic benefits to the host. SCFAs are proposed to exert metabolic benefits through the gut-brain axis, but the absence of cell-type specific tools has impeded our understanding of the molecular mechanism and neural circuitry. We identified expression of the SCFA-binding GPCR free fatty acid receptor 3 (FFAR3) in both vagal afferent and dorsal root ganglia (DRG) neurons that send messages to the central nervous system regulating autonomic function. We utilized a newly designed FFAR3 “floxed” mouse model for Cre Recombinase targeted deletion of this SCFA-binding GPCR in different populations of sensory neurons. These deletions of FFAR3 altered feeding behavior (Molecular Metabolism, 2021) and glucose homeostasis. Ex vivo and in vitro studies also suggest that FFAR3 signaling alters neuronal activity, possibly through intracellular Ca2+ signaling. Thus, we have begun to test the hypothesis that afferent neurons “sense” propionate produced by the gut bacteria upon fiber intake, via FFAR3, and this signaling modulates autonomic circuits. Overall, our data provides insights into distinct roles for FFAR3 in separate sensory neuron populations which may be therapeutically targeted to reduce food intake and improve glucose management.