Société de Neuroendocrinologie
SNE

46th Congress of the French Society of Neuroendocrinology

France-Canada Joint Congress

NICE, September 16-19, 2024

LE SAINT-PAUL
HÔTEL RESTAURANT SÉMINAIRES

Hôtel Le Saint-Paul
29 Bd Franck Pilatte
06300 Nice

UNIVERSITÉ CÔTE D'AZUR
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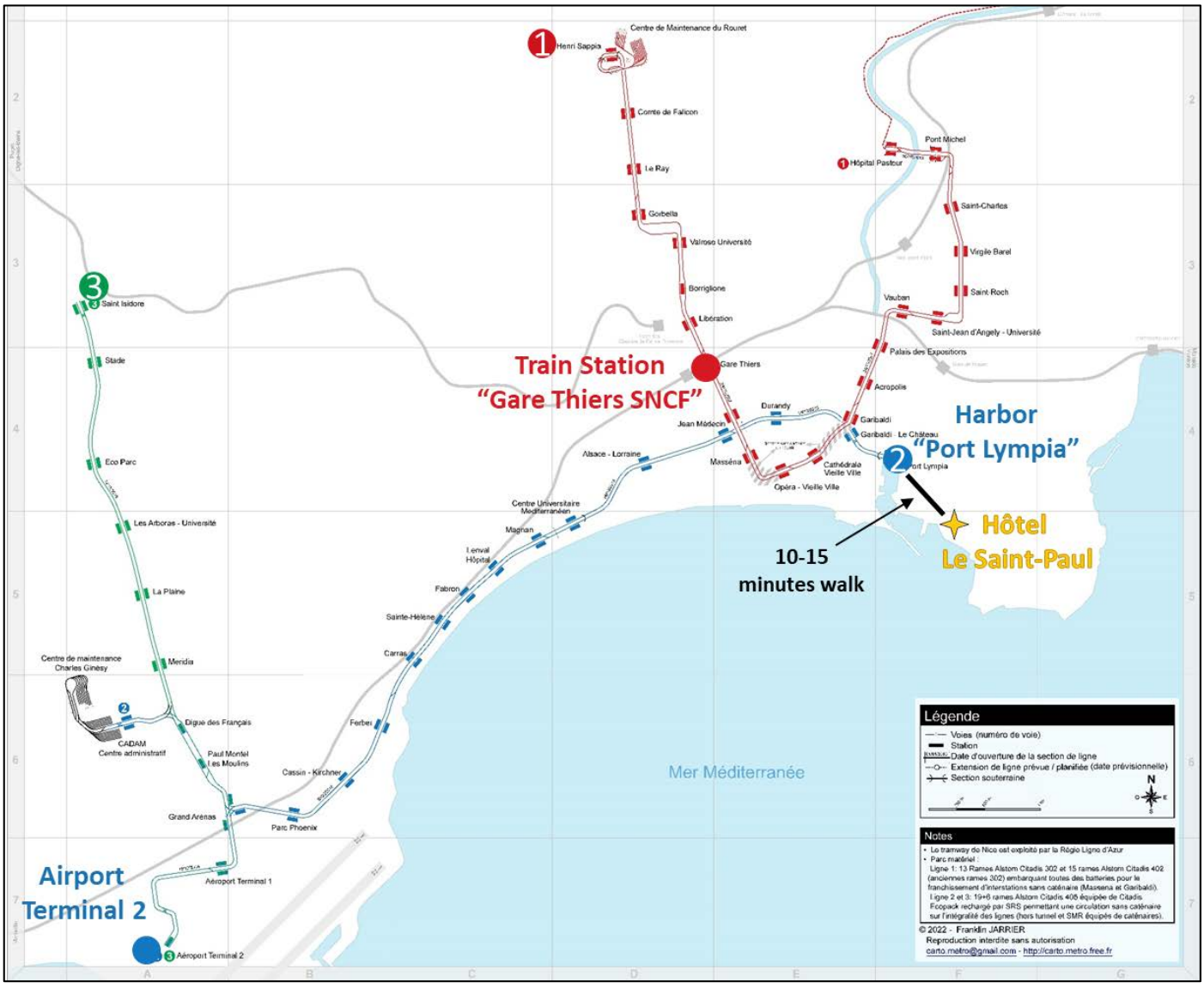
Inserm
VILLE DE NICE
MÉTROPOLE NICE CÔTE D'AZUR
06 DÉPARTEMENT DES ALPES-MARITIMES

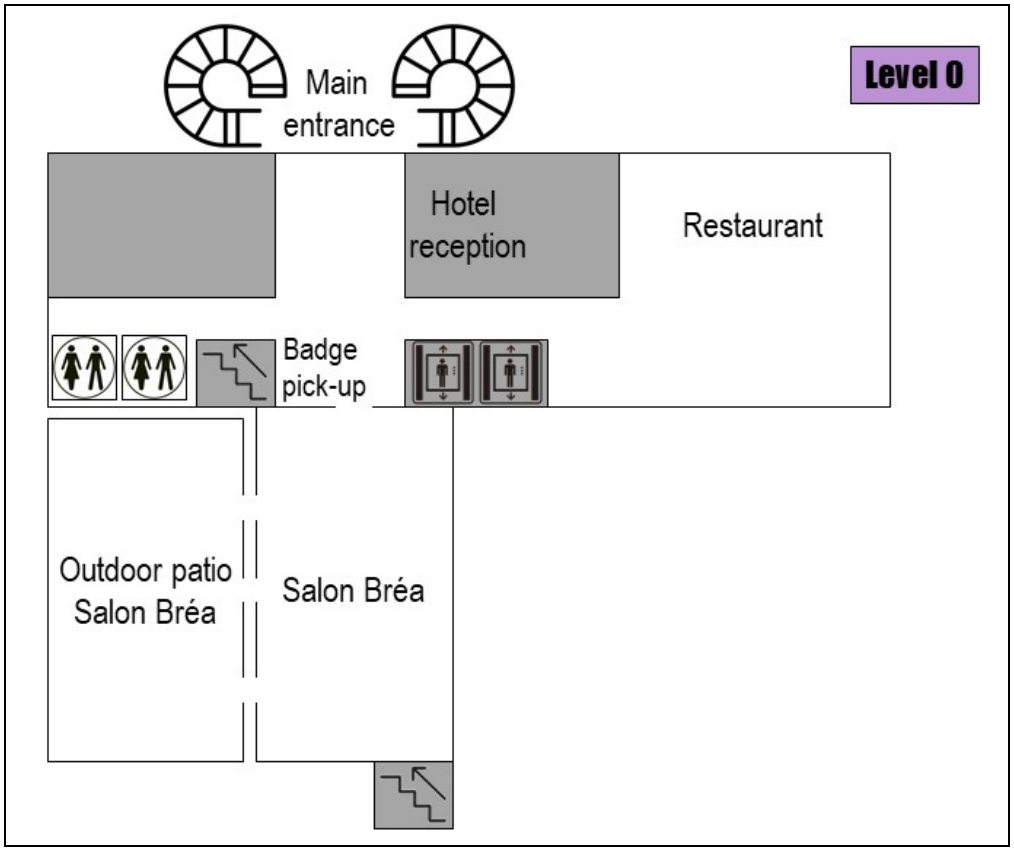
Getting to the conference venue

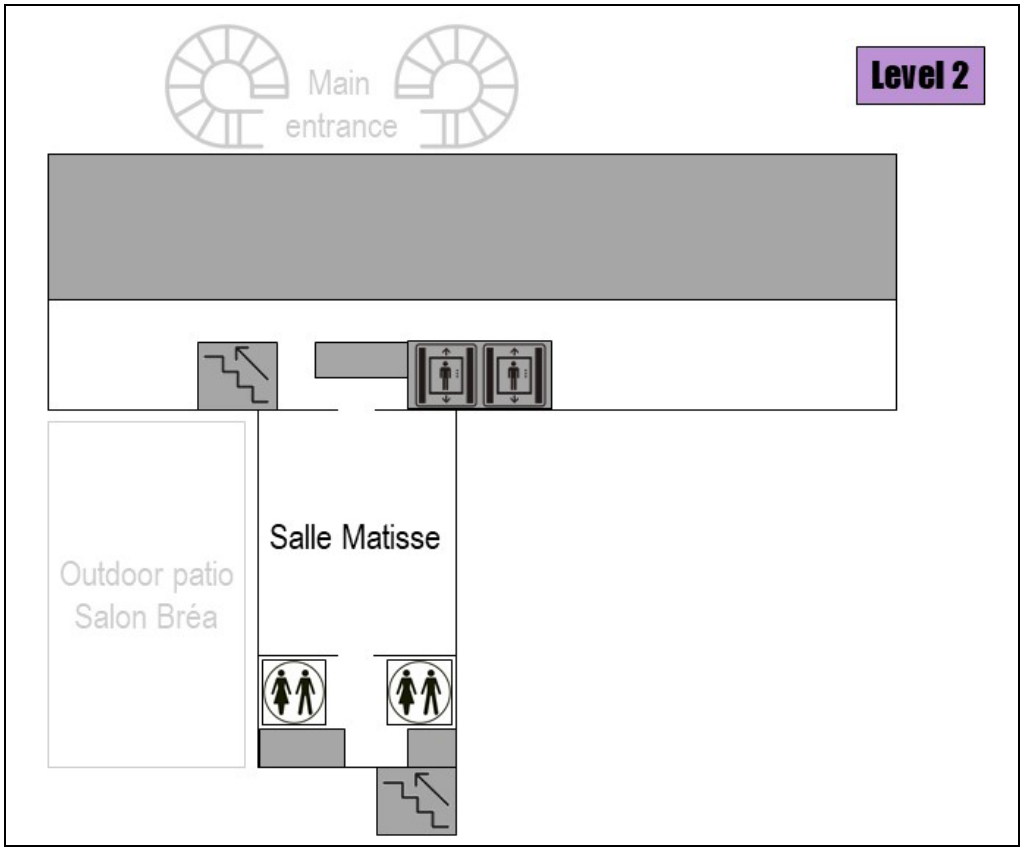
You can take line 2 of the Nice tramway to the "Port Lympia" stop, then walk 10 to 15 minutes along the seafront to reach the Hôtel Saint-Paul.



A rechargeable transport pass with 6 trips included is provided to all participants.

Floor plan of the conference hotel





Sponsors

Welcome to Nice for this 46th SNE

Dear Colleagues,

On behalf of the Organizing Committee and the members of the Scientific Council of the SNE, we are honored to welcome you to the 46th SNE Conference and 1st Joint France-Canada Conference, to be held in Nice from September 16 to 19, 2024.

Fifteen years after the last conference of the Society of Neuroendocrinology was held in Nice, we are delighted to welcome over 150 scientists of many nationalities to the Hôtel Saint-Paul on the Côte d'Azur.

This 3-day symposium will present the latest discoveries in Neuroendocrinology. The scientific program, elaborated by the SNE Scientific Committee, will include plenary lectures by renowned experts in the field of Neuroendocrinology, symposia on recent advances in our discipline, and oral and poster sessions dedicated mainly to young researchers. A SNE prize, a thesis prize, oral communication prizes, poster prizes, as well as travel grants will be awarded at the event thanks to the support of our sponsors. We would like to thank the Obélisque Foundation for the continuous support of young researchers.

We look forward to welcoming the French and international neuroendocrinology community at this congress, and are confident that the meeting will be beneficial both for the development of neuroendocrinology and for scientific exchanges between specialists in the field.

The Jacques Benoît lecture will be given by Pr Denise Belsham (Toronto, Canada) on "The amazing molecular diversity of hypothalamic neurons: Tackling mechanisms one neuron at a time", the Claude Fortier lecture will be given by Dr Serge Luquet (Paris, France) on "Susceptibility to modern food environment: a role for brain lipid sensing? "and the general public lecture will be given in French by Dr. Sakina Mhaouty-Kodja (Paris, France) on "Endocrine Disruptors: Research and Regulation".

We look forward to seeing many of you in person at the next 46th Colloque de la SNE in Nice in September.

Carole Rovère, Alexandre Caron and Clara Sanchez for the organization committee.

Scientific commitee

ANOUAR Youssef, Rouen (President)

BOURET Sébastien, Lille (Vice-President)

CARON Alexandre, Québec

COTA Daniela, Bordeaux

DESROZIERS Elodie, Paris

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MARTIN Agnès, Montpellier

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SHARIF Ariane, Lille (Treasurer)

TOLLE Virginie, Paris

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ROUX Marine, Valbonne

ROVERE Carole, Valbonne (President)

SANCHEZ Clara, Valbonne

VILLET Maxime, Valbonne

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Detailed program

MONDAY, SEPTEMBER 16, 2024

10h00 - 13h00 // Welcoming participants and registration
Entrance hall - Hôtel Saint Paul

10h00 - 13h00 // SNE Scientific Commitee
Salon Bonnard - Hôtel Saint Paul

13h30 - 14h00 // Opening ceremony
Salon Bréa - Hôtel Saint Paul

14h00 - 16h00 // Symposium 1 - "Sexual dimorphism in neuroendocrinology"
Chairs: Agnès Nadjar (Bordeaux, France), Carmelo Quarta (Bordeaux, France)

- 14h00-14h30 S1.1 Manuel Tena-Sempere (Cordoba, Espagne)
  Sex differences in the neuroendocrine control of puberty: Current knowledge and open questions
- 14h30-15h00 S1.2 Agnès Nadjar (Bordeaux, France)
  Sexual dimorphism in microglial nutrient sensitivity
- 15h00-15h30 S1.3 Alexandre Caron (Québec, Canada)
  Hypothalamic and Autonomic Control of Metabolism: Does Sex Matter
- 15h30-16h00 S1.4 Deborah M. Kurrash (Calgary, Canada)
  Sex differentiation programs of the embryonic hypothalamus

Salon Bréa - Hôtel Saint Paul

16h00 - 16h30 // Coffee break
Outdoor patio Salon Bréa - Hôtel Saint Paul

16h30 - 17h30 // Flash Talks
Chairs: Elodie Desroziers (Paris, France), Alexandre Benani (Dijon, France)

- 16h30-16h35 PF.1 Marie Barbier (Lausanne, Suisse)
  Untangling the complexity of POMC neurocircuits: anatomic, genetic and functional perspectives.
- 16h35-16h40 PF.2 Ludovica Cotellessa (Lille, France)
  Exposure to high anti-Müllerian hormone (AMH) levels during mini-puberty in mice induces Polycystic Ovary Syndrome-like defects in both sexes.
- 16h40-16h45 PF.3 Eleonora Deligia (Lille, France)
  Inhibition of transcytosis in tanycytes alters energy and glucose homeostasis.
- 16h45-16h50 PF.4 Louise Eygret (Bordeaux, France)
  Olfaction and feeding behaviour: Neuronal substrates underlying odour modulation of food intake regulating neuronal circuits.
- 16h50-16h55 PF.5 Thomas Ferrand (Rouen, France)
  Neurosecretion is finely tuned by molecular actors sorted at the Golgi membrane level in neuroendocrine cells.
- 16h55-17h00 PF.6 Justine Fredoc-Louison (Paris, France)
  Perinatal exposure to TBBPA interferes with the establishment of the thyroid axis at young age and the ability to cope with metabolic challenges in adulthood.
- 17h00-17h05 PF.7 Chloé Glachet (Liège, Belgique)
  Transgenerational alterations of energy balance and hypothalamic melanocortin system caused by a mixture of endocrine disrupting chemicals in rats.
- 17h05-17h10 PF.8 Emma Grosjean (Strasbourg, France)
  Impact of nighttime light pollution on female metabolism in a diurnal animal model.
- 17h10-17h15 PF.9 Marina Habib (Lyon, France)
  Modulation of intestinal gluconeogenesis by the perinatal nutritional environment.
- 17h15-17h20 PF.10 Amélie Joly (Lyon, France)
  Sex-dependent developmental and physiological trade-offs in response to juvenile malnutrition.
- 17h20-17h25 PF.11 Clarisse Quignon (Washington, United States)
  Effect of maternal hypothyroidism during gestation on the development of GnRH neurons in the offspring.
- 17h25-17h30 PF.12 Audrey Turmel (Québec, Canada)
  Noradrenergic control of proopiomelanocortin neurons.

Salon Bréa - Hôtel Saint Paul

17h30 // End of the day

19h00 - 20h00 // General Public Conference
"Endocrine Disruptors: Research and Regulation"
Sakina Mhaouty-Kodja (Paris, France)
Chairs: Carole Rovère (Valbonne, France)
Centre Universitaire Méditerranéen

20h00 // Aperitif Dinner

Centre Universitaire Méditerranéen

TUESDAY, SEPTEMBER 17, 2024

9h00 - 11h00 // Symposium 2 - "Therapeutic neuroendocrine strategies in Alzheimer's disease"

Chairs: Laurent Givalois (Montpellier, France), Emmanuel Planel (Québec, Canada)

9h00-9h30 S2.1 Geoffrey Canet (Montpellier, France / Québec, Canada)
Is Alzheimer's disease a stress-related disorder? Focus on the therapeutic potential of selective glucocorticoid receptors modulators.

9h30-10h00 S2.2 Frédéric Calon (Québec, Canada)
How metabolic hormones interact with the brain: therapeutic applications for Alzheimer's disease.

10h00-10h30 S2.3 Maud Gratuze (Marseille, France)
Unveiling the Brain's Chubby Secrets: Disrupted cholesterol and Lipid metabolism in Alzheimer's Disease.

10h30-11h00 S2.4 Emmanuel Planel (Québec, Canada)
Unveiling the thermoregulatory nexus: Exploring the intricate interplay between temperature dysregulation and Alzheimer's disease pathogenesis.

Salon Bréa - Hôtel Saint Paul

11h00 - 11h30 // Coffee break ☕
Outdoor patio Salon Bréa - Hôtel Saint Paul

11h30 -12h30 // Poster Session (even numbers)
Outdoor patio Salon Bréa (level 0) & Salle Matisse (level 2) - Hôtel Saint Paul

12h30 - 13h30 // Lunch 🍽
Restaurant - Hôtel Saint Paul

13h30 -14h30 // Oral Communications

Chairs: Stéphanie Fulton (Montréal, Canada), Stéphane Gasman (Strasbourg, France)

13h30-13h45 OC.1 Camille Allard (Bordeaux, France)
Unravelling the role of mitochondria-associated cannabinoid receptors type 1 (mtCB1) in glucose homeostasis: unexpected new partners for insulin secretion.

13h45-14h00 OC.2 Fernando Cazarez-Marquez (Tromso, Norvège)
c-fos induction in the choroid plexus, tanycytes and pars tuberalis is an early indicator of spontaneous arousal from torpor in a deep hibernator.

14h00-14h15 OC.3 Mélodie Devere (Rouen, France)
Glucose homeostasis and energy metabolism are impaired in orexins deficient mice.

14h15-14h30 OC.4 Manon Duquenne (Montréal, Canada)
Regulating corticosterone secretion: is it a fo(u)r stars service?

Salon Bréa - Hôtel Saint Paul

14h30 - 15h00 // Coffee break ☕
Patio extérieur Salon Bréa - Hôtel Saint Paul

15h00 - 16h00 // General Assembly
Salon Bréa - Hôtel Saint Paul

16h00 // End of the day

17h00 // Activities (SENSAS, Vieux Nice visit, Lazaret Cave visit)

WEDNESDAY, SEPTEMBER 18, 2024

9h00 - 10h00 // Claude Fortier Lecture

"Susceptibility to modern food environment: a role for brain lipid sensing?"

Serge Luquet (Paris, France)

Chairs: Sakina Mhaouty-Kodja (Paris, France), William Rostène (Paris, France)

Salon Bréa - Hôtel Saint Paul

10h00 - 10h30 // Coffee break

Outdoor patio Salon Bréa - Hôtel Saint Paul

10h30 - 12h30 // Symposium 3 - "New insights in the central action of thyroid hormones"

Chairs: Marie-Pierre Moisan (Bordeaux, France), Xavier Bonnefont (Montpellier, France)

10h30-11h00 S3.1 Karine Gauthier (Lyon, France)
Thyroid hormone control of thermogenesis: a dialog between the hypothalamus and the periphery.

11h00-11h30 S3.2 Daniel Bernard (Montréal, Canada)
Mechanisms of central hypothyroidism in IGSF1-deficiency syndrome.

11h30-12h00 S3.3 Xavier Bonnefont (Montpellier, France)
Alteration of the central circadian clock during hypothyroidism.

12h00-12h30 S3.4 Rachel Gineis (Bordeaux, France)
Memory deficit in mice fed a high fat high sucrose diet during adolescence linked to hypothyroidism in hippocampus.

Salon Bréa - Hôtel Saint Paul

12h30 - 13h30 // Lunch

Restaurant - Hôtel Saint Paul

13h30 - 14h30 // Poster Session (odd numbers)

Outdoor patio Salon Bréa (level 0) & Salle Matisse (level 2) - Hôtel Saint Paul

14h30 - 15h30 // Symposium 4 Young Researcher - "Maternal effect on plasticity of neuroendocrine functions"

Chairs: Rachida Ammari (Londres, Royaume-Uni), Cristina Miralpeix (Bordeaux, France), Clara Sanchez (Valbonne, France)

14h30-14h50 S4.1 Rachida Ammari (Londres, Royaume-Uni)
Hormone-mediated neural remodeling orchestrates parenting onset during pregnancy.

14h50-15h10 S4.2 Roberta Haddad Tovolli (Barcelona, Spain)
Neuronal circuits underlying maternal dietary habits and the programming of offspring health.

15h10-15h30 S4.3 Marialetizia Rastelli (Lille, France)
Maternal gut microbiome alteration has enduring effects on offspring's metabolic programming and neuroendocrine plasticity.

Salon Bréa - Hôtel Saint Paul

15h30 - 16h00 // Coffee break

Outdoor patio Salon Bréa - Hôtel Saint Paul

16h00 - 17h00 // Oral Communications

Chairs: Amandine Gautier-Stein (Lyon, France), Paolo Giacobini (Lille, France)

16h00-16h15 OC.5 Judith Estrada-Meza (Lausanne, Suisse)
Local translation as a molecular mechanism underlying tanycyte-neuron communication for energy balance regulation.

16h15-16h30 OC.6 Charlotte Jacquinet (Liège, Belgique)
Effects of in utero high fat and high sucrose diet exposure on postnatal growth and pubertal development.

16h30-16h45 OC.7 Alicia Sicardi (Lille, France)
GnRH, a fertile new pathway for the regulation of food intake.

16h45-17h00 OC.8 Thomas Torres (Paris, France)
Effects of minipuberty disruption on the expression of sexual behavior in female mice.

Salon Bréa - Hôtel Saint Paul

17h00 - 18h00 // SNE « Early Career" Prizes

Chairs: Patricia Parnet (Nantes, France) ; Sébastien Bouret (Lille, France)

17h00-17h30 Thesis Prize Clara Sanchez
Dietary fatty acid composition drives neuroinflammation and impaired behavior in obesity.

17h30-18h00 SNE Prize Cristina Miralpeix
Hypothalamic POMC neurons control competing behaviours.

Salon Bréa - Hôtel Saint Paul

18h00 // End of the day

19h00 // Bus Transfert

19h30 // Gala Dinner

Citadel of Villefranche-sur-Mer

THURSDAY, SEPTEMBER 19, 2024

9h00 - 9h30 // Homage to Denis Richard
By Alexandre Caron (Québec, Canada)
Salon Bréa - Hôtel Saint Paul

9h30 - 10h30 // Jacques Benoît Lecture
"The amazing molecular diversity of hypothalamic neurons: Tackling mechanisms one neuron at a time."
Denise Belsham (Toronto, Canada)
Chairs: Daniela Cota (Bordeaux, France), Youssef Anouar (Rouen, France)
Salon Bréa - Hôtel Saint Paul

10h30 - 11h00 // Coffee break ☕
Outdoor patio Salon Bréa - Hôtel Saint Paul

11h00-13h00 // Symposium 5 - "Neuro-modulator systems regulating metabolism"
Chairs: Virginie Tolle (Paris, France), Alexandre Caron (Québec, Canada)

11h00-11h30	S5.1 Natalie Michael (Québec, Canada)	Histamine: at the nexus of sleep and metabolism.
11h30-12h00	S5.2 Stéphanie Fulton (Montréal, Canada)	Leptin modulation of motivation and mood.
12h00-12h30	S5.3 Xavier Fioramonti (Bordeaux, France)	Serotonergic neurons are involved in the counter-regulatory response to hypoglycemia.
12h30-13h00	S5.4 Jérôme Leprince (Rouen, France)	From chemistry to neuroendocrinology: tools and breakthroughs in the understanding ODN role in the hypothalamic regulation of energy homeostasis.

Salon Bréa - Hôtel Saint Paul

13h00 - 13h30 // Closing ceremony
Salon Bréa - Hôtel Saint Paul

13h30 // Packed Lunch 🍽
Salon Bréa - Hôtel Saint Paul

Social program

Activities

Tuesday September 17, 2024, in the afternoon, we will offer you few activities. You will be able to choose one activity during the registration process. Note that there is a limited number of places available per activity.

Guided tour in Old Nice

Initially emerging as a resort destination, Nice is today classified as a UNESCO world heritage site. Discover the culture and rich history of Nice by exploring the waterfront and the old town. You'll learn a lot during this fun walking tour, while admiring the magnificent baroque architecture and medieval old town. You will be asked to choose between the two tours of offer: “When Nice invents the Riviera” and “Old Nice”.
10€/person

SENSAS: Sensory experience

In teams, your mission is to complete 6 sensory workshops. Put your senses to the test with one ultimate challenge: by being immersed in almost total darkness! How well do you know the unsuspected power of each of your senses? It will make you experience an even stronger moment, filled with joy, good humor... and a healthy dose of fear! He will also take care of taking as many photos as possible for you.
20€/person

Visit to the Lazaret cave

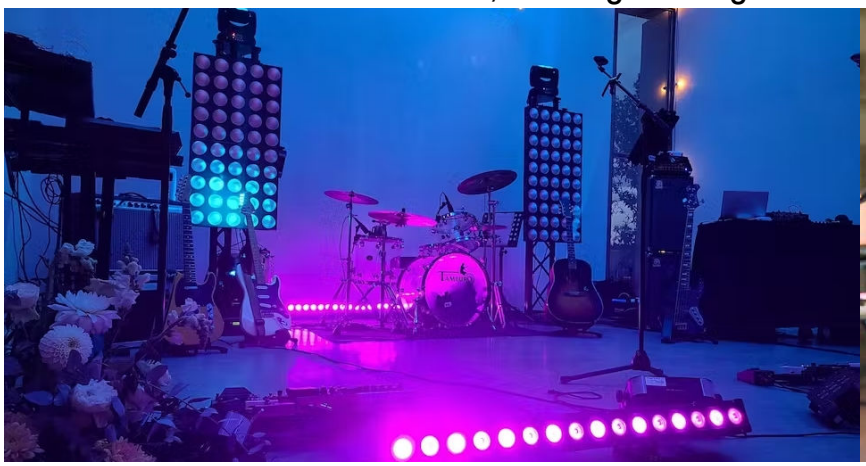
Discover the history of Lazaret man and his environment, existing aroung 120-190,000 years ago. The site tour lasts approximately 1 hour, to which a guided tour around the cave of approximately 45 minutes can be added. The collections of the prehistoric site of the Lazaret cave will be accessible to students and researchers during the visit.
Free activity

Gala dinner

Thursday September 18, 2024, we will have the pleasure of sharing a cocktail and a gala dinner at the citadel of Villefranche-sur-Mer. A “Folklore & Traditions” surprise will await you upon your arrival. You will be asked during registration to choose between the menu detailed below or a vegetarian alternative of the menu.

Transport from the congress hotel to the gala dinner place is provided by the organization via a bus transfer.
Departure time: 7pm at Hôtel Saint-Paul

And afterward, dancing evening with a live concert!!



Music band: Star Preacher

General Public Conference

Perturbateurs endocriniens : Recherche et Réglementation.

Endocrine disruptors : Research and Regulations

Mhaouty-Kodja Sakina, Research Director

Sakina Mhaouty-Kodja1

1. Sorbonne Université, CNRS UMR8246, INSERM U1130, IBPS, Neuroscience Paris Seine, Neuroplasticité des Comportements de Reproduction, Paris, France.

Depuis le milieu du 20ème siècle, l'activité humaine a généré une contamination de l'environnement par des substances chimiques destinées à la fabrication de produits à usages industriels et agricoles. Parmi ces polluants chimiques, certains désignés sous le nom de perturbateurs endocriniens sont capables d'interférer avec le système endocrinien et entraîner un effet néfaste sur les individus ou leur descendance. La perturbation endocrinienne représente un nouveau défi dans le cadre de la santé environnementale. Que désigne-t-on par système endocrinien et quel est son rôle dans l'organisme ? Que sont les perturbateurs endocriniens ? Sont-ils dangereux pour la santé humaine et l'environnement ? Leur usage est-il réglementé et comment ? Ces questions seront abordées dans le cadre de cette conférence.

Since the middle of the 20th century, human activity has led to the contamination of the environment by chemical substances used in the manufacture of industrial and agricultural products. Some of these chemical pollutants, known as endocrine disruptors, are capable of interfering with the endocrine system, with harmful effects on individuals or their offspring. Endocrine disruption represents a new challenge for environmental health. What is the endocrine system and what role does it play in the body? What are endocrine disruptors? Are they dangerous to human health and the environment? Is their use regulated, and how? These questions will be addressed at this conference.

Claude Fortier Lecture

Susceptibility to modern food environment: a role for brain lipid sensing?

Luquet Serge, Research Director

Cansell Celine1, Berland Chloé1, Montalban Enrica1, Benoit Simon1, Li Guangping1, Castel Julien1, Ansoult Anthony1, Martin Claire1, Trifilieff Pierre2, Walle Roman2, Bosh-Bouju Clementine2, Faure Philippe3 , Cebrian-Serrano Alberto4,5, Small Dana. M6,7,8, Gangarossa Giuseppe1, Luquet Serge1

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4. Institute for Diabetes and Obesity, Helmholtz Diabetes Center (HDC), Helmholtz Zentrum München, 85764 Neuherberg, Germany.
5. German Center for Diabetes Research (DZD), 85764 Neuherberg, Germany.
6. The Modern Diet and Physiology Research Center, New Haven CT, USA.
7. Department of Psychiatry, Yale University School of Medicine, New Haven CT, USA.
8. McGill University Health Center (RI-MUHC).

In the brain, neurons and glial cells are equipped with the necessary machinery to transport and metabolize nutritional lipids. Since neurons only uses glucose as energy substrate it has been postulated that lipids might act as signaling molecule. Lipid sensing was initially described in hypothalamus, and alter described in various brain structures including the reward dopaminergic system which is is instrumental to encode the reinforcing/rewarding aspects of feeding. In the reward circuit, DA-producing and dopaminoceptive neurons specifically express the lipoprotein lipase (LPL), an enzyme able to hydrolyze the dietary form of lipids, namely the triglycerides (TG), suggesting that circulating TG might modulate the activity of dopaminergic and dopaminoceptive neurons. By using in vivo central TG delivery, which mimics post-prandial increase of TG specifically in the brain, we have discovered that circulating TG act directly onto DA-D2 (DR2) receptors expressing neurons modulating the reinforcing and motivational values of feeding. In humans, we discovered that the neural responses to food cues show a significant correlation between postprandial increases in TG and the presence of Drd2/Taq1A genetic polymorphism. Taq1A polymorphism is one of the most commonly studied in psychiatry. TaqIA is located in the gene that codes for the Ankyrin repeat and kinase domain containing 1 kinase (ANKK1) near the dopamine D2 dopamine receptor (DR2) gene. It affects 30 to 80% of the population and its homozygous expression of the A1 allele correlates with a 30 to 40% reduction of striatal DR2, a typical feature of addiction, over-eating and other psychiatric pathologies. Using genetic approaches, we revealed that Ankk1 loss-of-function in dorsal and ventral striatum leads to alteration in learning, impulsive, and flexible behaviors resembling the endophenotypes described in A1 carriers. We also observed an unsuspected role of ANKK1 in striatal DR2-expressing neurons in the regulation of energy homeostasis and documented differential nutrient partitioning in humans with versus without the A1 allele. We are now investigating the consequences of an engineered point mutation in mice to produce humanized TaqIA mutation. Altogether, our data indicates that genetic variant of TaqIA greatly influence how the reward system response to modern food environment and particularly nutritional lipids to control behavior and metabolism.

Jacques Benoît Lecture

The amazing molecular diversity of hypothalamic neurons: Tackling mechanisms one neuron at a time.

Belsham Denise, Professor

Denise Belsham1

1. Departments of Physiology and Medicine, University of Toronto, Toronto, Ontario, Canada

The hypothalamus maintains whole-body homeostasis by integrating information from circulating hormones, nutrients and signaling molecules. Distinct neuronal subpopulations that express and secrete unique neuropeptides execute the individual functions of the hypothalamus, including, but not limited to, the regulation of energy homeostasis, reproduction, and circadian rhythms. Alterations at the hypothalamic level can lead to a myriad of diseases, such as type 2 diabetes mellitus, obesity, and infertility. The excessive consumption of saturated fatty acids can induce neuroinflammation, endoplasmic reticulum stress, and resistance to peripheral signals, ultimately leading to hyperphagia, obesity, impaired reproductive function, and disturbed circadian rhythms. This lecture focuses on the how the changes in the underlying molecular mechanisms caused by palmitate exposure, the most commonly consumed saturated fatty acid, and the potential involvement of microRNAs, a class of non-coding RNA molecules that regulate gene expression post-transcriptionally, can result in detrimental alterations in protein expression and content. Studying the involvement of microRNAs in hypothalamic function holds immense potential, as these molecular markers are quickly proving to be valuable tools in the diagnosis and treatment of metabolic disease.

SNE Prize

Hypothalamic POMC neurons control competing behaviours.

Miralpeix Cristina, Post-doctoral Researcher

Cristina Miralpeix1*, Abel Eraso-Pichot1*, Melissa Sadallah1, Victor Jouque1, Urszula Skupio1, Vincent Simon1, Philippe Zizzari1, Samantha James1, Carmelo Quarta1, Giovanni Marsicano1, Daniela Cota1

1. University of Bordeaux, INSERM, Neurocentre Magendie, U1215, F-3300 Bordeaux, France.
**These authors contributed equally*

Survival in natural habitats forces animals to constantly adapt their behavior according to their intrinsic needs and environmental conditions. This situation can put basic physiological responses in competition, forcing the animal to make a choice. For instance, a hungry animal in a threatening situation will favor fear responses over their motivation to eat to ensure survival. However, in this context, how the brain senses the inner state and a threatening situation to orchestrate an optimal survival response has been poorly studied. Within the hypothalamus, pro-opiomelanocortin (POMC)-expressing neurons classically promote satiety during energy surfeit and have a role in the physiological adaptations that occur during stressful and fearful events. Recent findings from our lab have demonstrated that POMC neurons activity is regulated by cannabinoid type 1 (CB1) receptors, key physiological determinants of synaptic and behavioral functions. Here, we hypothesized that CB1 receptor-dependent signaling in POMC neurons is at the intersection of fear and feeding responses. Mice lacking CB1 in POMC neurons POMC-CB1-KO, did not show any relevant change in food intake in basal condition compared to their control littermates. However, when POMC-CB1-KO mice were fasted and in a fearful situation (using fear-conditioning protocol), they displayed higher motivation for eating and decreased fear response than their control littermates. Immunofluorescence and chemogenetic studies showed that POMC activation is necessary for suppressing the motivation to eat in a threatening situation. However, POMC neurons without CB1 are hyperactive, possibly impairing proper decision-making. In addition, POMC neurons are a heterogeneous population that can express both inhibitory and excitatory neurotransmitters. We have observed that mice with impaired release of GABA in POMC neurons, also favor eating behavior over fear responses. Thus, these results suggest that CB1 receptors and GABA release in POMC neurons are key to balancing fear and feeding behaviours. Finally, since a threatening situation can activate the stress response and POMC neurons modulate stress hormones release through CRH neurons, we evaluated corticosterone plasma levels observing that corticosterone levels of POMC-CB1-WT and KO correlate with their eating behaviour and fear response. Therefore, we are now deciphering a POMC-to-CRH neurons circuit as a possible key to control competing behaviors.

SNE Thesis Prize

Dietary fatty acid composition drives neuroinflammation and impaired behavior in obesity.

Sanchez Clara, Post-doctoral Researcher

Clara Sanchez1, Cécilia Colson1,2, Nadine Gautier2, Pascal Noser3, Juliette Salvi4, Maxime Villet1, Lucile Fleuriot1, Caroline Peltier4, Pascal Schlich4, Frédéric Brau1, Ariane Sharif5, Ali Altintas3, Ez-Zoubir Amri2, Jean-Louis Nahon1, Nicolas Blondeau1, Alexandre Benani4, Romain Barrès1,3, Carole Rovère1

1. Université Côte d'Azur, Institut de Pharmacologie Moléculaire et Cellulaire, CNRS, France
2. Université Côte d'Azur, Institut de Biologie de Valrose, CNRS, INSERM, France
3. Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Denmark
4. Université Bourgogne Franche-Comté, Centre des Sciences du Goût et de l'Alimentation, CNRS, INRAe, France
5. Université de Lille, CHU Lille, Laboratory of Development and Plasticity of the Neuroendocrine Brain, Lille Neurosciences & Cognition, UMR-S 1172, Lille France

Nutrient composition in obesogenic diets may influence the severity of disorders associated with obesity such as insulin-resistance and chronic inflammation. Here we hypothesized that obesogenic diets rich in fat and varying in fatty acid composition, particularly in omega 6 (ω6) to omega 3 (ω3) ratio, have various effects on energy metabolism, neuroinflammation and behavior. Mice were fed either a control diet or a high fat diet (HFD) containing either low (LO), medium (ME) or high (HI) ω6/ω3 ratio. Mice from the HFD-LO group consumed less calories and exhibited less body weight gain compared to other HFD groups. Both HFD-ME and HFD-HI impaired glucose metabolism while HFD-LO partly prevented insulin intolerance and was associated with normal leptin levels despite higher subcutaneous and perigonadal adiposity. Only HFD-HI increased anxiety and impaired spatial memory, together with increased inflammation in the hypothalamus and hippocampus. Our results show that impaired glucose metabolism and neuroinflammation are uncoupled, and support that diets with a high ω6/ω3 ratio are associated with neuroinflammation and the behavioral deterioration coupled with the consumption of diets rich in fat.

Symposium 1

S1.1. Sex differences in the neuroendocrine control of puberty: Current knowledge and open questions

Tena-Sempere Manuel, Professor

Manuel Tena-Sempere1

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Puberty is a fascinating maturational event in the lifetime of any individual, which is under the precise control of complex neuroendocrine regulatory networks. These pathways transmit the regulatory effects of a wide variety of endogenous signals and environmental factors, including metabolic and nutritional cues, therefore allowing to precisely and timely regulate the complete activation of the secretory activity of GnRH (gonadotropin-releasing hormone) neurons in the basal forebrain, as key hierarchical element of the so-called hypothalamic-pituitary-gonadal (HPG) axis and major driving force for pubertal progression. While notable chronological and phenotypic differences exist between male and female puberty, there are also important commonalities, including the central role of GnRH neurons, and some of their major upstream regulators, in the neuroendocrine control of puberty. The latter prominently include kisspeptins, the products of Kiss1 neurons, which have been recently recognized as major gatekeepers and indispensable regulators of puberty onset in both sexes, by virtue of their capacity to activate GnRH neurosecretion. Admittedly, however, most of our current understanding on the ultimate mechanisms whereby puberty is centrally controlled derives from preclinical studies conducted mainly in females, while key aspects of the neurohormonal basis of male puberty are mostly inferred from female data. This might be especially relevant when addressing the control of puberty by nutritional cues, where direct inference of mechanisms from one sex to the other is hampered by the intrinsic differences in the sensitivity of female vs. male puberty to metabolic cues. Here, I will recapitulate our current understanding of basic neuroendocrine mechanisms for pubertal control, with particular emphasis on the current gaps of knowledge and open questions regarding potential sex differences in the brain mechanisms for pubertal control. Recognition of such differences (and gaps of knowledge) would help to illuminate new
topics of research, leading to a better understanding and management of pubertal disorders, not only in girls but also in boys.

Symposium 1

S1.2. Sexual dimorphism in microglial sensitivity to nutrients.

Nadjar Agnès, Professor

Nadjar Agnès1,2

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Microglia are the brain macrophages, eliciting multifaceted functions to maintain brain homeostasis across lifetime. To achieve this, microglia are able to sense a plethora of signals in their close environment. In our research, we explore the influence of nutrients on microglial function for several reasons: 1) Microglia exhibit all the necessary cellular machinery for nutrient sensing; 2) Dietary patterns have undergone significant changes in the past century, shifting towards high calorie diets; 3) This so-called “Western diet” correlates with a rise in neuropathologies, where microglia are recognized to play a substantial role.
During my presentation, I will share data illustrating how variations in nutrient intake can modify microglial function, leading to an exacerbation of synaptic pruning. These changes have profound implications for neuronal activity and subsequent behavior. Additionally, I will present previously undisclosed data shedding light on the mechanisms that underlie the impact of nutrients on microglia, particularly in the regulation of their metabolic activity.
Finally, I will share data that show how significantly all these responses vary depending on the sex of the animals.

Symposium 1

S1.3. Hypothalamic and Autonomic Control of Metabolism: Does Sex Matter?

Caron Alexandre, Professor

Silva Anisia1,2, Efole Bernie1,2, Lavoie Olivier1,2, Elmquist Joel3, Michael Natalie1,2, Caron Alexandre1,2

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The leptin-melanocortin system is one of the best appreciated neuronal pathways involved in the regulation of energy and glucose homeostasis. Evidence suggests sexual differences in the way this system influences metabolism. Thanks to the development of modern approaches allowing spatiotemporal, intersectional, and chemogenetic manipulations of melanocortin neurons, we now appreciate how complex and heterogenous this system is. Using an adult-inducible model, we previously reported that definitive pro-opiomelanocortin (POMC) neurons expressing leptin receptors play a pivotal role in liver metabolism, independently of changes in energy balance. More recently, we reported that leptin exerts both excitatory and inhibitory effects in hypothalamic POMC neurons. We also provided evidence that sex does not appear to be a major determinant of the basal properties and the leptin responsiveness of hypothalamic POMC neurons. However, despite evidence that POMC neurons regulate hepatic metabolism through the autonomic nervous system, the receptors and pathways involved in the central control of the liver are still unsettled. Moreover, whether sex differences exist in brain-liver communication is unknown. Based on recent tissue clearing studies, showing that neural innervations within the liver are of sympathetic nature, we hypothesized that adrenoceptors expressed by hepatocytes directly mediate the autonomic control of liver metabolism. We generated novel mouse models allowing specific deletion of adrenoceptors in hepatocytes. We found that selective deletion of hepatic alpha-1b adrenoceptor (Adra1b) exacerbated diet-induced obesity, insulin resistance and glucose intolerance in female, but not male mice. In obese females, this was accompanied by reduced hepatic gluconeogenic capacity and reprogramming of gonadal adipose tissue with hyperleptinemia. Our data highlight sex-dependent mechanisms by which the sympathetic nervous system regulates energy and glucose homeostasis through ADRA1B. Future investigations will determine whether these receptors mediate melanocortin-dependent control of liver metabolism.

Symposium 1

S1.4. Sex differentiation programs of the embryonic hypothalamus

M. Kurrash Deborah, Professor

Jing Zheng1,2,3 and Deborah Kurrasch1,2,3

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Arginine vasopressin (AVP) neurons in the hypothalamic paraventricular region (AVPPVN) influence sex-biased social behaviors in many species. In mice, neural sex differences become established around birth due to the secretion of testosterone from testes and its conversion to estrogen in sexually dimorphic brain regions. We discovered that AVPPVN neurons show sexual dimorphism by embryonic day 15.5 (E15.5), prior to the established critical window. Gestational exposure to estrogen or the estrogenic contaminant BPA from E7.5-E15.5 masculinizes female AVPPVN neurons, leading to lasting effects on adult brains, including the display of male-like traits. This masculinization occurs around embryonic day 11 (E11), in alignment with peak neurogenesis. Exposure to estrogen receptor antagonists from E14.5-E15.5 prevents masculinization in males. Combined, these findings reveal a new window of estrogen sensitivity that can influence embryonic neurodevelopmental programs.

Symposium 2

S2.1. Is Alzheimer's disease a stress-related disorder? Focus on the therapeutic potential of selective glucocorticoid receptors modulators.

Canet Geoffrey, Post-doctoral Researcher

Canet Geoffrey1,2,3

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Alzheimer's disease (AD) is characterized by the accumulation of β-amyloid peptides (Aβ) and the abnormal phosphorylation of tau protein in the brain. The cognitive deficits associated with AD correlates with an early disruption of the hypothalamic-pituitary-adrenal axis (HPA), resulting in the excessive production of glucocorticoids (GC) and subsequent impairment of glucocorticoid receptors (GR) signaling. In an acute model of AD induced by the intracerebroventricular injection of Aβ peptide oligomers (oAβ), we observed the dysregulation of the HPA axis along with cellular changes reminiscent of human AD pathophysiology. This enabled us to identify a vicious cycle where the disease induces an overproduction of GC, which in turn exacerbates AD pathophysiology. The objective of this study was to break this vicious cycle by using a new class of molecules known as selective GR modulators (sGRm).
First, we assessed the short- and long-term therapeutic potential of the sGRm CORT113176 in two complementary AD models: the acute oAβ model and the J20 transgenic mouse model (overproducing Aβ peptides). Subsequently, we employed sGRm as a tool to investigate the central role of GR in various AD-related signaling pathways. We examined the phosphorylation state of GR, its chaperone proteins (HSP90/70), the balance between amyloidogenic and non-amyloidogenic pathways, and the main enzymes involved in both GR and tau phosphorylation (GSK-3β, Cdk5, Calpain-1, Fyn).
Our findings indicated that CORT113176 can effectively prevent short- and long-term behavioral and molecular abnormalities associated with amyloid toxicity, including memory and synaptic deficits, elevated plasma GC levels, neuroinflammation, apoptosis, and Aβ production. Furthermore, our results suggest that GR plays a central role in the pathophysiology of AD, as these receptors are involved in the key pathways associated with oAβ toxicity.
In summary, our results underscore the significance of the HPA axis and GR in the pathophysiology of AD, potentially bridging the gap between amyloid toxicity and tau hyperphosphorylation. This research also highlights the promising approach presented by sGRm in breaking the vicious cycle between HPA axis dysregulation and amyloid toxicity, while restoring the fundamental role of GC and GR in maintaining homeostasis.
(This project is supported by France Alzheimer/FRC, Fondation Vaincre Alzheimer & the LabEx LipSTIC).

Symposium 2

S2.2. How metabolic hormones interact with the brain: therapeutic applications for Alzheimer's disease.

Calon Frédéric, Professor

Calon Frédéric1

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Alzheimer's disease (AD) is an age-related neurodegenerative disorder that shares risk factors with metabolic diseases. In this presentation, we will delve into the intricate relationship between metabolic hormones, including insulin, FGF21, and IGFBP2, and their interactions with the brain, with a particular emphasis on the role of the blood-brain barrier (BBB). We will explore preclinical research conducted in animal models, analyze post-mortem data from human AD samples, and examine fluid measurements in individuals experiencing early stage cognitive decline. More specifically, we will interrogate whether these metabolic hormones cross the BBB and how they induce signaling into cerebral cells. Finally, we will discuss the potential therapeutic applications, highlighting how the extensive therapeutic arsenal available for diabetes and obesity may provide opportunities for repurposing drugs for the treatment of AD.

Symposium 2

S2.3. Unveiling the Brain's Chubby Secrets: Disrupted cholesterol and Lipid metabolism in Alzheimer's Disease.

Gratuze Maud, Research Fellow

Gratuze Maud1

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Alzheimer's disease (AD) is one of the biggest scientific and socio-economic challenges of the 21st century. Currently, there is no cure. Aggregates of amyloid-β and tau protein are hallmarks of AD that lead to synaptic and neuronal loss as the basis for cognitive decline.
Interestingly, Alois Alzheimer initially identified a third distinctive pathological feature in Alzheimer's disease, but this aspect received limited attention from early researchers. Notably, individuals with Alzheimer's disease exhibit an increased presence of 'adipose inclusions' or 'lipoid granules' in their brains, indicating aberrant lipid metabolism. However, the profound link between lipid metabolism and AD only became apparent when the ε4 allele of the apolipoprotein E (APOE) gene emerged as the strongest genetic risk factor for the disease.
Moreover, extensive research spanning decades has unveiled intricate connections between lipid metabolism and fundamental Alzheimer's disease mechanisms, encompassing amyloid formation, energy deficits, oxidative stress, neuroinflammation, and myelin degradation.
In our discussion, we will explore the compelling evidence that defines the disturbances in lipid and cholesterol homeostasis in AD and examine the ways in which lipid metabolism contributes to the pathogenesis of the disease, ultimately affecting disease risk. These findings hold promise for a future where we can combat Alzheimer's effectively by addressing the complex interplay between lipids and brain health.

Symposium 2

S2.4. Unveiling the thermoregulatory nexus: Exploring the intricate interplay between temperature dysregulation and Alzheimer's disease pathogenesis.

Planel Emmanuel, Professor

Emmanuel Planel1

1. Université Laval, Faculté de médecine, Département de psychiatrie et neurosciences, Québec, Canada

Hormonal control of sleep and body temperature involves a complex interplay of various hormones regulated by the hypothalamus and other endocrine glands. In Alzheimer's disease (AD), tau pathology in the hypothalamus can disrupt these critical functions, contributing to symptoms such as sleep disturbances and altered thermoregulation. The impairments in thermoregulation and sleep are interrelated. Disturbances in body temperature regulation can exacerbate sleep problems, and poor sleep can further disrupt thermoregulation. Interestingly, several studies have shown that repeated exposure to heat through sauna sessions is inversely associated with AD. Sauna use is associated with well-being and relaxation, as well as improved sleep and increased body temperature. Therefore, we hypothesized that body temperature might have an effect on certain neuropathological features of AD, such as the tau protein.
Here, we demonstrate that temperature variations during the sleep-wake cycle regulate the phosphorylation and secretion of tau protein in mice and correlate with tau levels in the blood and cerebrospinal fluid in humans. Furthermore, we show that temperature can affect tau pathology levels and its alternative splicing. These data suggest that sauna use could delay tau-mediated neurodegeneration by correcting misalignments in sleep and core body temperature associated with thermoregulatory disturbances and sleep disorders in aging and early stages of AD. Thus, various forms of thermotherapy might offer promising therapeutic strategies for AD and other tauopathies.

Symposium 3

S3.1. Thyroid hormone control of thermogenesis: a dialog between the hypothalamus and the periphery.

Gauthier Karine, Research Director

Zekri Yanis1, Rial-Pensado Eva2, Guyot Romain1, Lopez Miguel2, Flamant Frédéric1, Gauthier Karine1

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Cold exposure and High Fat Diet feeding trigger thermogenesis to maintain body temperature and limit weight gain. T3 efficiently induces thermogenesis and hypothyroidism is associated with hypersensitivity to cold and diet induced obesity. TR are expressed in merely every tissues and T3 was described to induce thermogenesis either directly in the metabolic tissues or in the hypothalamus to increase SNS output. We used the Cre/loxP system to identify the cells and the signalling pathways responsible for T3 thermogenic action under physiological conditions. T3 signalling was selectivily inhibited in neurons or in mature brown adipocytes by the simultaneous mutation of Thra and Thrb. Both cold and diet induced thermogenesis were impaired in the BAT selective mutants whereas neuron mutants were only more sensitive to diet induced obesity. This corelates with an increase of D2 activity in both BAT and hypothalamus in response to HFD, only in BAT in response to cold. In addition the direct T3 target genes in BAT involved in cold response were determined using transcriptomics approaches. They all belong to pathways important for heat production.
Altogether it suggests that a local increase of T3 concentration participates to increase thermogenic processes in different tissues depending on the physiolocal conditions.

Symposium 3

S3.2. Mechanisms of central hypothyroidism in IGSF1-deficiency syndrome.

Bernard Daniel, Professor

Bernard Daniel J.1

1. Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec.

Loss-of-function mutations in the X-linked immunoglobulin superfamily, member 1 gene (IGSF1) are now recognized as the most common cause of congenital central hypothyroidism in humans. Igsf1 knockout mice also exhibit central hypothyroidism and have been instrumental in determining underlying disease mechanisms. IGSF1 is a transmembrane protein of unknown function highly expressed in the anterior pituitary gland, with enrichment in thyrotrope cells. Thyrotropin (TSH) production is significantly reduced in pituitaries of Igsf1 mice, whereas their hypothalamic thyrotropin-releasing hormone (TRH) expression is normal to slightly elevated. Thus, a pituitary defect appears to underlie central hypothyroidism in IGSF1 deficiency. The precise nature of the defect is not yet clear, however. In this lecture, I will discuss our recent efforts to resolve IGSF1 function in the pituitary using transcriptomic and proteomic approaches. The results may finally uncover how IGSF1 loss leads to TSH deficiency and central hypothyroidism.

Symposium 3

S3.3. Alteration of the central circadian clock during hypothyroidism.

Bonnefont Xavier, Research Fellow

Bonnefont Xavier1,2

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Our circadian clock keeps us in tune with the day-night cycle by regulating our behavior and physiology with a period close to 24 hours. This endogenous period is encoded genetically, which accounts for the diversity of human circadian phenotypes (chronotypes): the clock ticks faster in early chronotypes (morning larks) than in late chronotypes (night owls). However, chronotype can change with age or pathological conditions, indicating that other, as yet unknown, mechanisms beyond circadian clock genes are involved. Sporadic observations indicate that hypothyroidism may alter chronotype in both human patients and laboratory animal. We investigated the origin and consequence of such circadian alterations in a mouse model of induced hypothyroidism.
We observed that mice fed with a low-iodine diet, enriched with the antithyroid drug propylthiouracil (PTU), display a shorter circadian period in running-wheel activity under constant darkness, as compared to control mice. Those hypothyroid mice also exhibit an elevated level of anxiety in behavioral tests. Using in vivo calcium imaging in freely-moving mice, we found that this phenotype is associated with a reversible desynchronization of circadian cell rhythms in the suprachiasmatic nuclei (SCN), where the central pacemaker is located. Taken together, our findings in hypothyroid mice suggest that normal thyroid hormone levels regulate cell-cell coupling in the SCN to set the chronotype, and contribute to good mental health.
Supported by Fédération pour la Recherche sur le Cerveau (FRC, Neurodon 2021)

Symposium 3

S3.4. Memory deficit in mice fed a high fat high sucrose diet during adolescence linked to hypothyroidism in the hippocampus.

Ginieis Rachel, Post-doctoral Researcher

Rachel Ginieis1, Jean-Christophe Helbling1, Mariano Ruiz-Gayo2, Guillaume Ferreira1, Etienne Challet3, Marie-Pierre Moisan1

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The consumption of calorie-rich diet has adverse effects on short and long-term memory, especially when introduced early in life when the brain is still maturing. Time-restricted feeding (TRF) without calorie restriction has proven to be an efficient strategy to reduce the deleterious effects of diet-induced obesity on metabolism. TRF was also shown to be beneficial to restore long-term memory in Alzheimer rodent models. Here, we provide evidence that four weeks of TRF restore the rhythmicity of some metabolic parameters together with short and long-term memory in mice fed a high fat-high sucrose (HFS) diet since weaning. Hippocampal translatome analyses indicated that impaired memory of mice under ad libitum HFS diet is accompanied by changes in genes associated with thyroid hormone signaling and astrocytic genes involved in the regulation of glutamate neurotransmission. TRF restored the diurnal expression variation of part of these genes and intra-hippocampal infusion of T3, the active form of thyroid hormone, rescued the memory performances of ad libitum HFS diet-fed mice. Thus, TRF demonstrates positive effects on both metabolism and memory in mice fed an obesogenic diet, highlighting this nutritional approach as a powerful tool in addressing obesity and its related comorbidities in mice. The analogous time-restricted eating in humans is an easy to implement lifestyle intervention that should now be tested in obese adolescents with memory alterations.

Young Researcher Symposium 4

S4.1. Hormone-mediated neural remodeling orchestrates parenting onset during pregnancy

Ammari Rachida, Post-doctoral Researcher

Rachida Ammari1, Francesco Monaca1, Mingran Cao1, Estelle Nassar1, Patty Wai1, Nicholas A Del Grosso1, Matthew Lee1, Neven Borak1, Deborah Schneider-Luftman2, Johannes Kohl1

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During pregnancy, physiological adaptations prepare the female body for the challenges of motherhood. Becoming a parent also requires behavioral adaptations that include changes in the brain and underlying networks. Such adaptations can occur as early as during pregnancy, but how pregnancy hormones remodel parenting circuits to instruct preparatory behavioral changes remains unknown. We used patch clamp recordings of Galanin neurons in the Medial Preoptic Are of the Hypothalamus (MPOAGal) neurons to unravel the synaptic changes that sustained pregnancy induced changes.We found that action of estradiol and progesterone on galanin (Gal)–expressing neurons in the mouse medial preoptic area (MPOA) is critical for pregnancy-induced parental behavior. Whereas estradiol silences MPOAGal neurons and paradoxically increases their excitability, progesterone permanently rewires this circuit node by promoting dendritic spine formation and recruitment of excitatory synaptic inputs. This MPOAGal-specific neural remodeling sparsens population activity in vivo and results in persistently stronger, more selective responses to pup stimuli. Pregnancy hormones thus remodel parenting circuits in anticipation of future behavioral need.

Young Researcher Symposium 4

S4.2. Neuronal circuits underlying maternal dietary habits and the programming of offspring health.

Haddad Tovolli Roberta, Research Fellow

Haddad-Tovolli Roberta1

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Maternal physiological and behavioural adaptations during pregnancy and lactation are set to provide an adequate environment for the correct growth and nurture of the infant. Disturbances in this delicate balance during critical periods of embryonic and perinatal development may exert life-long influences on disease predisposition in early life and adulthood. In this talk, I will describe our latest findings on the dynamic rearrangements taking place in the maternal brain underlying distinctive feeding behaviours during pregnancy. In addition, we will discuss how maternal unbalanced dietary habits, including HFD exposure, food cravings and emulsifiers consumption directly influence the development of key neuronal centers that control feeding and metabolism, as well as its impact in neuropsychiatric health.

Young Researcher Symposium 4

S4.3. Maternal gut microbiome alteration has enduring effects on offspring's metabolic programming and neuroendocrine plasticity.

Rastelli Marialetizia, Post-doctoral Researcher

Rastelli Marialetizia1, Catherine Michel2 , Isabelle Grit2, Patricia Parnet2, Sebastien G. Bouret1

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The alarmingly high prevalence of obesity and type 2 diabetes, particularly in children, highlights the need to better understand the mechanisms involved in the development of these pathological conditions. Previous studies showed that alterations in the maternal nutritional environment disrupt the development of hypothalamic circuits with enduring metabolic consequences in the offspring. Recent evidence also linked maternal gut microbiome with offspring's brain development and behavior. Nevertheless, whether the maternal gut microbiome(mGM) affects the development of offspring's hypothalamic circuits with short- and long-term consequences on hypothalamic function remains unknown. Here, we examined the consequences of impairment of mGM on physiological and neurodevelopmental outcomes in the offspring. To this aim, we developed a mouse model of maternal dysbiosis during gestation and lactation by administering a cocktail of large spectrum antibiotics(ABX) in dams. The aim was to target critical phases of the hypothalamic development,that include embryonic neurogenesis,postnatal circuit formation and hypothalamic barriers maturation. We first validated the model by confirming that during gestation, lactation and up to weaning the abundance of gut bacteria was markedly reduced in ABX-treated dams compared to controls. Maternal body weight during gestation,litter size or litter sex ratio were not affected by the treatment. A battery of metabolic tests were performed to examine the consequence of maternal dysbiosis on the offspring's metabolic regulation. mGM alteration slows pre-weaning offspring body weight gain. However,the offspring of antibiotic-treated dams(off_ABX) display a catch-up growth between weaning and adulthood,mainly due to an increase in longitudinal growth. At adulthood,male off_ABX develop metabolic alterations. Adult female off_ABX exhibit delayed puberty onset,but no metabolic impairments. In addition,preliminary results suggest that off_ABX present neuroanatomical changes of the blood-hypothalamic barrier in the median eminence, which is at the crossroad between the brain and the periphery and plays a crucial role in regulation of metabolism. Together, these results support the hypothesis that mGM contributes to the development of the neuroendocrine hypothalamus with both short- and long-term consequences on metabolic regulation and reproductive functions in the offspring associated with structural changes of the blood-hypolathamic barrier

Symposium 5

S5.1. Histamine: at the nexus of sleep and metabolism.

Michael Natalie, Associate Professor

Natalie J Michael1, Alexandre Caron1, Charlotte E. Lee2, Carlos M. Castorena2, Syann Lee2, Jeffrey M. Zigman2, Kevin W. Williams2, Joel K. Elmquist2

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Histaminergic neurons reside in the tuberomammillary nucleus in the posterior hypothalamus. They project extensively throughout the central nervous system and provide the sole source of neuronal histamine to the brain. Functioning more as a neuromodulator than a traditional fast neurotransmitter, histamine can influence diverse populations of neurons, signaling via multiple metabotropic histamine receptors. While the histaminergic neurons are best recognised for their role promoting arousal and regulating transitions between sleep and wakefulness, the central histaminergic system is also implicated in energy homeostasis. Despite the ability of histamine to influence energy intake and energy expenditure, whether histaminergic neurons can detect changes in energy status remains underexplored. Using transgenic mouse models in combination with single neuron recordings and in vivo physiological techniques, we explored the ability of histaminergic neurons to detect metabolic signals encoded by the melanocortin system, one of the brain's major systems detecting changes in energy state. We determined that melanocortin receptor activation with melanotan II (MTII) excites the histaminergic neurons. Furthermore, we demonstrate that blockade of the melanocortin-induced excitation of histaminergic neurons dramatically enhances the anorexigenic effects of MTII. These findings suggests that melanocortin-induced excitation of the histaminergic neurons may act naturally as a brake, or negative feedback loop, to the normal feelings of satiety induced by melanocortin receptor activation. Our work highlights an underappreciated link between metabolic signals and the wake-promoting histaminergic neurons.

Symposium 5

S5.2. Leptin modulation of motivation and mood.

Fulton Stéphanie, Professor

Stéphanie Fulton1

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In a manner corresponding to energy status, leptin exerts diverse effects on behavior. This presentation will cover evidence amassed illuminating leptin's influence on brain reward circuitry, including midbrain dopamine neurons, and on several goal-oriented behaviors vital to the preservation of energy reserves. Low leptin levels serve as a key driver of appetitive behavioral actions and can reinforce stimulus-response connections that propel anticipation for and engagement in behaviors such as feeding, running and foraging - effects that can be reversed by leptin administration. Beyond direct observations of motivated behavior, we also show that lack of leptin signaling in these circuits gives rise to negative affective states such as anxiety. As will be discussed, this concomitant effect of low leptin on emotions can be conceived as another biological installation serving to rebuke stagnation to favor behaviors that restore energy. These diverse effects of leptin illustrate the potency of this hormone to serve as a multifarious signal influencing numerous aspects of behavior in a manner responsive to and consistent with the organism's metabolic state.

Symposium 5

S5.3. Serotonergic neurons are involved in the counter-regulatory response to hypoglycemia.

Fioramonti Xavier, Research Director

Hugo Martin1, Adeline Coursan1, Justine Lallement2, Mathieu Di Miceli3, Janany Kandiah2, Ilyès Raho2, Jasmine Buttler4, Jean-Philippe Guilloux5, Philippe De Deurwaerdere4, Sophie Layé1, Vanessa Routh H.6, Bruno P. Guiard7, Christophe Magnan2, Céline Cruciani-Guglielmacci2, Xavier Fioramonti1

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Objectives. Intensive insulin therapy provides optimal glycemic control in patients with diabetes. However, intensive insulin therapy causes so-called iatrogenic hypoglycemia as a major adverse effect. The ventromedial hypothalamus (VMH) has been described as the primary brain area initiating the counter-regulatory response (CRR). Nevertheless, the VMH receives projections from other brain areas which could participate in the regulation of the CRR. In particular, studies suggest a potential role of the serotonin (5-HT) network. Thus, the objective of this work is to determine the contribution of 5-HT neurons in CRR control.
Methods. Complementary approaches have been used to test this hypothesis in quantifying the level of 5-HT in several brain areas by HPLC in response to insulin-induced hypoglycemia, measuring the electrical activity of dorsal Raphe (DR) 5-HT neurons in response to insulin or decreased glucose level by patch-clamp electrophysiology; and measuring the CRR hormone glucagon as an index of the CRR to the modulation of the activity of 5-HT neurons using pharmacological or pharmacogenetic approaches.
Results. HPLC measurements show that the 5HIAA/5HT ratio is increased in several brain regions including the VMH in response to insulin-induced hypoglycemia. Patch-clamp electrophysiological recordings show that insulin, but not decreased glucose level, increases the firing frequency of DR 5-HT neurons in the DR. In vivo, both the pharmacological inhibition of 5-HT neurons by intraperitoneal injection of the 5-HT1A receptor agonist 8-OH-DPAT or the chemogenetic inhibition of these neurons reduce glucagon secretion, suggesting an impaired CRR.
Conclusion. Taken together, these data highlight a new neuronal network involved in the regulation of the CRR. In particular, this study shows that DR 5-HT neurons detect iatrogenic hypoglycemia in response to the increased insulin level and may play an important role in the regulation of CRR.

Symposium 5

S5.4. From chemistry to neuroendocrinology: tools and breakthroughs in the understanding ODN role in the hypothalamic regulation of energy homeostasis.

Leprince Jérôme, Research Fellow

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Endozepines designate a family of peptides including diazepam-binding inhibitor (DBI) and its processing fragments such as ODN, that have been isolated for their ability to interact with the benzodiazepine (BZ) binding site at the GABA-A receptor. At this allosteric site, BZ enhance the action of GABA, whereas DBI and ODN reduce. Consequently, the central effects of ODN have long been described as inducing anxiety, increasing conflict and generating aggressive behavior in rodents. Recent data also support ODN role in neurogenesis through this negative allosteric mechanism. We have previously demonstrated that cultured rat astrocytes contain and release substantial amounts of DBI-related peptides and that ODN acts as an autocrine factor controlling the intracellular [Ca2+] through activation of a receptor pharmacologically different from canonical BZ binding sites, that likely belongs to the GPCR family. These data suggest that ODN presents other effects mediated by this receptor, which require the development of specific tools, particularly an antagonist. To this end, we studied ODN structure-activity relationships to identify peptide molecular determinants responsible for the activation of astroglial cells. We demonstrated that the C-terminal octapeptide is the shorter truncated analog of ODN possessing a full biological activity, and that Leu15 is essential for GPCR activation. By combining several modifications, we rationally designed cyclo[DLeu5]OP (LV-1075), which totally prevents the ODN-evoked [Ca2+] increase in astrocytes. With this singular tool, we explored novel central effects of ODN. Based on the significant expression of DBI mRNA in the hypothalamus, we showed that intracerebroventricular (icv) injection of ODN reduces food intake in rodents and that concomitant administration of LV-1075 completely reverses this effect. Since then, our understanding of ODN anorexigenic effect has significantly expanded, participating directly in the demonstration of the involvement of glial factors in the central regulation of energy balance. Currently, our research is focused on employing alternative routes of administration for our GPCR-agonist analogs to reduce food intake. Simultaneously, we intensify our efforts to develop probes aimed at characterizing the GPCR involved in the metabolic effects of ODN. We recently designed a first fluorescent probe for covalently transferring its tag to the receptor on astrocytes, paving the way for GPCR identification.

Oral communication

OC1. Unravelling the role of mitochondria-associated cannabinoid receptors type 1 (mtCB1) in glucose homeostasis: unexpected new partners for insulin secretion.

Allard Camille, Associate Professor

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The endocannabinoid system, which includes cannabinoid receptors type 1 (CB1R), has a key role in the regulation of glucose homeostasis. CB1R are highly expressed in the brain but also to a lesser extend in the pancreas, two essential organs contributing in the maintenance of physiological glycaemia, thanks to inter-organ humoral and neural communications. CB1R do not only localize at the plasma membrane (pmCB1), but also at the mitochondrial membrane (mtCB1). pmCB1 and mtCB1 play different roles in the regulation of cognitive and behavioral responses. Of note, available evidence on the role of CB1R in the modulation of insulin secretion is conflicting.
Hence, the goal of our work was to understand the relative contribution of pmCB1 and mtCB1 to glucose homeostasis. For this purpose, we used an animal model expressing a mutant form of CB1 (named DN22-CB1) which lacks in vivo mitochondrial localization and functions, but maintains pmCB1-related signaling.
We observed that DN22-CB1 mice are hyperglycemic in basal conditions (chow diet) and display reduced plasma insulin, while retaining insulin sensitivity. Insulin secretion measured in vivo is then abrogated in DN22-CB1 mice under high-fat diet (HFD). Neural recordings after glucose injection suggested no alteration in vagal signaling in DN22-CB1 mice. Glucose-stimulated insulin secretion data obtained from isolated islets of chow-fed DN22-CB1, full CB1-KO and their control littermates suggest that both pmCB1 and mtCB1 participate to the regulation of insulin secretion in complex ways. We observed profound differences in protein content, endocannabinoids content, and cells' kinome activity in response to glucose in pancreatic DN22-CB1 islets. Further analyses are ongoing to reveal the specific underlying mechanisms involved in this response dependent on subcellular CB1 pools. These studies will pinpoint novel molecular mechanisms regulating glucose-dependent insulin secretion, possibly leading to new pharmacological targets against type 2 diabetes.

Oral communication

OC2. c-fos induction in the choroid plexus, tanycytes and pars tuberalis is an early indicator of spontaneous arousal from torpor in a deep hibernator.

Cazarez-Marquez Fernando, Post-doctoral Researcher

Markussen Fredrik Andreas Fasth1, Cazarez-Marquez Fernando1, Melum Vebjørn Jacobsen1, Hazlerigg David1, Wood Shona1

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Hibernation is an extreme state of seasonal energy conservation, reducing metabolic rate to as little as 1% of the active state. During the hibernation season, many species of hibernating mammals cycle repeatedly between the active (aroused) and hibernating (torpid) states (T–A cycling), using brown adipose tissue (BAT) to drive cyclical rewarming. The regulatory mechanisms controlling this process remain undefined but are presumed to involve thermoregulatory centres in the hypothalamus. Here, we used the golden hamster (Mesocricetus auratus), and high-resolution monitoring of BAT, core body temperature and ventilation rate, to sample at precisely defined phases of the T–A cycle. Using c-fos as a marker of cellular activity, we show that although the dorsomedial hypothalamus is active during torpor entry, neither it nor the pre-optic area shows any significant changes during the earliest stages of spontaneous arousal. Contrastingly, in three non-neuronal sites previously linked to control of metabolic physiology over seasonal and daily time scales – the choroid plexus, pars tuberalis and third ventricle tanycytes – peak c-fos expression is seen at arousal initiation. We suggest that through their sensitivity to factors in the blood or cerebrospinal fluid, these sites may mediate metabolic feedback-based initiation of the spontaneous arousal process.

Oral communication

OC3. Glucose homeostasis and energy metabolism are impaired in orexins deficient mice.

Devere Mélodie, PhD Student

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The orexin system consists of two neuropeptides, orexin A and orexin B (also known as hypocretin-1 and hypocretin-2), encoded by the same polypeptide precursor, and their two receptors orexin/hypocretin 1 and orexin/hypocretin 2. Orexins are biologically active neuropeptides that were found to control feeding behaviour and glucose homeostasis. However, despite the various studies undertaken to determine the precise role of orexins, the results reported vary depending on the experimental conditions, and the role of orexins and the mechanisms involved remain unclear. To go further, in the present study we investigated, the impact of altered endogenous orexin production on the regulation of energy and glucose metabolism using a mouse model deficient for the prepro-orexin gene.
Surprisingly, despite a decrease of food consumption, in males, orexin deficiency induces a significant increase in body weight compared to the wild-type mice. This is associated with an alteration of the body composition, as males and females orexin deficient mice have an increased fat mass compared to the wild-type littermates. Nevertheless, no significant differences of global energy expenditure and locomotor activity were measured.
Glucose homeostasis is also impaired in the absence of orexins, since glucose tolerance is reduced and insulin secretion and sensitivity are diminished. In addition, the livers of the male orexin-KO mice are significantly larger and heavier with more adipose tissue than the wild type mice. Interestingly, orexin deficient mice present an increase of the hepatic glucose production and an alteration of the expression of liver enzymes playing a key role in gluconeogenesis and glucogenolysis, in fed and fasted conditions.
To sum up, the orexin deficency leads to decrease in food intake, glucose tolerance and insulin sensitivity, as well as an increase in fat storage, and hepatic glucose production, which is more pronounced in males than in females. These findings further support the idea that orexins are a key regulator of energy metabolism. In particular, they appear to play an important role in maintaining the body's glucose homeostasis and could be an interesting therapeutic target in the context of 'diabesity'.
Key words: orexins; feeding behaviour; energy expenditure; glucose homeostasis

Oral communication

OC4. Regulating corticosterone secretion: is it a fo(u)r stars service?

Duquenne Manon, Post-doctoral Researcher

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Energy homeostasis and stress response involve constant adaptation, which recruits much of the same circuitry. One of the major contributors to this adaptation is the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for regulating the production and secretion of glucocorticoids (cortisol in humans and corticosterone in rodents). Disruption of this dynamic neuroendocrine circuitry, which is regulated by the PVN, directly contributes to the development of metabolic disorders and anxiety. Recent findings from our lab indicate that astrocytic GR activity suggest an important role of astrocytic GR activity in regulating synaptic and behavioural responses to stress. Despite these data, the involvement of astrocytes in the regulation of the HPA axis remains poorly understood. Therefore, we set out to test the hypothesis that astrocytic GR signalling may be important for regulating corticosterone secretion.
For that, we generated transgenic mice to induce astrocyte-specific deletion of GR in a brain wide manner (AstroGRKO mice). Metabolic phenotyping was then performed on both female and male mice before and after a metabolic challenge. In basal conditions, AstroGRKO mice were found to have an increased fat mass associated with a higher ZT2 corticosteronemia than controls. However, the behavioural and metabolic consequences of this phenotype differed between sexes. Following a 16-hour fasting/refeeding test, we observed a slower recovery from body weight loss in AstroGRKO males and the absence of the characteristic corticosterone response to fasting. Interestingly, this phenotype was absent in females, suggesting once again distinct roles of astrocyte GR signalling between sexes. To determine the mechanism underlying astrocytic GR-dependent corticosterone secretion, we investigated astrocytic reactivity and c-fos immunoreactivity changes in critical hypothalamic regions. Our findings suggest that astrocytic GR signalling in the PVN may be a key factor in the observed phenotype. To investigate this further, we employed a viral approach (AAV-GFAP:cre) to selectively reduce the expression of GR in PVN astrocytes.
Overall, our results indicate, for the first time, that astrocytic GR signalling plays a critical role in the maintenance of circadian secretion of corticosterone and adaptation to metabolic stress in a sex-dependant manner.

Oral communication

OC5. Local translation as a molecular mechanism underlying tanycyte-neuron communication for energy balance regulation.

Estrada-Meza Judith, Post-doctoral Researcher

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Energy balance requires a fine-tuned crosstalk between the periphery and the central nervous system. In the hypothalamus, tanycytes line the walls and floor of the third ventricle and extend their processes into brain parenchyma. This strategic location allows tanycytes to integrate peripheral metabolic cues and modulate neuronal function in consequence. Here, we investigate local translation as a molecular mechanism underlying tanycyte-neuron communication for energy balance regulation.

We use a wide variety of technologies including electron microscopy, puromycin, live imaging, In Situ Hybridization and immunofluorescence to study translation in tanycytes. We show the presence of endoplasmic reticulum, mitochondria, the mRNAs of multiple genes that regulate energy balance and translating ribosomes throughout tanycyte processes, strongly suggesting that local translation takes place in tanycytes. We also show that the nutritional context modifies the tanycytic ultrastructure for local translation. Interestingly, using electron microscopy 3D models, we highlight that at the interface of tanycyte-neuron contacts, both cells are enriched in endoplasmic reticulum-plasma membrane and endoplasmic reticulum-mitochondria contacts. These types of contact sites participate in intracellular calcium homeostasis, and tanycyte calcium transients have been shown to trigger tanycyte-neuron communication. Using live calcium imaging, we show that the nutritional context also modulates tanycyte calcium transients. Finally, preliminary results suggest that the molecular mechanism linking tanycytic nutritional status and local translation is calcium.

Our results suggest that tanycyte processes contain ultrastructure that could participate in tanycyte-neuron communication via calcium homeostasis and the distal localization of protein synthesis.

Oral communication

OC6. Effects of in utero high fat and high sucrose diet exposure on postnatal growth and pubertal development.

Jacquinet Charlotte, PhD Student

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The prevalence of obesity continues to rise worldwide. It comes with a growing concern about the effect of a high-fat diet during pregnancy on child's health. We therefore investigated the effects of a high fat-high sucrose (HFHS) diet during gestation on pubertal development and reproduction in offspring using a rat model.
Dams were exposed to HFHS (45% fat, 40% sugar) ad libitum 5 weeks before mating until 1 week after the birth of pups. We studied the effect of HFHS diet in utero on female and male pup growth and pubertal development. Animals were studied at postnatal day (PND) 25 (juvenile females) or PND 35 (juvenile males), at puberty, 24 hours after puberty (post-pubescent) and during adulthood.
Juvenile female and male pups exposed to HFHS diet during gestation showed a lower body weight compared to controls. Females had a lower weight from PND14 to PND 42 (2way ANOVA: F (3,48) = 5,371 p-value = 0,0029). Moreover, juvenile females exposed to HFHS in utero had a lower gonadal white adipose tissue (gWAT) (t-test, p-value =0,0015, mean +- SD: 0,007 +- 0,002) compared to control (mean +- SD: 0,027 +- 0,015). Lower gWAT (t-test, p-value = 0,0005, mean +- SD: 0,10 +-0,04) persisted in post-pubescent females exposed to HFHS compared to control females (mean +- SD: 0,21+- 0,05).
Exposed males had a lower weight from PND 21 to PND42 (2way ANOVA: F (3,54) = 2,872, p-value = 0,0446). However, gWAT weight was only decreased (Mann-Whitney, p-value = 0,0289, U=9, mean rank CTL: 10,71, mean rank HFD: 5,62), mean +- SD: 0,37 +-0,02) in post- pubescent males exposed to HFHS in utero compared to controls.
Gestational exposure to HFHS diet did not affected pubertal timing in females or males. Juvenile females exposed to HFHS in utero had a lower ovary weight (t-test, p-value =0,018, mean +- SD: 0,013 +- 0,001) compared to control (mean +- SD: 0,017 +- 0,003) females, but ovaries weight in post-pubescent females was no more affected. Post-pubescent males exposed to HFHS in utero had a lower testis weight (t-test, p-value = 0,016, mean +- SD: 0,84 +-0,08) compared to controls (mean +- SD: 1,01 +- 0,085).
In conclusion, exposure to HFHS diet in utero impaired postnatal growth in male and female juveniles. It did not appear to affect puberty timing but testis weight was decreased in HFHS exposed males while ovarian weight was not affected.

Oral communication

OC7. GnRH, a fertile new pathway for the regulation of food intake.

Sicardi Alicia, PhD Student

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Eating disorders are multifactorial and complex diseases with no effective long-term treatment. Patients suffering from these pathologies show severe alterations in their reproductive function such as dysmenorrhea and fertility problems even after remission. The hypothalamus is the seat of regulation of many vital functions including reproduction and energy metabolism. An interconnection exists between them. The reproductive function is orchestrated by GnRH neurons. The way in which metabolic state can modulate the function of GnRH neurons is well documented. Indeed, it is known that in the presence of a disturbed energy balance due to both an excess and a lack of energy reserves, reproduction and hence GnRH neuronal activity is shut down. In contrast, the existence of an inverse link is much less clear. To investigate whether GnRH neurons can regulate metabolism, we generated mice in which activity-dependent exocytosis, including GnRH secretion, is blocked by the Cre recombinase-dependent expression of the Clostridium botulinum neurotoxin serotype B light chain (Gnrh1::cre; iBot). Gnrh1::cre; iBot mice show a drastic decrease in food intake as well as deregulation of body weight and other metabolic parameters. A 15-day treatment restoring the physiological rhythm of GnRH secretion in these mice rescues these alterations. Beyond state-of-the-art approaches, such as ultrahigh field 17.2T magnetic resonance imaging, as well as more classical neuroanatomical and physiological approaches are being used to untangle the role of GnRH in the regulation of food intake and eating behavior. Overall, our results show an involvement of the reproductive hormone GnRH in the regulation of eating behavior and raise the intriguing possibility that pulsatile GnRH therapy holds potential for the management of eating disorders.

Oral communication

OC8. Effects of minipuberty disruption on the expression of sexual behavior in female mice.

Torres Thomas, PhD Student

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Background
The development of nervous structures governing sexual behavior relies on a tight regulation by sex steroids during early organizational windows. In rodents, a critical perinatal period during which fetal and neonatal testosterone surges occur has been identified and widely studied in males. In contrast, data are lacking for females, whose ovarian activity starts later in the postnatal period. The minipuberty period has recently been described in female mice, corresponding to a transient activation of the gonadotropic axis, with high levels of estradiol. This study investigated the role of this minipubertal period in the organization of female sexual behavior.
Methods
For this purpose, we transiently disrupted the minipubertal estradiol surge between postnatal days 10 and 17, using two pharmacological models: 1) a daily injection of 10 µg of Ganirelix®, a gonadotropin-releasing hormone (GnRH) antagonist, and 2) a daily injection of 50 µg of letrozole (a reversible aromatase inhibitor) in the absence or presence of 0.1 mg of flutamide (a non-steroidal anti-androgen). We assessed puberty initiation, estrous cyclicity and expression of sexual behavior (olfactory preference, ability to attract male, lordosis), along with locomotor activity and anxiety-related behaviors in female mice.
Results
Disruption of minipuberty by these two pharmacological methods did not impact puberty initiation. Adult estrus cyclicity was mildly disturbed by both treatments with changes in duration of metestrus or diestrus phases. Behavioral assessment of ovariectomized and hormonally primed females showed minor modifications of some components of sexual behavior. Olfactory preference of Ganirelix-treated mice was slightly reduced, and letrozole/flutamide-treated females showed a reduced ability to attract males compared to controls. These effects had no impact on lordosis behavior. Interestingly, while locomotor activity was unchanged, an increased anxiety state was observed in letrozole-treated female mice compared to controls.
Conclusions
Overall, this study showed that pharmacological disruption of minipuberty had only minor effects on adult female reproductive function and behavior. This period therefore does not seem to be a key organizational window for female sexual behavior. Nevertheless, estradiol released at minipuberty appears to participate in the organization of neural structures involved in anxiety-related behavior.

Poster - Flash Talk

PF1. Untangling the complexity of POMC neurocircuits: anatomic, genetic and functional perspectives.

Barbier Marie, Post-doctoral Researcher

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The melanocortin system, including hypothalamic pro-opiomelanocortin (POMC)-expressing neurons has been involved in the control of energy and glucose homeostasis, and in cardiovascular functions. Such a variety of functions suggests high heterogeneity of POMC neuronal system at both anatomic and genetic levels. In line with this, hypothalamic POMC neurons project into several brain areas and to spinal cord, and recent studies confirmed a strong genetic variability in POMC neurons subpopulations in mice. Interestingly, some evidence suggests a correspondence between the genetic heterogeneity of POMC neurons subpopulation with their projections. Nonetheless, such a level of details has never been reached to describe POMC neuronal network and most of published data have been generated in males and absent or marginalized in females. Regarding the sexual dimorphism in the prevalence of pathologies caused by alteration of energy and glucose homeostasis, and cardiovascular functions, it is urgent to better describe the POMC neuronal system in both male and female mice. In this study, we aim to untangle the complexity of hypothalamic neuronal network and to assess whether POMC subcircuits support specific functions by using anatomical, genetic and functional approached in male and female mice. To achieve the goals of this study, we will 1. Provide an exhaustive description of hypothalamic POMC neurons distribution and projections pattern in both female and male mice, 2. Create a 3D Connect-seq mapping integrating anatomic, genetic and spatial components in an interactive atlas and 3. Associate the identified Connect-seq to specific functions.
This project will employ neuronal tracing combined with transcriptomics, optogenetics, along with physiological and behavioral approaches. Collectively, the overarching goal of this research is to provide new anatomic and genetic basis, summarized in an interactive atlas, to develop new technical tools to precisely study the functions mediated by POMC neurons subcircuits. This will also emphasize the importance of considering, and including both sexes in preclinical studies.

Poster - Flash Talk

PF2. Exposure to high anti-Müllerian hormone (AMH) levels during mini-puberty in mice induces Polycystic Ovary Syndrome-like defects in both sexes.

Cotellessa Ludovica, Post-doctoral Researcher

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Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy affecting women worldwide, leading to various long-term cardio-metabolic repercussions. Despite its significant impact, there is currently no cure, emphasizing the urgent need for effective treatments. Gestational excess of androgens and anti-Müllerian hormone (AMH) is common in women with PCOS and preclinical studies have demonstrated that abnormal exposure to these hormones during prenatal development can cause PCOS-like traits in adult female offspring. However, it is unclear if there is also a critical period of susceptibility to PCOS during early postnatal life. Interestingly, AMH levels have been found to be significantly higher during mini-puberty in both daughters and sons of mothers with PCOS compared to infants of non-PCOS women. To elucidate whether elevated AMH levels during infancy in offspring of women with PCOS are a byproduct or a driving force behind the condition, we developed an innovative mouse model by exposing otherwise healthy mice to AMH during mini-puberty. We showed that such treatment induced PCOS-like reproductive and metabolic defects in females and males alike.
Additionally, we developed a pharmacological approach that showed beneficial effects on both reproductive and metabolic PCOS-related defects.
These findings suggest that exposure to elevated serum AMH levels during mini-puberty plays a causal role in the pathophysiology of PCOS. They also identify a window of opportunity for developing novel therapeutic preventive strategies for PCOS.

Poster - Flash Talk

PF3. Inhibition of transcytosis in tanycytes alters energy and glucose homeostasis.

Deligia Eleonora, Post-doctoral Researcher

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Objective: In Western society, high-caloric diets rich in fats and sugars have fueled the obesity epidemic and its related disorders. Disruption of the body-brain communication, crucial for maintaining glucose and energy homeostasis, arises from both obesogenic and genetic factors, leading to metabolic disorders. Here, we investigate the role of hypothalamic tanycyte shuttles between the pituitary portal blood and the third ventricle cerebrospinal fluid in regulating energy balance.
Methods: We inhibited vesicle-associated membrane proteins (VAMP1-3)-mediated release in tanycytes by expressing the botulinum neurotoxin type B light chain (BoNT/B) in a Cre-dependent manner in tanycytes. This was achieved by injecting either TAT-cre in the third ventricle or an AAV1/2 expressing Cre under the control of the tanycyte-specific promoter diodinase 2 into the lateral ventricle of adult mice.
Results: In mice fed a standard diet, targeted expression of BoNT/B in adult tanycytes blocks leptin transport into the mediobasal hypothalamus and results in increased food intake, abdominal fat deposition, and elevated leptin levels. Additionally, BoNT/B expression in adult tanycytes promotes fatty acid storage, leading to glucose intolerance and insulin resistance, despite increased insulin secretion in response to exogenous glucose boluses in vivo and in isolated pancreatic islets.
Conclusions: These findings underscore the central role of tanycytes in brain-periphery communication and highlight their potential implications in the development of type 2 diabetes. Our tanycytic BoNT/B mouse model provides a robust platform for studying prediabetic conditions and exploring the mechanistic contribution of tanycytes to metabolic disorders, offering insights into therapeutic approaches for managing these diseases. Recognizing the impact of tanycytic transcytosis on hormone transport opens new avenues for targeted metabolic therapies.

Poster - Flash Talk

PF4. Olfaction and feeding behaviour: Neuronal substrates underlying odour modulation of food intake regulating neuronal circuits.

Eygret Louise, PhD Student

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A growing proportion of the population is having problems maintaining a stable body weight. Therapeutic drug strategies deployed to modulate food intake are often accompanied by side effects. Olfactory system plays an important role in food intake, thus it could offer safer alternative strategies to regulate eating behaviour. Food intake is essentially regulated by the hypothalamic neurons of the melanocortin network: AgRP (Agouti Related Peptide) and POMC (Pro-opiomelanocortin) neurons, respectively orexigenic and anorexigenic. Previous studies showed that the presentation of food rapidly modulates the activity of these neurons in mice even before eating suggesting the involvement of sensory cues in this modulation. However, the determinants of this modulation have not been identified. Our study presents the modulatory effects of appetitive odorant molecules on hypothalamic neurons involved in the control of food intake.
We first selected attractive food odorants on both males and females. Afterwards, appetitive effect of the chosen odours was tested in cages that automatically monitored food intake. The electrical properties of POMC and AgRP neurons were characterized using patch-clamp electrophysiology on brain slices from mice previously exposed to the most appetitive odours.
We identified attractive food odours that increased food intake without preliminary association with food in males and females. The POMC neurons recorded in animals exposed to these same odours showed a modulation of their electrical activity during patch-clamp experiments, differentially in males and females. In the AgRP neurons, we recorded less impact of the odour exposure in both males and females.
Our results show the modulatory effect of food related odorants on AgRP and POMC neuron physiology. They highlight the integration of hedonic signals in the regulation of food intake by the arcuate nucleus melanocortin network.

Poster - Flash Talk

PF5. Neurosecretion is finely tuned by molecular actors sorted at the Golgi membrane level in neuroendocrine cells.

Ferrand Thomas, PhD Student

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Neuroendocrine cells orchestrate physiological processes by releasing neurohormones through a regulated secretory pathway supported by secretory granules. These organelles are generated by budding from the trans-Golgi (TGN) membrane and store neurohormones. Among all soluble proteins sorted during secretory granules biogenesis, the glycoprotein chromogranin A (CgA) is of particular interest as it is i) a precursor for biologically active peptides, ii) used as a biomarker of neuroendocrine tumors, and iii) involved in neuropeptide aggregation and sorting. We demonstrated that CgA favors TGN membrane remodeling via its interaction with phosphatidic acid (PA), essential for granule formation and exocytosis. Another study showed CgA might regulate fusion pore expansion and neurohormone release in chromaffin cells, without investigating CgA/PA interaction.

Using synthetic PA photo-crosslinkers, we identified CgA as a major PA interactant in chromaffin cells, interacting with both mono- and poly-unsaturated PA forms. Confocal and transmission electron microscopy showed CgA interaction with the plasma membrane of stimulated chromaffin cells. Total Internal Reflection Microscopy (TIRF-M), a live-cell imaging technique, revealed release kinetics of WT CgA-GFP and CgA without its PA-binding domain (CgAΔPABD)-GFP. The mutant is released faster than WT CgA, indicating the importance of CgA/PA interaction at the plasma membrane during neurosecretion.

Using carbon fiber amperometry on chromaffin cells overexpressing WT CgA-GFP or CgAΔPABD-GFP, we studied catecholamine secretion dynamics. We observed an increase in catecholamine release in cells overexpressing WT CgA-GFP, but not CgAΔPABD-GFP, suggesting CgA/PA interaction regulates secretory granule size or catecholamine loading. Moreover, WT CgA-GFP overexpression increased fusion pore lifetime, indicating a role in fusion pore expansion. Finally, confocal microscopy showed accelerated endocytosis in stimulated chromaffin cells overexpressing CgA, suggesting involvement in exocytosis/endocytosis coupling, crucial for recycling granule material post-exocytosis.

These findings highlight the critical role of CgA/PA interactions along the secretory pathway, showing CgA/PA interaction finely tunes neuroendocrine secretion at various stages.

Poster - Flash Talk

PF6. Perinatal exposure to TBBPA interferes with the establishment of the thyroid axis at young age and the ability to cope with metabolic challenges in adulthood.

Fredoc-Louison Justine, PhD Student

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Obesity incidence is increasing worldwide. It does not only result from excess calorie intake and sedentary lifestyle. Environmental endocrine disrupting chemicals (EDCs) could also be involved, deregulating fat storage and energy balance. Thyroid hormones (THs) play major role in metabolic homeostasis. They are well known to control all aspects of metabolism, acting both centrally and in peripheral metabolic organs to control lipid and carbohydrate metabolism, as well as metabolic-cellular mechanisms such as mitochondrial activity and thermogenesis. The hypothalamus-pituitary-thyroid (HPT) axis, which controls both metabolic and TH homeostasis, is set up during development. Any perinatal perturbation of this axis could have major metabolic consequences at the adult age. EDCs such as TBBPA (a flame-retardant affecting TH signalling) are detected in human amniotic fluid and milk, threatening early development of the hormonal systems. In a previous study, we have shown that exposure to TBBPA during gestation causes changes in HPT axis regulation shortly after birth, but we did not investigate consequences on adult homeostasis. Here, we studied if perinatal exposure to TBBPA interferes with the ability of two mouse strains with different thyroid and metabolic capacities, the C57BL/6J and the WSB/EiJ mice, to cope with western diet at the adult age. Pregnant dams received 10 mg/kg/d TBBPA or vehicle for 4 weeks (last week of gestation through lactation). The progeny followed either a standard or a western diet (WD) from 2 to 6 months of age. We compared the metabolic responses of the two strains treated or not with the chemical exposure and/or the diet. We have shown that TBBPA exposure transiently lowers the circulating TH levels at young age but these levels were recovered at adult age. In C57BL/6J strain, perinatal TBBPA exposure combined with WD at adult age leads to more pronounced weight gain, perturbed glucose homeostasis and changes in adipose tissues (histological aspect and mitochondrial respiration assessed by Seahorse mitostress test), while WSB/EiJ mice do not experience these effects of TBBPA. Our results reveal the obesogenic effect of a perinatal TBBPA exposure in a genetic background dependent manner, providing a proof of principle that perinatal period is very sensitive to environmentally relevant EDC exposure, and that interfering with the setup of thyroid axis during perinatal period could have dramatic consequences on health in adulthood.

Poster - Flash Talk

PF7. Transgenerational alterations of energy balance and hypothalamic melanocortin system caused by a mixture of endocrine disrupting chemicals in rats.

Glachet Chloé, PhD Student

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The prevalence of obesity has been rising worldwide for several decades. Obesity is associated with multiple risk factors, such as a lack of physical exercises, unbalanced diet, but also genetic or environmental factors such as developmental exposure to endocrine disrupting chemicals (EDC). Our recent data have indicated that transgenerational exposure to a mixture of EDC disrupted the hypothalamic control of puberty and reproduction in F3 female rats. The aim of the current study is to characterize the effects of a transgenerational exposure to such mixture of EDC on energy balance in male rats. Wistar dams (F0) were orally exposed to a mixture of 13 anti-androgenic or estrogenic EDC at environmentally relevant doses starting 2 weeks before mating, during gestation and until lactation. Third generation males (F3) were then exposed to a high fat diet (HFD, 45% fat) between 3 and 6 months of age (n= 14 for standard diet controls (CNN) and EDC (ENN), n= 13 for HFD controls (CHFD) and EDC (EHFD)).

F3 males ancestrally exposed to EDC showed a significantly higher body weight than the control group during the adulthood. This increased weight gain (Mean body weight ± SD: CNN: 570.2 ± 24.1 g; CHFD: 593.5 ± 29.3 g; ENN: 628.5 ± 38.1 g; EHFD: 630.5 ± 48.1 g) was associated with a significant increase in food intake (CNN: 34.7 ± 0.8 g; CHFD: 21.9 ± 1.1 g; ENN: 36.7 ± 3.02 g; EHFD: 25.8 ± 4.4 g). Consistently, the ratio of gonadic gonadic white adipose tissue weight over body weight (WATg) (Mean WATg weight ± SD: CNN: 0.011 ± 0.001 g; CHFD: 0.013 ± 0.002 g; ENN: 0.013 ± 0.003 g; EHFD: 0.014 ± 0,002 g) and average adipocyte size (Mean adipocyte size ± SD: CNN: 3051 ± 369 µm²; CHFD: 4020 ± 627 µm²; ENN: 4507 ± 341 µm²; EHFD: 4304 ± 1127 µm²) was increased after the transgenerational EDC exposure. From a mechanistic perspective, the study of the hypothalamic pathway controlling the energy balance (melanocortin system) showed a consistent decrease of the axonal fiber density of POMC neurons (α-MSH) controlling satiety, going from the arcuate nucleus to the paraventricular nucleus of the hypothalamus of F3 males before HFD exposure (Mean α-MSH fiber density ± SD: CTRL: 0.032 ± 0.002; EDC: 0.028 ± 0.002).

In conclusion, transgenerational exposure to a mixture of EDC leads to an obesogen-like phenotype in F3 males, coupled with an alteration of the hypothalamic melanocortin system controlling energy balance.

Poster - Flash Talk

PF8. Impact of nighttime light pollution on female metabolism in a diurnal animal model.

Grosjean Emma, PhD Student

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Metabolic functions are closely linked to circadian rhythms through reciprocal interactions. Although the population is increasingly exposed to nighttime light pollution, shift work has a negative impact on health, increasing the risk of metabolic disorders. In addition, there are gender differences when it comes to light pollution. The aim of this project is to assess the metabolic impact of nocturnal light pollution on female diurnal rodents, Arvicanthis ansorgei, whose daily temporal organisation is similar to that of women, taking into account the effects of nocturnal light (LAN) and circadian desynchronisation (jetlag).
A cohort of females was subjected to glucose tolerance tests and monitored in metabolic cages (food intake, locomotor activity) for 1 standard week (12 h light-12 h darkness), the first week and after one month of exposure to LAN, jetlag or the control condition. Another cohort was hosted in actimetric cages continuously. The jetlag protocol corresponds to a phase of 10 h of delayed light period for 4 days, then 10 h of advanced light period for 3 days (corresponding to a standard light phase), and the LAN protocol corresponds to 4 days with 6 h of light added in the middle of the night, then 3 standard days. Animals were sacrificed at different time points (at 2 months) and the blood, brain, and liver were collected for qPCR analysis (clock genes, and metabolism) and dosages (hormones, and metabolites).
Acute effects (1st week): light pollution leads to differences in eating behaviour (daytime meal/total meal ratio) over the week. Jetlag increases fasting glycaemia and night-time eating behaviour from 1 week.
Chronic effects (1 month): Individuals exposed to jetlag show a decrease in glucose tolerance, an increase in fasting glycaemia and nocturnal food intake. Those exposed to LAN showed no detectable effects on these parameters.
Chronic effects (2 months): Interday stability of locomotor activity rhythm is drastically reduced under the chronic jetlag protocol and moderately under the LAN protocol. Blood analyses show that average cholesterol levels are higher, average DAPI levels are lower than in the control group. Clock and metabolism genes in the liver are disturbed (rhythmicity, average levels) under light pollution.
In conclusion, light pollution (jetlag, LAN) has a deleterious impact on metabolism with more drastic effects for the jetlag group.

Poster - Flash Talk

PF9. Modulation of intestinal gluconeogenesis by the perinatal nutritional environment.

Habib Marina, Post-doctoral Researcher

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The de novo production of glucose by the intestine, i.e intestinal gluconeogenesis (IGN), is an essential function for maintaining metabolic health by transmitting nutritional cues to the hypothalamus. The induction of IGN protects adult mice against diet-induced diabetes and obesity, whereas its absence can lead to pre-diabetic states. Epidemiological and experimental studies evidenced the link between the nutritional and hormonal disturbances during the perinatal period and the development of metabolic and cognitive disorders. Moreover, maternal nutritional habits during gestation and/or lactation could modulate not only the “in-utero programming of metabolic pathways”, but also the composition of maternal milk. These signals regulate the development of key organs, particularly the hypothalamus. Interestingly, IGN peaks within the first few weeks of life. We showed that genetic induction of IGN from post-natal day 1 (P1), but not from P15, modulates the neuronal development of hypothalamic nuclei involved in energy homeostasis and protects adult mice from high-fat diet-induced weight gain. Proteins and metabolites produced by the microbiota from dietary fibers induce intestinal gluconeogenic genes in adults. We thus suggest that milk nutrient, enriched in proteins and carbohydrates with fiber properties, supplied by the mother could induce perinatal IGN. We sought to identify whether maternal diet during gestation and lactation might regulate the neonatal IGN peak. For this aim, G6pc1 and Pck1 expression, two key genes involved in gluconeogenesis, were analyzed in C57BL6J pups aged of 5 days (J5) and 9 days (J9) (maximal and minimal expression, respectively), born to dams fed a standard diet (CONT), a high-fat high sucrose diet (HFHS) or a high-fat high sucrose diet enriched with soluble fibers (HFHS+FOS). Our preliminary results suggested that IGN peak was significantly maintained in HFHS+FOS pups (p=0,03, two-way Anova), and to a lesser extent in HFHS pups. The Pck1 relative expression remained unchanged between different groups of pups. Thus, these results suggest that maternal diet might influence neonatal intestinal gene expression. Ultimately, understanding the mechanisms leading to IGN neonatal activation could pave the way to exploring its therapeutic potential through early-life dietary modifications.

Poster - Flash Talk

PF10. Sex-dependent developmental and physiological trade-offs in response to juvenile malnutrition.

Joly Amélie, PhD Student

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Protein malnutrition during infancy still affects more than 150 million children worldwide. It has long-lasting consequences on the organism, including stunted growth and metabolic dysfunction. Human data demonstrate that sex is a biological risk factor for stunting, with boys being more susceptible than girls. However, the biological basis of the sex-dependent susceptibility to juvenile protein malnutrition have only been sparsely investigated. Using a mouse model of juvenile malnutrition, we tested the hypothesis that the physiological response to protein scarcity is sex-dependent. To this aim, weanling mice were fed a control or an isocaloric low-protein diet during 5 weeks.

At the end of the procedure, malnourished male mice were stunted (8% shorter than controls) and wasted (30% lighter) with consistent alterations of the somatotropic axis. On the contrary, malnourished females displayed minimal weight and size growth retardation. Multi-scale metabolic phenotyping, including measures of energy balance, metabolic tests and liver transcriptomic analysis showed that metabolic adaptation to protein malnutrition is sexually dimorphic and revealed that males and females respond to malnutrition by regulating distinct metabolic pathways.

However, the apparent adaptation of females to low-protein feeding comes at the expense of an optimal sexual maturation. Indeed, malnourished females display a disrupted puberty, i.e., delayed vaginal opening and first estrus, decreased uterus weight and altered estrus cycle. In contrast, the sexual maturation of males, i.e., preputial separation, testis weight and sperm count, is not affected by malnutrition.

Our data suggest that juvenile mice differentially allocate their energy resources in response to protein malnutrition depending on their sex, with males investing in sexual maturation and females in growth and metabolic maintenance. Interestingly, production of the hepatokine Fibroblast Growth Factor 21 (FGF21) is differentially regulated in malnourished males and females, suggesting a sexually dimorphic role for this hepatokine in the response to juvenile malnutrition. We are currently investigating the potential role of FGF21 in regulating the neuroendocrine pathways mediating this trade-off and will report our results at the conference.

Poster - Flash Talk

PF11. Effect of maternal hypothyroidism during gestation on the development of GnRH neurons in the offspring.

Quignon Clarisse, Post-doctoral Researcher

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Thyroid hormones (TH) play a key role in fetal brain development and congenital hypothyroidism can cause severe neurodevelopmental disorders. However, embryos don't produce their own TH before mid-gestation, thus, early neurological development processes relies on maternal TH production. GnRH neurons are born in the olfactory placodes and migrate into the brain during this critical period of maternal TH dependency. We hypothesized that a disruption of maternal TH production during gestation might alter the development of GnRH neurons in the offspring, possibly causing long-term reproductive defect. Pregnant mice were treated with methimazole (MMI) to induce mild hypothyroidism during their gestation. ED12/13 embryos were collected from control or treated females, to study proliferation and migration of GnRH neurons. In these embryos, maternal hypothyroidism resulted in a decreased number of GnRH neurons, but migration of the remaining GnRH neurons was normal. Staining with a proliferation marker showed reduced cell proliferation in the brain of embryos collected from MMI-treated mothers, as well as the olfactory placodes, correlating with the reduced number of GnRH neurons found in this region. To assess the long-term effect of maternal hypothyroidism on reproductive functions, we compared physiological and neuronal parameters in pups born from treated and control females. MMI-treated females had reduced litter size suggesting increased reabsorption/miscarriages due to hypothyroidism. Pups born from hypothyroidic mothers had normal post-weaning growth and regular oestrus cycles. Although the number of GnRH neurons seems to be normal in the offspring, these animals have an increased amount of estrogen receptors in the arcuate nucleus at adult stage. Together, these results show the importance of maternal TH for GnRH neurons proliferation during embryonic development. Despite the reduction in GnRH neurons proliferation caused by gestational maternal hypothyroidism seems to be compensated in adult offspring, disruption of thyroid hormones during development can have long-term effect on various neuroendocrine systems, possibly leading to hormonal imbalance and reproductive dysfunctions.

Poster - Flash Talk

PF12. Noradrenergic control of proopiomelanocortin neurons.

Turmel Audrey, M.Sc Student

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Rationale: In 2022, 43% of adults worldwide were overweight or obese and this prevalence increases every year according to WHO. The central nervous system plays a key role in maintaining energy homeostasis, deregulation of which can cause obesity. In particular, the arcuate nucleus of the hypothalamus contains a neuronal population expressing proopiomelanocortin (POMC), which is involved in the control of energy balance and glucose homeostasis. Evidence suggests that the activity of POMC neurons can bqe regulated by the orexigenic neurotransmitter norepinephrine through adrenergic receptors. However, the mechanism by which adrenergic receptors expressed by POMC neurons influence energy balance and glucose homeostasis remains elusive. Aim: To determine the metabolic role of adrenergic receptors expressed by POMC neurons. Methods: In situ hybridization was performed on mouse coronal brain slices to analyze the rostro-caudal distribution of adrenergic receptors and to quantify co-expression with Pomc. We also developed a transgenic mouse model to specifically delete adrenergic receptors from POMC neurons. Cohorts of mice were fed with different obesogenic diets and a complete metabolic phenotyping was performed. Results: More than half Pomc neurons of the arcuate nucleus co-express a specific adrenergic receptor. Results obtained from our first animal cohorts do not support that this receptor is required for POMC neurons to influence energy balance. However, male mice lacking this receptor in POMC neurons are more glucose intolerant and have an altered insulin sensitivity. Conclusion: The next steps of the project will allow us to further understand the involvement of adrenergic receptors expressed by POMC neurons in the regulation of energy balance and glucose metabolism. We will determine whether the orexigenic effects of centrally administered norepinephrine remain in the absence of specific adrenergic receptors in POMC neurons.

Poster

P13. SELENOT, an essential ER-resident thioredoxin-like protein, as a therapeutic target in obesity and type 2 diabetes.

Abgrall Azénor, PhD Student

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SELENOT is a new thioredoxin-like protein involved in endoplasmic reticulum (ER) stress, which has been shown to intervene in the regulation of insulin and POMC production. Obesity is a worldwide prevalent metabolic disease characterized by a deregulation of energy homeostasis that could be linked to ER stress and associated impairment of the production of metabolism-regulating hormones, including alpha-MSH and insulin. In the present study, we hypothesized that a SELENOT-based treatment could improve metabolic alterations and reverse the negative effects of obesity and type 2 diabetes. To assess the metabolic impact of SELENOT and its therapeutic potential against obesity and associated comorbidities such as diabetes, we administrated a SELENOT-derived therapy 3 times a week to mice fed a high-fat diet (HFD). Then, we monitored different metabolic parameters. Our preliminary results revealed a tendency of slowing down the weight gain in HFD mice after this treatment. Moreover, treated mice showed a significant decrease in HFD-induced hyperglycemiacompared to control mice treated with saline. Histological studies analyzing fat content in organs of these mice indicated a decrease also in the lipidic content in the organs of mice receiving the treatment compared to control mice. These preliminary results demonstrate the impact of SELENOT in the control of energy homeostasis since SELENOT therapy appears to exert beneficial effects in obesity in mice. These results suggest that SELENOT therapy could be considered for further therapeutic development in obesity and type 2 diabetes.

Poster

P14. Deleterious consequences of TBBPA on functional remyelination.

Butruile Lucile, Associate Professor

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Over the past 40 years, thousands of endocrine disruptors (EDCs) have been introduced into our environment, leading to constant human exposure, from early development to aging. These EDCs have harmful effects on the endocrine system by interfering with the physiological action of hormones. Among them, tetrabromobisphenol A (TBBPA) is used as a flame retardant in various polymer materials. TBBPA is of environmental and health concern due to its persistence in the environment, bioaccumulation potential, and toxic effects. TBBPA is also known to interfere with thyroid hormone (TH) signaling. Neurodevelopment, and especially the generation of oligodendrocytes, the myelin-forming cells in the central nervous system, are controlled by TH. Consequently, a disturbance in TH pathway could alter the (re)myelination capacity. Functional myelin repair depends notably on (i) thyroid hormone (TH)-dependent generation of new myelinating oligodendrocytes derived from adult neural stem cells (NSCs), and (ii) the liver X receptor (LXR)-mediated local synthesis of cholesterol, the basic lipid constituent of myelin membrane.
Our overarching aim was to assess the potential adverse effects of TBBPA on remyelination capacities and on the fine-motor skills linked to remyelination capacities. To this end, we combined ex vivo (organotypic cerebellar slices) and in vivo approaches in two groups of vertebrates (xenopus and mouse) to assess how TBBPA by disrupting TH-signaling alter functional remyelination.
By combining our double ex vivo (mouse cerebellar slices) and in vivo (Xenopus tadpole optic nerve) approaches we were able to demonstrate that i) TBBPA strongly inhibited remyelination and ii) the functional consequences of TBBPA-induced impairment of remyelination in Xenopus, including reduced swimming speed, distance traveled and visual avoidance of a virtual collision. Finally, these deleterious effects of TBBPA on functional remyelination were rescued by co-exposure of TBBPA with TH or LXR agonist. In conclusion, our data illustrated that TBBPA negative effect on remyelination involved modulation of both TH and LXR action. Although direct evidence linking TBBPA to demyelinating diseases in humans is still limited, our study suggests that TBBPA exposure may contribute to demyelinating conditions related to deregulation of the TH and LXR pathways.

Poster

P15. Tanycyte-derived extracellular vesicle annexin A1 modulates microglia and neuronal functions to control energy balance.

Dali Rafik, PhD Student

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Energy balance requires accurate crosstalk between the periphery and the central nervous system. In the hypothalamus, specialized ependymoglial cells called tanycytes line the walls and the floor of the third ventricle and extend their processes into the brain parenchyma. Thanks to their strategic location, tanycytes integrate peripheral signals about the metabolic state and modulate neuronal function accordingly. However, how tanycytes communicate with neural cells remains largely unknown.

Our pilot experiment highlighted Annexin A1 (ANXA1) as a candidate tanycyte signaling molecule modulating neural cell activity and gene expression in response to energy imbalance. Here, we show that ANXA1 is expressed along the third ventricle, mainly by dorsal tanycytes and classical ependymal cells. Tanycyte ANXA1 expression and localization are regulated by energy imbalance in vivo and in vitro. Notably, our in vitro experiments show that ANXA1 colocalizes with the CD9 marker in the presence of glucose, suggesting its secretion through extracellular vesicles during positive energy balance. Proteomic analysis on isolated tanycyte-derived extracellular vesicles confirms the presence of ANXA1 in extracellular vesicles, among classical vesicular proteins. Using publicly available single-cell and single-nuclei RNA sequencing data, we next sorted microglia and neurons as putative targets of tanycyte ANXA1: notably, tanycyte ANXA1 modulates microglia number and morphology and SF1-expressing neuron activation. These neural modulations finally impact brown adipose tissue thermogenesis in response to feeding.

Our results put in light a tripartite communication between tanycytes, microglia, and neurons to modulate energy balance. This study constitutes a first step in understanding the different exchanges between hypothalamic networks to control energy balance.

Poster

P16. The preoptic Kisspeptin/nNOS/GnRH (KiNG) neuronal network regulates rhythmic LH release through a dual activation-inhibition mechanism.

Delli Virginia, Post-doctoral Researcher

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Gonadotropin-releasing hormone (GnRH) neurons are the final common target of a complex network of cells cooperating for the central control of reproduction. The balance between excitatory and inhibitory transsynaptic and non-synaptic inputs is crucial for the maintenance of the GnRH rhythms: the pulse and the surge. The precise mechanisms behind this remain under debate. In this work, we challenge the hypothesis that excitatory and inhibitory inputs from kisspeptin and neuronal nitric oxide (NO) synthase (nNOS)-expressing neurons orchestrates GnRH release, in a microcircuit that we call the Kisspeptin/nNOS/GnRH (KiNG) neuronal network. Our work specifically focuses on the role of nNOS neurons located in the organum vasculosum laminae terminalis (OV) and the median preoptic nucleus (MePO). nNOS and kisspeptin neurons interact anatomically and functionally, with the kisspeptin receptor (Kiss1r) being differentially regulated in nNOS-expressing neurons across the female estrous cycle. Using a novel viral tool allowing for the measurement of NO/cGMP levels with exquisite sensitivity, we demonstrate that kisspeptin is able to induce NO-dependent cGMP production in the OV/MePO, including in GnRH neurons in vivo. Using electrophysiological, genetic, chemogenetic and pharmacologic approaches, we reveal that NO production from nNOS neurons in the OV/MePO is needed to fine-tune the GnRH/LH response to kisspeptin, and specifically to turn off GnRH release, thus generating pulses. Our findings provide valuable insights into the tripartite KiNG neuronal network governing the regulation of the GnRH/LH pulse and surge.

Poster

P17. Cellular and molecular mechanisms underlying the disruption of sexual behavior in female mice exposed to environmentally relevant doses of phthalates.

Desroziers Elodie, Associate Professor

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Phthalates are ubiquitous in the environment, due to their widespread use as plasticizers, in cosmetics and as adjuvants in herbicides. In humans, exposure to phthalates causes fertility disorders. We have previously shown that chronic exposure of adult females to DEHP alone at 5 or 50 g/kg/d, or to DEHP in an environmental mixture reduced female reproductive behavior including olfactory preference, partner attraction and lordosis behavior (female sexual typical behaviour) (Adam et al., 2021).These behavioral alterations were associated with reduced number of progesterone receptor-immunoreactive (ir) cells in the neural circuitry underlying female sexual behavior including the ventromedial hypothalamus (VMH). Herein, this study endeavour to investigate the cellular and molecular targets of phthalate exposure in the brain regions involved in sexual behavior in female mice, with a particular focus on glial cells. For this purpose, we performed a proteomic analysis of the ventromedial hypothalamus and found 341 proteins differentially expressed between the vehicle group and DEHP-exposed groups. Following a gene ontology analysis, we identified changes in proteins implicated in different cellular functions including neuroplasticity and neuroinflammation. Brain sections processed from female mice exposed were used to perform immunohistochemistry against cell types involved in neuroinflammatory processes, i.e. astrocytes (GFAP) and microglia (IBA-1). In the VMH, we observed an increase of total GFAP-ir with no changes in the number of GFAP-ir cells in phthalate-exposed female mice compared to the vehicle group, suggesting an astrocyte reactivity as similarly observed in male mice exposed to phthalates under similar experimental conditions (Ducroq et al., 2023). Oppositely, we did not find any effect of phthalate exposure on total IBA-1 immunoreactivity nor on IBA-ir cells number after microglia phenotype characterization (ameboid, stout, thick and ramified) compared to vehicle suggesting that phthalates exposure do not trigger microglia activation in female mice contrary to our findings in male mice (Ducroq et al, 2023). These data together with the current analyses aiming to decipher the cellular and molecular targets of phthalate exposure will be presented and discussed, with a particular focus on similarities and differences with previously analyzed males.

Poster

P18. Effects of intranasal administration of an analogue of the gliopeptide ODN on energy expenditure and glucose homeostasis.

Dlimi Omayma, PhD Student

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Compelling evidence shows that endozepines, including DBI and its processing fragment ODN, contribute to the regulation of energy balance. Produced by glial cells, ODN exerts a potent anorexigenic effect by targeting canonical hypothalamic pathways via the activation of a still unknown G protein-coupled receptor (GPCR). Furthermore, it is well accepted that nasal brain drug delivery can be, in some cases, an effective route overcoming the blood brain barrier obstacles. Hence, we chose this route to centrally deliver OP, an ODN-derived analog developed in the laboratory, for modulating energy homeostasis in mice.
Our data reveal that chronic intranasal (i.n.) administration of OP (20 or 10 µg) in mice fed a normal chow (NC) or a high-fat diet (HFD) induced a significant effect on fuel selection as evidenced by a markedly reduced respiratory quotient, a higher fat oxidation level and a longer distance covered. These results suggest improved adaptation to aerobic exercise, favoring fat oxidation over carbohydrates for energy source. The chronic effects of OP on metabolic parameters were consistent with the observed loss of body weight during chronic OP treatment and implied that increased energy utilization plays a crucial role in the anti-obesity actions of OP. Similar to intracerebroventricular administration of ODN, i.n. administration of OP (2 µg) showed a significant increase in c-Fos labeling in the paraventricular, arcuate, and ventromedial nuclei, brain regions known to be implicated in energy and metabolism homeostasis.
Obesity frequently correlates with glucose intolerance leading to high glycemia, and studies have shown that endozepines enhance glucose tolerance in mice. Intranasally OP-treated (10 µg) mice, fed NC or HFD, exhibited increased glucose tolerance. However, i.n. administration of OP (10 µg) significantly reduced basal glycemia of mice fed HFD but not in mice fed NC. This finding supports previous data demonstrating an endogenous tone of endozepine which maintains basal glycemia. Indeed, in mice treated with a ODN-GPCR antagonist, higher glycemia is observed. Finally, to determine whether the anorexigenic effect of OP is partially due to visceral discomfort associated to the i.n. route of administration, a conditioned taste aversion assay was performed in normally fed mice. Our results indicate that the reduction in body weight observed in OP-instilled mice was not due to visceral malaise.

Poster

P19. A set of miRNAs regulates exocytosis in pheochromocytoma, a neuroendocrine tumor.

Drissa Inès, Post-doctoral Researcher

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Calcium-regulated secretion of hormones and neuropeptides by cells within the neuroendocrine system is essential for regulating vital physiological functions, including metabolism, growth, and reproduction. Pheochromocytomas (PCCs) are rare neuroendocrine tumors of the adrenal medulla gland that secrete high levels of catecholamines into the bloodstream, leading to clinical manifestations such as hypertension. This hypersecretion of catecholamine is due to both tumor burden and dysfunction of exocytosis, the final step of the regulated secretory pathway (RSP). However, the etiology of hypersecretory PCC activity is poorly understood. Several studies suggest that miRNAs, as post-transcriptional inhibitors, play a role in the control of the RSP. To investigate this possibility, we first built ExoDB, a general network of interactions between miRNAs and their target mRNAs involved in exocytosis. To do this, we developed a bioinformatics approach that combines the use of prediction and co-expression software. Applied to miRNA and gene differentially expressed in human PCC, we were able to identify an ExoDB subnetwork in which 31 miRNAs and 41 genes, involved in the exocytosis process, are deregulated in PCC compared to the normal adrenal medulla. To determine the regulatory capacity of these miRNAs, we developed a secretion assay based on a luminescent reporter (hGH1-Nluc) specifically expressed in the dense-core secretory vesicles of the rat PCC-derived PC12 cell line (PC12-2luc). Thus, under resting and stimulated (Ba2+) conditions, we observed that 20 of these 31 rat miRNAs inhibited secretion (-30% to -71%) following their transfection. Moreover, these miRNAs fall into 3 functional groups (resting and/or stimulated), suggesting that they regulate different stages of exocytosis. Several miRNA:mRNA interactions were experimentally validated at transcriptomic level (RT-qPCR), corroborating the inhibitory effects of miRNAs on exocytosis. To better understand the role played by these miRNAs on exocytosis, we then studied miR-34a-5p, one of the most connected miRNAs in the ExoDB network, using carbon fiber amperometry on bovine chromaffin cells in primary culture. Overexpression of bta-miR-34a-5p inhibited the number of exocytic events and slow down their kinetics (-34%). This study provide a solid basis for a better understanding of the dysregulation of secretion mechanisms in neuroendocrine tumors such as PCC.

Poster

P20. Effect of weight loss on the epigenetic remodeling of human sperm transposable elements.

Dumargne Marie-Charlotte, Post-doctoral Researcher

Marie-Charlotte Dumargne1,2, Romain Barrès1,2

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In 2023, nearly half of French adults were overweight or obese. European surveys recently reported that despite being on a diet, 70% of the people attempting to lose weight in the past 12 months did not achieve clinically meaningful weight loss. Transposable elements (TEs), commonly referred to as jumping genes, occupy more than half of the human genome. Their mobility generates structural variation with potential pathogenic consequences when their insertion disrupts important genes functions. Human sperm TEs escape DNA methylation reprogramming during gametogenesis and therefore carry potential to transmit epigenetic information from one generation to the next. Given the acceleration of obesity prevalence, we hypothesize that insertions of TE and/or epigenetic remodeling participate in the obesity pandemic. More particularly, we hypothesize that obesity spurs mobile elements activity which in turn leaves an epigenetic imprint on their jumping way that predispose the offspring genomic make-up to easier weight gain. To characterize the effects of a diet-induced weight loss on the human sperm young transposable elements, we sequenced the sperm of men with obesity using long-read Oxford Nanopore sequencing. We detected 1,549 TE insertions of the most actives sub-families, which affected 591 genes. Among these, 21 were located in promoters or exons and 570 were introners. Potential functional impact was evaluated with gene annotation and enrichment analysis, which suggested a strong relationship with genes involved in lipid and carbohydrate metabolism, muscle process and neurogenesis. As spermatozoa are haploid, the sequencing reads directly correspond to the fraction of cells carrying a TE insertion at that position. Comparison from before versus after weight loss revealed that TE insertions were never present in all reads and tended to decrease after the diet intervention suggesting that TE insertions only occur in a subpopulation of spermatozoa. The type of structural variants (insertion, deletion, inversion, duplication or translocation) and the tissue origin (germline, de novo or somatic) are currently being explored and will be presented.

Poster

P21. Target receptor identification of ODN and its role in glial regulation of hypothalamic leptin transport.

Duraisamy Karthi, Post-doctoral Researcher

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Obesity has become a global epidemic, surpassing undernutrition and infectious diseases as the leading contributor of ill health worldwide. Addressing this crisis requires new therapeutics and interventions. Our team in Rouen has discovered that octadecaneuropeptide (ODN) and its analogue (OP) significantly reduce food intake and promote weight loss in animal models. These effects are mediated by a still unidentified G protein-coupled receptor (GPCR) expressed in glial cells. Traditionally, energy homeostasis and weight regulation have been attributed to leptin-sensitive neuronal populations in the arcuate nucleus and the nucleus tractus solitarius. The novel glial mechanism involving ODN/OP and a GPCR offers promising therapeutic potential, particularly since most marketed drugs target GPCRs.
Our study aims to achieve two primary objectives: (1) identifying and characterizing the specific GPCR responsible for ODN/OP effects, and (2) exploring the role of this GPCR in facilitating leptin uptake in the brain. ODN is a gliopeptide known to modulate GABAAR at micromolar concentrations, causing anxiogenic and orexigenic effects. However, at nanomolar concentrations, ODN stimulates astrocytes to mobilize intracellular calcium, an effect inhibited by pertussis toxin, indicating G protein involvement. We developed an ODN-GPCR antagonist, cyclo(1–8)[DLeu5]OP, and demonstrated that the anorexigenic effect of ODN/OP is mediated by this receptor. Using a NASA-Cy3-tagged ODN/OP probe, we aim to identify the specific GPCR in cultured astrocytes by permanently transferring the Cy3 tag from the peptide to the target GPCR. Functional tests, including proliferation assays, ELISA, and western blot analysis, confirmed the probe's efficacy.
Another crucial aspect of our research is understanding how ODN/OP enhance leptin uptake in the brain. Preliminary data indicate that intranasal administration of OP facilitates leptin transport, increasing leptin receptor (LepR) expression and activating POMC pathways, despite an observed increase in NPY and AgRP expression. This dual activation suggests that OP can enhance energy homeostasis by promoting leptin action in the brain. Additionally, proteomics studies after intranasal administration of OP shed light on overall protein changes in the hypothalamus, elucidating the mechanisms by which OP modulates leptin signalling pathways. These findings underscore the potential of ODN/OP as therapeutic targets for obesity treatment.

Poster

P22. Role of steroid 5α-reduction in cerebroprotection at the acute phase after stroke in male mice.

Guennoun Rachida, Research Director

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Ischemic stroke is a leading cause of disability and death worldwide, and age is the main non-modifiable factor. Given that, neuroactive steroids play a key role in cerebroprotection, we investigated the effect of age and stroke on steroidome, sensori-motor performances, and neuron degeneration. Three- and 18-month-old C57BL/6JRj male mice were used in a model of ischemic stroke by middle cerebral artery occlusion for 1 hour followed by reperfusion (MCAO/R) and analyses were performed at 6 hours after MCAO. Using gas chromatography-tandem mass spectrometry, we showed that (1) brain and plasma concentrations of the main 5α-reduced metabolites of progesterone, 11-deoxycorticosterone, and corticosterone were lower in old than in young mice; (2) after MCAO/R, brain concentrations of progesterone, 5α-dihydroprogesterone, and corticosterone increased in young mice; and (3) after MCAO/R, brain concentrations of 5α-reduced metabolites of progesterone, 3α5α-tetrahydrodeoxycorticosterone, and 3β5α-tetrahydrodeoxycorticosterone were lower in old than in young mice. These lower levels of 5α-reduced steroids were associated with increased sensori-motor deficits and degenerating neurons in old mice compared to young mice. Our observations strongly suggested that steroid 5α-reduction play a role to cope with cerebral ischemia. Thus, we investigated the effects of finasteride, a 5α-reductase inhibitor. Three-month-old C57BL/6JRj male mice received either finasteride (50 mg/kg of body weight) or its vehicle 1h prior to MCAO and histological outcomes, neurological deficits and steroid concentrations were assessed at 6 hours post-MCAO. Finasteride treatment diminished drastically brain and plasma concentrations of 5α-reduced steroids but also modified concentrations of some of their precursors and of some 5β-reduced steroids. Comparatively to vehicle-treated mice, finasteride-treated mice exhibited worsened stroke outcomes, as seen with an increased infarct volume, decreased neurological score and decreased time spent on the Rotarod, together with decreased density of activated astrocytes in external capsule and stria terminalis.
Altogether, our results strongly suggest an important cerebroprotective role of the 5α-reduced neuroactive steroids at the acute phase after cerebral ischemia in male mice

Poster

P23. Hypothyroidism and memory impairments in mice fed obesogenic diet: differential exon usage analysis.

Helbling Jean-Christophe, Engineer

Jean-Christophe Helbling1, Rachel Ginieis1, Enrica Montalban1, Marie-Pierre Moisan1

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The early consumption of calorie-rich diet disrupts circadian rhythms and has adverse effects on memory, yet the effects of time-restricted feeding (TRF) and the underlying molecular mechanisms are unknown. Our study in male mice demonstrates that four weeks of TRF restore the rhythmicity of metabolic parameters and prevents memory impairments in mice fed a high fat-high sucrose (HFS) diet since weaning. Hippocampal translatome analyses indicate that impaired memory of mice under ad libitum HFS diet is accompanied by changes in genes associated with thyroid hormone signaling and astrocytic genes regulating glutamate neurotransmission during memory formation. A differential exon usage analysis revealed that an exon of thyroid hormone receptor alpha (Thralpha) is differentially used in mice fed HFS diet compared to normal chow but rescued in mice fed HFS under a time-restricted feeding regimen (HFS TRF). This result was comforted by the measure of Thr alpha isoforms mRNA expression. Similarly, 2 exons of BDNF receptor 2 (Ntrk2 gene encoding for TrkB) are differentially used in mice fed control or HFS TRF diet while no splicing events occur for Ntrk2 in HFS ad lib mice. While no significant changes were noted for the full-length TrkB isoform mRNA expression between diets, the truncated TrkB-T1 isoform mRNA appeared differentially regulated according to diet and regimen. Furthermore, Ntrk2 gene expression was found co-regulated with a number of thyroid hormone target genes during memory formation, among which astrocytic genes regulating glutamate neurotransmission. Since BDNF-TrkB-T1 signaling is involved in astrocytes' maturation, it may be possible that HFS diet affects memory through dysregulation of astrocytes development.

Poster

P24. Tanycytic Slit2 signaling directs wiring of oxytocin axons in the mediobasal region of the hypothalamus.

Jasinski Claire, PhD Student

Claire Jasinski1 , Sreekala Nampoothiri1 , Jessica Klucznik1 , Emilie Caron1 , Vincent Prévot1 and Sebastien G. Bouret1

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The hypothalamus plays a critical role in a variety of physiological and behavioral processes, including feeding. The architecture of hypothalamic neural circuits requires the tight temporal and regional regulation of expression for specific sets of genes. However, the molecular mechanisms underlying the formation of hypothalamic neural projections remain elusive. Growing axons must choose a path to follow and must decide the direction to go on this path to innervate a particular nucleus and area. The rate and direction of axon growth are defined by cell-cell interactions and diffusible chemorepulsive and chemoattractive cues. Several families of guidance molecules have been identified including netrins, semaphorins, and slits. We recently characterized the anatomical distribution of Slits in the mouse hypothalamus and found that Slit2 mRNA was heavily expressed in hypothalamic tanycytes, which are known to act as barrier properties. Here, we examined the role of Slit2 in tanycytes during adult life using a viral approach. We first performed immunohistochemical stainings for neural systems that pass near the tanycytic barrier, i.e., oxytocin, vasopressin, and GnRH. The distribution pattern of GnRH- and vasopressin-immunopositive fibers appeared normal in Slit2TanKO mice. However, Slit2TanKO mice often displayed oxytocin-positive fibers near the tanycytic layer of the third ventricle at the level of the arcuate nucleus, which was rarely seen in Slit2Con mice. These neuroanatomical alterations were accompanied by metabolic consequences: Slit2TanKO mice had increased fat mass and reduced lean mass compared to the Slit2Con mice. Given the importance of the oxytocinergic system in behaviors, we are currently exploring the consequences of tanycytic Slit2 deletion in social behavior. This study reveals a new role for Slit2 in the wiring of oxytocin axons and suggests that this system is still remarkably plastic during adult life.

Poster

P25. Role and mechanisms of leptin transport by microglia in the median eminence.

Joffre Bérengère, PhD Student

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Leptin is a hormone secreted by adipose tissue which acts in the median eminence (ME) of the hypothalamus to induce satiety and regulate appetite. In pathological condition such as obesity, leptin is produced in large quantities, but its action is impaired. This is known as leptin resistance and the reasons of this phenomenon are still not totally understood.
One hypothesis is that leptin's access to its targets is impaired. Previous work has proposed that tanycytes, which are specialized hypothalamic ependymoglial cells, lining the floor of the third ventricle, convey leptin to the ventricle lumen by transcytosis after leptin crosses fenestrated vessels. Microglia, the resident immune cells of the central nervous system, plays a pivotal role in the development of hypothalamic inflammation in obesity. As leptin modulates microglia activity, we wondered whether microglia could alter leptin availability in the ME. To address this question, we performed in vitro pulse-chase experiments with primary cultures of microglia from the ME using fluorescent leptin. Confocal microscopy analysis showed that leptin is rapidly endocytosed by microglia and reaches EEA1-positive endosomes before being sorted into Rab11-positive ones. Leptin colocalizes only partially with the Rab7-positive endosomes and the lysosomal marker Lamp1. Elisa assays showed that leptin is released by microglia, indicating that leptin does not reach the degradative pathway once endocytosed, but is rather released by microglia. Whether leptin trafficking is altered in condition of neuro-inflammation will be further addressed by studying the role of saturated fatty acids on microglia, one contributor to leptin resistance.

Poster

P26. Identification of oxytocin-antigen mimetic protein in lactobacillus and its validation in an animal model of autism.

Lahaye Emilie, PhD Student

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Oxytocin (OT) is a neuropeptide hormone playing a key role in promoting social interactions. Deficient OT signaling was associated with autism spectrum disorders (ASD). Recently we showed that immunoglobulin G (IgG) serves as an OT carrier protein modulating OT receptor activation. In this study, we tested our hypothesis that OT-binding IgG can be stimulated by homologous antigens produced by commensal gut bacteria and, therefore, can modulate social and anxiety-like behavior relevant to ASD. Targeted proteomic approach using OT-antibodies was applied to the total proteome of Lactobacillus salivarius. Mass spectrometry-identified OT-like target proteins have been synthesized and used for immunization of BTBR mice, a genetic model of ASD. Effects of immunization on social and repetitive behavior was analyzed using 3-chambers and self-grooming tests, respectively, and on anxiety by the open-field and elevated plus maze tests. Plasma levels of OT-reactive IgG and hypothalamic concentration of OT peptide were measured by ELISA. An about 50 kDa OT-like positive protein spot was consistently detected in the proteome of L. salivarius resulting in identification of 3 OT-like candidate proteins with molecular weight of 48, 43 and 50 kDa, among which only the 48-kDa protein displayed OT-like immunoreactivity. Immunization of BTBR with the corresponding recombinant proteins resulted in increased plasma levels of OT-reactive IgG by all 3 proteins but increased hypothalamic OT concentration only by the 48 kDa protein. Behavioral tests revealed significantly reduced repetitive and locomotor behavior effects of all 3 OT-like proteins but increased sociability and reduced anxiety only by the 48-kDa protein. The study identified an oxytocin-antigen mimetic protein produced by Lactobacillus salivarius which can improve OT-like signaling and OT-mediated behavior suggesting its putative application as a new therapeutic strategy against ASD.

Poster

P27. Multi-scale analysis of the genomic role of Estrogen Receptor α in immature pituitary gonadotrope cells.

Le Ciclé Charles, PhD Student

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The pituitary gland, present in all vertebrates, is responsible for the homeostatic balance of many physiological functions through the production of distinct hormones by six endocrine lineages. The appearance of these lineages is a stepwise differentiation process driven by the expression of specific transcription factors. In vertebrates, reproductive function is under the control of pituitary gonadotrope cells, which regulate gonadal activity by secreting the gonadotropins LH and FSH. Gonadotrope differentiation has been shown to be under the tight control of Nr5a1 expression, the earliest known marker of the gonadotrope cell fate. In a recent work (Pacini et al, Epigenetics Chromatin. 2019), we demonstrated that during gonadotrope differentiation, the Nr5a1 epigenetic regulation of expression is strongly dependent on estrogen receptor alpha (ERα)-mediated estrogen signaling. Interestingly, ERα is emerging as a key epigenetic regulator of many endocrine cell lineages and proteins interacting with ERα appear to be critical for modulating its activity.
In this project, we aimed to characterize the role of ERα genomic activity as well as the one of ERα protein partners in the control of early gonadotrope cell commitment. To do so, we set up a multi-scale analysis of ERα function in an in vitro model of immature gonadotrope αT3-1 cells. We notably characterized ERα target genes by RNAseq analysis, identified ERα cis-regulatory target regions by Chromatin Immuno-Precipitation assay and finally, characterized ERα interactome by proximity-dependent labeling assay. By in silico bio-informatic analysis, we then identified the cis-regulatory regions of estrogen regulated genes including those potentially co-regulated by ERα and its partners. Our results highlight that ERα gene regulatory network encompasses over 2500 genes in immature gonadotrope cells, many of them being involved in the regulation of key cellular processes of gonadotrope differentiation such as cellular migration. We specifically identified key partners, such as the Chromodomain Helicase DNA Binding Protein 7 which could be essential for ERα regulation of gonadotrope cell differentiation.
Overall, deploying a multi-scale analysis allowed us to infer ERα gene regulatory networks involved in gonadotrope differentiation. From these data, we identified many of ERα potential roles in gonadotrope differentiation and pinpointed potential key unsuspected partners in the regulation of these processes.

Poster

P28. A Hypothalamic Functional Atlas of Cell-Cell Communication.

Lopez Rodriguez David, Research Fellow

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The hypothalamus, as a hub for the reproductive and metabolic functions, is a highly specialized and interconnected region. Cell-cell interactions play an essential role in maintaining hypothalamic homeostasis and functionality. Here, we aim at establishing the first functional communication atlas of hypothalamic cell populations.
We generated a novel approach, using publicly available single cell RNAseq datasets to evaluate intercellular cell-cell communication and its association to intracellular functional signals. Multiple datasets are integrated together or split by conditions: feeding, fasting, high fat diet or by sex differences. A web interactive tool allows to visually explore the data.
In our atlas, ligand-receptor intercellular communication between two cell populations are associated to intracellular functional signals, allowing to determine activated or inactivated pathways and transcription factors at the source or target populations. To improve the biological relevance of the model, scores of communication plausibility (i.e. connectivity) were integrated in the model. Therefore, different scores can be obtained from our model: (1) an intercellular communication score (ligand-receptor interaction), (2) an intracellular pathway communication score (pathways activated/inactivated by the intercellular communication) and (3) an intracellular transcription factor communication score (TFs activated/inactivated by the intercellular communication).
The atlas can be used to infer differences in hypothalamic functional communication between hypothalamic cells originating from animals undergoing different metabolic challenges or according to sex differences.

Poster

P29. Combined effect of a high-fat diet and phthalates on the central control of male sexual behavior.

Mahiddine Lina, PhD Student

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The decrease in male fertility observed since the beginning of the 20th century in Western countries could be linked to changes in diets and exposure to molecules from industry, such as endocrine disruptors and among them, phthalates. We evaluated the
combined effects of a high fat/high fructose diet (HFHF) and an environmental mixture of phthalates, on male murine sexual behavior. 4 groups of adult male C57Bl/6J mice were exposed to: control diet (CD), control diet associated with an environmental mixture of phthalates (CD Mix), HFHF diet, and HFHF diet coupled with the mixture of phthalates (HFHF Mix). Metabolic monitoring (weight, OGTT, ITT) confirms the induction of metabolic alterations with HFHF diets, but only the HFHF Mix diet alters the efficiency of sexual
behavior, with a significant decrease in the number of animals reaching ejaculation and an increase in mating latency. These alterations are associated with a decrease in testicular, seminal glands and Tyson glands weights. No effects were recorded on locomotion activity. Interestingly, only the HFHF Mix diet induced a loss in discrimination towards female counterparts in olfactive preference test. The effect of the HFHF Mix on the cellular and molecular markers of the mPOA, the main integrating center in the control of male sexual behavior, are explored. Our results demonstrate a synergistic eFect of an HFHF diet and phthalates at doses relevant for human exposure, on sexual behavior, which could be explained by an alteration in the mPOA neural network.

Poster

P30. Central SELENOT expression regulates gonadotrope axis function, sexual behavior and fertility in male and female mice.

Mallouki Ben yamine, Post-doctoral Researcher

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Reproductive disorders are associated with neuroendocrine dysregulation in the hypothalamic-hypophysis-gonadal (HHG) axis, which can result from a defective production and action of the neuropeptide gonadotropin-releasing hormone (GnRH), the master regulator of reproduction. We have previously shown that SELENOT, a new thioredoxin-like selenoprotein highly expressed in endocrine and neuroendocrine cells, plays a role in hormone secretion. However, whether SELENOT is involved in neuroendocrine regulatory mechanisms that impinge on vital functions such as reproduction, is totally unknown. We found that brain SELENOT deficiency results in a very strong decline in fertility and impaired sexual behavior in both male and female mice. In the brain, increased number of GnRH immunoreactive neurons is observed in the hypothalamic preoptic area and in their terminals in the median eminence of both male and female mice. This leads to a marked increase in luteinizing hormone (LH), testosterone (T) and estradiol (E2) levels, and a decrease in folliculo-stimulating hormone (FSH) level in male mice. While female animals exhibit impaired estrous cyclicity and a polycystic ovary syndrome (PCOS)-like phenotype, with an increase in LH and T levels and a decrease in FSH and E2 levels. SELENOT deficiency impairs LH pulse secretion in both males and females. These phenotypes are reverted after administration of a GnRH antagonist. These results demonstrate for the first time the direct role of a selenoprotein in the neuroendocrine control of reproduction and identify a new mechanism in the brain impacting GnRH neuron activity, whose deficiency leads to male and female reproductive dysfunction.

Poster

P31. Effects of food and sleep realignment onto circadian rhythms on memory functions in adolescent patients with obesity.

Moisan Marie-Pierre, Research Director

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Time-Restricted Eating (TRE) is a nutritional intervention approach that emphasizes the realignment of meal timing onto circadian rhythms, without caloric restriction. This intervention has increased in popularity over the past decade as a potential treatment for metabolic pathology such as obesity, essentially because it does not require individuals to count calories in order to improve their health. Most TRE studies have primarily focused on the metabolic benefits of TRE in adults, largely neglecting the potential benefits of this approach on obese adolescents. Furthermore, TRE effects on brain health such as cognitive functions, anxiety, and depression have never been analyzed. The aim of the present study is to evaluate the impact of TRE on memory and mood of adolescents suffering from obesity. Obese patients aged between 12 and 17 years are recruited from the obesity specialized center of Bordeaux children hospital. A first home-based study focuses on the patients' habits in terms of food intake temporality and sleeping behavior. Based on these data, patients are either classified as synchronized or desynchronized using a cluster analysis method. Then, both groups of patients undergo 4 weeks of nutritional rehabilitation in a specialized clinic, during which the daily food intake window is restricted to10h30 (from 8.30 am to 7pm). Memory tests are conducted at the start and at the end of their clinical stay to determine any improvements following this intervention. We hypothesize that re-aligning obese adolescents' eating and sleeping schedules onto their circadian rhythms induce relative greater beneficial effects on memory performances in desynchronized patients than their synchronized counterparts. Aligned with this hypothesis, the first set of results revealed that desynchronized patients showed improved performances on 20-minute delayed memory tasks (verbal and pattern recognition memory), while synchronized patients showed no difference after 4 weeks of 10h30 TRE. While these results are preliminary, in the greater scheme of things, this study aims to provide new insights into the therapeutic value of circadian rhythm realignment on sleep quality and memory consolidation processes in adolescents with obesity.

Poster

P32. Unveiling tanycytes as immunocompetent brain cells: The conduit for sex-biased physiology.

Nampoothiri Sreekala, Post-doctoral Researcher

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Energy balance and metabolism differ in males and females. However, there is a paucity of understanding of sex-specific and ovarian cycle-influenced metabolic outcomes, the cornerstone of public health and human well-being. The mediobasal hypothalamus acts as a hub for the exchange of systemic metabolic and reproductive signals through molecularly distinct cell types localized in the region. Using single cell RNA sequencing, we investigated the profound impact of sex, ovarian cycle, and high-fat diet on the transcriptional landscape of the cells of the mouse median eminence and the periventricular region, particularly tanycytes, the gatekeepers of metabolic and reproductive signals in the hypothalamus. Among tanycytic subtypes, we discovered a unique sexually dimorphic “innate immune cell state” of tanycytes primarily driven by the ovarian cycle in female mice rather than the metabolically challenging high-fat diet in males. We found that the immunocompetent tanycytes chemoattract leukocytes and communicate with microglia while being equipped with the molecular machinery to guard the brain from excessive inflammation, which recurs every 4-5 days in cycling female mice. The cyclic immune state of tanycytes is reminiscent of the acute and cyclic leukocytic influx in the vagina at dioestrus, unveiling the hitherto unknown vaginal-brain axis. Obesity in males, on the other hand, triggers an adaptive immune response in tanycytes, opening a new frontier of investigation in HFD-induced hypothalamic neuroinflammation. This discovery of tanycytes as sexually-dimorphic immunocompetent cells and their temporal relation with the reproductive cycle of female mice shall revolutionize our understanding of sex-biased neurological, metabolic and inflammatory diseases.

Poster

P33. GnRH neurons sectional, Electrophysiological and Biomolecular characterization in rats.

Nasri Nabil, PhD Student

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The Hypothalamic-Pituitary-Gonadal (HPG) axis controls reproduction in mammals. The Gonadotropin-releasing hormone (GnRH) neurons, located in the hypothalamus, play a crucial role in controlling reproductive function by secreting GnRH into the hypothalamic-pituitary portal blood system. When GnRH reaches the anterior pituitary, it stimulates gonadotroph cells to secrete the gonadotropins Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) into the bloodstream. LH and FSH then regulate gonadal gametogenesis, folliculogenesis (in females), and the production of steroid hormones such as estradiol, progesterone, and testosterone. These hormones exert feedback control, either negative or positive, on hypothalamic GnRH release. It has been established that GnRH must be secreted in a pulsatile manner, and changes in GnRH pulse frequency and amplitude significantly impact gonads functionality, altering gametogenesis and sexual hormone secretion. The use of LH secretion as a proxy for GnRH is the standard method to measure GnRH levels and pulse frequency in humans and animal models. In animal models, the LH measurement was previously only possible through challenging venous catheterization surgery, but the introduction of mouse tail-tip bleeding techniques has significantly improved the ability to conduct detailed assessments of pulsatile hormone secretion in rodents. However, to date, the mouse remains the single species from which all our recent functional conclusions are drawn. Therefore, the detailed characterization of rat GnRH release as an experimental model is essential for broadening our understanding of the HPG axis in different reproductive physiological states.
This study advances our understanding of the Hypothalamic-Pituitary-Gonadal axis in rats, complementing existing mouse models. We successfully characterized LH pulsatility profiles in rats under various conditions using high-resolution sampling techniques. Our novel transgenic rat model, expressing GFP under the GnRH promoter, enabled precise identification and isolation of GnRH neurons, facilitating detailed electrophysiological measurements and genetic profiling. These advancements provide a more comprehensive view of the HPG axis across species and physiological states, laying the groundwork for future studies in reproductive biology and potential therapeutic interventions.

Poster

P34. Cellular and molecular effects of exposure to BPA alternatives in hippocampal neurons derived from human induced pluripotent cells.

Naulé Lydie, Research Fellow

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Bisphenol A (BPA) is used in epoxy resins and a wide variety of polycarbonate containers for the storage of foods and beverages. Health concerns have been raised concerning BPA leaching from plastic. In 2017, BPA has been classified as a substance of very high concern (SVHC) by the European Chemical Agency (ECHA) for its endocrine-disrupting properties. In this context, adverse effects were identified on learning and memory, via an estrogenic mode of action. As a result of restrictions on the use of BPA, many BPA substitutes have been developed, such as bisphenols P, AP, E, S, Z. Other halogenated bisphenols such as TCBPA are used as flame retardants. These alternative bisphenols share structural similarities with BPA, yet data on their toxicity are scarce and incomplete. The goal of this project is to use hippocampal neurons derived from human induced pluripotent stem cells (hiPSCs) to assess the effects of a chronic treatment of BPA and BPA substitutes (BPAP, BPE, BPP, BPZ,BPS-MAE, TCBPA), at the cellular and molecular levels. Hippocampal neurons were generated from hiPSCs adapting previously reported protocols. Inhibition of WNT, transforming growth factor-β (TGFβ) and bone morphogenetic protein (BMP) signaling pathways, followed by a treatment with a WNT pathway activator leads to the differentiation of hiPSCs into hippocampal neural progenitors (hNPCs) within 28 days. BDNF treatment of hNPC promotes neuronal maturation. RT-qPCR analyses showed that octamer-binding transcription factor 4- (OCT-4) expressing hiPSCs differentiated with high efficiency into hNPCs expressing NPC marker NESTIN and hippocampal progenitor markers prospero homeobox 1 (PROX1) and zinc finger and BTB domain containing 20 (ZBT20). Furthermore, the neuronal marker microtubule associated protein 2 (MAP2), and hippocampal markers ELAV like RNA binding protein 2 (ELAVL2) and glutamate ionotropic receptor kainate 4 (GRIK4) were expressed in mature hippocampal neurons at day 43. These hNPCs were treated chronically with increasing doses of BPA and BPA substitutes (starting in a first step with BPAP, BPE and BPZ) over a 14-day period. Cell viability and cytotoxicity tests are under analysis. The cells will also be subjected to a battery of developmental neurotoxicity tests. In addition, gene expression of potential key gene targets as well as DNA methylation will be analyzed in treated cells.

Poster

P35. Role of ephrinb3 in POMC neurons in the control of energy and glucose homeostasis.

Pajot Clémentine, PhD Student

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POMC-expressing neurons have been primarily described as controlling feeding behavior, but accumulating evidence also showed a crucial role of these neurons in the control of glucose homeostasis, notably hepatic glucose production and insulin secretion. For this, and in addition of being able to sense peripheral signals such as leptin, POMC neurons receive direct upstream excitatory (glutamate) and inhibitory (GABA) inputs coming from a plethora of brain areas. A recent study from our group specifically showed that the modulation of a well-known actor of glutamatergic synapse formation called EphrinB1 during development, led to reduced number of glutamatergic inputs into POMC neurons, impaired glutamatergic-dependent activity and insulin secretion in response to hyperglycemia. Interestingly, EphrinB1 and two other members of EphrinB family, EphrinB2 and EphrinB3, are still expressed in POMC neurons of adult mice. Indeed, EphrinB family members are involved in glutamatergic synaptic plasticity by modulating for instance synapse density and glutamatergic synapse stabilization. Here, we focused our study on EphrinB3, as it showed the highest level of expression in POMC neurons of adult male mice compared to EphrinB1 and EphrinB2. To determine the role played by EphrinB3 in the control of synaptic plasticity of POMC neurons, we chose to modulate EphrinB3 expression by stereotactic viral infusion. We either overexpress (Pomc-Efnb3-OE) or knock-down (Pomc-Efnb3-KD) Efnb3 (gene encoding EphrinB3) in POMC neurons of male adult mice, and exposed the animals to high fat diet (HFD), a potent modulator of synaptic plasticity of POMC neurons. We first measured the spontaneous postsynaptic excitatory currents (sEPSC) of POMC neurons in animals overexpressing Efnb3. Next, regarding the role of POMC neurons in controlling energy and glucose homeostasis, we evaluated several parameters such as body weight, body composition, food intake, glycemia, and glucose tolerance. Interestingly, Pomc-Efnb3-OE male mice showed altered AMPA-dependent sEPSC of POMC neurons compared to control mice. In addition, Pomc-Efnb3-OE male mice displayed greater body weight gain, associated with with an increased fat mass compared to control mice. In order to identify the molecular mechanisms underlying such altered physiological outcomes, we performed a single cell RNA-sequencing experiment on sorted POMC neurons in both Pomc-Efnb3-OE and control mice. Study of the mechanistic insight is ongoing.

Poster

P36. Preconceptional paternal nutrition influences metabolism and behavior in the offspring.

Pignol Marie, PhD Student

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Environmental factors such as physical activity, nutrition and pollutants influence the health of the reproductive system as well as the epigenetic program carried by gametes (oocytes and spermatozoa). Our laboratory and others have shown that nutritional factors before conception influence the phenotype of the offspring for at least two generations. In a context where the effect of maternal nutrition before and during pregnancy is widely studied, there are strong evidence about paternal nutrition factors in epigenetics reprogramming. A majority of studies investigating parental effects have observed sex-specific effects for both metabolic and behavioural traits in the offspring as a result of altered preconceptional paternal diet. Fathers fed low protein-high carbohydrate diets generate anxiety phenotype in male offspring, while metabolic traits and fat distribution of females were driven by differences in paternal dietary fat. However, the mechanisms by which paternal nutrition rewires the developmental programming of the offspring towards an altered behavioural phenotype are unknown. We hypothesize that the protein level rewires the epigenetic make-up of spermatozoa, which in turn modulates the development of the central nervous system in the offspring. To address this hypothesis, male mice were fed on iso-caloric diets with different macronutrient compositions designed by using the nutritional geometry framework. Fathers were mated with female mice fed with standard diet to generate offspring fed with standard diet. Over a period of several weeks, weight gain, food intake, metabolism and behavior was assessed and sperm samples analyzed to determine the epigenetic changes associated with the different diets. We observed metabolic impairment and weight gain of male offspring from fathers fed with high-protein diet, and anhedonia and memory deficit as well. Food intake and cognition level of female offspring were affected by fathers fed on low-protein diet. These results confirm that macronutrients balance in paternal preconceptional nutrition, in particular protein level, is essential for cognitive development. We aim to identify the epigenetic and developmental mechanisms as well as the anatomical features of the brain that may be responsible for the observed behavioral phenotypes in the offspring.

Poster

P37. Cell-to-Cell communication of hypothalamic network controlling reproduction from existing single cell RNA sequencing dataset.

Renard Margot, PhD Student

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Gonadotropin hormone- releasing hormone (GnRH) neurons are essential to mammalian reproduction. The development of their cell population, their migration, the establishment and function of their mature network are required for puberty and fertility. Human and murine studies have been instrumental to identify genes involved either in GnRH neuron fate specification or migration or homeostasis of their network. Though, the exact molecular mechanisms remain largely unknown.

In collaboration with another lab, we have built an in silico tool that infer the cell-to-cell communication dynamics in the mouse hypothalamic nuclei based on published datasets of high-throughput RNA sequencing of single cells. This inference rely on a connectivity score calculated based on the gene expression of Ligand and Receptors in source and target cell population from the dataset, on the hypothalamus neuroanatomy, and on the classification of genes ensembles as functional signaling cascades in the cell. These informations were retrieved from freely available resources and curated to be integrated in our Cell-to-Cell communication tool.

We use it to associate the molecular signature of cells from GnRH neuron network to the physiological state of the organism. We identify signaling cascades partaking in the modulation of GnRH neurons activity, amongst these, potential new factors involved in the crosstalk of metabolism and GnRH network are first validated using available data from databases and literature, most relevant gene targets will be selected for an in vivo validation study.

Poster

P38. Hyperactivation of YAP in tanycytes stimulates proliferation and alters energy metabolism.

Roux Mathilde, PhD Student

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In the adult mammalian brain, the hypothalamus has been identified as a neural stem cell (NSC) niche, in which newborn neurons integrate circuits controlling energy homeostasis. Putative NSCs of this niche are the tanycytes, specialized radial ependymoglial cells lining the 3rd ventricle (3V), which are also key components for the regulation of energy balance. A proposed candidate for the regulation of tanycyte NSC properties is the Hippo pathway (HP), a major signaling pathway involved in organ growth and stem cell control. Previous work of the lab has shown that all core components of the HP are expressed in adult mouse tanycytes. We therefore thought to explore whether the HP controls tanycyte NSC properties and impacts energy metabolism.

To do so, we used an in vivo model of hyperactivation of Yes-associated protein (YAP), the main effector of the pathway, in tanycytes, thanks to the intracerebroventricular injection of an adeno-associated virus 1/2 coding for a constitutively active mutant form of YAP (YAPCA) driven by the tanycyte-specific deiodinase 2 promoter. Mice were subsequently injected with the thymidine analog bromodeoxyuridine (BrdU) and sacrificed after 2 months in order to assess cell proliferation and differentiation. Immunodetection of BrdU showed that the expression of YAPCA in tanycytes markedly stimulated cell proliferation in the mediobasal hypothalamus, associated to increased vimentin staining along the 3V border, suggesting a disorganization of the tanycyte border. Co-immunodetection of different lineage markers (Sox2 for progenitors, HuC/D for neurons, S100β for astrocytes, Olig2 for oligodendroglial lineage cells) was performed to determine the fate of newborn cells and showed that most remained in a progenitor state, and that YAPCA did not favor the entrance in any cell lineage over the others. In agreement with neuroanatomical data, RT-qPCR analysis on tanycytes isolated by fluorescence-activated cell sorting revealed that YAPCA enhanced the expression of genes involved in cell cycle progression such as cyclin dependent kinase 6 or cyclin D1. YAPCA expression in tanycytes also increased mice bodyweight, fat mass, food and water intake, while glucose homeostasis was not affected.

Altogether, our results show that YAP regulates the proliferation of adult tanycytes and that forced activation of tanycyte proliferation impacts energy homeostasis.

Poster

P39. Postprandial hypertriglyceridemia promotes satiety via microglia inflammasome activation.

Salvi Juliette, PhD Student

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Context. Overfeeding causes significant cellular stress in all organisms, linking nutrition and inflammation. Indeed, regular consumption of high-calorie high-fat foods triggers a systemic immunological, and promotes metabolic disorders such as obesity. Recent studies have shown that this inflammatory response also occurs in the brain. Furthermore, the food-related brain inflammatory response can be detected very early, at the time scale of a meal. However, the physiological value of the postprandial inflammatory response (PIR) in the brain is totally unknown.
Aim. This study involves characterizing the PIR in the hypothalamus, a brain structure that coordinates physiological responses to maintain body energy homeostasis and that is highly sensitive to postprandial metabolic signals, in mice.
Results. Using immunostaining, 3D reconstruction and morphometric analysis, we showed that microglia, resident immune cells in the brain, can change their shape rapidly after a meal, and this phenomenon is exacerbated by a fatty meal. This results in an increase in cell process length, number of branches and complexity. Interestingly, microglial reactivity is reversible, regioselective, and appears in males only. In addition, cell sorting of hypothalamic microglia reveals a specific increase in IL-1β mRNA expression in these cells. To better understand the role of reactive microglia in the PIR, we generated AscMgKO mutant mice in which the Asc gene, an essential component of the intracellular inflammasome, is specifically deleted in microglia. Interestingly, AscMgKO mice have no phenotype and eat normally on a standard diet, but they become hyperphagic on a high-fat diet. AscMgKO mice also exhibit greed for fat in 2-food choice and gustometer paradigms. This suggests that the postprandial microglial inflammatory response that appears during overfeeding has a positive valence, stimulating satiety and maintaining energy balance. The aberrant feeding behavior found in AscMgKO mice is not present in female mice, indicating sexual dimorphism in this physiological response.
Conclusion. Thus, the PIR appears in the hypothalamus after a meal, and is exacerbated by a fatty meal. It is characterized by the reactivity and pro-inflammatory phenotype of microglia which is found in males only. The brain PIR is a plasticity-related mechanism that has an adaptive physiological value, limiting food intake under caloric pressure.

Poster

P40. Effect of maternal exposure to polychlorinated biphenyls and polybrominated diphenyl ethers on dentate gyrus function and development.

Sevrin Elena, PhD Student

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Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are two families of thyroid disruptors associated with cognitive alterations in humans and rodents. To better understand the mechanisms underlying these alterations, we studied the function and development of granule cells in the dentate gyrus after perinatal exposure to BDE-47 compared to Aroclor 1254 (PCBs). Dams were orally exposed to a daily dose of 6 mg/kg of Aroclor 1254, 0.03 mg/kg of BDE-47, 1 mg/kg of BDE-47, or corn oil (control) from the sixth day of pregnancy until 21 days after the birth. Exposure to the low dose of BDE-47 did not affect the expression of selected markers of oxidative and endoplasmic reticulum stresses in male or female newborn neurons. On the contrary, exposure to Aroclor 1254 significantly increased the expression of two markers of the unfolded protein response (data are mean+/-SEM, Atf4: p=0.045, CTL=1.17+/-0.81, ARO=2.45+/-1.22; Xbp1: p=0.049, CTL=1.097+/-0.36, ARO=1.95+/-0.84) in male mice newborn neurons. RNA sequencing in newborn neurons collected from BDE-47-exposed or control mice revealed that the expression of only a few genes was affected by exposure to BDE-47, whereas previous data showed that Aroclor 1254 exposure leads to an increase in expression of numerous genes. To study neuronal activation in the dentate gyrus after stimulation by running, we used stereotaxic injection of virus with conditional Cre recombinase that drove expression of Cre-dependent TdTomato in activated cells. There was a significant increase in activated cells (Fos/Tdt+) after exercise, but exposure to BDE-47 did not alter this expected increase (SB=superior blade, IB=inferior blade, RUN=running, HC=homecage; 2-way ANOVA p exercise=0.03, p exposure=0.96, p interaction=0.92; CTL SB HC=67680+/-28987, CTL SB RUN=98265+/-47649, CTL IB HC=59780+/-23743, CTL IB RUN=87340+/-43868, BDE SB HC=56580+/-14101, BDE SB RUN=113130+/-101760, BDE IB HC=48695+/-14667, BDE IB RUN=100313+/-918710). Exposure to Aroclor 1254 decreased Tdt+ cell density, but there was no interaction between running and exposure (p exercise=0.06, p exposure=0.03, p interaction=0.76; ARO SB HC=51349+/-19959, ARO SB RUN=57732+/-12135, ARO IB HC=37008+/-18475, ARO IB RUN=47766+/-15613). In conclusion, despite structural similarities between PBDEs and PCBs and both families being associated with cognitive alterations, our results suggest that BDE-47 acts through different pathways compared to Aroclor 1254.

Poster

P41. Seasonality of hypothalamic neurogliogenesis in Syrian hamsters: what are these new cells?

Sicot Louise, PhD Student

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Neurogliogenesis is a continuous adaptive process, from embryonic stages to adulthood, which can be influenced by various environmental factors (stress, aging, exercise, or diet). An important environmental factor that most species are exposed to is seasonal change in photoperiod, humidity, temperature, and food availability. In order to ensure species survival, individuals anticipate these variations by relying on the consistent annual variation in the photoperiod, the period of day when an organism is exposed to light. The brain integrates photoperiodic variation through a polysynaptic network, resulting in the nocturnal production of melatonin. The melatoninergic message is processed by the hypothalamus to adapt biological functions to seasons. Recent studies have shown that the hypothalamus exhibits persistent neurogliogenesis in adults with photoperiodic variations. In this context my project will test the hypothesis that hypothalamic cell proliferation may play a role in the seasonal regulation of biological functions in the Syrian hamster.
I found that cell proliferation increases in the hypothalamus and in the subventricular and subgranular areas, the two main neurogenic niches in adults, following the transfer from long (spring, summer) to short photoperiod (autumn, winter), with a maximum observed one week after the transfer. By contrast, cell proliferation in these areas is not modified during the opposite short to long photoperiod transfer.
In order to characterize the fate of these proliferating cells, I am phenotyping the newly born cells in the brain of adult male Syrian hamsters. Animals were sacrificed at different time points following the photoperiodic transfer, 5 weeks after the injection of a DNA intercalator, 5-bromo-2'-deoxyuridine (BrdU). Dual labeling of BrdU with neural markers (immature and mature neurons, astrocytes and oligodendrocytes) will help to track and identify fate of photoperiod-induced new cells.

Poster

P42. Immunoneutralization of enterobacterial ClpB protein protects mice against activity-based anorexia.

Thomas Benjamin, M.Sc Student

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BACKGROUND AND OBJECTIVES:
Anorexia nervosa (AN) is an eating disorder characterized by food self-deprivation and excessive physical activity. Development of effective biopharmacological treatment of AN is hampered by insufficient knowledge of its pathophysiology. Recently, a key role of ClpB, a 96 kDa heat-shock enterobacterial protein in the origin of AN was proposed, based on ClpB molecular mimicry with α-MSH, an anorexigenic neuropeptide. To further validate this hypothesis, in the present study we determined if immunization against ClpB can influence the development of activity-based anorexia (ABA) in mice, an animal model of AN.
METHODS:
4 groups of C57Bl6- male mice were used. 2 groups were immunized with 25 µg of E. coli ClpB in an adjuvant. Prior to immunization, to induce immune tolerance for ClpB, one group received ClpB protein (25 µg/mL) in drinking water for 10 days. In two control groups, mice received the adjuvant only or 0.9% NaCl. All mice were placed in individual Biodaq cages equipped with a running wheel and were exposed to an ABA protocol consisting of progressive decrease of food access to 4 h/day during the last 8 days. Plasma levels of ClpB, α-MSH and their reactive IgG were determined by ELISA. Surface plasmon resonance was used to measure IgG affinity for these molecules.
RESULTS :
As expected, ClpB immunized mice showed increased production of anti-ClpB and α-MSH-reactive IgG, characterized by their lower affinity. Importantly, the ClpB and α-MSH antibody production was abolished in mice orally tolerized with ClpB. Moreover, plasma levels of ClpB protein was increased only in ClpB-tolerized mice. Behavioral analysis revealed higher food intake and reduced food anticipatory physical activity in ClpB immunized mice as compared to the control groups resulting in a significant reduction of body weight loss during the 4 h- food restriction period.
CONCLUSIONS :
Taken together, these results demonstrate that immunoneutralization of bacterial ClpB efficiently protects mice from ABA suggesting a novel therapeutic strategy for AN.
Acknowledgement : The study was supported by the EU ERANET Neuron and ANR, France MiGBAN project, Nr 01EW1906A “Microbiome Gut-Brain Axis in Anorexia Nervosa” and by the Transversal Microbiota Program (PTM-2) of Inserm, France.

Poster

P43. GHSR-deficient female mice fail to adapt the circadian patterns of physical activity in response to a chronic activity-based anorexia nervosa model.

Tolle Virginie, Research Fellow

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Anorexia Nervosa (AN) is a psychiatric disorder characterized by voluntary food restriction, resulting in severe undernutrition that has been associated with circadian rhythms alterations. Yet, mechanisms that link circadian rhythm shifts to abnormal eating regulation in AN are poorly understood. Plasma ghrelin concentrations, an orexigenic hormone secreted by the stomach and acting through the GHSR (Growth Hormone Secretagogue Receptor), is elevated in AN despite restraint eating. We aimed to test the hypothesis that GHSR signaling contributes to altered circadian pattern observed in AN. For this purpose, we first assessed whether morning versus evening chronotypes were unevenly distributed in patients with AN (n=22), bulimia nervosa (n=15) and healthy controls (n=9). We next recorded the pattern of physical activity in 8-week old female GHSR deleted (Ghsr-/-, n=8) and wild-type (Ghsr+/+, n=14) mice housed in cages equipped with running wheels and exposed to quantitative food restriction, mimicking AN metabolic signature. We demonstrated that morningness/eveningness distribution was uneven in the three groups of subjects (Fisher c^2= 9.50, df=4, p=0.05), a difference mainly driven by an excess of morningness in patients with AN (54.5%) compared to the rest of the sample (16.7%) (Chi^2=7.26, df=1, p=0.007). In Ghsr+/+ mice, the shift toward higher daytime running activity and lower night-time running activity, induced by food restriction, was impaired in Ghsr-/- mice that maintained predominant activity during the night (Repeated measures Anova: Genotype effect, p=0.0035; Time effect, p<0.0001 and Time x Genotype effect p<0.0001), suggesting a lack of capacity to adapt patterns of circadian activity to chronic food restriction. These data suggest an interaction between altered circadian pattern and AN and indicate that GHSR signaling deficiency may play a critical role in adapting circadian patterns of activity to the undernutrition state in this disorder.

Poster

P44. Characterisation and expression of urotensin I and urotensin II in the caudal neurosecretory system of the small-spotted catshark Scyliorhinus canicula.

Tostivint Hervé, Professor

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The caudal neurosecretory system (CNSS) is a neuroendocrine complex specific to fish. In teleosts, the neuroendocrine neurons of the CNSS, called Dahlgren cells, are located in the terminal segments of the spinal cord and project to a neurohemal organ, the urophysis, from which several hormones are released. The major urophyseal hormones are urotensin 1 (UI), related to corticotropin-releasing hormone (CRH), and urotensin 2 (UII), related to somatostatin (SST). In cartilaginous fishes, the CNSS organization is simpler than in teleosts due to the absence of urophysis. Dahlgren cells project into a diffuse neurohemal region located at the ventral base of the spinal cord. Such an organization is considered as primitive.
The goal of the present study was to provide more insight into the CNSS in cartilaginous fish, which has been poorly studied so far. For this purpose, we used the small-spotted catshark Scyliorhinus canicula, as a model. We first cloned the cDNAs encoding for both catshark UI (uts1) and UII (uts2). This search led us to demonstrate the existence of two copies of the uts1 gene, uts1a and uts1b, tandemly arranged on the same chromosome. We then determined by RT-qPCR the expression pattern of the uts1a, uts1b, and uts2 genes in various catshark tissues. Our results revealed that uts1a and uts2 genes are primarily expressed in the caudal spinal cord. Uts1a gene was also found to be relatively strongly expressed in ovary and testis. In contrast, uts1b transcript was only detected at very low levels in all tissues examined, suggesting that the corresponding gene is undergoing pseudogenization. Further study by in situ hybridization showed that uts1a and uts2 genes are co-expressed in Dahlgren cells. The final part of our study aimed to follow by in situ hybridization the expression of uts1a and uts2 genes during development. Uts2 transcript was detected as soon as the hatch, suggesting that the CNSS is, at least in part, already functional at this stage.
In conclusion, our work indicate that, as in teleosts, UI and UII are the major secretory products of the CNSS in cartilaginous fish.
Fundings : Réseaux Initiative Normandie (RIN) Normandie Terre et Mer (to P.S.) et Actions Tremplin du Muséum (to H.T.)

Poster

P45. Dietary protein restriction disrupts hypothalamic neurogenesis in fetal rats.

Vancamp Pieter, Post-doctoral Researcher

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Fetal programming refers to the concept that suboptimal conditions during early life predispose individuals to non-communicable diseases in adulthood. Epidemiological studies have linked inadequate protein availability for the fetus to an elevated risk of metabolic disorders, although the mechanistic origins remain elusive. We hypothesized that this risk could stem from anatomical anomalies originating during prenatal development of the hypothalamus, a brain region that governs the energy balance and food intake. We subjected pregnant rat dams to either a standard diet containing 20% protein or a severely protein-restricted isocaloric diet (4%) including a 4-week pre-conceptional protein restriction of 8%. We focused on two time points within the 22-day in utero period: gestational day 15 (G15), characterized by a peak in neurogenesis, and G17 when neuronal subtypes emerge. Dams and fetuses on the low-protein diet gained less weight, indicating intrauterine growth restriction. Single-cell RNA-seq on hypothalamic progenitors dissected from G15 fetuses and grown in culture, allowed us to identify neuronal subtypes and assess the impact of protein restriction. We detected 500 down- and 39 upregulated genes in protein-deprived cells associated with processes such as cell cycle regulation, cellular metabolism and apoptosis. Although EdU-pulse labeling did not show altered proliferation rates at G15 in vivo, western blots revealed reduced mTOR protein levels, a key amino acid sensor promoting differentiation. Additionally, a population of Isl1+ cells in the single-cell RNA-Seq dataset, precursors of arcuate nucleus neurons, including POMC and NPY, was smaller and exhibited downregulation of genes involved in differentiation, as confirmed by qPCR. At G17, bulk RNA-Seq on dissected hypothalami revealed a similar pattern of predominantly downregulated transcripts enriched in similar cellular processes identified at G15. Immunostaining showed a reduction in the number of POMC neurons in vivo and a decrease in synaptogenesis. Future experiments will assess NPY neuronal differentiation and explore the methylation status of the Pomc promoter. Collectively, our data provide insights into how fetal protein deficiency during critical windows of hypothalamic development could lead to programmed metabolic dysfunction later in life. These findings could guide revisions of dietary recommendations for pregnant women and inform strategies to prevent poor metabolic programming.

Poster

P46. Implication of a portal vein to brainstem circuit in the modulation of food intake by intestinal gluconeogenesis.

Videlo Jasmine, PhD Student

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Glucose is a fundamental molecule in the lifetime of all mammals and requires constant regulation. Thus, in the absence of dietary inputs, the body is able to produce its own glucose through three organs: the liver, kidneys and intestine.
Intestinal gluconeogenesis (IGN) leads to the liberation of glucose in the portal vein. Since the early 70s, numerous studies have studied the effect of infusing glucose directly into the portal vein on feeding behavior. Our lab demonstrated that portal glucose infusion at a rate mimicking IGN induces hypothalamic activation, independently of the vagus nerve, to reduce the size of the next meal. However, mechanisms linking detection, transmission and integration of this nervous signal that induces satiety remain to be investigated.
In this study, we showed that a portal glucose infusion mimicking IGN induces activation (measured by C-FOS staining) of two brainstem nuclei: the solitary nucleus (NTS) and the parabrachial nucleus (PBN). Both nuclei are targeted by vagal and spinal nerves and control food intake, in part by informing the hypothalamus. Thus, we measured food intake after a portal glucose infusion in mice with denervated spinal afferents. In contrast to sham mice in which portal glucose induced satiety, spinal denervated mice showed no change in food intake.
Spinal nerves mainly express the calcitonin gene-related peptide (CGRP). Using immunostainings on whole portal vein, we showed a dense network of CGRP-positive fibers surrounding the vein. Furthermore, in CGRP-/- mice, portal glucose infusion no longer induced PBN activation. Of note, CGRP neurons in the lateral PBN have been implicated in aversive-related decrease in food intake. However, we showed that neurons activated in the PBN by a portal glucose infusion mimicking IGN are non-CGRP neurons.
Finally, by using stereotactic adenovirus injection to control neuronal activity in the NTS or PBN, we showed that inactivation of either blunted the effect of portal glucose infusion on food intake. Importantly, inactivation of one thwarted the portal-glucose induced activation of the other. Thus, both nuclei could be activated in parallel or sequentially to target the hypothalamus.
Our results showed that spinal afferents expressing CGRP are needed for portal glucose detection and signaling to both the PBN and the NTS. They shed light on the importance of the brainstem and non-CGRP neurons in the PBN in the regulation of feeding behavior by IGN.

Poster

P47. Physical activity as a means of regulating glucose homeostasis in situation of chronic caloric restriction.

Viltart Odile, Professor

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Anorexia nervosa (AN) is a complex psychiatric disorder characterized by self-food-restriction leading to dramatic weight loss and severe somatic complication, often associated with hyperactivity. The lifetime prevalence rates of AN might be up to 4% among females and the mortality rate is among the highest in the psychiatric disorders. However, patients with restrictive AN are often protected against hypoglycemia despite a low energy status, suggesting significant metabolic adaptations to maintain energy homeostasis.
Our study aims to better apprehend metabolic adaptations to chronic caloric restriction by investigating glucose homeostasis and evaluating gluconeogenesis (GNG), using a murine model of chronic food restriction (FR) combined with voluntarily access to a running wheel (FRW) mimicking the metabolic symptoms described in AN.
We used 4 groups of C57BL/6J female mice (n=6 per group). The FR and FRW groups underwent a 30% reduction in their diet (3 days) followed by 50%, up to 20 days. The control groups had free access to food, with (ALW) or without access to the wheel (AL). We assessed glucose metabolism through glucose and insulin tolerance tests, and measure GNG rate with the administration of precursors such as pyruvate, glycerol, lactate and glutamine. We also measured plasma insulin levels and hypothalamic mRNA expression of genes involved in the regulation of energy metabolism, using qPCR.
FR and FRW mice lost weight rapidly over the first 2 weeks, then reaching a plateau. They did not develop hypoglycaemia. FR and FRW mice showed a marked increase in glucose tolerance, and paradoxically responded less to the GNG substrates compared to AL and ALW mice. FRW mice showed better recovery kinetics than FR mice. FR and FRW mice had increased basal insulin concentrations and insulin resistance. Both FR and FRW mice showed increase in mRNA expression of AgRP, NPY and CRH, of leptin-, ghrelin- and insulin- receptors, of fatty acid synthase and of GLUT4, whereas the mRNA expression of POMC is decreased.
We consider that, in response to FR, mice have rapid glucose uptake that did not allow detection of the rise in blood glucose levels when submitted to tolerance tests. We suggest that glucose administrated or produced by GNG is consumed -or stored- within minutes. We evidenced a more efficient use of glucose as an energy source, especially in FRW mice, whose precise mechanisms remain to be determined.
Supported by “Institut Benjamin Delessert”.

Poster

P48. Targeted proteomic approach to identify oxytocin-like bacterial proteins in human gut microbiota as putative biomarkers of autism spectrum disorders.

Wallart Lisa, Post-doctoral Researcher

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Background and objective: Autism (ASD) is a neurodevelopmental disorder that appears in early childhood lacking specific biomarkers and efficient treatment. The gut microbiota has recently become a topic of research of putative biomarkers in neuropsychiatric disorders including ASD. In this study, we hypothesized that the human gut microbiota produces proteins homologous to oxytocin (OT), a neuropeptide involved in regulation of social behavior and affected in ASD.
Method: We applied a targeted proteomic approach to identify microbiota-derived OT-like proteins in fecal samples of children with ASD and healthy controls (HCs). Total bacterial protein was extracted from cultured fecal microbiota samples and separated by 1- or 2-dimensional gel electrophoresis followed by immunodetection with polyclonal oxytocin antibodies. Positive spots were identified by mass-spectrometry (MS).
Results: By comparing the individual samples from both study groups, we found that all of them consistently displayed an OT-like immunopositive protein spot at about 70 kDa. Moreover, one OT-positive spot at about 55 kDa was present only in female HCs. The MS identification of OT-positive spots has yielded putative protein targets. The identified OT-like protein targets are currently validated for their specificity.
Conclusion: For the first time, we revealed a constitutive production of OT-like bacterial proteins in human gut microbiota suggesting their physiological role in the oxytocinergic system. Moreover, the presence of such OT-like bacterial proteins seems to be sex-specific and deficient in the microbiota of ASD patients suggesting that such proteins can become both biomarkers and therapeutic targets of ASD.
Acknowledgement: The study received support from “GEMMA” project (ID 825033) funded by the European Commission in the frame of the Horizon 2020 program (call H2020-SC1-BHC-03-2018) and Inserm PTM2 Program, France.

Poster

P49. An atalas of Thyroid hormone responsive genes in the hypothalamus at single cell level.

Wu Shijia, PhD Student

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Thyroid hormones (TH) are crucial for energy homeostasis and metabolism. Thyroid hormone receptors (TR), including TRα and TRβ, are widely expressed in the central nervous system. However, how TR regulates energy balance in the hypothalamus, one of the most important brain regions involved in the central control of feeding and energy expenditure, remains poorly understood. We treated two groups of mice with propyl–thio-uracyl to make them hypothyroid. One group of mice was treated with TH for 24h. We then used single nucleus RNA sequencing (snRNA-seq) to analyze the TH response of mediobasal hypothalamic cells. We found that this response varies among cell types. Astrocytes stand out as being the most sensitive. We also performed bulk RNA-seq on sorted GABAergic neurons and astrocytes. These additional analyses confirm that there is no correlation between the number of differentially expressed genes and the level of expression of TH signaling genes. Overall, snRNA-seq revealed the precise transcriptional diversity of TH in different cell types within the hypothalamus. This atlas will serve to further explore the molecular mechanisms underlying the central regulation of metabolism by TH.

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46th Conference of the Society of Neuroendocrinology – Joint France-Canada conference
September 16-19, 2024 – Nice, France

Program at a glance

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