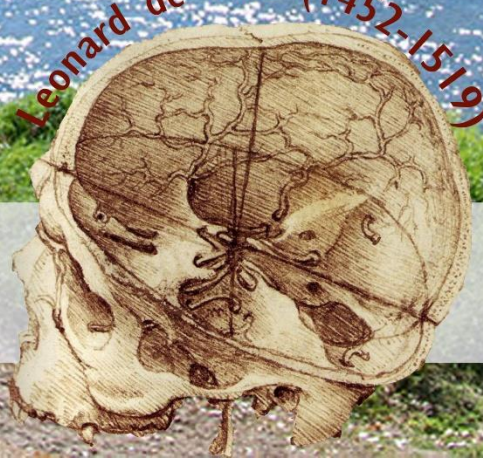
43ème colloque de la Société de Neuroendocrinologie

TOURS 2019

2-4 octobre
Salle Thélème, Université de Tours



Renseignements:
https://www.societe-neuroendocrinologie.fr/

Partenaires

Fondation Planiol

Bienvenue en Touraine, sur les bords de la Loire, pour ce 43ème colloque de la SNE.

Merci à la Société de Neuroendocrinologie de nous avoir fait confiance pour l'organisation de ce colloque, après le 34ème en 2007 et le 6ème en 1976. Avec le Conseil Scientifique de la Société, nous vous proposons un programme des plus attractifs avec 5 symposiums, 2 séances de communications orales et près de 50 posters, sans oublier la prestigieuse lecture Jacques Benoit qui sera présentée par **Valérie Simonneaux** (INCI Strasbourg). Parmi les thèmes abordés citons les interactions entre la sphère digestive, les hormones du métabolisme, et le cerveau, en lien avec les pathologies cérébrales, un domaine peu exploré au cours des colloques de la SNE. Nous avons laissé une large place aux jeunes chercheurs avec **une présentation flash de 10 posters**, **2 séances de communications orales** et **un symposium confié à Sophie Croizier et Nour Mimouni** que nous remercions pour leur engagement et dynamisme. Le Prix de la SNE sera attribué à **Elodie Desroziers,** ancienne doctorante dans l'UMR Physiologie de la Reproduction et des Comportements à Nouzilly, et actuellement en Nouvelle Zélande dans le Laboratoire de Rebecca Campbell.

Ce 43ème colloque de la SNE a été organisé avec l'aide de **la Structure Fédérative de Recherches de Neuroimagerie Fonctionnelle** (FED 4226) qui regroupe 26 équipes de recherches de Tours, Orléans et Poitiers, évoluant dans le domaine des Neurosciences, et où se retrouvent les neuroendocrinologistes Tourangeaux. Afin de promouvoir les travaux de notre discipline auprès du public de Tours, une conférence grand public ayant pour titre « Stress et Dépression » sera donnée par **le Professeur Catherine Belzung** directrice de l'UMR Imagerie et Cerveau (Inserm-Univ Tours) au sein de la SFR.

Nous remercions ici chaleureusement les nombreux soutiens académiques et privés dont nous bénéficions ainsi que toutes les personnes qui se sont impliquées au sein du Comité d'Organisation, de l'Université de Tours et du secrétariat de la SFR FED4226.

Nous vous souhaitons un excellent congrès riche en échanges scientifiques et nous espérons que vous prendrez le temps de vous attarder à Tours et sa région pour y découvrir (ou redécouvrir) ses vignobles et châteaux. Tours est située au cœur des jardins de la France, c'est une ville chargée d'histoire : ancienne cité gallo-romaine, ancienne capitale du royaume de France…. La vallée de la Loire est inscrite au patrimoine mondial de l'UNESCO depuis novembre 2000.

Autant de bonnes raisons pour y séjourner quelque temps.

Yves Tillet pour le comité d'organisation

Droits Réservés Office de Tourisme

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Alexandre Surget (UMR U1253, Univ Tours),

Avec la participation des étudiants du M2 « Biologie de la Reproduction » de l'Université de Tours.

Programme détaillé

Mercredi 2 octobre

14H00 - 14H30 : Ouverture du 43ème Colloque de la SNE

14H30 - 16H30 : Symposium 1 : **Microbiote-Intestin-cerveau: régulations psychoneuro-endocrines et implications pathologiques**

Chairs : Ms Darnaudéry, Muriel (Bordeaux University, INRA UMR1286 NUTRINEURO) et Benani Alexandre (CSGA, UMR 6265 CNRS-INRA-Université de Bourgogne)

- **S1.1** Food controls mood by inducing gut-brain neural circuits par Amandine Gautier-Stein, (Inserm 1213,Lyon)
- **S1.2** The neuropeptide 26RFa: a novel actor in the peripheral and hypothalamic regulation of glucose homeostasis par Nicolas Chartrel (Inserm U1239, Rouen University).
- **S1.3** Stimulation of the vagus nerve: impact on intestinal diseases with psychiatric comorbidities par Bruno Bonaz (Inserm U 836, Grenoble, France)
- **S1.4** The microbiota-gut-brain axis in developmental and neurodegenerative diseases? par Michel Neunlist, (INSERM UMR 913, Nantes, France)

16H30 - 17H00 : Pause café

17H00 - 18H00 : Présentations « flash » de 10 posters

19H00 - 21H00 : Conférence grand public : Stress et dépression par le Prof Catherine Belzung (INSERM U1253, Tours, France)

Jeudi 3 octobre

8H30-10H30 : Symposium 2 : **Insulin and related-peptides action in the brain: a reciprocal and unexpected link between energy metabolism dysfunctions and alzheimer disease**

Chairs: Didier Vieau (UMR Inserm UMR-S1172,"Alzheimer & Tauopathies", JPARC, Univ. Lille-Nord de France), David Blum (Inserm UMR-S1172, "Alzheimer & Tauopathies" JPARC, University of Lille, France)

- **S2.1** Insulin-induced regulation of mitochondrial proteostasis in the brain is crucial for metabolism and brain health par Andre Kleinridders (German Institute of Human Nutrition, Department of Central Regulation of Metabolism, Berlin, Germany)
- **S2.2** Insulin-like growth factor signalling in the brain and neuroprotection par Saba Aïd (Inserm U938, Sorbonne University, Paris, France)
- **S2.3** The impairment of insulin signalling in Alzheimer disease: focus on Tau protein par David Blum (Inserm UMR-S1172, "Alzheimer & Tauopathies" Jean-Pierre Aubert Research Centre, University of Lille, France)
- **S2.4** Tau hyperphosphorylation results in intraneuronal accumulation of oligomeric insulin and induces insulin resistance par Angel Cedazo-Minguez (Sanofi)

10H30 - 11H00 : Pause café

11H00 - 12H00 : Communications orales libres

Chairs : Alexandre Surget (Inserm U1253, Université de Tours) et Nicolas Chartrel (Inserm U1239, Rouen University)

- **O1** Therapeutic potential of a new selective glucocorticoid receptor modulator in the prefrontal cortex in Alzheimer's disease rat par Geoffrey Canet et al. (Inserm U1198 – Université de Montpellier, EPHE, Montpellier)
- **O2** Molecular mechanisms of hormones secretion in neuroendocrine tumor from the adrenal medulla par Stephane Gasman (INCI, Université de Strasbourg, CNRS)

- **O3** Impact of type 2 diabetes-associated mood disorders on the electrical properties of brain serotoninergic neurons par Hugo Martin et al. (Univ. Bordeaux, INRA, NutriNeuro, UMR 1286, Bordeaux)
- **O4** ERa-activated pituitary enhancer is mandatory for Sf-1 expression during early gonadotrope lineage specification par Vincent Pacini et al (UMR 8251, Université Paris Diderot, CNRS, Inserm Paris)

12H30 - 13H30 : Déjeuner et posters

13H30 - 14H30 : Assemblée Générale de la SNE

14H30 - 16H00 : Symposium « Jeunes chercheurs »

Chairs : Nour Mimouni (Laboratory of Development and Plasticity of Neuroendocrine Brain, Jean-Pierre Aubert Research Center, U1172, Lille, France) et Fanny Langlet (University of Lausanne, Center for Integrative Genomic, Lausanne, Switzerland)

- **SJC1** L'injonction éthique en recherche : mode ou nécessité ? par Patrick Gaudray (CNRS, Membre du Comité Consultatif National d'Ethique)
- **SJC2** INTime: Predictability of individual circadian phase during daily routine for medical applications of circadian clocks par Matei Bolborea (Medical School, Warwick University, Coventry, United Kingdom) :
- **SJC3** Glutamatergic synapse formation in POMC neurons and regulation of metabolism par Sophie Croizier (University of Lausanne, Center for Integrative Genomic, Lausanne, Switzerland)

16H00 – 16H30 : Prix de la SNE par Elodie Desroziers et al. (University of Otago, Dunedin, NZ), Chronic activation of arcuate GABA neurons leads to reproductive dysfunction: potential implication for PCOS.

16H30-17H00 : Pause café

17H00-18H00 : Conférence Jacques Benoît par le Dr Valérie Simonneaux (INCI Strasbourg), A timely Kiss drives reproductive rhythms.

20H00 : Repas de Gala

Vendredi 4 octobre

8H30-10H30 : Symposium 3, **Neurogenèse et régulations neuroendocrines**

Chairs : Alexandre Surget (U1253 INSERM, Université de Tours) et Martine Migaud (INRA UMR 85, CNRS, UMR7247, Université de Tours, IFCE, Nouzilly).

- **S3.1** Neurogenesis-dependent regulation of HPA axis and relevance for stress-related disorders par Alexandre Surget (UMR iBRain, Inserm 1253 Tours)
- **S3.2** Adult neural stem cells, new players in the reproductive function par Martine Migaud (UMR PRC, INRA Nouzilly)
- **S3.3** Steroid modulation of neurogenesis : Focus on radial glial cells in zebrafish par Elisabeth Pellegrini (Université Rennes, Inserm, EHESP, Irset Rennes, France)
- **S3.4** Amylin and brain develoment in the early postnatal period and in adulthood par Thomas Lutz (Institute of Veterinary Physiology, Université de Zurich)

10H30 - 11H00 : Pause café

11H00 - 12H00 : Communications orales libres

Chairs: Youssef Anouar (Inserm U1239, Rouen University) et Ariane Sharif (Laboratory of Development and Plasticity of Neuroendocrine Brain, JPARC, U1172, Lille, France)

- **O5** Development of metabolic disturbances in a mouse model of polycystic ovary Syndrome, par Nour El Houda Mimouni et Paolo Giacobini (INSERM, U1172, Jean-Pierre Aubert Research Center, Lille, France)
- **O6** Effect of High-Fat Diet on pituitary inflammation and gonadotrope activity par Salma Tazi et al. (UMR 8251, Université Paris Diderot, Université Sorbonne Paris Cité, CNRS, Inserm, Paris)
- **O7** Reproductive and socio-sexual behaviors regulation by Gai2 signal transduction in mice par Anne-Charlotte Trouillet et al. (UMR PRC, INRA CNRS IFCE, Université de Tours, Nouzilly, France)
- **O8** Intestinal gluconeogenesis exerts metabolic benefits by activating the leptin signaling pathway and CGRP neurons par Justine Vily Petit et al

(INSERM U1213 Nutrition, diabète et cerveau – Université Claude Bernard - Lyon I – France)

12H00 - 14H15: Déjeuner et visite poster

14H15 - 16H15 : Symposium 4, **Genre et stéroïdes sexuels dans les comportements et la neuroprotection**

Chairs : Arnaud Nicot (CRTI-UMR1064 INSERM-Université de Nantes, CHU Nantes) et Laurence Dufourny (INRA UMR 85, CNRS, UMR7247, Université de Tours, IFCE, Nouzilly)

- **S4.1** Molecular and cellular mechanisms regulated by androgens: a possible contribution to increasing the risk of developing ASD in boys par Amélie Piton (IGBMC & Université de Strasbourg, France)
- **S4.2** GPER1/estrogen receptor crosstalk and implications for anxiety and social behaviour par Nandini Vasudevan (University of Reading, United Kingdom)
- **S4.3** Stroke cerebroprotection by endogenous progesterone and its intracellular receptors par Rachida Guennoun (INSERM U1195/Université Paris-Sud, France)
- **S4.4** Promoting neurosteroid synthesis by a TSPO ligand par Yvette Akwa (INSERM U1195 /Université Paris-Sud, Ville, France)

16H15 - 16H30 : Clôture du Congrès – remise des Prix

Résumés

Conférence grand public

Stress et dépression

Catherine Belzung
iBrain, UMR 1253 Inserm-Université de Tours, France

La dépression est l'une des pathologies les plus fréquentes puisqu'on estime qu'une personne sur 6 en souffrira au moins une fois au cours de sa vie. De nombreux travaux portent sur la recherche des causes sous-jacentes, et l'un des facteurs les mieux identifié est le stress, puisque ce dernier multiplie par 10 le risque de développer un premier épisode dépressif chez l'adulte. La dépression est caractérisée par divers altérations cérébrales (en particulier des zones de régulation du stress) et hormonales (en particulier des hormones du stress), constituant un genre de cercle vicieux puisque la dépression est à la fois causée par le stress et à l'origine d'un dysfonctionnement des mécanismes de lutte contre le stress

Conférence Jacques Benoît

A timely Kiss drives reproductive rhythms

Valerie Simonneaux

Institut des Neurosciences Cellulaires et Intégratives, CNRS & Université de Strasbourg, France

Reproduction, like many other biological functions, exhibits marked daily and seasonal rhythms in order to anticipate and adapt breeding activity to environmental challenges. In recent years, studies investigating the neuroendocrine mechanisms driving rhythms in reproduction have unveiled the pivotal role of hypothalamic neurons expressing RF-amide peptides, notably kisspeptin but also RF-related peptide3, in integrating and forwarding daily and seasonal cues to the reproductive system. This conference will discuss the current knowledge on the effect and role of these neuropeptides on the mammalian hypothalamo-pituitary-gonadal axis and describe how it is involved in the daily control of ovulation in females and long term adaptation of reproduction in seasonal breeders.

Prix de la SNE

Chronic activation of arcuate GABA neurons leads to reproductive dysfunction: potential implication for PCOS.

Elodie Desroziers, Sabine Hessler, Melanie Prescott, Chris Coyle, Allan E. Herbison and Rebecca E. Campbell
Center for Neuroendocrinology and Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin, NZ.

Polycystic ovary syndrome (PCOS) is the most common form of anovulatory infertility worldwide, affecting 1 in 10 women. Although commonly considered an ovarian disorder, the brain is a critical contributor to PCOS pathogenesis. Women with PCOS exhibit elevated cerebrospinal fluid GABA levels and preclinical models of PCOS exhibit increased GABAergic input to gonadotropin-releasing hormone neurons (GnRH-N), which orchestrate the hypothalamo-pituitary-gonadal axis. The arcuate nucleus (ARN) is postulated as the anatomical origin of elevated GABAergic innervation; however, the functional role of this circuit is undefined. The present study aimed to test the hypothesis that increased activity in ARN GABA neurons underpins the reproductive dysfunction of PCOS. To investigate the effect of selective activation of ARN GABA-N on GnRH-N activity and fertility we used chemogenetic tools coupled with a Cre-lox approach in mice. The designer receptor hM3Dq was specifically expressed in ARN GABA-N via stereotaxic injection in vesicular GABA transporter (VGAT-Cre) mice. The delivery of the designer drug (CNO) to activate hM3Dq was coupled with serial tail-tip blood sampling to measure luteinizing hormone (LH) secretion as a readout of GnRH secretion. Acute stimulation of ARN GABA fibers adjacent to GnRH neurons resulted in a significant and long-lasting increase in LH secretion. Chronic activation of ARN GABA neurons impaired estrous cyclicity, decreased corpora lutea number, increased circulating testosterone and resulted in a trend toward increased LH pulse frequency similar to the PCOS condition. Altogether, these results support the hypothesis that ARN GABA neurons are a functional component of the GnRH neuronal network and suggest that elevated activity in this circuit can drive reproductive dysfunction similar to PCOS.

Symposium 1

Microbiota-Gut-Brain axis: from psycho-neuroendocrinology to pathology

S1.1 Food controls mood by inducing gut-brain neural circuits

Flore Sinet[1,2,3], Maud Soty[1,2,3], Juliane Zemdegs[4], Bruno Guiard[4], Judith Estrada[1,2,3], Gaël Malleret[5], Marine Silva[1,2,3], Gilles Mithieux [1,2,3,6], ***Amandine Gautier-Stein*** *[1,2,3,6]*

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[5]Forgetting and Cortical Dynamics, Lyon Neuroscience Research Center, University Lyon, Lyon, France.
[6] Senior authors

Hanger (a mix of hunger and anger) is a word popularly used to describe a common familiar feeling associating disquiet, irritability and anger in the context of hunger, conveying the assumption that food availability and mood may be tightly linked phenomena. Indeed, several studies have suggested that diet, especially one enriched in microbiota-fermented fibers or fat, regulates mood-related behavior. The underlying mechanisms are currently unknown. We previously reported that certain macronutrients (fermentable fiber and protein) regulate energy homeostasis via the activation of intestinal gluconeogenesis (IGN), which generates a neural signal to the brain. Using behavioral tests, we show here that both fiber- and protein-enriched diets exert beneficial actions on mood-related behavior. These benefits do not occur in mice lacking IGN. Consistently, IGN-deficient mice display hallmarks of mood disorders, including decreased hippocampal neurogenesis, basal hyperactivity and decreased retro-control of the hypothalamic-pituitary-adrenalaxis, which are associated with increased expression of corticotropin releasing hormone in the hypothalamus and decreased expression of the glucocorticoid receptor in the hippocampus. These neurobiological alterations are corrected by portal glucose infusion mimicking IGN. Thus, IGN translates nutritional information allowing the brain to finely coordinate energy metabolism and behaviour.

S1.2 The neuropeptide 26RFa: a novel actor in the peripheral and hypothalamic regulation of glucose Homeostasis

Nicolas Chartrel[1]*, Mouna El Mehdi[1], Marie-Anne Le Solliec[1], Saloua Cherifi[1], Arnaud Arabo[1], Julie Maucotel[1], Hind Berrhamoune[1,2], Alexandre Benani[3], Emmanuelle Nedelec[3], Jérome Leprince[1] ,Youssef Anouar[1], Gaëtan Prévost[1,2], Marie Picot[1].*

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[2]Normandie Univ, UNIROUEN, Rouen University Hospital, Department of Endocrinology, Diabetes and Metabolic Diseases, 76000 Rouen, France
[3]Centre des Sciences du Goût et de l'Alimentation, Unité Mixte de Recherche CNRS, INRA, Université de Bourgogne, Dijon, France.

The neuropeptide 26RFa and its receptor, GPR103, form a hypothalamic system known to strongly stimulates food intake. This peptidergic system also regulates glucose homeostasis at the periphery, 26RFa acting as an incretin. As the hypothalamus plays an important role in the control of glucose homeostasis, we investigated whether 26RFa may be implicated in the hypothalamic regulation of glucose homeostasis. We found that hypothalamic 26RFa exerts an anti-hyperglycemic effect similar to that observed peripherally, that is associated with an insulinotropic activity of the neuropeptide. In addition, this central anti-hyperglycemic effect of 26RFa is partially abolished by a central administration of a GPR103 antagonist and in 26RFa knock out mice. To understand how the 26RFa/GPR103 peptidergic system is involved in the central glycemic regulation, we examined whether the expression and the secretion of 26RFa by hypothalamic neurons

may be regulated by factors known to control glucose homeostasis. Using mouse hypothalamic explants, we showed that insulin strongly stimulates 26RFa secretion by hypothalamic neurons. We also found that hypothalamic 26RFa-neurons express the insulin receptor, that insulin induced c-fos expression in these neurons and that the central anti-hyperglycemic effect of insulin is partially abolished by the GPR103 antagonist and in 26RFa knock out mice. Together, these data reveal, for the first time, that the hypothalamic 26RFa/GPR103 system plays a pivotal role in the hypothalamic regulation of glucose homeostasis, notably by acting as a relay of insulin signalization in the brain.

Key-words: neuropeptide; hypothalamus; glucose homeostasis; insulin; glucoregulatory system

S1.3 Stimulation of the vagus nerve: impact on intestinal diseases with psychiatric comorbidities.

Bruno Bonaz

Service d'Hépato-Gastroentérologie, CHU Grenoble Alpes et Grenoble Institut des Neurosciences (GIN), Inserm U1216, Université Grenoble Alpes, Grenoble

The vagus nerve (VN), the longest nerve in the body, is part of the autonomic nervous system. It provides the link between the central nervous system and the digestive tract. It is a mixed nerve with 80% afferent and 20% efferent fibers respectively. The VN has anti-inflammatory properties in response to immune stress via its afferents activating the hypothalamic-pituitary adrenal axis and its efferences through the cholinergic anti-inflammatory pathway. It also has anti-depressive and anti-nociceptive properties, particularly via its central afferents to the nucleus of the solitary tract located in the brainstem. These properties of the VN can be used in the treatment of inflammatory bowel disease (IBD, Crohn's disease and ulcerative colitis) and irritable bowel syndrome (IBS) using invasive or non-invasive (transcutaneous or trans-auricular) VN stimulation (VNS). These digestive pathologies are bio-psycho-social models with a role of stress in their physiopathology and vagal dysautonomia (hypotonia in particular). There are 30-50% depressive and traumatic antecedents in childhood / adolescence in IBS, and a depressive connotation in IBD. VNS is used in the treatment of drug refractory epilepsy and depression. Recent pilot studies have shown an interest of VNS in the treatment of these digestive disorders through its anti-inflammatory, anti-depressive, and anti-nociceptive properties. VNS could therefore be used as a non-drug therapeutic approach of IBD and IBS. Complementary therapies, and especially hypnosis, which stimulate the VN, are also of interest in the management of these digestive disorders.

S1.4 The microbiota-gut-brain axis in developmental and neurodegenerative diseases

Michel Neunlist

Inserm U1235 'The enteric nervous system in gut and brain diseases'

The perinatal period is a key developmental period in life during which environmental and genetical factors interact and contribute to the building of organs, and in particular of the brain. In this context, the gut which represents one of the largest surface open to our environment (and contains also the second largest number of neurons besides the brain) plays an increasingly recognized role in the development and maturation of the brain. In particular, the gut microbiota has been shown to be a central regulator of both gut and brain maturation during this period of life. Conversely, early life alterations in microbiota composition has been linked to the development of various gut and brain disorders. Besides affecting brain development, gut microbiota is also increasingly considered as an (co)-actorof neurodegenerative brain disorders such as Parkinson's diseases. These findings have lead the development of novel therapeutical approaches based on the use of pre/probiotic to restore gut and brain functions.

Symposium 2

Insulin and related-peptides action in the brain: a reciprocal and unexpected link between energy metabolism dysfunctions and alzheimer disease

S2.1 Insulin-induced regulation of mitochondrial proteostasis in the brain is crucial for metabolism and brain health

André Kleinridders

German Institute of Human Nutrition Potsdam-Rehbruecke, Central Regulation of Metabolism, Arthur-Scheunert-Allee 114-116, 14558 Nuthetal, Germany and German Center for Diabetes Research (DZD), Ingolstaedter Land Str. 1, 85764 Neuherberg, Germany

Brain insulin action modulates brain function regulating a variety of metabolic and behavioral outcomes ranging from controlling body weight development up to modulating cognition and emotional behavior. Conversely, brain insulin resistance is linked to obesity, impaired memory formation and neurodegenerative diseases. A common feature of reduced insulin action and neurodegeneration is the occurrence of mitochondrial dysfunction and oxidative stress. We show that insulin directly improves mitochondrial function in the brain by regulating mitochondrial proteostasis but not biogenesis. Interestingly, a dysregulated mitochondrial proteostasis with a reduction of mitochondrial chaperones and proteases are an early event of insulin resistance in high fat diet fed mice and coincides with obesity development. Knockdown of these proteins in the brain are sufficient to induce insulin resistance suggesting that counteracting this dysregulation ameliorates metabolism. Indeed, treating high fat diet fed mice with intranasal insulin improves mitochondrial proteostasis and metabolism. In addition, mutations of the insulin-induced mitochondrial chaperones Hsp60 and Hsp10 are linked to neurodegenerative diseases in humans and their reduced expression in mice cause behavioral alterations which have been observed in neurodegenerative diseases. Taken all together, we describe a novel function of brain insulin action in controlling mitochondrial proteostasis thereby improving metabolism and supporting neuronal health.

S2.2 Insulin-like growth factor signalling in the brain and neuroprotection

***Saba Aïd**, Jean-Christophe FRANÇOIS and Martin HOLZENBERGER*

Saint-Antoine Research Center, UMR 938, INSERM and Sorbonne University, 75012 Paris, France.

Despite structural and functional homology, insulin-like growth factor (IGF) and insulin pathways have different metabolic and survival functions, especially within the aging brain. The pleiotropic hormone IGF-I through its receptor (IGF-1R) is an important regulator of organismal longevity that controls growth, metabolism and stress resistance. I will discuss recent works from our lab and others showing that long-term suppression rather than enhancement of IGF signalling supports long-term neuronal function and resistance to Aβ proteotoxicity during aging. Notably, we demonstrated that limiting neuronal IGF signalling efficiently slows down Alzheimer disease (AD) progression, alleviates amyloid pathology and prevents cognitive deficits in Alzheimer-like mice, specifically by enhancing Aβ clearance. At the cellular level, loss of IGF signalling in differentiated neurons leads to marked changes in cellular homeostasis and morphology, with enhanced synaptic neurotransmission and preserved cognitive functions. We also recently identified a convergent transcriptomic signature between early stage AD neurons and adult-onset IGF-1R-deficient neurons resistant to Aβ proteotoxicity, highlighting similar genetically regulated defence mechanisms of these neurons. Therefore, brain IGF-I resistance observed post-mortem in AD is possibly not the primary cause, but rather represents an endogenous defence mechanism for surviving neurons to limit further damage due to Aβ proteotoxicity. A better understanding of the

molecular mechanisms underlying IGF-related neuroprotection, and how it contrasts from insulin signalling, is warranted to help design novel and better-targeted therapeutical strategies against AD.

S2.3 The impairment of insulin signalling in Alzheimer disease: focus on Tau protein

David Blum

Inserm UMR-S 1172, 1 place de Verdun 59045 Lille Cedex

Brain insulin resistance is a cardinal feature of AD. Brains from AD patients exhibit a reduced responsiveness to insulin, correlated with memory deficits. Brain insulin resistance seen in the AD brain could favor the development of AD lesions themselves but also partly explain the metabolic disturbances of AD patients. The mechanisms that trigger insulin unresponsiveness in the AD brain are largely unknown. Previous studies supported the involvement of Abeta oligomers as a potential trigger, presumably through inflammatory-mediated processes. In sharp contrast, until recently, the role of Tau remained completely unknown. In the present presentation, we will provide our recent data related to the relationship between Tau and brain insulin signaling as well as discuss its potential role in dementia.

S2.4 Tau hyperphosphorylation results in intraneuronal accumulation of oligomeric insulin and induces insulin resistance.

Patricia Rodriguez-Rodriguez and ***Angel Cedazo-Minguez.***

Karolinska Institutet, Department of Neurobiology, Solna, Sweden and Sanofi, Rare and Neurologic Diseases Research TA, Chilly-Mazarin, France

Insulin signaling deficiencies in in the brain are directly linked to the progression of neurodegenerative disorders but very little is known about underlying molecular mechanisms. We found that insulin in oligomeric form is neurons bearing hyperphosphorylated tau-bearing neurons. This is seen in Alzheimer disease and several other tauophaties. The intraneuronal accumulation of insulin follows the tauopathy progression and depends upon tau hyperphosphorylation. Oligomeric insulin accumulation results in signs of insulin resistance and in decreased insulin receptor levels. We propose that insulin retention in hyperphosphorylated tau-bearing neurons is a causative factor for the insulin resistance observed in Tauopathies. This novel neuropathological concept with important therapeutic implications will be discussed during the presentation.

Symposium 3
Neurogenèse et régulations neuroendocrines

S3.1 Neurogenesis-dependent regulation of HPA axis and relevance for stress-related disorders.

Alexandre Surget

iBrain, U1253 INSERM, Université de Tours; Parc de Grandmont Bât L, 37200 Tours, France

Stress is not always detrimental: it promotes adaptation, drives motivation or helps individuals to perform better and to deal with challenging experiences. However, when it becomes excessive or chronic, stress can lead to the emergence of pathophysiological conditions. Stress-related disorders represent one of the leading causes of health problem, disability and economic burden worldwide. Despite solid progress in the last decade, the precise mechanisms causing their pathophysiology and remission remain poorly understood. Using animal models and translational studies, we investigated the neurobiological mechanisms underlying stress integration, stress-related disorders and their treatments, focusing on the role of adult hippocampal neurogenesis. Our results contributed to unravel the functional involvement of hippocampal neurogenesis in stress response and antidepressant effects. We notably demonstrated how adult-generated neurons are recruited by antidepressants to reestablish an efficient hippocampal control on HPA axis. Altogether, our research participated to provide a mechanistic framework explaining population dynamics under stress conditions, and how hippocampal circuits and outputs operate into larger systems to regulate stress systems, and notably HPA axis.

S3.2 Adult neural stem cells, new players in the reproductive function

Lucile Butruille[1], Martine Batailler[1], Marie-Line Cateau[1], Ariane Sharif[2], Valérie Leysen[2], Vincent Prévot[2], Pascal Vaudin[1], Delphine Pillon[1] and ***Martine Migaud***[1]

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In adult mammals, neural stem cells are found mainly in three neurogenic regions, the subventricular zone of the lateral ventricle (SVZ), the subgranular zone of the dentate gyrus of the hippocampus (SGZ), and the hypothalamus. In the SVZ and the SGZ, neural stem/progenitor cells (NSPCs) display astroglial characteristics and express a large panel of NSPCs markers including glial fibrillary acidic protein (GFAP). The selective ablation of these GFAP+ NSPCs results in a decrease in cell proliferation in vitro and in vivo. In the caudal hypothalamus, GFAP+ NSPCs are localized among a subset of the specialized radial glia-like cells called tanycytes and within the parenchyma. We used transgenic mouse lines to study the role of the GFAP+ NSPCs in the function of reproduction. We show that, in the neurosphere assay, the GFAP-expressing cells exhibit a neurogenic potential and their selective ablation leads to a significant decrease in the cell proliferation rate. In vivo, the selective elimination of GFAP+ NSPC results in decreased testicular weight and plasma testosterone concentration and leads to vacuolization of seminiferous tubes associated with an alteration of the spermatogenesis and the inhibition of sexual behavior. In the central nervous system, NSPC GFAP ablation results in a marked decrease in the number of GnRH-immunoreactive neurons and fibers in the pre-optic area and the median eminence respectively. These data indicate that adult hypothalamic neurogenesis plays a key role in the regulation of reproductive function.

S3.3 Steroid modulation of neurogenesis : Focus on radial glial cells in zebrafish

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In adult teleost fish, the brain exhibits several proliferative regions and provide a unique model to investigate the role of estradiol on adult neurogenesis. Indeed, brain aromatase activity is much stronger compared to other vertebrates. Therefore, using adult zebrafish, we showed that the brain is a true steroidogenic organ producing a wide range of neurosteroids. We demonstrated that aromatase B (AroB, the cerebral form of aromatase in fish, encoded by the cyp19a1b gene) is strongly expressed in radial glial cells (RGC), which are progenitor cells that give rise to new cells able to migrate and differentiate into mature neurons. We established that AroB-RGCs express estrogen and progesterone receptors, which make them target for those hormones. To investigate the role of estradiol on neurogenesis, adult zebrafish were treated with molecules interfering with the endogenous estrogenic signaling. We showed that estradiol inhibits the proliferative activity and the migration of new-generated cells. Using a transgenic zebrafish line expressing GFP in AroB-RGCs, we also investigated the impact of estrogenic and progestagenic compounds detected in aquatic environment on larval neurogenesis. Results revealed that estradiol, progesterone and norethindrone (a synthetic progestagen) affect proliferative and apoptotic activities in the brain of exposed larvae. Altogether, our findings provide general knowledge about the mechanisms that underlie teleost neurogenesis and its regulation by steroids. We also demonstrated that steroid compounds released in aquatic environment disrupt larval neurogenesis, raising questions about developmental impairments and physiological and behavioral impacts later in adulthood.
Supported by the European project Lifecycle and TC2N, ANR Need and Proof.

S3.4 Amylin and brain development in the early postnatal period and in adulthood

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The pancreatic hormone amylin acts in the area postrema (AP) and arcuate nucleus (ARC) to control food intake. Similar to leptin, amylin has also been shown to influence the development of brain cells and to contribute to axonal fiber outgrowth in parts of the brain that are relevant for metabolic control. E.g., endogenous amylin seems to be necessary for the promotion of axonal pathway development and axonal fiber outgrowth from the AP→nucleus tractus solitarius (NTS) and from ARC→ hypothalamic paraventricular nucleus (PVN). Further, we found that acute and chronic amylin treatment upregulated genes such as NeuroD1 that are involved in cell proliferation and neurogenesis in the AP. This was consistent with the observation that exogenous amylin infusion for 4 weeks increased neurogenesis in adult rats in the AP. It was however interesting to note that endogenous amylin seems to have a different role in fetal brain development because between day embryonic E12 and postnatal P2, amylin did not influence neurogenesis processes but contributed to the birth and the fate of microglial cells in the ARC and AP. Given the role of hypothalamic microglial interleukin-6 as a mediator of amylin's effect to increase leptin sensitivity, this finding will deserve further research.

Symposium 4

Genre et stéroïdes sexuels dans les comportements et la neuroprotection

S4.1 Molecular and cellular mechanisms regulated by androgens: a possible contribution to increasing the risk of developing ASD in boys.

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Intellectual Disability (ID) and Autism Spectrum Disorders (ASD) are two neurodevelopmental disorders (NDD) with many genetic and phenotypic overlaps and a high sex bias, with more boys affected (1,4x more for ID and 4x for ASD). For a long time, the contribution of mutations on the X chromosome was put forward to explain this sex bias. However, genetic investigations performed in individuals with DI/ASD did not observe a significant difference between girls and boys in the proportion of pathogenic mutations on the X chromosome, confirming that these mutations cannot explain the excess of boys with ID or ASD. We therefore chose to study another hypothesis, more environmental, that could make the male brain more susceptible to the development of NDD: the role of androgens during brain development. We studied the effect of these male hormones in human neuronal precursors (hNSCs) derived from embryonic stem cells (in collaboration with Istem) and representing cortical progenitors and observed that androgens increase the proliferation of hNSCs and protect against cell death during their differentiation into neurons in depleted environment. They also demonstrated that androgens, via their receptor (androgen receptor), regulate the expression of several hundred genes in hNSCs with, among them, an enrichment of genes known to be differentially expressed in the cortex of individuals with ASD. The regulation of these genes by androgens during brain development and the effect of androgens on the regulation of proliferation and survival of neural precursors may therefore contribute to the increased sensitivity of the male brain, exposed to other genetic or environmental factors, to develop a NDD.

S4.2 GPER1 / estrogen receptor crosstalk and implications for anxiety and social behaviour

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Estrogens are required for the display of social behaviours via receptors that are expressed in nuclei of the brain social behaviour network. 17β-estradiol, the endogenous estrogen, signals via both genomic and nongenomic pathways. Genomically, estrogens bind classical, intracellular nuclear receptors such as the estrogen receptor α (ERα) and ERβ to regulate transcription. In the non-genomic pathway, a membrane estrogen receptor (mERs) whose identity is still controversial signals rapidly from the plasma membrane to activate kinases and calcium flux. Our laboratory has demonstrated a coupled signalling pathway where rapid non-genomic signaling by 17β-E potentiates transcription via the phosphorylation of the ERα may drive some social behaviours.
Although ERα and ERβ are themselves present on the cell membrane, novel candidate mERs include the former orphan receptor GPER1/GPR30 whose localization and function in the brain is relatively unknown. Recently, we showed that the rapid activation of GPER1, leads to anxiolytic behaviours in male, but not female mice, suggesting that this receptor and pathway promotes sexually dimorphic behaviours. In females, we showed that GPER1 activation is sufficient for the classical 17β-E-driven reproductive behaviour, lordosis. We suggest that GPER1 upregulation of spinogenesis in both sexes is an important mechanism for these behaviours. Lastly, we

also show localization of GPER1 in a novel system of differentiated neurons and astrocytes from mouse embryonic stem cells; the implications of this localization and the molecular mechanisms including possible crosstalk with ERα that drive these behaviours will be discussed.

S4.3 Stroke cerebroprotection: role of endogenous progesterone and its intracellular receptors

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Sex steroids regulate brain function in both physiological and pathological states. The brain responds to injury with protective signaling and our results show that steroids are a part of these endogenous counteracting processes. I will summarize our recent findings concerning the effects of ischemia on the endogenous levels of steroids and the role of neural progesterone receptors (PR) at the acute phase after stroke in young and aging mice of both sexes (Zhu et al., 2017). We used steroid profiling by gas chromatography-tandem mass spectrometry for exploring adaptive and sex-specific changes in brain steroid levels after stroke. To assess whether endogenous progesterone and 5α-dihydroprogesterone, both ligands of PR, contribute to the resistance of neural cells to ischaemic damage, we selectively inactivated PR in the central nervous system by using the Cre-lox strategy. Our results highlight the key role of the endogenous progesterone, its metabolites and neural PR in acute cerebroprotection after stroke. In addition, our findings revealed marked sex differences in brain steroid levels and stroke outcomes in young but not in aging mice. Exploiting endogenous cerebroprotective mechanisms is a major therapeutic challenge for ischaemic stroke. Our data strongly suggest that ligands of PR or agents targeting their downstream signaling could be developed for cerebroprotection after stroke and that their use should be optimised specifically for each sex.

Reference : Zhu X, Fréchou M, Liere P, Zhang S, Pianos A, Fernandez N, Denier C, Mattern C, Schumacher M, Guennoun R. J Neurosci, 37, 10998-11020

S4.4 Promoting steroid synthesis by a TSPO ligand

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The mitochondrial 18-kDa translocator protein (TSPO) is predominantly expressed in steroid-synthesizing tissues such as gonads, adrenal glands and brain. It has been mainly associated to cholesterol transport and steroidogenesis and provides a valuable target for selectively upregulating the synthesis of neuroactive steroids. TSPO ligands such as etifoxine (Stresam, Biocodex laboratories) have gained a lot of attention in the last decade as therapeutic agents against anxiety-related disorders and neuronal injuries. Etifoxine possesses anxiolytic-like, neuroprotective and neurodegenerative properties in rodents and is clinically approved for the treatment of anxiety. Besides enhancing GABAA receptor function, etifoxine has previously shown its high efficacy in increasing steroid levels in the brain of male rats, presumably via TSPO binding and activation. However, only few steroids were analyzed and the regulatory action of etifoxine on steroid production was not characterized in detail. In the present work, dose-response and acute and chronic time-course experiments were performed; concentrations of key steroids were quantified by gas chromatography-mass spectrometry in adult Sprague-Dawley male rat brain and plasma after intraperitoneal injections of etifoxine. A whole steroid profiling was then established in brain, plasma, testis and adrenal gland after an acute administration of etifoxine. We now provide a precise and complete panel of steroids regulated by etifoxine that could be useful in therapeutic research.

Symposium Jeune Chercheur

SJC1 - L'injonction éthique en recherche : mode ou nécessité ?

Patrick Gaudray
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La recherche scientifique (et médicale) a ceci de paradoxal qu'elle est, par certains de ses excès, en partie responsable de l'envahissement d'une véritable injonction éthique, avec son lot formalisme, de comités, de régulations, dont les institutions scientifiques sont garantes, en un mot de ce qui est souvent perçu par les scientifiques eux-mêmes comme un frein au développement de la science. Une éthique de la recherche existe-t-elle ? Doit-elle exister ? La tension entre liberté académique et responsabilité du chercheur est-elle constitutive de l'éthique de la recherche ou d'une éthique en recherche ? La réflexion éthique a pour fonction de remettre en question les certitudes, les pouvoirs, les pensées dominantes et les modes, mais aussi d'articuler valeurs et pratiques. Nul ne peut en faire l'économie, et encore moins les chercheurs qui ont une responsabilité singulière dans les progrès des connaissances et des techniques que la société attend d'eux pour tenter d'en faire un progrès pour l'humain.

SJC2 - INTime: Predictability of individual circadian phase during daily routine for medical applications of circadian clocks

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**Contributed equally to the work*

Background: Circadian timing of treatments can largely improve tolerability and efficacy in patients. Thus, drug metabolism and cell cycle are controlled by molecular clocks in each cell, and coordinated by the core body temperature 24-hour rhythm, which is generated by the hypothalamic pacemaker. Individual circadian phase is currently estimated with questionnaire-based chronotype, center-of-rest time, dim light melatonin onset (DLMO), or timing of CBT maximum (acrophase) or minimum (bathyphase).
Methods: We aimed at circadian phase determination and read-out during daily routine in volunteers stratified by sex and age. We measured (i) chronotype; (ii) q1min CBT using two electronic pills swallowed 24-hours apart; (iii) DLMO through hourly salivary samples from 18:00 to bedtime; (iv) q1min accelerations and surface temperature at anterior chest level for seven days, using a tele-transmitting sensor. Circadian phases were computed using cosinor and Hidden-Markov modelling. Multivariate regression identified the combination of biomarkers that best predicted core temperature circadian bathyphase.
Results: Amongst the 33 participants, individual circadian phases were spread over 5h10min (DLMO), 7h (CBT bathyphase) and 9h10 min (surface temperature acrophase). CBT bathyphase was accurately predicted, i.e. with an error <1h for 78.8% of the subjects, using a new digital health algorithm (INTime), combining time-invariant sex and chronotype score, with computed center-of-rest time and surface temperature bathyphase (adjusted R-squared = 0.637).
Conclusion: INTime provided a continuous and reliable circadian phase estimate in real time. This model helps integrate circadian clocks into precision medicine and will enable treatment timing personalisation following further validation.

SJC3 - Glutamatergic synapse formation in POMC neurons and regulation of metabolism

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The overweight and obesity pandemics are major public health concerns. In 2016, the global prevalence of overweight adults reached 39% (WHO). The body weight is continuously regulated by tight control of the balance between energy intake (food intake) and energy expenditure (exercise, thermogenesis). A brain region called hypothalamus is the cornerstone regulating this process and in particular the arcuate nucleus (ARH) made of two main neuronal populations: the anorexigenic (appetite-supressing) pro-opiomelanocortin (POMC)-expressing neurons and the orexigenic (appetite-stimulating) Neuropeptide Y/Agouti-related peptide (NPY/AgRP)-co-expressing neurons. Their activity is controlled excitatory (glutamate) and inhibitory (GABA) inputs originating from several brain areas. The PVH is one of the main source of glutamatergic inputs onto POMC neurons. We showed that PVH projections reached the ARH at postnatal day 14 and potentially make synapse with POMC neurons. At this age, we identified by RNA-sequencing *Efnb1* and *Efnb2* as enriched in POMC neurons when compared to NPY/AgRP neurons. Interestingly, these two members of Ephrin family are involved in glutamatergic synapse formation in hippocampus. By using *in vitro* and *in vivo* approaches, we highlighted a specific role of EphrinB1 (*Efnb1*) and EphrinB2 (*Efnb2*) in glutamatergic synapse formation in POMC neurons and in the control of energy metabolism and glucose homeostasis.
This data provide valuable information on the role of glutamatergic inputs onto POMC neurons and emphasize the importance of the development to built normal and functional neuronal networks.

Communications orales

O1 - Therapeutic potential of a new selective glucocorticoid receptor modulator in the prefrontal cortex in Alzheimer's disease rat.

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In Alzheimer's disease (AD), cognitive and psychological symptoms are associated with an early deregulation of the hypothalamic-pituitary-adrenal (HPA) axis, elevated circulating glucocorticoids (GC) and GC receptors (GR) signalling impairment.
In an acute model of AD intracerebroventricularly-injected with Aβ peptide oligomers (oAβ), we analyzed the impact of amyloid toxicity in the prefrontal cortex (PFC), and evaluated the therapeutic potential of a new selective GR modulator (CORT113176, Corcept Thera- peutics). This structure is altered in AD, involved in the control of HPA axis and in cognitive processes. In addition, GR are highly concentrated in PFC, suggesting a high sensitivity of this region to the HPA axis deregulation.
We found that CORT113176 reversed oAβ-induced apoptotic processes, neuroinflamma-tion, synaptic deficits and amyloidogenesis, and restored GC plasma levels. Interestingly, we showed that oAβ inhibits the non-amyloidogenic pathway via the overactivation of the Rho-associated coiled-coil kinases (ROCK) / 3-phosphoinositide-dependent kinase 1 (PDK1) pathway. We found that CORT113176 normalized the HSP70/HSP90 (heat shock protein) ratio and the Src kinase Fyn, and restored activity of kinases involved in both GR activation and Tau hyperphosphorylation, i.e. GSK3b, Cdk5 and Calpain-1.
In conclusion, this study highlighted that the HPA axis, GC and GR, due to their pri- mordial role in the maintenance of homeostasis, are key actors in the etiology of AD and prime targets to tackle the course of the pathology.
(This project is supported by France Alzheimer/FRC, Fondation Vaincre Alzheimer & the LabEx LipSTIC)

O2 - Molecular mechanisms of hormones secretion in neuroendocrine tumor from the adrenal medulla

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Neuroendocrine tumors (NETs) are neoplasms arising from hormone/peptide-secreting cells. Although NETs are heterogeneous, a common critical feature is the dysfunction of the secretory activity leading to hypersecretion. Pheochromocytomas (pheo) are NETs that arise from chromaffin cells of the adrenal medulla, which are characterized by an excess of catecholamine secretion, leading to hypertension, cardiomyopathy and high risk of stroke. Although this aspect is well known by clinicians, it has never been explored at the cellular and molecular level.
In order to investigate the mechanisms leading to aberrant secretion of catecholamines we have compared, between healthy chromaffin cells and pheochromocytoma cells, both the ex- ocytic activity and the expression level of proteins involved in the exocytic machinery. To do so, we have combined the highly sensitive carbon fiber amperometry technique on single cells with quantitative proteomic of tissue resection. We have demonstrated that hyperse- cretion is a direct consequence of a deregulation of the catecholamines secretion and we have identified several candidates involved in the changes leading to uncontrolled secretion.
This work has been supported by a Ligue Contre le Cancer (CCIR-GE), by a USIAS (Uni- versity of Strasbourg Institute for Advanced Study) and by the ANR "SecretoNET" research grants to SG.

O3 - Impact of type 2 diabetes-associated mood disorders on the electrical properties of brain serotoninergic neurons

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Major Depressive Disorder (MDD) and Type-2 Diabetes (T2D) are diseases of major health concern. Recent epidemiological studies indicate that MDD is now considered as a comorbidity of T2D with serious detrimental health outcomes. Despite this, the mechanisms linking these two pathologies remain largely unknown. As the brain's serotoninergic (5-HT) system is involved in the pathophysiology of depression, we hypothesized that T2D can affect this network. Thus, we aimed to determine whether emotional behavior, serotoninergic neurotransmission and electric properties of 5-HT neurons are altered in a nutritional model of T2D-associated mood disorders, and if the insulin-sensitizing agent metformin can rescue these alterations. We assessed depressive-like and anxiety-like behavior in mice fed a high fat diet (HFD) for 16 weeks and treated for 4 weeks with metformin (300mg/kg; p.o) or vehicle control. The electrical activity of Dorsal Raphe Nucleus 5-HT neurons was assessed by patch clamp electrophysiology on brain slices from Pet1-cre-mcherry mice to specifically visualize 5-HT neurons. We observed depressive-like and anxiety-like behaviors in HFD-fed mice. Moreover, we observed that intrinsic properties of 5-HT neurons were altered by HFD feeding. In both cases, electrophysiological and behavioral alterations were reversed in part by the metformin treatment. In conclusion, these results show that HFD-induced mood disorders are associated with impaired 5-HT neuronal excitability. Interestingly, improving metabolic outcomes with the insulin-sensitizing agent metformin is sufficient to reduce emotional disorders and rescue 5-HT neuronal excitability, supporting the hypothesis that impairment in 5-HT neuronal activity in response to HFD-induced T2D is underlying associated mood disorders.

O4 - ERα-activated pituitary enhancer is mandatory for Sf-1 expression during early gonadotrope lineage specification.

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Gonadotrope differentiation is a stepwise process taking place during pituitary development and abnormalities in this process lead to hypogonadotropic hypogonadism and infertility. The early step of gonadotrope lineage specification is characterized by the expression of the SF-1 transcription factor. However, molecular mechanisms triggering Sf-1 expression in gonadotrope precursors are still poorly understood. Previous studies suggested that Sf-1 pituitary expression is under the control of a gonadotrope-specific enhancer. In this work, we reconsidered the implication of this enhancer at the earliest step of gonadotrope specifi- cation.
Using ATAC chromatin accessibility analyses on three cell lines recapitulating gradual stages of gonadotrope differentiation (progenitors, immature and mature gonadotropes) and in vivo on developing pituitaries, we demonstrated that a yet undescribed enhancer is transiently recruited during gonadotrope specification. Using CRISPR-Cas9, we demonstrated that this enhancer is mandatory for the emergence of Sf-1 expression during gonadotrope specification. Furthermore, we showed that the enhancer activation is dependent upon estrogens acting through ERα and that binding of ERα on a highly conserved sequence amongst mammals, is crucial for

chromatin remodeling of Sf-1 enhancer and promoter, leading to RNA polymerase recruitment and transcription.
This study identifies the earliest regulatory sequence involved in gonadotrope lineage specifi- cation in mammals and highlights the key epigenetic role played by ERα in this differentiation process.

O5 – Development of Metabolic Disturbances in a Mouse Model of Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is a chronic complex disorder that affects more than one in ten women. Women with PCOS suffer symptoms of excess androgen, reproductive dysfunction and metabolic disturbances. Metabolic features include insulin resistance (IR), hyperinsulinaemia, impaired glucose tolerance, type 2 diabetes (DM2) and obesity. The true underpinnings of metabolic disturbances in PCOS remain complex and somewhat unclear. We recently generated a new animal model which recapitulates the major PCOS cardinal neuroendocrine reproductive features, by exposing the animals to high concentration of Anti-Mullerian Hormone during their fetal life.
In this study, we examined the metabolic characteristics of the PCOS-like female mice across postnatal development and uncovered that they develop an age-related increase in body weight correlated with an increase in food intake as well as fasting glucose levels, im- paired glucose tolerance and insulin resistance.
Furthermore, we checked the expression levels of key peptides involved in the central hy- pothalamic control of energy homeostasis and food intake. Interestingly, we detected a significant decrease of *anorexigenic* proopiomelanocortin (*POMC*) mRNA in the brains of PCOS females as compared to controls.
These results support the hypothesis that PCOS might originate *in utero* and that an al- tered hormonal milieu during early life could disrupt the hypothalamic neuronal circuits controlling reproduction and metabolism.

O6 - Effect of High-Fat Diet on pituitary inflammation and gonadotrope activity

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Nutritional disorders lead to obesity and also to alterations of reproductive capacities notably by affecting the hypothalamo-pituitary activity. Our previous works indeed demon- strated that fatty acids (FA) can target the pituitary to alter gonadotropin synthesis and secretion. Recent studies have shown that FA in fat-rich diets trigger hypothalamic inflam- mation, as already described in metabolism-linked organs that would play a major role in alterations of the central control of energy homeostasis. However, no studies have yet in- vestigated whether FA excess mays also lead to pituitary inflammation. Our goal was to characterize such inflammation in male Wistar rats submitted during 13 weeks to a High- Fat Diet (HFD) enriched or not with DHA (an omega3 polyunsaturated FA). HFD was associated with a disruption of gonadotrope activity as evidenced by a decrease of mRNA levels of pituitary gonadotropin beta-subunits and of hypothalamic GnRH. Surprisingly, we observed a decrease in the expression of inflammatory marker genes such as TNFalpha and IL1beta in the pituitary of these rats. Moreover, we highlighted a different inflammatory response under a HFD enriched with DHA as the expression of the gene encoding COX2 was increased in pituitary and hypothalamus as was the one of IL1beta in hypothalamus. Gonadotrope activity was also differentially

affected in this group as only pituitary Fshb transcripts were down-regulated without modification of GnRH mRNA levels. Our study thus confirms the deleterious effect of HFD on gonadotrope activity and emphasizes that pituitary inflammatory response is different depending on the FA content.

O7 - Reproductive and socio-sexual behaviors regulation by Gαi2 signal transduction in mice.

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In mammals, the olfactory system modulates reproductive and socio-sexual behaviors mainly by the detection of chemosignals (pheromones) by dedicated neurons of the vomeronasal organ (VNO). At least two populations of VNO receptor cells detect pheromones through two families of G-protein-coupled receptors, V1Rs and V2Rs. Whether Gαi2 plays a key role as the primary G protein α-subunit mediating V1Rs ligand detection remains unknown. To address this point, we created a conditional knockout mouse for Gαi2 gene in all olfactory marker protein (OMP)-expressing cells. Using calcium imaging, we found that Gαi2-/- VNO neurons do not detect small organic molecules and steroid derivatives, indicating that Gαi2 is required for sensory transduction in V1R-expressing vomeronasal neurons. Furthermore, male mice mutant for Gαi2 display enhanced male-male aggression and increased neural activity in the medial amygdala (MeA), and bed nucleus of the stria terminalis (BNST). By contrast, these mice showed reduced infant-directed aggression and enhanced parental behavior, as well as decreased activity in MeA neurons and elevated neural activity in the medial preoptic area (MPOA). These data show that Gαi2+ vomeronasal neurons and the brain circuits activated by these neurons play a central role in balancing territorial and infant-directed aggression of male mice. Conditional ablation of Gαi2 did not induce major alterations in sexual behavior in both females and males. Clearly, Gαi2+ vomeronasal neu- rons are dispensable for sexual preference and mounting behavior, and thus the importance of V1Rs for basic sexual behaviors has been overestimated.

O8 - Intestinal gluconeogenesis exerts metabolic benefits by activating the leptin signaling pathway and CGRP neurons

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Intestinal gluconeogenesis (IGN) exerts metabolic benefits, inducing satiety and energy expenditure and improving glucose control. Interestingly, leptin, a key anorexigenic hormone, exhibits comparable metabolic effects. The sensing of glucose produced by the intestine in the portal vein signals to the brain areas, such as the parabrachial nucleus expressing the neuropeptide CGRP (calcitonin gene-related peptide), a potent inhibitor of food intake.

We studied the central mechanisms involved in the beneficial effects of IGN by investigating the role of leptin and calcitonin-related peptide CGRP.

We evaluated the effect of portal glucose infusion mimicking IGN on: 1/ food intake and 2/ STAT3-phosphorylation, a key protein of the leptin pathway in the hypothalamus, with or

without an inhibitor of this phosphorylation (AG490). The effect of portal glucose infusion was also studied in leptin- (Ob/ob mice) or CGRP- (CGRP-/- mice) deficient mice.

We report that the portal glucose signal decreases food intake (about of 30%) and plasma glucose by activating STAT3-phosphorylation especially in the arcuate nucleus. These ef- fects are absent in mice treated with AG490, suggesting a key role for the leptin pathway. Importantly, portal glucose counteracts the hyperphagic behaviour of Ob/ob mice, reduc- ing their food intake, while the STAT3-phosphorylation is induced. Metabolic benefits and hypothalamic STAT3-phosphorylation take place upon portal glucose infusion in CGRP-/- mice.

In conclusion, portal glucose signalling involves the STAT3 phosphorylation, independently of the presence of leptin, and depends on the anorexigenic neuromediator CGRP. The causal link between the two phenomena is currently being investigated.

Poster

P1 - Effects of phthalates on female reproductive behaviors and neuroendocrine responses

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Over the last decades, a massive increase of environmental contamination with endocrine disrupters has been recorded. Among these molecules, phthalates are of great concern since they are widely encountered in the environment, particularly the DEHP (di-2-éthylexyl ph- thalate). Phthalates can induce reproductive dysfunctions, including an altered reproductive behavior in adult male mice (Dombret *et al.*, 2017). In the present study, our aim is to in- vestigate the effects of phtalates on female reproductive behaviors. Adult female mice were fed with food containing a vehicle, DEHP at 5 µg/kg/day (close to the environmental expo- sure) or 50 µg/kg/day (tolerable daily intake dose), or a mixture of phthalates close to the environmental exposure. Results show prolonged estrous cycle duration in phtalates-exposed mice, particularly the estrus and diestrus stages. Moreover, male mice are less attracted by females exposed to phtalates – both awake or anesthetized – and emit a lower number of ultrasonic vocalizations in their presence. In addition, phtalates-exposed females show an altered olfactory preference towards male mice and they exhibit a decreased lordosis quotient, a position adopted during copulation. This may be explained by the lower number of neurons expressing the progesterone receptor in the ventromedial hypothalamus, a key region in the expression of lordosis posture. These data strongly suggest that adult exposure to an environmental anti-androgenic compound can affect the female neural structures involved in female reproduction.

P2 - Contribution of exposure to environmental doses of anti-androgenic endocrine disruptors belonging to the phthalate family, on the neurovascularunitin male mouse brain

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Phthalates are considered to be one of the major group of endocrine disruptors which display an anti-androgenic activity**,** leading to a decline in male reproductive health**.** The pivotal role of sex steroid hormones in male reproductive and non-reproductive functions are well documented. Our team has recently shown that neural circuitry underlying male sexual behavior is vulnerable to adult exposure of di (2-ethylhexyl) phthalate (DEHP) at a dose close to environmental exposure. These alterations trigger by the androgen receptors **(**AR) down-regulation which is accompanied by an increased astrocyte reactivity. In parallel, we have shown that testosterone depletion-mediated AR down-regulation in adult male mice after castration, results in up-regulation of inflammatory molecules which is associated with an increased blood-brain barrier (BBB) leakage in cerebral capillaries. The BBB is a highly regulated specific interface maintaining cerebral homeostasis. Cerebral vessels are target tis- sues of sex steroid hormones as they express their receptors. In the current study, we studied the effects of chronic exposure to environmental doses of phthalates on the neurovascular unit in adult male mouse. We focused on two sensitive-hormone cerebral regions, the hy- pothalamic medial preoptic area and the CA1 region of the hippocampus, compared with the region of the cortex which expresses much less AR. We investigated the impact of a 6 week- oral exposure to DEHP alone at doses of 5 and 50 µg/kg/day or in a phthalate mixture. We mainly explored the function and structure of the BBB: permeability, endothelial tight junctions, trans-endothelial vesicular transport pathway and basal lamina.

P3 - SELENOT regulates POMC expression in hypothalamic neurons

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The arcuate nucleus of the hypothalamus is involved in feeding behavior. It is close to the median eminence, a blood-brain barrier-free area allowing peripheral factors to inform hypothalamic structures about the energy status. Neurons expressing the prohormone POMC are among the first neurons exposed to peripheral signals. In patients suffering from anorexia nervosa or obesity, low plasma levels of α-MSH, a POMC-derived peptide, are measured (1). Low circulating levels of α-MSH also correlate with diminished leptin and insulin sensitivity in a mouse model of diet-induced obesity (DIO). Hypothalamic inflammation and endoplas- mic reticulum (ER) stress are reported in DIO mice, leading to redox status alteration and hypothalamic nutrient sensing impairment. Selenoproteins, which are for most of them antioxidant enzymes, exert an important role in the maintenance of energy homeoastasis. In particular, Selenoprotein T (SELENOT) regulates insulin secretion and glucose tolerance (2). High SELENOT transcript levels have been reported in POMC neurons by cell type-specific transcriptomics studies, but the role of SELENOT in POMC neurons and related metabolic diseases is still unknown. Using a POMC cell line derived from the mouse hypothalamus, we found that SELENOT expression is increased twice in response to anorexic signals (insulin or leptin stimulation) or lipotoxic stress (palmitate treatment). In addition, SELENOT de- pletion disrupted cell trafficking and provoked ER stress, leading to POMC accumulation. These findings support a role of SELENOT in POMC neuron physiology. Further studies are ongoing to understand the function of SELENOT in these neurons and its effect in food intake regulation.

P4 - Regulation of tumor angiogenesis by chemerin and its receptor CMKLR1

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Chemerin is a multifunctional protein characterized initially in the host laboratory as a chemoattractant factor for leukocyte populations. Its main functional receptor is ChemR23/CMKLR1, but GPR1 and CCRL2 have also been described as chemerin receptors, although their signaling properties appear limited. Chemerin and CMKLR1 were shown to display anti- tumoral properties in animal models and our group identified an original mechanism by which chemerin interferes with cancer progression by inhibiting the efficient vascularization of the tumors and their growth. The control of neoangiogenesis is a key element in tumor progression, and the interaction between pericytes and endothelial cells is an essential com- ponent in this process. The aim of the present proposal is to investigate more precisely how chemerin affects angiogenesis and more precisely the dialog between endothelial cells and pericytes, *in vitro* and *in vivo*, using a set of established or newly developed genetic models in mouse. We also evaluate the therapeutic potential of CMKLR1 agonists as therapeutic agents in combination with other inhibitors of tumoral angiogenesis. Altogether, we aim to validate the chemerin system as a target for therapeutic intervention in the frame of hu- man cancer. We have so far demonstrated that chemerin expression *in vivo* is as efficient as anti-tumoral agent as an inhibitor of the VEGF receptor tyrosine kinase activity used in the clinic, and have demonstrated that chemerin also affects angiogenesis in two tumoral paradigms, including the *ex vivo* aorta ring assay, and *in vivo*, the post-natal development of the retinal blood vessel network.

P5 - NLRP3 facilite le contrôle de l'appétit chez la souris

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L'obésité est une maladie inflammatoire chronique dans laquelle des médiateurs pro-inflammatoires favorisent le dysfonctionnement d'organes métaboliquement actifs. Bien que les effets délétères de ces signaux soient connus à long terme, le rôle de la réponse inflamma- toire postprandiale transitoire est encore largement méconnu. L'objectif est d'évaluer le rôle de la réponse inflammatoire postprandiale sur le contrôle de la prise alimentaire. Afin d'initier une réponse inflammatoire postprandiale, des souris C57Bl/6j ont été nourries avec une diète hypercalorique et hyperlipidémique (HFD). Après introduction de la diète pro-inflammatoire, le comportement alimentaire des animaux a été enregistré pendant 24h. Différentes interventions pharmacologiques ou génétiques ont été réalisées afin d'apprécier les effets de la réponse inflammatoire postprandiale sur le comportement alimentaire. L'endotoxémie, caractéristique de la réponse inflammatoire postprandiale, a été inhibée par traitement antibiotique déplétant le microbiote intestinal. L'action du LPS bactérien sur la voie de sig- nalisation TLR4 a été inhibée par blocage pharmacologique ou délétion du gène codant le récepteur TLR4. L'activation de la voie de signalisation de l'inflammasome NLRP3 a été inhibée par injection ip de l'antagoniste MCC950 ou délétion du gène codant NLRP3. La réponse microgliale hypothalamique a également été recherché. Nos résultats montrent que la déplétion du microbiote ou l'inhibition de la signalisation du TLR4 avant l'introduction de l'aliment HFD n'a pas eu d'incidence sur le comportement alimentaire et l'activation microgliale centrale. L'inhibition de NLRP3 a augmenté la prise alimentaire sur 24 heures. Ainsi, l'inflammation postprandiale favoriserait le contrôle homéostatique de la prise alimen- taire et limiterait la consommation excessive de calories.

P6 - Endocrine regulations of subordinate females during dominant gestations in slender-tailed meerkats

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In obligate cooperative species, breeders need the presence of non-breeding helpers for their offspring to survive. In meerkats (*Suricata suricatta*), the dominant pair of each group monopolizes reproduction, but subordinate females are physiologically able to breed as well. In order to prevent them from giving birth at the same time, pregnant dominant females become very aggressive toward subordinate females, even more as parturition approaches. Here, we used noninvasive methods to investigate the hormonal response underlying the behavioral reproductive suppression in subordinate females during the gestation of a dominant female. Fecal progestagens have been shown to reflect the reproductive function in female meerkats. Feces were collected from captive and wild subordinate females. After extraction, the progestagen levels were measured using an enzyme immunoassay. Our results show a sig- nificant decrease in the progestagen levels of the subordinate females during the dominant's gestation. This decrease is stronger during the second half of the gestation. These results suggest that the reproductive system in subordinate females is strongly regulated during the gestation of the dominant female. Indeed, a decrease in progestagens can prevent females from establishing or maintaining a pregnancy. Recent evidence also show that fecal gluco- corticoid metabolites are higher in subordinate meerkats during the gestation of a dominant, which along with our results would suggest that high stress levels are down-regulating the reproductive axis in subordinate meerkats.

P7 - Preclinical evidence for a role of Apelin in the comorbidity of diabetes and major depression

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Epidemiological studies suggest the existence of a bidirectional link between diabetes and depression. Since the prevalence of depression is twice higher among diabetic patients than the general population, we raised the possibility that insulin sensitivity could be a key process underlying this comorbidity. Accordingly, our pre-clinical data demonstrated that type 2 diabetic obese mice harbor behavioral hallmarks of depressive-like behaviors, mem- ory deficits and antidepressant drug resistance. On this ground, the identification of targets regulating peripheral and/or central insulin signaling, is a new avenue for the development of innovative therapeutic strategies in the field of mood disorders.
Apelin is the endogenous ligand for the G-protein-coupled receptor (APJ) known to improve insulin sensitivity. The localization of APJ in limbic structures is another argument in favor of a potential role of this peptide in emotional processes. However, such association has never been clearly demonstrated.
In the present study, we evaluated the effect of the constitutive genetic inactivation of Apelin on emotional and cognitive response in basal conditions or after exposure to an high fat diet (HFD). In basal conditions, we found that Apelin KO mice develop a prediabetic state while displaying minor neurobehavioral changes. However, after 6 weeks of HFD, mutants were

more prone to metabolic impairments including insulin resistance accompanied by a marked depressive-like phenotype compared to control mice. Collectively, these results suggest that apelin could have beneficial effects on mood but further experiments are warranted to decipher the mechanisms underlying those effects potentially involved in comorbid diabetes and depression.

P8 - Efficient metabolic control could protect against hypothyroidism-induced neuro-inflammationand cognitive alterations

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Thyroid hormones (THs) are important regulators of metabolism through their action in many organs, including brain and liver. Hypothyroidism is characterized by low energy ex- penditure and a decrease in lipid and carbohydrate metabolism. Moreover, hypothyroidism could promote neuro-inflammation and is linked with cognitive impairments. Metabolism dysregulations are also known to favour neuro-inflammation by increasing peripheral inflam- mation. Recently, TH dysfunction has been associated with neurodegenerative diseases and even identified as a possible risk factor for Alzheimer's disease. In this context, we hypothesized that an altered TH status could trigger the onset of neurodegeneration by disrupting metabolic homeostasis, and then promoting neuro-inflammation. To test this hypothesis, we analyzed the impact of hypothyroidism in mice on metabolism, peripheral/central inflammation, and cognitive functions. Therefore, we compared WSB/EiJ mice strain, characterized by obesity resistance due to its hypermetabolic phenotype, with C57BL/6J mice which are prone to high-fat-diet induced obesity. After induction of hypothyroidism by propylthiouracil treatment for seven weeks, we checked the lipid metabolism of eu- or hypothyroid mice of each strain. Preliminary results showed an increase of cholesterol levels in hypothyroid mice for both strains, contrary to triglycerides levels which decreased only in hypothyroid C57BL/6J mice. In liver, expression of key metabolic genes was downregulated in both hypothyroid strains. Further, we evaluated central inflammation by measuring microglia/astrocyte activa- tion in the hippocampus: WSB/EiJ mice appeared to have less activated microglia/astrocyte than C57BL/6J mice. Our data would emphasize the importance of maintaining metabolic and thyroid homeostasis to prevent the development of neuro-inflammation and subsequent cognitive impairments.

P9 - Fasting induces astroglial plasticity in the olfactory bulb glomeruli of rats: evidence for a role of astrocytes in the sensory regulation of food intake

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The morphological plasticity of astrocytes plays an active role in situations requiring adaptive changes in neurotransmission. We hypothesized this may occur in the modulation of olfactory sensitivity involved in food intake regulation. Olfaction participates to the sensation of hunger and satiety by changing the perception and value of food flavors. The olfactory system is reciprocally influenced by the metabolic state, being more active in starving animals, whereas satiety reduces olfactory acuity. Astrocytes are particularly important in the glomerular layer of the olfactory bulb (OB), the first step of integration of the olfactory signal. To test whether they are involved in the

metabolic sensing of the olfactory system, we compared the astroglial processes deployment in fed and fasted rats. Astroglial spreading was markedly increased in fasting rats (+40%), as compared to fed rats, in the glomeruli of all regions of the OB, and this increase was reversed by an intra-peritoneal administration of the anorexigenic peptide PYY3-36 or glucose. Direct application of the orexigenic peptides ghrelin and NPY on OB acute slices, resulted in an increased astroglial deployment, whereas application of PYY3-36 triggered astroglial retraction within the glomeruli. These results demonstrate that astrocytes of the OB glomeruli change their processes deployment accord- ing to the metabolic state of the rats, under the influence of food intake regulatory peptides. This plasticity may be part of the mechanism by which the olfactory system adapts to food intake. Our study highlights a new implication of the morphological plasticity of astrocytes in the context of feeding regulation.

P10 - Influence of the microbiota and a high fat diet transition on glomerular regulations in the olfactory bulb in rats

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Germ-free rodents are resistant to diet induced obesity, emphasising the importance of microbiota on the central control of food intake. Among the mechanisms possibly involved, we have evaluated whether the olfactory system, which participates to the sensation of hunger and satiety by changing the perception and value of food flavors, could be influenced by the microbiota. For this, we have compared several neuronal and glial regulations in the olfactory bulb (OB), in conventional (C) or germ-free (GF) rats submitted to a 2-days high fat diet transition (HF) or maintained on a chow diet (C). HF diet transition induced an increase in energy intake during the first 24h followed by a return to basal food intake within 2 days. This adaptation to HF diet was weaker in GF rats than in C rats. We measured several markers of plasticity in the OB glomerular layer, by immunohistochemistry: astrocytes deployment, dopaminergic and serotoninergic activity, and number/ramification of microglia. We found no striking changes of these markers in response to the lack of microbiota or to the HF transition. Nervertheless, we observed a slight decrease in the dopaminergic activity in response to HF in C rats but not in GF rats, and a slight decrease in microglia ramification in GF rats under HF diet. Our results indicate that the lack of microbiota is not associated with major changes in the glomerular regulation of olfaction, but that subtle olfactory modulations may contribute to the impact of microbiota on dietary behaviour.

P11 - Inducing PCOS in sheep : Physiological and behavioral consequences of a prenatal exposure to testosterone in Ile-de-France ewe lambs

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PCOS (Polycystic Ovary Syndrome) is the most common hormonal abnormality affecting ~7% of reproductive-age women. This syndrome can lead to infertility, metabolism disor- ders but also to anxiety disorders. Prenatal exposure to testosterone is a cause of PCOS and testosterone-treated ewes during pregnancy are known to induced a good model for PCOS syndrome in daughter female lambs. Hence we treated 40 ewes with testosterone propionate during the second third of gestation and we

obtained 28 PCOS ewe lambs that will be compared for their physiology and behavior to 27 Control lambs born at the same period.
Regular blood sampling in all young females will enable a fine monitoring of their reproductive activity, by assaying the progesterone the levels of which reflect ovarian activity. In addition, 22 PCOS and 20 Control lambs were submitted to different behavioral tests such as the Open Field test and the Novel Object test. Open Field test was performed on two consecutive days to test the habituation ability of the females.
Results showed a diminished habituation capacity in PCOS lambs. When confronted to a Novel Object, latency before touching the object was 2 times more elevated in PCOS than in Control lambs. Moreover, PCOS females had increased levels of cortisol in comparison to Control females. This anxiety does not seem to be linked to impaired cognitive performance as 11 PCOS and 10 Control were compared in a modified Detour Task (cognitive test) and their results were similar, with a comparable learning curve.

P12 - Cellular organization of the sheep hypothalamic neurogenic niche and associated microvasculature across season.

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A neurogenic niche is defined by a specific anatomical location in which stem cells can be directed into mitosis ensuring cell lineage fate and maintain stem cell stock or stay in quiescent state in response to internal microenvironment and external systemic stimuli.
In adult mammalian brain, neurogenesis has been recently shown to occur around the third ventricle, near to the lumen in basal hypothalamus. Interestingly basal hypothalamus har- bors several common components with other neurogenic niches, in particular a fenestrated vascular network characteristic of a loose blood-brain barrier. Moreover, hypothalamus is a crucial crossroad for the regulations of physiological function such as reproduction and serves as the operator of the neuroendocrine system by secreting hormones into the blood to induce the release of pituitary hormones. In sheep, our seasonal model, both proliferation rate and the number of neuroblasts are higher during short photoperiod corresponding to the breeding season, suggesting that inducible factors can trigger the increase in hypothalamic neurogenesis. We hypothesize that these inducible factors can be associated to the proximal vascular network.
In this present work, we focus on the relationship between hypothalamic blood vessels and neural stem cells across seasons using an immunohistochemical technique followed by the development of an image-processing analysis to measure the distances between them.
In addition, the wholemount technique is performed in order to map the cellular organization of the third ventricular wall by using tight junction and stem cell markers in relation with the blood vessel arborization pattern depending on the seasons.

P13 - Transcriptomic sex differences in the brain of Japanese quail show distinct regional patterns of response to gonadectomy and/or testosterone treatment

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Genetic differences and different hormonal exposure explain sex differences in physiology and behavior in vertebrates. The genes underlying these differences are largely unknown, especially in birds. The present study investigated transcriptomic sex differences in three brain regions (medial preoptic nucleus [POM], ventromedial nucleus of the hypothalamus [VMN] and nucleus taeniae of the amygdala [TnA]) of adult male and female Japanese quail left gonadally intact or gonadectomized and treated with testosterone (GDX+T). Overall, POM showed the largest number of differentially expressed genes (DEG). As expected, some DEG responded to GDX+T (T sensitive), while others did not (T-insensitive). Moreover, a third category of genes emerged that did not differ in gonadally intact subjects but became different upon GDX+T, suggesting that T (or ovarian hormones) actively "repress" some otherwise sexually-dimorphic genes. Some DEG were identified in only one nucleus and tended to be more T-sensitive, particularly in the POM which, surprisingly, had female-bias from autosomes and male-bias from the Z chromosome. In contrast other DEG, most of them T-insensitive, were common to several nuclei. DEG common to POM and VMN were most abundant, being mostly male-biased and located on sex chromosomes. Most DEG common to all nuclei are only expressed in females, suggesting they are located on chromosome W. Three patterns of DEG thus emerge in response to testosterone: T-sensitive, T–insensitive, and DEG normally repressed by T, each depending on neuroanatomical and chromosomal location, representing sets of candidate genes that could explain fundamental behavioral sex differences in adult birds.

P14 - Le dimorphisme sexuel de la concentration plasmatique de la LH et de la FSH à mi-gestation est associé à un dimorphisme sexuel de l'expression hypophysaire de LHB, de FSHB et de GnRHR

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A mi-gestation, les hormones LH et FSH dans le sang de cordon chez les fœtus filles sont proches de celles observées chez une femme ménopausée. Chez le fœtus male, la LH plasmatique est proche des concentrations observées chez l'adulte alors que la FSH est indosable. Ce dimor- phisme sexuel a disparu à 35 semaines de grossesse. Le but de ce travail était de comparer les niveaux d'expression hypophysaire des gènes de l'axe gonadotrope et plus largement du transcriptome entre les foetus filles et garçons.
Les ARN ont été extraits à partir d'hypophyse provenant de fausses couches tardives ou d'interruptions médicales de grossesse. A mi-gestation (17-20 WG), nos résultats montrent un dimorphisme sexuel de l'expression de *LHB*, de *FSHB en accord avec les concentrations plasmatiques*, mais également de *GnRHR*. Une analyse du transcriptome par microarray (Affimetrix) a montré l'expression différentielle de 118 gènes dont 96 codants et 22 non- codants. Une analyse fine des gènes différentiellement exprimés suggère que le timing de la transition epithélio-mesenchymateuse (EMT) survient plus précocément dans l'hypophyse du fœtus fille par rapport aux garçons.
Le dimorphisme sexuel de la concentration de la LH et de la FSH dans le sang de cordon à mi gestation est associé à un dimorphisme sexuel de l'expression des gènes codant pour les sous unités beta des gonadotrophines mais également de *GnRHR*. Cela pose la question du mécanisme sachant que l'environnement hormonal diffère peu entre les fœtus garçons et les fœtus filles à mi-gestation.

P15 - L'expression de PER2 est en avance de phase dans le syndrome de Smith-Magenis

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Le syndrome de Smith-Magenis est l'association d'un retard mental, d'anomalies du développement et du rythme veille-sommeil. Ce syndrome est du à une délétion de 3,5 Mb en 17p11.2. Les anomalies du sommeil associent des endormissements diurnes, un réveil très matinal. Un décalage du pic plasmatique de mélatonine à 12h00 est également observé. Dans ce travail, nous avons analysé l'expression de gènes de l'horloge dans les fibroblastes de patients SMS par rapport à un groupe contrôle. Dix enfants SMS âgés de 7 a 12 ans et 10 enfants contrôles ont été sélectionnés. Une biopsie cutanée a été réalisée pour mettre en culture les fibroblastes synchronisés par dexametha- sone. Les ARNm de *BMAL1*, *PER1* et *PER2* ont été quantifies par qRT-PCR, 1 heure après la synchronisation (PS), puis toutes les 4 heures pendant 56 heures. Dans les cellules contrôles, *BMAL1* et *PER2* oscillent avec une période de 24 heures alors que l'oscillation de *PER1* disparait 40 heures PS. L'analyse fine des oscillations montre un premier pic à 20h PS pour *PER1* (10/10) et à 24 h PS pour *PER2* (10/10). L'analyse dans les cultures SMS montre une avance du premier pic de *PER2* à 20h PS (7/10) sans modification de la phase du premier pic de *PER1* (10/10).
Une avance de phase de *PER2* est donc observée dans les fibroblastes cutanés des enfants SMS ce qui suggère fortement que l'avance de phase de la sécrétion de mélatonine est due à une anomalie du contrôle des gènes de l'horloge.

P16 - Does kisspeptin analog (C6) stimulate the release of gonadotropins in the mare?

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The kisspeptin is a key factor controlling ovulation in several species of mammals, but it fails to trigger ovulation in the mare. C6 is a kisspeptin analog with a half-life longer than the endogenous kisspeptin and capable of inducing ovulation in small ruminants. The aim of this study was to evaluate in the mare the effect of a single injection of C6 on the release of gonadotropins. We conducted two experiments and we collected jugular blood samples to measure LH and FSH plasma concentration. In a first experiment, eight cyclic Welsh pony mares (200-370kg) received an intramuscular injection of 50nmol of ovine C6 (oC6). In these experimental conditions, C6 had not effect on LH and marginally increased FSH concentration. In a second experiment, four acyclic Welsh pony mares (200-370kg) received an intravenous injection of 150nmol of equine C6 (eC6). eC6 and oC6 sequences differ in one amino acid. The eC6 increased rapidly the LH and FSH plasma concentration (before injection (mean±SEM) : 0,16±0,031 et 2,33±0,35 ng/mL versus 0h-4h after injection 0,34±0,035 et 3,82±0,47 ng/mL respectively). Mares with follicles smaller than 20mm at the time of injection showed a more pronounced response. These preliminary results suggest that the effect of C6 could be depend on: the physiological status, the dose, the route of administration and/or the type of C6 used. News experiments would allow to establish if C6 would trigger ovulation in the mare.

P17 - Prenatal androgen excess impairs sexual behavior in adult female mice: perspective on sexual dysfunction in PCOS

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Polycystic ovary syndrome (PCOS) is the most common anovulatory infertility disorder, affecting 1 in 10 women of reproductive age worldwide. PCOS is characterised by high circulating androgen levels, oligo- or anovulation, and polycystic ovaries. Recent epidemiological studies indicate that PCOS patients also experience sexual dysfunction, such as

decreased sexual desire, increased sexual dissatisfaction and gender dysphoria. Very little is currently understood about the development of female sexual behaviour in androgen excess states such as PCOS. Prenatally androgenized (PNA) animal model of PCOS exhibit an adult hyper- androgenism, impaired sensitivity to progesterone signalling in the brain and alterations in the neuronal network regulating reproductive function. Here, we aimed todetermine whether the PNA mouse model of PCOS exhibits typical female sexual behaviour. PNA females exhibited an overall reduction in lordosis quotient compared to VEH females ($p< 0.01$). These data suggest that increased androgen receptor mediated signalling during the prenatal period impairs sexual differentiation of the female brain and behaviour in addition to other PCOS features. To date, using cfos expression as an indicator of neuronal activation, no significant differences have been found in different brain regions known to be involved in the control of sex behaviour (MnPOA, VMHvl, MeA and BNSTpm). Further investigations will : 1) determine whether androgen excess impairs other components of female sexual behaviour such as partner preference and 2) define which neuronal circuit could be targeted by androgen excess in the PNA mouse model of PCOS.

P18 - Neural effect of a chronic adult exposure to di-(2-ethylhexyl) phthalate (DEHP) in male mouse.

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Phthalates are frequently detected pollutants in the environment due to their extensive use in the manufacture and processing of several products like plastics. Phthalates are endocrine disruptors; it is a substance that interferes with the normal hormonal mechanisms that allow a biological organism to interact with its environment. This results in a large contamination of adult individuals in industrialized countries as well as wildlife. Our team has recently shown that adult exposure to low doses phthalate close to environmental doses, alters the emission of ultrasonic vocalizations, lowers male attractiveness and delays the initiation of mating (Dombret et al. 2017; Capela et al. 2019). This vulnerability is not due to changes in circulating levels of testosterone or the integrity of the gonadotropic axis, but rather to a down-regulation of the androgen receptor in the neural circuit involved in the expression of sexual behavior. This receptor plays an important and complementary role with the estrogen alpha-receptor in the activation of those behaviors by testosterone (Raskin et al. 2009; Picot et al. 2014). In this context, we study the neural effects on sexual behavior of a 6 week- oral chronic exposure to di-(2-ethylhexyl) phthalate (DEHP) at doses of 5 µg/kg/day (dose corresponding to environmental exposure) or 50 µg/kg/day (tolerable daily intake) or to a phthalate mixture.

P19 - Chronic central infusion of apelin decreased LH levels but did not affect gene expression in KNDy neurons.

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Central control of reproduction relies on the hypothalamic integration of several exogenous and endogenous stimuli allowing LH and FSH release from pituitary cells controlled by GnRH secretion. This latter is driven by modulatory neurons that relay steroid feedback and metabolic status. Among them, kisspeptin (KP) neurons both sensitive to metabolic status major and major players in eliciting GnRH release are found in the arcuate

nucleus (ARC) as well as apelin neurons. This latter hormone is known to exert a prominent role in metabolic regulation, and was reported to decrease LH secretion. In the present study, we sought to check for an influence of apelin on KP neurons both anatomically and functionally through several experiments. Regarding KP neurons, we observed using immunocytochemistry neuroanatomical contacts between apelin fibers and KP neurons of the ARC of male rats. In a functional experiment, we treated male mice for 2 weeks with intracerebroven- tricular infusion of apelin and found a decrease of LH levels in treated mice but no effect on gene expression levels of KP, neurokinin and dynorphin in microdissected ARC between treated and control animals. Similarly, no effect was noted on testicular weight, glycemia and body weights. These results suggest that apelin effect on LH secretion do not pass through a modulation of genes expressed in KP neurons in male rodents but we cannot rule out a modulation of the secretory activity of these neurons. Further studies are underway to assess whether downstream populations are also affected by apelin.

P20 - Intestinal gluconeogenesis controls the neonatal development of the hypothalamus

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In adults, intestinal gluconeogenesis (IGN) regulates energy homeostasis in part by modulating hypothalamic leptin signaling. In neonates, IGN is induced during the time-window of hypothalamic axonal elongation, which depends on a neonatal leptin surge. We hypothe- sized that the neonatal pic of IGN also regulates this axonal elongation.
Neonatal IGN was stimulated by the overexpression of the catalytic unit of the glucose-6- phosphatase (IoverexpG6pc) one day after birth. Axonal elongation was studied by mea- suring AgRP(Agouti-related protein) and POMC (Proopiomelanocortin) fiber area in hy- pothalamic nuclei in 20-day-old IoverexpG6pc pups exposed to either a standard or high-fat high-sucrose (HFHS) diet during gestation and lactation. The metabolic consequences of the neonatal IGN induction were studied in 10-week-old IoverexpG6pc mice challenged with a HFHS diet during 4 weeks. IoverexpG6pc littermates were used as control.
Fiber area did not change in IoverexpG6pc pups exposed to a standard perinatal diet, despite increased neonatal leptin levels. Pups born to dams fed a perinatal HFHS diet exhibited increased AgRP and decreased POMC fiber area in the paraventricular nucleus. Interestingly, IoverexpG6pc mice were protected from these alterations. Indeed, neonatal IGN induction restored AgRP but not POMC fiber area in IoverexpG6pc mice fed a perinatal HFHS diet. Regarding metabolism, 10 week-old IoverexpG6pc mice showed better glucose and insulin tolerance than littermates when challenged with a HFHS diet.
Neonatal IGN protects from the hypothalamic AgRP fiber alterations induced by a perina- tal obesogenic diet and improves adult metabolic flexibility. The beneficial role of IGN on metabolism seems thus to extend to the developmental period.

P21 - Membrane estrogen receptor alpha is implicated in the control of fertility.

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Estrogens act through both nuclear and membrane-initiated signaling. Estrogen receptor alpha (ERα) is critical for reproduction, but the relative contribution of its nuclear and membrane signaling is unclear. To address this question, we characterized the reproductive phenotype of a knock-in mouse model (ERα-C451A backcrossed in the CD1 background) in which ERα's palmitoylation site is mutated resulting in a loss of function of membrane ERα

(mERα). ERα-C451A females present several reproductive abnormalities. While their LH response to ovariectomy does not differ from this of wildtype females, ERα-C451A fe- males present an altered response to estrogens indicative of a dysregulated negative feedback. ERα-C451A females do not show a pre-ovulatory LH surge and the associated activation of kisspeptin and GnRH neurons in response to estrogens unless they are treated with proges- terone. However, when left gonadally intact and mated with a wildtype male, these females become pregnant suggesting they are able to ovulate without exogenous progesterone. Yet, they present multiple gestational defects resulting in a decreased or total absence of pups in the nest depending on the strain. Daily weighing and scheduled ultrasound confirmed that ERα-C451A females (C57Bl6) do get pregnant and carry live pups. However, fewer implan- tation sites were found and developmental arrest occurred in some embryos before embryonic day 9. Parturition also appears to occur later in these females. Therefore, although mERα participates in the activation of the neuronal circuits leading to LH secretion, its ablation does not prevent ovulation, but induces gestational defects resulting in lower or no live birth.

P22 - Role of endogenous 5α-dihydroprogesterone in cerebroprotection at theacutephaseaftercerebral ischemia

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Stroke is a major cause of mortality and disability worldwide. Acute phase is critical as 2 million neurons are lost each minute. Using a middle cerebral artery occlusion /reperfu- sion (MCAO/R) model, our team has recently shown a marked increase in brain levels of 5α-dihydroprogesterone (5α-DHP) in male mice 6 hours following cerebral ischemia (Zhu *et al.*, 2017). The present study aimed to investigate the hypothesis that this increase could be an endogenous cerebroprotective process in response to ischemia.
5α-DHP is formed from progesterone by 5α-reductases (5α-Rs). Finasteride, a 5α-Rs in-hibitor, was administered to male C57Bl/6J mice 1 hour before MCAO/R and its effects on steroids levels and behavior were analysed at 6 hours post-MCAO. Finasteride efficiently reduced 5α-DHP concentration to basal levels, as confirmed by gas chromatography coupled to tandem mass spectrometry (GC-MS/MS) analysis. Interestingly, finasteride increased motor deficits as shown by neurological score, grip strengh test and Rotarod test and tended to increase lesion volume. At the cellular level, finasteride treatment impacted the density of neurones, astrocytes, oligodendrocytes and microglia, as shown by immunofluorescence analysis using NeuN, GFAP, Olig2 and Iba1 antibodies, respectively.
Overall, our observations point to an important potential role of 5α-DHP in the cerebro-protective mechanisms at the acute phase after cerebral ischemia. This should be confirmed by reversing the effect of finasteride by the administration of 5α-DHP.
*Reference***:** Zhu et al., (2017), *The Journal of Neuroscience*, 37(45):10998-11020

P23 - Mixtures measured in human, disrupt brain gene expression in *Xenopus laevis*

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Thyroid hormones are essential for normal brain development where they influence, through specific embryonic and post-natal periods all the steps of brain development. In adults, TH roles are essential to brain function and to general metabolism (thermogenesis, fat burning, etc.) Endocrine disrupting chemicals (EDCs) harm human health both as single molecules and as mixtures. Most research on

EDCs is done on individual chemicals whereas we are exposed to mixtures of numerous and possibly interacting molecules. As multiple EDCs are reported among classes of chemicals we are exposed to, we questioned the thyroid hormone disrupting effect of common chemicals.
We hypothesized that a common mixture of molecules is not inert and that a developmental exposure could lead to adverse effects later on. We recreated a mixture of 15 compounds commonly found in Human beings and tested them at the concentration measured in amniotic fluid and study the effects on thyroid hormone signaling and adverse effects on an amphibian model.
After 8 days of exposure to either thyroid hormone (T4 10nM) or to the mixture showed that an increase in proliferation in the neurogenic zones and a diminished tadpoles' motility. We then explored gene expression in tadpoles' brains and quantified mRNA level by a genome wide analysis. Surprisingly we showed that T4 or the mixture of 15 molecules showed significant gene alteration with an overlap on TH-dependent genes. Finally, we showed that t behavior. These results highlight the necessity to take into consideration mixture effects in both experimental studies and risk assessment.

P24 - Impaired welfare in sport horses: identification of marker genes

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As part of a project to assess the overall welfare of sport horses, a multidisciplinary approach combining behavior, intestinal microbiota, transcriptome and animal health stud- ies were performed on 202 sport horses. Four major behavioral disorders were identified: behavioral stereotypes, anxiety, apathy and aggression towards human. Among these 202 horses, 12 contrasted for anxiety (6 high and 6 low) were selected for transcriptomic analy- sis. Between high and low anxiety groups, 387 differentially expressed genes were identified. Upstream regulator analyses with Ingenuity Pathway Analysis and Enrichr have shown that these genes are involved in RNA metabolism and splicing, gene expression, cell cycle, and cell death/survival pathways and cell development. All these functions are related to cellular stress responses that are regulated by microRNAs and alternative splicing of pre-RNA, themselves controlled by RNA binding proteins. We are currently in the process of selecting the genes particularly involved in these pathways in order to perform a cross-correlation analysis between behavior, transcriptomic and microbiote data to identify marker genes of impaired welfare in sport horses.

P25 - Ghrelin stimulation of self-renewal of adult mouse stem cells from both brainstem area postrema and prostate epithelium

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Area postrema (AP) is the neurohemal

nucleus of the dorsal vagal complex (DVC), the brainstem integrator of autonomic reflexes, known to harbor a niche of neural stem cells. Ghrelin is the appetite-stimulating hormone, acting at the DVC level, and was reported to stimulate adult neurogenesis in the forebrain. Using Flourescent-Activated Cell Sor- tiing (FACS) of freshly dissociated cells from AP *vs* subventricular zone (SVZ) of adult mouse after labelling of neuropoiesis stage markers, we observed enrichment of AP cells in Lex(bright)/EGFR-negative (ie quiescent stem) cells as compared with SVZ. We addressed effects of ghrelin or its agonist JMV2894 on stem cells of AP *vs* prostate of adult mouse, using sphere assays. Microdissected AP and minced prostate from adult male mice were dissociated in DMEM/F12 or complete PrEGM (Lonza) media respectively, both supplemented with EGF (40ng/mL) and bFGF (20ng/mL). Resulting floating spheres were counted and passaged 3 subsequent times, giving rise to novel spheres at each generation. Various doses of ghrelin were added once at each plating. Ghrelin significantly increased the number of secondary spheres from both tissues, up to 4 times above control according to a bell-shaped dose-response curve. It demonstrates that ghrelin stimulates self-renewal of neural stem cells from AP and of epithelial stem cells from prostate, with a peak dose of 10nM. Expression of ghrelin receptor was detected by RT-qPCR on RNA extracts of pelleted proliferating spheres.
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P26 - In vitro study of glucocorticoid receptors involvement in hippocampal amyloid toxicity

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In Alzheimer's disease (AD), cognitive deficits are associated with an early deregulation of the hypothalamic-pituitary-adrenal (HPA) axis associated with elevated circulating gluco- corticoids (GC) and receptors (GR) signaling impairment. In an acute model of AD obtained after an intracerebroventricular injection of an oligomeric solution of amyloid peptides (oA*β*), we evidenced a deregulation of the HPA axis. In this model, we showed that a new selective GR modulator (CORT113176 - *Corcept Therapeutics*) restored HPA axis functionality and reversed AD hallmarks.
Here, to decipher some of the underlying mechanisms associated with Ab toxicity and GC in the hippocampus, we developed a model of primary neuronal culture. Hippocampal cells were obtained from rat embryos (day 17). After 6 days *in vitro* (6DIV) neurons were treated with GC, oAb (7DIV) and finally, CORT113176 or mifepristone (RU486, the non-selective GR antagonist of reference) (8DIV).
We first determined effective doses of GC and oAb treatments on hippocampal cells. We analysed some morphological parameters (neurites length, pyknotic cells...), cell viability, cytotoxicity, and finally GR, pGR (S211) and caspase 3 expression. Then, we evaluated cumulative deleterious effects of GC (at sub-effective dose) and oAb (at effective dose) and the capacity of GR ligands to reverse this toxicity.
We showed that GC and oAbexhibited cumulative deleterious effects on some parameters analysed, which could be reversed by CORT113176. These findings reinforce our hypothesis about HPA axis, GC and GR involvement in the induction and/or the development of AD, and bring new therapeutic strategies to tackle AD.

P27 - Chromogranin A - phosphatidic acid interaction promotes secretory granule biogenesis and neuroendocrine secretion

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Previous studies demonstrated that chromogranin A (CgA) promotes neurohormone ag- gregation and mediates secretory granule biogenesis at the *trans*-Golgi network level in neu- roendocrine cells but the mechanisms involved remain obscure. Here, we investigate the possibility that CgA acts synergistically with specific membrane lipids to trigger secretory granule formation. We show that CgA preferentially interacts with strip-immobilized PA. In secretory cells, we observe that Golgi PA is involved in the biogenesis of CgA-containing granules and we identify PA (36:1) and PA (40:6) as predominant species in Golgi and gran- ule membranes. Moreover, a bioinformatic analysis of CgA sequence predicts a PA-binding domain (PABD) and we show that, through this PABD, CgA is able to bind liposomes en- riched with PA (36:1) or PA (40:6) and to regulate secretory granule biogenesis. Interestingly, we observe that this interaction promotes liposome membrane deformation and remodeling. Furthermore, we demonstrate that depletion of CgA PABD or PLD1 activity significantly alters secretory granule formation in neuroendocrine cells. These results suggest that CgA controls remodeling and curvature necessary for secretory granule budding in neuroendocrine cells. In conclusion, CgA appears as a linker between neurohormone aggregates and Golgi membrane to generate secretory granules and then supporting neuroendocrine secretion. *This work was supported by institutional funding from INSERM, University of Rouen-Normandie, Région Normandie and the European Regional Development Fund (ERDF) (DO-IT2015 program), and grant from the Medical Research Foundation (FRM) (project number DEI20151234424).*

P28 - Peculiar tanycyte subcellular domains face hypothalamic neurons

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Tanycytes are highly specialized ependymal cells that line the bottom and the lateral walls of the third ventricle. In contact with the cerebrospinal fluid through their cell bodies, they send processes into the arcuate nucleus, the ventromedial nucleus and the dorsomedial nucleus of the hypothalamus. In this study, we combined transgenic and immunohistochemi- cal approaches to investigate the neuroanatomical interactions between tanycytes and neural cells present in hypothalamic parenchyma.

By stereotactically infusing TAT-CRE in the lateral ventricle of adult Rosa26-floxed stop tdTomato mice, we induced the expression of tdTomato in tanycytes, in order to analyze cell morphology. This allowed the observation of peculiar subcellular compartments along tanycyte processes -including spines, swelling, as well as en-passant boutons. Moreover, our data indicate that tanycyte endfeet form bouton-like shapes contacting both vessels and neurons, and in particular NPY and POMC neurons in the arcuate nucleus. Remarkably, these structures contain ribosomes, mitochondria, diverse vesicles, and transporters suggest- ing tanycyte/neuron and tanycyte/vessel communications.

Together, our results lay the neuroanatomical basis for tanycytes/hypothalamic neural cells

interactions that will be useful to further understand cell-to-cell communications involved in the regulation of neuroendocrine functions.

P29 - Acute central administration of 26RFa has antihyperglycemic effect in obese and hyperglycemic mice

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The neuropeptide 26RFa is known to be involved both in the regulation of energy metabolism and glucose homeostasis. It has been demonstrated that 26RFa acts as an incretin and also exhibits a central antihyperglycemic effect. However, the incretin effect of 26RFa is totally abolished in obese and hyperglycemic mice while the 26RFa central effect on glycemia remains unknown in this model.

The aim of this study is to investigate the central role of 26RFa under pathophysiological conditions such as obesity and diabetes.

First, we investigated the high fat diet impact on the hypothalamic expression of 26RFa and its receptor (GPR103). C57Bl/6JRj mice were submitted to high fat diet for 30, 60 or 120 days, 26RFa system in the hypothalamus was analysed by RT-qPCR. No significant alteration of 26RFa/GPR103 hypothalamic expression was found whatever the high fat diet duration.

Then, we performed glucose tolerance tests in high fat mice under acute intracerebroventricular 26RFA/HEPES injection. A significant antihyperglycemic effect was found in 26RFa treated mice. Because insulin secretion was not significantly altered in the 26RFa treated mice, the antihyperglycemic effect of the peptide seems to be explained by a modification of insulin sensitivity. Further studies are in progress to clarify this hypothesis.

Altogether, these data demonstrate that the central antihyperglycemic effect of 26RFA subsists in obese and hyperglycemic mice contrary to the loss of incretin effect. Further studies are now warranted to evaluate the benefit effect of central 26RFa chronic administration in diabetic models.

Key words: 26RFa, Obesity, diabetes, glucose homeostasis, CNS

P30 - Chronic intranasal insulin treatment in mice leads to the development of brain insulin resistance.

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Intranasal insulin (INI) has demonstrated benefits for patients with cognitive impairment and has been proposed as a potential therapy for the treatment of obesity. While globally well tolerated and showing beneficial behavioral outcomes, some evidences have pointed to the potential development of insulin resistance in humans. Brain insulin action modulates synaptic transmission, improves memory and reduces anxiety. Conversely, insulin resistance is linked to increased anxiety and anhedonia behavior. Although insulin resistance represents an important health threat, chronic INI effects on brain physiology were not further

studied in a mouse model.
Eight week-old male and female mice received a daily dose of INI (1.75UI) or saline (SAL) for 5 weeks. Anxiety and exploration were assessed after a final acute intranasal insulin or saline application. Particularly, the novelty-suppressed feeding test, the dark-light box and the openfield tests were performed. Following the last day of application, mice were sacrificed, brain regions dissected and processed for the study of the insulin receptor signaling pathway by western blot and qPCR.
Acute INI treatment had anxiolytic effects in males and females compared to the SAL-treated animals. Chronic INI-treated mice showed a reduction of the anti-anxiolytic properties of insulin. Moreover, chronic INI reduced the appetite suppressing effect of insulin. Finally, biochemical markers of insulin sensitivity were dampened in chronic INI treated mouse brain. Our study confirm the anxiolytic effect of nasal insulin administration, but chronic INI may have long-term deleterious consequences that should be further characterized in order to assess the safety of this method of application.

P31 - Differential effects of oxytocin on olfactory, hippocampal and hypothalamic neurogenesis in adult sheep

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New neurons are continuously added in the dentate gyrus of the hippocampus, the olfactory bulb and the hypothalamus of mammalian brain. In sheep, while the control of adult neurogenesis by the social environment or the photoperiod has been the subject of several studies, its regulation by intrinsic factors, like hormones or neurotransmitters is less documented. We addressed this question by investigating the effects of central oxytocin admin- istration on hippocampal, olfactory and hypothalamic neurogenesis. Endogenous markers, Ki67, Sox2 and DCX were used to assess cell proliferation, progenitor cells density and cell survival respectively in non-gestant ewes receiving a steroid treatment followed by intrac- erebroventricular injections of either oxytocin or saline. The results showed that oxytocin treatment significantly decreases the density of neuroblasts in the olfactory bulb, increases the density of neuroblasts in the ventromedian nucleus of the hypothalamus while no change is observed in both ventral and dorsal dentate gyrus. In addition, no change in the density of progenitor cells is found in the three neurogenic niches. These findings show for the first time that in females, oxytocin can regulate adult neurogenesis by acting on neuroblasts but not on progenitor cells and that this regulation is region specific.

P32 - Tanycyte-Neuron Lactate Shuttle: a new mechanism controlling food intake?

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The strategic location of the tanycytes of the arcuate nucleus of the hypothalamus (ARH) at the interface between the glucose-containing cerebrospinal fluid (CSF) and glucose- sensitive proopiomelanocortin (POMC) neurons raises the possibility that tanycytes play a role in hypothalamic glucose detection mechanisms. However, the existence of metabolic coupling between ARH tanycytes and POMC neurons has never been explored. Here, we investigated whether ARH tanycytes could form a network of interconnected cells in which lactate, produced from glucose circulating in the CSF, could diffuse to POMC neurons to modulate their electrical

activity. Using mice in which Cx43 is selectively knocked out in tanycytes (Cx43KoTanycytes) and wildtype (WT), we demonstrated that ARH tanycytes are indeed connected with each other and that energy substrates such as glucose can dif- fuse in the syncytium. Disruption of Cx43 in tanycytes leads to the loss of the ability of glucose to diffuse between tanycytes and to an increase in food intake, as shown using metabolic cages. Interestingly, electrophysiological studies showed that spontaneous activity in POMC neurons is significantly altered in Cx43KoTanycytes POMC-Cre:ROSA-tdTomato mice. Furthermore, we showed that 76% of POMC neurons use endogenous lactate, which they metabolize into pyruvate, as an energy substrate to maintain their electrical activity. Moreover, the bath application of lactate in Cx43KoTanycytes POMC-Cre:ROSA-tdTomato mice is able to rescue spontaneous firing activity in POMC neurons. Overall, our results suggest the existence of metabolic coupling between the ARH tanycytes and POMC neurons that appear to form a functional glia-to-neuron network regulating feeding.

P33 - Pregnancy promotes the addition of new oligodendroglial lineage cells in the rat hypothalamus

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The success of pregnancy involves a high degree of brain plasticity, including increased neurogenesis in the subventricular zone/olfactory bulbs that promotes maternal behaviour. The hypothalamus recently emerged as another germinal niche producing new neurons and glial cells in the postnatal brain. Given the central role of the hypothalamus in the control of reproduction and physiological adaptations to pregnancy, we explored whether cell neo- genesis occurs in the rat maternal hypothalamus.

Analysis of cell proliferation using the thymidine analogue BrdU showed that hypothalamic proliferation varies across the estrous cycle, with a peak in diestrus 2, which precedes the pre-ovulatory surge leading to ovulation. Cells born in diestrus 2 preferentially survived if females became pregnant. This differential survival was selectively seen in the medial preop- tic area (mPOA), a hypothalamic region acting as a hub in the onset of maternal behaviour. Co-immunofluorescent labelings showed that 14 days after their birth, most BrdU+ cells in the mPOA expressed Sox2 and Olig2, and a fraction of them expressed NG2, indicating an oligodendrocyte progenitor cell phenotype. The fraction of BrdU+ cells co-expressing Olig2 and NG2 was higher in pregnant versus non-pregnant rats. Moreover, BrdU+ cells were fre- quently found morphologically associated with neuron cell bodies, some of which expressed parvalbumin or Estrogen Receptor a.

Altogether, our data show that pregnancy is associated with the production of oligoden-droglial lineage cells in the mPOA that associate with neurons, and raise the possibility that gliogenesis may contribute to modulating the activity of neuronal networks involved in the onset of maternal behaviour.

P34 - In vivo effects of ghrelin and its agonist JMV2894 on feeding behavior and neurogenic proliferation of brainstem area postrema in adult male mouse

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Area postrema (AP) is the neurohemal nucleus of the dorsal vagal complex (DVC) i.e. the brainstem integrator of satiety and vomiting reflexes. The rodent DVC was shown to harbor a neurogenic niche with adult genesis of new neurons, intrinsic neural stem cells in AP, radial glia-like astrocytes. Although unknown, the physiological role of this adult neurogenic niche seems related with appetite since AP neurogenesis was enhanced *in vivo* by the anorexigenic hormone amylin (Liberini et al 2016). Ghrelin is the stomach-secreted orexigenic hormone of Mammals, acting directly on DVC. Ghrelin was reported to stimulate neural stem cell proliferation in the forebrain niches, in vitro and in vivo. In the present study, we addressed in vivo action of ghrelin and its degradation-resistant agonist JMV-2894 (Bresciani et al 2017) on both feeding behavior and BrdU-labelled AP neurogenesis. Tothis aim, groups of 8-week-old mice were housed individually in metabolic cages and treated with daily subcutaneous injections of either JMV2894 (320mg/kg) or ghrelin (120mg/kg) or saline (controls) during 3 weeks, combined with daily intraperitoneal BrdU injections (100mg/kg) during the 1st week. Both JMV-2894 and ghrelin treatments triggered significant increases of food intake (by factors 3 and 4 respectively above control) during the 4 first hours after injection each day of treatment. Meal frequencies were significantly altered by ghrelin. AP neurogenic proliferation was assessed on post-mortem brains of the experimental animals, by BrdU immunohistochemistry on serial slices throughout DVC.

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P35 - Molecular mechanisms of leptin transport across the tanycytes of median eminence

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Leptin is a hormone secreted by adipose tissue that acts in the central nervous system to regulate appetite. This dialogue between the periphery and the brain is essential to maintain energy homeostasis but is impaired in obese people. We have recently hypothesised that this so-called leptin-resistance, could be the consequence of a defective leptin transport into the brain. The median eminence, a hypothalamic structure located below the third ventricule contains specialized ependymoglial cells called tanycytes. These cells line the floor of the third ventricle and contact the fenestrated vessels in the median eminence. It has been proposed that tanycytes act as " gatekeepers " by regulating the access of blood-borne signals to the hypothalamus, and are involved in leptin transport for release into the cerebrospinal fluid from where leptin-sensitive regions can be reach. However, the cellular and molecular mechanisms controlling leptin internalization, its transcytosis as well as its release from apical site of the tanycytes remain unknown. Using fluorescence and electron microscopy on primary cultures of rat tanycytes, we are deciphering the endocytic route taken by leptin. Moreover, in order to maintain the cell polarity in vitro, we are implementing tanycytes culture in basal membrane extract gels. Finally, leptin release from tanycytes was monitored by ELISA assay and we focused on the role of vesicule-associated membrane proteins (VAMPs), components of SNARE complex, which is a key component of the exocytotic machinery in glial cells. Altogether, these data constitute a promising start toward the understanding of

the leptin journey in tanycytes.

P36 - The Hippo signalling pathway in tanycytes

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The Hippo signalling pathway is an evolutionarily conserved pathway critical for the con- trol of organ growth, stem cell function, regeneration and tumour suppression. In particular, it has been shown to regulate the properties of neural stem/progenitor cells (NPC) during embryonic development. Accumulating data suggest that tanycytes, ependymoglial cells lin- ing the floor of the third ventricle, are hypothalamic NPC in the postnatal brain. However, the molecular control of tanycyte NPC properties remains largely unknown.
In order to explore whether the Hippo pathway controls tanycyte NPC properties, we first examined the expression of core components of the Hippo pathway in rodent tanycytes. Immunofluorescent stainings showed that adult mouse tanycytes express the transcriptional co-activator Yes-associated protein (YAP), a downstream effector of the Hippo pathway, *in situ*. Western blot experiments and immunofluorescent labelings revealed the presence of YAP and of its binding partners, the TEA domain-containing sequence-specific transcription factors (TEAD1, 2 and 4) in primary cultures of rat tanycytes. Analysis of cell proliferation by flow cytometry using propidium iodide and an anti-Ki67 antibody showed that primary rat tanycytes enter the cell cycle in response to XMU-MP1 and amb1, which are two acti- vators of the Hippo pathway acting at an upstream and a downstream level of the pathway, respectively.
Altogether, our results show that tanycytes express components of the Hippo pathway and proliferate *in vitro* in response to Hippo pathway activators. Experiments are ongoing to evaluate whether activation of the pathway also regulates tanycyte proliferation *in vivo*, as well as their neurogenic potential.

P37 - Role of hypothalamic tanycyte VEGF-A secretion in the establishment of obesity in female mice

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Obesity is a worldwide problem that besides impacting human health produces economic and social damages. One key component of the pathology is the brain's resistance to hormones that is in part due to the impaired access of peripheral signals to their first cerebral target: the arcuate nucleus of hypothalamus (ARH).
A previous study from the laboratory showed that ARH access of peripheral signals is regulated via the secretion of VEGFa by tanycytes, specialized hypothalamic ependymoglial cells lining the third ventricle (3V) and sending projections to the ARH vessels. VEGFa secretion is glucose-dependant and modulates the permeability of blood vessels supplying the ARH, and thus the access of peripheral signals to neurons regulating energy homeostasis.
This study aims to determine the role of tanycyte VEGFa in the access of peripheral signals to the ARH during the establishment of obesity.
For this purpose, VEGFa secretion was specifically invalidated in tanycytes after the injection of cre –recombinase in the 3V of $Vegfa^{loxP/loxP}$ mice ($Vegfa^{TAN\ -/-}$). $Vegfa^{TAN\ -/-}$ female mice were monitored for the body weight, food intake and oestrus cycle before and after a high fat diet challenge. $Vegfa^{TAN\ -/-}$ mice were compared to $Vegfa^{loxP/loxP}$ mice injected with vehicle ($Vegfa^{TAN\ +/+}$).

Our preliminary results suggest that the invalidation of VEGFa secretion by tanycytes protects against the body weight gain and fat tissue production. In other words, ARH vessel plasticity and increase in their permeability may contribute to the establishment of obesity.

P38 - Dietary arachidonic acid induces alterations in gut microbiota and expression of astrocytic marker GFAP in male Balb/C mice.

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Arachidonic acid (ARA) is the second polyunsaturated fatty acid in the brain. ARA intake is associated with consumption of animal origin products and seems to be underestimated in western diet. A previous study in our laboratory showed that a diet containing 1% ARA increased the sensitivity of male Balb/C mice to the neurotoxicity of the amyloid-β peptide oligomers, considered as the main Alzheimer's disease agents. The objective of this study was to evaluate the impact of dietary ARA intake on brain functions through gut microbiota modifications and alteration of gut-brain communications. For this, two groups of male BalB/C mice were orally fed with moderately high fat diet, i.e., HL-ARA (15% lipid without ARA) and HL+ARA (15% lipid with 1% ARA) and the third group was fed on standard diet (Std-ARA, 5% lipids without ARA) during 9 weeks. No significant difference was observed in weight gain among the 3 groups except an increase in mesenteric fat tissue in HL-ARA diet group. An increase in Bifidobacteriaceae group (potentially anti-inflammatory) in gut microbiota of HL-ARA diet group was noted compared to standard diet group. This increase in Bifidobacteriaceae was correlated to high lipid contents in diet but this effect was reversed in HL+ARA diet group. No modifications in inflammatory markers were highlighted in plasma and feces samples of the three groups. Contrariwise, higher expression levels of the Glial fibrillary acidic protein were observed in hippocampus of HL+ARA group. It could be interesting to further investigate alterations of the gut-brain communications including neuroendocrine signals.

Keywords: Arachidonic acid, moderate high fat diet, intestinal microbiota, inflammation, gut-brain axis

P39 - Characterization of the reproductive physiology in the vole Arvicola terrestris.

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The fossorial water vole (*Arvicola terrestris*) is a rodent of the family of the Cricetidae. These voles live in galleries dug in meadows. The reproductive physiology of water vole is not well characterized but the literature suggests that they are probably seasonal breeders, which implies strong regulations of their hypothalamic-pituitary-gonadal (HPG) axis. To explore this hypothesis, we are performing a monthly monitoring of various physiological parameters on animals captured on the field. Our first results show a significant increase of genitals weight on males and females between February and June, followed, in females, by an

increase of the gestation rate. Our results show also a significant increase from February to April of the surface of their lateral scent glands, which are sensitives to androgens.
Finally, we are also evaluating neuronal expression of two hypothalamic neuropeptides, namely kisspeptin and RFRP-3, which are known to modulate reproductive activity through HPG axis regulation.

P40 - Disclosing neuroendocrine mechanisms of seasonality, a step towards genetically modified models.

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Previous studies on seasonal mammals have highlighted the role of melatonin for synchronizing reproductive activity with the seasons. Melatonin controls thyroid stimulating hormone (TSH) production from the pituitary *pars tuberalis* so that its secretion is higher under long summer days. TSH in turn acts on tanycytes, to regulate the balance in deio- dinase2/3 activities leading to increased hypothalamic concentration of T3. Although this melatonin-driven TSH/T3 signal is pivotal for synchronizing reproduction with the seasons, T3 cellular targets have not been established.
In hamsters, two hypothalamic peptides known to regulate GnRH neurons, kisspeptin and (Arg)(Phe)related peptide (RFRP), are inhibited by melatonin in short days adapted sexu- ally inactive Syrian hamsters, but whether this seasonal regulation depends on a direct effect of T3 is unknown.
Because studies on hamsters are limited by the lack of genetically modified models, we explored whether mice, although showing no overt seasonal functions, could help disclosing the link between hypothalamic T3 and kisspeptin/RFRP.
First, we observed that melatonin-deficient C57 mice supplemented with melatonin at night display the same melatonin-dependent regulation of TSH, Dio2/3 and RFRP than hamsters. Next, by comparing the effect of melatonin supplementation in wildtype or mutated C57 for the T3 receptor TRalpha, we found that in mice lacking TRalpha, melatonin no longer inhibits RFRP expression.
Altogether our data indicate that mice, like seasonal mammals, are able to integrate the melatonin signal up to the hypothalamic RFRP and that the melatonin-driven inhibition of RFRP neurons appears to depend on the effect of T3 on TRα.

P41 - Design and synthesis of new pharmacological tools to characterize and localize the kisspeptin receptor GPR54 (KissR1)

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Introduction
In mammals, the kisspeptin (Kp) system activates the reproductive axis. However, its pharmacology is only partially known. To refine our knowledge we have created new tools based on modifications of the endogenous ligand Kp10.
Methods
Four Kp analogs were synthesized (TMV-33-2a, TMV-34, TMV-160A and TMV160B) bearing modifications to improve the pharmacodynamics, to tag the molecule (biotin insertion) and capable of binding covalently the

receptor (furan insertion). In vitro activity was evaluated by a calcium mobilization assay in HEK-293 transfected with the human GPR54. In vivo activity was assessed in adult male mice and in ovariectomized and estrogen replaced female mice by measuring the plasmatic concentration of LH by ELISA.

Results and conclusions

All analogs were active in vitro (TMV-33-2a EC50=7nM, TMV-34 EC50=0.05nM, TMV-160A et TMV160B EC50<1 pM) and elicited an increase of LH from 20 minutes after injection. In the male the LH increase triggered by TMV-34 was of short duration. On the other hand, TMV-33-2a caused an LH increase lasting more than 8 hours. In the female TMV-34 has little effect, conversely the other analogs stimulated a prolonged LH increase.

These results show that it is possible to create Kp analogs with improved pharmacodynamics that are potentially capable of binding covalently the receptor and eventually detectable. Studies to better characterize these new tools and their interaction with the receptor are planned.

P42 - Effect of lipid nature on the establishment of a diet-induced obesity and associated neuroinflammation in mice

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Obesity, the fifth leading global risk factor for mortality, is a serious public health problem. It is associated with "low-grade" systemic inflammation and many studies are devoted to understanding the mechanisms causing obesity. Some of them shows that deregulation in the brain could be responsible for this syndrome and others have shown that in addition to the peripheral inflammation, a local hypothalamic inflammation was found in obese animals fed a high fat diet (HFD), leading to eating disorders. More specifically, certain lipids are responsible for this inflammation and the degree of hypothalamic inflammation induced by these lipids depends on the quality of their fatty acids. At the cellular level, exposure to excess nutrients leads to activation of astrocytes and microglia which have a preventive role at first but can become harmful in the long term and lead to obesity.

The purpose of this study was to characterize the impact of lipids nature on obesity development and associated inflammation.

To do this, we fed mice over 4, 8 or 12 weeks with animal or vegetable HFD with different omega6/omega3 ratios. We characterized obesity development and inflammation induced by these diets enriched in saturated fatty acid (SFA) or polyunsaturated fatty acid. We showed that SFA-enriched HFD induce a severe obesity and a deregulated glucose homeostasis, associated with an increased hypothalamic orexigenic peptides expression and a neuroinflammation. Moreover, we have demonstrated that omega6/omega3 ratio doesn't seem to influence the weight gain but is correlated with neuroinflammation associated with microglial reactivity in the hypothalamus.

P43 - Tanycyte AMPKα1/α2 ablation modulates hypothalamic hormone sensitivity

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AMP-activated protein kinase (AMPK) is a known regulator of cellular and whole-body

energy homeostasis. In the hypothalamus, it has been described that AMPK mediates ghrelin, glucose-like peptide 1 and thyroid hormone induced changes in metabolism related neuropeptides secretion. However, in order to reach their hypothalamic targets, peripheral hormones must first cross the blood-brain barrier (BBB); transcellular transport via tanycytes, specialized glial cells of the hypothalamus, appears to be one of the routes used by these signals to enter the brain. Tanycytes line the floor of the 3rd ventricle (3V) and send processes towards the external zone of the median eminence where reside fenestrated capillaries; they have been shown to act as a physical barrier preventing the free diffusion of circulating molecules into the cerebrospinal fluid (CSF). AMPK being a key energy sensor and tanycytes putative channels for the transport of peripheral metabolic signals into the brain, here we sought to study the role of AMPK expression in tanycytes at the blood-CSF barrier interface in the median eminence (ME) of the hypothalamus.
Tanycyte specific AMPK ablation in mice induced changes in food intake, body weight and energy expenditure. Those metabolic modifications are accompanied with an increased hormonal sensitivity which could like be related to the changes in blood-brain barrier permeability we observe in these mice.

P44 - See-through the brain: 3Dimensional Imaging of the Neuroendocrine Circuits Controlling Reproduction in Mice

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The proper functioning of the reproductive axis guarantees the survival of a species, and fertility in mammals is controlled by a population of gonadotropin-releasing hormone (GnRH) neurons located in the hypothalamus. These neurons integrate several signals from their interactors and release GnRH in the hypothalamo-pituitary portal circulation to stimu- late gonadotropin secretion in the pituitary. In mice, GnRH neurons are born in the olfactory placodes around embryonic day 10.5 (E10.5), then migrate during the embryonic life from the nasal region towards the brain, using olfactory/vomeronasal nerve projections as guides. In the brain, the majority of the GnRH neurons migrate ventrally and settle in the hypothalamus, where they show little activity until puberty onset.
Most studies on GnRH neurons migration and their interactions in the brain were conducted on sections. Thus, there was a significant loss of information when trying to study the entire network involved in the control of fertility. Clearing and 3D-imaging techniques developed these last ten years are useful tools to allow easier visualisation and analysis of both physiological and pathological conditions at the network and organ scale.
Here, using whole-mount immunolabelling combined with tissue clearing and light-sheet mi- croscopy, we analysed the ontogenesis, migration, and axonal targeting of GnRH neurons in mice from embryonic development to adulthood. Moreover, using transgenic mouse lines, we identified unexpected extrahypothalamic populations expressing GnRH, GnRH receptor, and kisspeptin in the postnatal mouse brain. These data raise the intriguing hypothesis that GnRH could be implicated in the modulation of multiple brain functions.

P45 - Effect of the prebiotic lactulose on neurogenesis in a sheep model of early-life stress

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The olfactory bulb and the hippocampus represent the main regions in the mammalian brain where new neurons continue to be added throughout life. Early-life stress affects the neurogenesis process in these areas. Gut microbiota modulates hippocampal neurogenesis and both probiotics and prebiotics supplementation can prevent the stress-induced reduction in hippocampal neurogenesis. The impact of gut microbiota and its modifications on olfactory neurogenesis has not been explored yet. Here, we investigate the effect of the prebiotic lactulose – an artificial disaccharide – on bulbar neurogenesis in maternally deprived lambs, a sheep model of early-life stress.

Twenty-four female lambs were separated from their mothers 24 hours after parturition and randomly assigned to the Prebiotic group (P, N=12) or the Control group (C, N=12), housed separately. P lambs were fed with lactulose-supplemented (1%) artificial milk, while C lambs with non-supplemented artificial milk. At eleven weeks of age, olfactory neurogenesis was investigated by quantifying the number of neuroblasts (visualized with doublecortin (DCX) immunostaining) in the granular layer of the main olfactory bulb (MOB). DCX-positive cells were counted manually in frontal sections of the left MOB (four per animal) using Mercator software.

The number of DCX-positive cells observed in the granular layer of the left MOB did not significantly differ (unpaired t-test: $t(71)=1.54$, $P=0.128$, two-tailed) between P lambs (mean ± SEM = 35.18 ± 2.17 cells/mm2) and C lambs (31.31 ± 1.45 cells/mm2).

We found no evidence that lactulose supplementation affects olfactory neurogenesis in maternally deprived lambs. However, we are currently investigating whether lactulose modulates hippocampal neurogenesis.

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