NutriNeuro lab presents

2017 Doc/Postdoc day

Nutrition: Time does matter…

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2017 Doc/Postdoc Day – Nutrition: Time does matter…

Program

9h30 ***Coffee break***

10h00 - 12h00 Session 1 Early-life
Chair: Essi, Lison, Marianela, Charlotte

Marion Rincel: social behavior impairments in males and hyper-anxiety in females are associated with gut microbiota changes in a neurodevelopmental two-hit model in mice

Quentin Leyrolle: N-3 PUFAs deficiency alters brain development.

Fabien Ducrocq: Impact of n-3 PUFA deficiency on motivation and mesolimbic dopamine transmission

Roman Walle: Interaction between membrane lipids and heteromers of receptors: impact on the functionality of mesolimbic dopaminergic transmission

12h00-13h30 ***Lunch Break***

13h30 - 15h30 Session 2 Adolescence to aging
Chair: Marion, Quentin, Fabien, Roman

Marianela Santoyo-Zedillo: Is the effect of adolescent high-fat diet on memory related to alteration of hippocampal-amygdala connectivity?

Lison Huet: Role of inflammation in the physiopathology and treatment response of depressive disorders

Charlotte Rey: Involvement of n-3 PUFA-derived lipid mediators in the resolution of brain inflammation

Essi Biyong: Effect of vitamin A supplementation in Alzheimer's disease prevention.

15h30 ***Conclusions***

Abstracts

Social behavior impairments in males and hyper-anxiety in females are Associated with gut microbiota changes in a neurodevelopmental two-hit Model in mice

Marion Rincel[1], Philippe Aubert[2], Julien Chevalier[2], Pierre-Antoine Grohard[2], Élodie Lévy[1], Camille Monchaux de Oliveira[1], Lilian Basso[3], Grégoire Chevalier[4], Nathalie Vergnolle[3], Michel Neunlist[2], Marion Leboyer[5], Gérard Eberl[4], Sophie Layé[1], Hélène Boudin[2], Patricia Lepage[6], Muriel Darnaudéry[1]

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There is a bidirectional communication between brain and gut and dysfunctions of the gastrointestinal tract are a common feature of numerous neuropsychiatric diseases. Various early life events (infection, stress…) can affect brain development and participate to the etiology of neuropsychiatric disorders such as schizophrenia, anxiety and affective disorders. Recently, gut microbiota alterations during development have been hypothesized to affect brain development. The long lasting impact of early life adversity, especially the combinatory effects of multiple early environmental factors, on gut microbiota, as well as potential differential effects between genders remain to be explored. Here we examined the effects of early life adversity on behavior, gut function and microbiota composition in males and females using a two-hit animal model in C3H/HeN mice combining maternal infection (Lipopolysaccharides injection at embryonic day 17, LPS) and maternal separation (3hr per day from postnatal day (PD)2 to PD14, MS). At adulthood, offspring exposed to LPS+MS displayed marked sexual dimorphism in behavioral as well as gastro-intestinal phenotypes. LPS+MS males showed impaired social behavior but intact anxiety-like behavior. In contrast, social interaction was not affected in LPS+MS females, but they were hyper-anxious relative to controls. These effects were accompanied by increased transcellular intestinal permeability in males, but not in females. Finally, 16S-based microbiota profiling revealed higher proportions of *Lactobacillus*, *Alloprevotella, Porphyromonas, Bacteroides and* unclassified *Firmicutes* genera and lower proportions of unclassified *Lachnospiraceae and* unclassified *Porphyromonas in* LPS+MS male mice compared with controls. In LPS+MS females, *Muscispirillum and Lactobacillus* genera were decreased. In conclusion, our work demonstrates a marked sexual dimorphic effect in a double-hit model of early life adversity, both on behavior and on gut microbiota. Further studies are needed to unravel the implication of the gut microbiota alterations reported here in the expression of the behavioral phenotypes associated with early inflammation combined with maternal stress.

N-3 PUFAs deficiency alters brain development.

Leyrolle Q[1,2], Sere A[1], Aubert A[1], Bosch-Bouju C[1], Dejean C[3], Schwendimann L[2], Gressens P[2], Layé S[1], Nadjar A[1].

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Neurodevelopmental disorders are thought to be due to pathophysiological processes occurring in the brain prior to the emergence of clinical symptoms, such as white matter or synaptic abnormalities. In addition, there are lots of evidence demonstrating a role for lipids in neurodevelopmental disorders. Polyunsaturated fatty acids (PUFAs) constitute the major class of lipids in the brain and have been linked to neurodevelopment. Polyunsaturated fatty acids (PUFAs) are essential fatty acids that mammals need to obtain through the diet. Imbalanced maternal dietary intake in PUFAs is an environmental risk factor for neurodevelopmental disorders such as autism, schizophrenia and immune related diseases. We postulated that developmental n-3 PUFA deficiency disrupts the shaping of neuronal networks leading to long lasting behavioral deficits.

We fed pregnant mice with n-3 PUFA deficient diet over the gestation and lactation period. White matter integrity was assessed by diffusion tensor imaging (DTI) and immunohistochemical measurements in offspring both during brain maturation and at adulthood. Brain connections integrity was also assessed by *in vivo* electrophysiology and EEG recordings. Our data showed decreased connectivity between brain structures. We also evaluated synaptic density and function and found impairment at that level as well. This was correlated to behavioral alterations at adulhood. Overall our data suggests that n-3 PUFAs deficiency alters the shaping of neuronal network both at the cellular and structural level. These alterations lead to various deficits in cognitive and emotional behavior.

Impact of n-3 PUFA deficiency on motivation and mesolimbic dopamine transmission

Fabien Ducrocq, Roman Walle, Clementine Bosch-Bouju,Asma Oummadi,Suzanne van der Veldt,Gabriel Barreda, Agnès Aubert,Rolando Meloni, Sophie Layé,Véronique De Smedt and Pierre Trifilieff

Supporting the implication of lipids for optimal brain function, normal aging as well as various and very distinct pathologies are associated with changes in brain lipid composition and in particular a decrease in the content of docosahexaenoic acid (DHA), the main n-3 polyunsaturated fatty acid (PUFA) in the brain. In animal models, chronic deficiency in n-3 PUFAs leads to various behavioral and neurobiological changes, including an alteration of monoaminergic transmissions. However, the mechanisms responsible for such modifications and the behavioral impact have been overlooked.

We showed that 1) developmental n-3 PUFA deficiency leads to motivational deficit accompanied by an increased expression of the dopaminergic D2 receptor (D2R), selectively in the ventral striatum (NAc), 2) reduction of D2R levels in the NAc worsened the motivational deficit, 3) n-3 PUFA deficient animals are insensitive to amphetamine-induced enhancement of motivation as well as aripiprazole-induced decrease of motivation and 4) D2R-dependent signaling seems to be blunted, despite increased expression of the receptor. Altogether, these data led us to hypothesize that the increased D2R expression under n-3 PUFA deficiency is a compensatory mechanism to impaired D2R-dependent signaling. Surprisingly, our electrophysiological experiments showed that D1 - but not D2 - expressing medium spiny neurons (MSNs) displayed a reduction of excitability. However, knowing that D2 MSNs are crucial for the control of D1 MSNs excitability, the impairment of D2R-dependent signaling could be directly responsible for the decreased D1 MSNs excitability. We are currently testing this hypothesis by 1) dissecting D2R-dependent signaling in response to an agonist, 2) determining if potentiating D2R pathways can reverse the motivational deficit, and 3) studying the link between D2 pathway alterations and reduction of D1 MSNs excitability with electrophysiological methods. Finally, using transgenic approaches, we will address whether alterations of n-3 PUFA levels selectively in D2R-expressing neurons is necessary and sufficient to lead to motivational deficits.

Interaction between membrane lipids and heteromers of receptors: impact on the functionality of mesolimbic dopaminergic transmission

Roman Walle[1], Fabien Ducrocq[1], Asma Oummadi[1], Sophie Layé[1], Peter Vanhoutte[2, 3,4], Véronique De Smedt-Peyrusse[1], Pierre Trifilieff[1]

Essential omega-3 polyunsaturated fatty acid (n-3PUFA), such as docosahexaenoic acid (DHA),are decreased in several neuropsychiatric disorders, however the implication of such alteration in PUFA levels in the etiology of psychiatric symptoms is unclear. Our group has obtained strong evidence that developmental n-3 PUFA deficiency in mice leads to impairment in dopamine signaling in the nucleus accumbens that could account for the behavioral alterations in reward processing in these animals. Nevertheless, the underlying cellular mechanisms are still unclear.

N-3 PUFAs modulate cell membrane properties, thereby affecting the functionality of transmembrane proteins like G protein-coupled receptors (GPCRs). Accordingly, our group has shown that membrane PUFAs directly modulate the binding affinity of the dopamine D2 receptor through conformational changes. Moreover, a recent study suggests that membrane composition in PUFAs modifies the membrane dynamic of the D2 receptor, therefore altering its heteromerization. Growing body of evidence highlight a crucial – though overlooked – role of receptor heteromers in the modulation of signaling in physiological and pathological conditions. The aim of this project is to assess the impact of membrane PUFA composition on heteromerization of dopamine receptors. *In vivo*, thanks to the use of a proximity-ligation assay (PLA) we will screen the effect n-3 PUFAs deficiency on the integrity of receptor complexes with particular relevance for brain disease, such as A2A/D2R, CB1/D2R, D3R/D1R, NMDA/D2R and NMDA/D1R. Based on these findings, pharmacokinetic and signaling pathway of heteromers of interest will be assessed by Bioluminescence Resonance Energy Transfer (BRET) and biochemical approaches *in vitro* and *in vivo*. Finally, using an interfering peptide strategy, we will study the functional roles of these heteromers *in vivo*. This work could reveal for the first time that membrane n-3 PUFAs impacts brain function through alteration of receptor heteromers, which may have important implications for some neuropsychiatric conditions.

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Is the effect of adolescent high-fat diet on memory related to alteration of hippocampal-amygdala connectivity?

Santoyo-Zedillo, Marianela

PhD supervisors: Guillaume Ferreira (NutriNeuro)/Gustavo Pacheco-Lopez (UAM, Mexico)

The prevalence of childhood and adolescent obesity is increasing at an alarming rate and an emerging aspect concerns the neurocognitive consequences of early-onset obesity. Data obtained in animal models indicate that obesogenic diet, in particular high-fat diet (HFD) consumption during adolescence, but not at adulthood, induces bidirectional effects on memory functions. Whereas it impairs hippocampal plasticity and hippocampal-dependent spatial/relational memories (Boitard et al., 2012, 2014), it enhances amygdala plasticity and amygdala-dependent aversive memory (Boitard et al., 2015). Moreover, adolescence is characterized by important changes in functional connectivity between brain structures (see Gee et al., 2013; Vink et al., 2014). According to the fact that impaired hippocampal-amygdala functional connectivity during adolescence has been associated with neuropsychiatric disorders in humans (Cullen et al., 2014) and that reciprocal connections between hippocampus and amygdala clearly sustains emotional and memory functions in rodents (Felix-Ortiz et al., 2013; Zhang et al., 2014), a thorough characterization of hippocampal-amygdala connectivity dysfunctions in the context of adolescent obesity is needed.

The present PhD project will be performed in animal models in France and Mexico in the context of the clinical and experimental OBETEEN project. We will use in Mexico functional neuroimaging to evaluate the impact of HFD consumption on hippocampal-amygdala functional connectivity at different time during adolescence. In France we will first combine pharmacogenetic (DREADDs) and behavioural approaches to manipulate hippocampal-amygdala connections to investigate the effects on HFD-induced alterations. Finally, we will study the impact of exercise on hippocampal-amygdala connextivity in adolescent HFD-fed animals.

Role of inflammation in the physiopathology and treatment response of depressive disorders

Lison Huet

Many data in the literature indicate that depression and metabolic disorders such as obesity are associated with various immune alterations, including an increase in the production of markers of inflammation. Despite this data, only few information exists regarding the involvement of inflammatory processes in the physiopathology and treatment response of depressive disorders and the influence of metabolic disorders on this relationship. Thus, the main objective of my thesis are to investigate the relationship between markers of inflammation and metabolic factors in the physiopathology of depression and its responsiveness to antidepressant treatment. To do so, we will 1) assess the relationship between adiposity, inflammatory status and neuropsychiatric condition in obese patients before bariatric surgery compared to non-obese subjects, then we will 2) analyze the impact of weight loss induced by bariatric surgery on the inflammatory profile and neuropsychiatric symptoms in these same subjects. In a second step, we will try to confirm these results in patients with unipolar or bipolar depression. The objectives of this study will be 3) to evaluate the relationship between systemic inflammation and depressive symptoms in these patients and 4) to determine the influence of inflammatory and metabolic processes on the response to antidepressant treatment and the risk of relapse in the same patients. For each patient, a comprehensive neuropsychiatric assessment will be performed before and at regular intervals after surgery or initiation of antidepressant treatment. Blood samples will be collected for the measurement of inflammatory markers and related metabolic pathways.

Involvement of n-3 PUFA-derived lipid mediators in the resolution of brain inflammation

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Neuroinflammation is the protective response against diverse insults to control and promote tissue repair. Several factors are implicated in this active defense reaction but dysfunction of this mechanism can cause multiple damages in the brain. Specialized pro-resolving mediators (SPM) derived from n-3 polyunsaturated fatty acids (n-3 PUFA), such as resolvins (Rv), and n-6 PUFA-derived lipid mediators emerge as key regulators in physiologic pathways. Accumulated evidence show the involvement of SPM in the protective role assigned to their precursors against inflammation.

The aim of the project is to determine the implication of these oxidized lipids mediators called oxylipins in the regulation of lipopolysaccharide (LPS)-induced neuroinflammation. We first evaluated the anti-inflammatory activities of RvD1 and RvE1 in microglia cells *in vitro*. Then, we investigated the effect of cerebral treatment with RvD1 and its precursors on neuroinflammation in mice. Finally, we were focused on the consequences following the modulation of dietary PUFA intake on fatty acid composition and localization in the brain and most notably, in glial cells, and on oxylipins synthesis in the brain during inflammation.

We found that resolvins decrease inflammation in microglial culture through miRNA dependent mechanism for RvD1 and the regulation of NFKB signaling pathways for RvE1. Then, we developed a model of intra-cerebro-ventricular administration of RvD1 and its precursors followed by peripheral LPS challenge. Our results showed that DHA decrease inflammation in the hippocampus but RvD1 have no effect in these conditions that need to be improved in further experiments. Finally, n-3 PUFA-deficient, balanced and supplemented diets change fatty acid and phospholipid molecular species contents and oxilipins concentrations in the brain. N-3 supplemented diet prevents the synthesis of the pro-inflammatory n-6 PUFA-derived lipid mediators in response to LPS.

To conclude, we demonstrate that oxilipins may play a role in the regulation of neuroinflammation. Further investigations are required to complete these promising results.

Effect of vitamin A supplementation in Alzheimer's disease prevention.

E. Biyong; F. Dumetz; S. Alfos; C. Bosch-Bouju; V. Pallet

As life expectancy has extended, different forms of pathological cognitive decline have arisen including dementia. Alzheimer's disease (AD) is nowadays the most abundant case of dementia and currently affects 40 millions of people wolrdwide, a worrysome amount that would reach 100 million by 2050. This disease is characterized by extracellular aggregates of beta amyloid, a small fibrillar peptide, and intracellular accumulation of neurofibrillary tangles consecutive to abnormal hyperphosphorylation of Tau protein, both phenomenons causing neuronal damage and death leading to cognitive impairments, especially learning and memory processes.

Body of evidence shows the onset of AD is associated with a downregulation of retinoid signaling at many levels: peripheral but also central. The ligand-activated retinoic acid receptors (RAR) control the expression of genes implicated in the clearance of beta amyloid aggregates. Thus, a decrease of retinoic acid synthesis participates in the enhancement of the amyloidogenic process. Moreover, an increase of hypothalamic pituitary adrenal (HPA) axis activity has been described in Alzheimer patients and animal models, which is also admitted to be associated with the retinoid signaling downregulation.

The goal of this project is to better understand the ability of nutritional and pharmacological vitamin A supplementations to avoid neurobiological, endocrine and cognitive disorders specific to the disease, on 2 murine models of AD. The first model is induced by a single i.c.v. injection of beta amyloid peptide, and the second model is transgenic (3xTg-AD). We will target effects of these supplementations on neurobiological and molecular aspects related to HPA axis activity and reactivity, to pathways associated with the activation of RARs, and to the mechanisms and features underlying Alzheimer's disease.

Considering nutritional supplementation could be able to delay the onset of the pathology, thus decreasing the number of AD patients, vitamin A supplementation is a promising way to participate in the prevention of Alzheimer's disease.