9th EDITION

NUTRINEURO ANNUAL MEETING

FEBRUARY 20st 2020

SCIENTIFIC PROGRAM

9h00 WELCOMING OF PARTICIPANTS

9h30-11h00 Session 1. Nutrition & Mood disorders (Chair: Marine, Anaïs, Hugo, Mathilde H., Sofia)

. Sofia Cussotto : The role of Brain IDO and the Microbiota in Fluoxetin Response.*

Barbara Rani: Role of brain histamine in the effects of a diet to prevent social defeat stress-induced cognitive and neuropsychologic modifications.*

. Mathieu Di Miceli: Dietary approaches to target depression: influence of omega-3 diets on synaptic plasticity within the nucleus accumbens.

. Inês Delgado: Impact of dietary habits on stress-induced cognitive alterations in healthy adults.

. Camille Monchaux De Oliveira: Mood disorders and therapeutic response: underlying mechanisms and nutritional modulation by saffron active ingredients (*Crocus Sativus* L.).

11h00-11h20 COFFEE BREAK

11h20-12h30 Session 2. Nutrition & Diseases (Chair: Barbara, Mathieu, Inês, Camille)

. Marine Persillet: Sleep/wake activity in the lewy bodies mouse model of Parkinson's disease.*

. Anaïs Marie: Implication of vitamin A in neuroprotection of dopaminergic neurons in a rat model of Parkinson's disease.

. Mathilde Henry: Role of glucocorticoids in emotional alterations associated with type 2 diabetes in Goto-Kakizaki rats.

. Hugo Martin: Impact of type 2 diabetes-associated mood disorders on the electrical properties of brain serotoninergic neurons.

12h30 – 14h00 LUNCH RESTAURANT "LA PASSERELLE"

14h00-14h15 Presentation of Master 2 students – Promotion 2020

14h15-15h30 Session 3. Nutrition & Executive functions (Chair: Katherine, Fanny, Moïra, Mathilde C)

. Anna Petitbon: Implication of nucleus accumbens dopaminergic and glutamatergic receptor heteromers in goal-directed behavior.*

. Eva Ducourneau: Role of hippocampal CB1 receptors in obesogenic diet-induced memory impairments.*

. Ioannis Bakoyiannis: Deciphering the role of hippocampal and amygdala efferent pathways in memory changes induced by obesogenic diet intake throughout adolescence.

. Andrea Contini: Impact of n-3 PUFA deficiency on executive control: likely implication of cortical dopaminoceptive signal

15h45-17h00 Session 4. Nutrition & Neuroinflammation (Chair: Anna, Eva, Andrea, John)

. Katherine Picard: Role of microglia in sleep/wave cycles.*

. Fanny Decoeur: Role of PUFAs in microglia-oligodendrocyte interactions during brain development.

. Moïra Rossitto: Essential omega-3 acids tune microglial phagocytosis of synaptic elements in the developing brain.

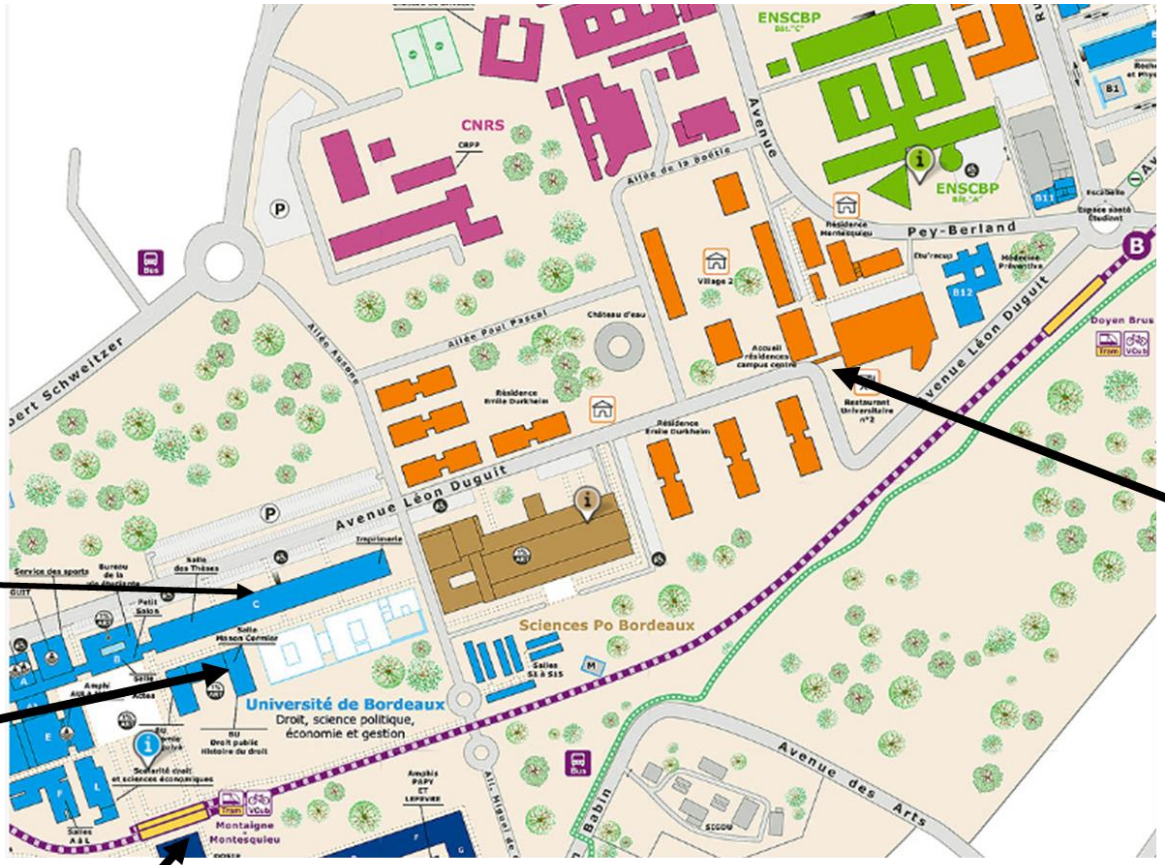
. Mathilde Chataigner: Impact of marine-derived products on age-related cognitive decline prevention.

17h00-20h FESTIVITIES (organized by students and post-docs) – GAMES / COCKTAIL

*** = short presentations**

AMPHI CORMIER, Campus Pessac

Tram B – arrêt Montesquieu-Montaigne



La galerie (animations)

Salle Manon Cormier (conférences)

Tram B (Montesquieu – Montaigne)

RU La Passerelle (lunch)

ABSTRACTS

The Role of Brain IDO and the Microbiota in Fluoxetine Response

Sofia Cussotto, Muriel Darnaudery, Sylvie Vancassel, Nathalie Castanon, Lucile Capuron

The prevalence of depressive disorders is growing worldwide, reaching a lifetime prevalence of 21% in developed countries. The large proportion of depressed patients who do not respond to conventional antidepressant (AD) treatments, and the increasing rate of chronic medical conditions associated with vulnerability to depressive comorbidities urge for new treatment therapies. Accordingly, better knowledge on the pathophysiology of depression and mechanisms underlying treatment response are urgently needed. There is strong evidence for a role of inflammation in the development of depression and increasing data suggests also its involvement in the response to AD. One pathway likely to contribute to this effect consists of the activation, by inflammatory factors, of the enzyme indoleamine-2,3-dioxygenase (IDO). The intestinal microbiota is also increasingly recognised as a potential player involved in the inter-individual differences in response to medications.

In the present study, we aim to evaluate the role of IDO in the acute response to fluoxetine, a commonly prescribed SSRI. The effect of 30 mg/kg fluoxetine on an acute stressor (forced swim test) will be recorded in adult mice and the animals will be subsequently allocated to a "responder" or "non-responder" group. Following a 3-weeks wash-out period, fluoxetine will be tested again in the FST in non-responders, this time in combination with 1-MT, a selective IDO inhibitor. Immunological status will be evaluated, as well as inflammation in brain regions of interest such as the hippocampus, striatum or the prefrontal cortex. The microbiota of responders and non-reponders will be examined for the detection of potential markers of treatment outcome. Based on our hypothesis, acute blockade of IDO should improve the fluoxetine response in non-responders, and the microbiota might be differentially altered in the two subgroups.

ROLE OF BRAIN HISTAMINE IN THE EFFECTS OF A DIET TO PREVENT SOCIAL DEFEAT STRESS- INDUCED COGNITIVE AND NEUROPHYSIOLOGIC MODIFICATIONS

Rani B.[1], Bonfiglio F. [1], Provensi G.[1], Schmidt S.D.[3], Blandina P.[1], Corradetti R. [1], Passani M.B.[2] Costa A.[4]
[1]Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence, 50139, Florence, Italy;
[2]Department of Health Sciences, University of Florence, 50139, Florence, Italy;
[3]Memory Center, Pontifical University of Rio Grande do Sul, 90619-900, Porto Alegre, Brazil.
[4]Faculty of Biology, Medicine and Health. School of Medicine. University of Manchester
barbara.rani@unifi.it

Evidence indicate that a diet rich in polyunsaturated ω-3 fatty acids (ω-3 PUFA) has positive effects on cognitive functions and resilience to stress responses. Here, we investigated the effect of ω-3 PUFA (0.545g/100g)/Vitamin-A (45 IU/g) enriched diet (*ED*) in the modification of cognitive functions and synaptic plasticity induced by chronic social defeat stress (CSDS), focusing on the role of the central histaminergic system.

We evaluated the effect of the *ED* on the cognitive performance of histamine deficient mice ($HDC^{-/-}$) and wild type littermates ($HDC^{+/+}$) subjected to CSDS. Non-stressed mice of both genotypes served as controls. CSDS consists of agonistic social confrontations between an aggressive CD-1 and an experimental C57BL6/J mouse, repeated daily for 10 days. At the end of the stressful procedure, social avoidance of the aggressive mouse by subordinate animals was measured. Cognitive performance was tested by using the Novel Object Recognition test (NOR) and the Novel Object Location Test (NOL). In addition, we estimated synaptic plasticity in CA1 hippocampus by measuring the magnitude of fEPSP LTP induced by theta bursts *in vitro*. The expression of hippocampal synaptophysin was also measured.

We found that social behaviour was greatly affected by the CSDS protocol: In the SIT invariably, stressed $HDC^{+/+}$ and $HDC^{-/-}$ mice spent less time approaching an aggressive CD1 mouse. The CSDS protocol worsened the memory for the familiar object/location of both genotypes. The *ED* prevented these deficits only in $HDC^{+/+}$ as the diet was ineffective in $HDC^{-/-}$ mice. Stress increased LTP amplitude in both genotypes, and this modification was prevented by the ED in $HDC^{+/+}$ mice only. Finally, the ED increased synaptophysin expression only in stressed $HDC^{+/+}$, but not in stressed $HDC^{-/-}$ mice.

Our data suggest that peripheral signals generated by the diet converge onto the central histaminergic system that provides the necessary central signalling to prevent stress-induced cognitive and neurophysiologic modifications.

Dietary approaches to target depression: influence of omega-3 diets on synaptic plasticity within the nucleus accumbens.

Mathieu Di Miceli[1], Maud Martinat[1], Marion Graland[1], Renee Clausing[1], Louisa Linders[1], Vicky Nicolas[1], Richard Bazinet[2], Ken Mackie[3], Olivier Manzonni[4], Clémentine Bosch-Bouju[1] & Sophie Layé[1].

[1] Laboratoire NutriNeuro. UMR INRA 1286. Université de Bordeaux. Bâtiment UFR Pharmacie. 146 rue Léo Saignat. 33076 Bordeaux Cedex. France.
[2] Department of Nutritional Sciences. Medical Sciences Building. 1 King's College Circle. Toronto. Ontario. M5S 1A8. Canada.
[3] Gill Center for Biomolecular Science. Psychological and Brain Sciences. Multidisciplinary Science Building II. Indiana University Bloomington. Bloomington. Indiana. USA.
[4] INMED, INSERM U1249, Université Aix-Marseille. Marseille, France.

Worldwide, depression affects about 350 million people per year and represents the first leading cause of disability. Antidepressant drugs do exist, but their efficacy remain weak in 2/3 of patients. Therefore, there is an urgent need for alternative strategies, and dietary approaches have been the focus of recent attention. Indeed, the role of n-3 polyunsaturated fatty acids (PUFAs) in the pathophysiology of mood disorders are under scrutiny. However, the mechanisms underlying the potential protective effects of n-3 PUFAs in depression are poorly understood, limiting their use in patients. Therefore, there is a need in conducting preclinical studies in order to understand how n-3 PUFAs can exert beneficial effects on depressive symptoms. Since depressive-like behaviours are paralleled with altered synaptic plasticity within the nucleus accumbens of mice [**1**], the purpose of our research is to examine the potential roles of n-3 PUFAs in the modulation of accumbal synaptic plasticity.
We performed whole-cell patch-clamp *ex vivo* electrophysiology on accumbal GABAergic medium spiny neurons in mice, following 8 weeks of either enriched of balanced n-3 PUFAs diets, starting at weaning (*ad libitum*).
Our results indicate that n-3 dietary intake can directly modulate endocannabinoid-dependant plasticity in medium size spiny neurons within the nucleus accumbens. The underlying mechanisms are currently under investigation, with a focus on CB_1R- and GPR_{55}-dependant pathways.
This project will therefore provide a further understanding of the link between n-3 PUFAs, depressive behaviour and synaptic functions.

1. Bosch-Bouju C, Larrieu T, Linders L, Manzoni OJ, Layé S. Endocannabinoid-Mediated Plasticity in Nucleus Accumbens Controls Vulnerability to Anxiety after Social Defeat Stress. Cell Rep. 2016 02;16(5):1237–42.

Impact of dietary habits on stress-induced cognitive alterations in healthy adults

Inês Delgado[a], Sandra Dexpert[a], Julie Sauvant[a], Lucile Capuron[a]

[a] Univ. Bordeaux, INRA, Bordeaux INP, NutriNeuro, UMR 1286, F-33000, Bordeaux, France

Stress is a fundamental biological response that is associated with alterations in cognitive processes. Interestingly, unhealthy dietary habits have been hypothesized to potentiate this effect. Not only diet is closely interrelated to stress reactivity, but it is also increasingly recognized that poor nutrition affects cognitive function. Accordingly, the present work, performed in the frame of the AMBROSIAC JPI project, aims at investigating the effect of diet as a modulator of stress-induced cognitive alterations in a group of healthy adult subjects.

Fifty healthy adult volunteers were recruited. Participants were stratified in two groups: healthy (balanced diet) *versus* unhealthy (unbalanced diet group), according to their adherence to the French nutritional recommendations, assessed by the "*Programme National Nutrition et Santé*" (PNNS) questionnaire. Cognitive function was evaluated through performance on the tests of Paired-Associated Learning (PAL), Visual Recognition Memory (VRM), Rapid Visual Information Processing (RVP) and Spatial Span (SSP) from the CANTAB battery. Assessments were performed before and after exposure to the psychological stressor Trier Social Stress Test (TSST). Stress response was evaluated by salivary cortisol and blood pressure.

The TSST produced a significant endocrine and autonomic stress response, independent of dietary habits. Exposure to TSST was also associated with cognitive alterations in the CANTAB battery, notably in the form of impaired performance on the VRM test and improved scores on the RVP, SSP and PAL tests. While these stress-induced alterations were apparent in both diet groups, participants with unbalanced diet exhibited lower performance on the PAL and VRM tests in comparison to participants with healthy dietary habits. Further analyses are being conducted to unravel the mechanisms that mediate this effect.

Mood disorders and therapeutic response: underlying mechanisms and nutritional modulation by saffron active ingredients (*Crocus sativus* L.).

C. Monchaux de Oliveira1,2, S. Vancassel1, L. Pourtau2, D. Gaudout2, L. Capuron1, N. Castanon1
1 Bordeaux University, NutriNeuro lab, INRA UMR 1286, Bordeaux, France
2 Activ'Inside, Beychac-et-caillau, France

Mood disorders (depression, anxiety) represent a major public health concern and display a continuously rising prevalence. In addition, a large proportion of patients develops important side effects and/or does not respond properly to conventional antidepressant treatments. These issues highlight a need to better understand the physiopathology of mood disorders and to develop further therapeutic strategies. In that context, nutritional approaches appear as particularly promising candidates. This notably concerns saffron administration, since its beneficial effects on health have already been reported in the literature. Indeed, clinical studies have shown mood improvement in depressed patients after administration of saffron extracts either alone (*Noorbala et al.*, 2005) or together with conventional antidepressants (*Lopresti et al.*, 2019). Similarly, saffron extract administration was reported to reduce depressive-like behavior in preclinical studies (*Wang et al.*, 2009), suggesting that saffron likely interfere with some of the neurobiological systems known to be involved in mood disorders. However, the mechanisms underlying these beneficial effects of saffron on mood remain unknown.

In that context, this project aims to study in preclinical models the role of saffron in the prevention and/or treatment of emotional alterations and to decipher the underlying mechanisms. For this purpose, these studies are performed in different animal models of depression, either induced by stress exposure or related to inflammatory conditions, notably obesity.
First experiments aimed to identify the conditions of administration and a behaviorally effective dose of saffron in control mice. We are now investigating the behavioral and neurobiological impact of saffron extract in animal models of depression. The next step will aim to explore the effects of a saffron/antidepressant co-administration to determine if saffron can help improving the therapeutic response to antidepressants. Altogether, this study should provide useful information on the physiopathology and treatment of mood disorders and on the therapeutic relevance of nutritional interventions.

Sleep/wake activity in the Lewy bodies mouse model of Parkinson's disease

Marine Persillet[1,2], Fanny Decoeur[3,4], Benjamin Dehay[1,2], Agnès Nadjar[3,4] and Erwan Bézard[1,2]

[1]Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France [2]CNRS, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France [3]Université de Bordeaux, Nutrition et Neurobiologie Intégrée, UMR 1286, Bordeaux, France [4]INRA, Nutrition et Neurobiologie Intégrée, UMR 1286, Bordeaux, France

Parkinson's disease (PD) is characterized by the loss of dopaminergic (DA) neurons of the substantia nigra pars compacta (SNc) and the presence of cytoplasmic inclusions named Lewy Bodies (LB) containing notably misfolded alpha-synuclein (□-syn). Although primarily a movement disorder, PD patients exhibit a myriad of non-motor symptoms. Sleep/wake alterations, such as rapid-eye movement (REM) sleep behavioral disorder (RBD), REM loss or increased day time sleepiness, may occur in the prodromal phase of PD. They are even considered as predictors of PD. While neurotoxin-based experimental models recapitulate both motor and non-motor symptoms, their poor face validity with regard to the neurodegenerative process make them unsuitable for investigating the likelihood of a relationship between progression of neurodegeneration, progression of the □-syn pathology and occurrence of sleep/wake issues.

We here take advantage of the recently developed LB mouse model of parkinsonian degeneration to investigate the potential occurrence of sleep/wake deficits as the pathology develops. Wild-type mice were injected with LB, containing pathological α-syn, extracted from the brain of PD patients leading to a progressive loss of DA neurons (LB mice). Control mice were injected with a fraction devoid of aggregated □-syn, extracted from the same patients (NoLB mice). Mice were implemented with a device recording both cortical neuronal activity (ElectroEncephaloGraphy, EEG) and neck muscles contractions (ElectroMyoGraphy, EMG) enabling the discrimination of sleep/wake cycle stages: wake, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Recording sessions were performed once a month for 48h over a 4-month period. Alteration of the sleep/wake cycles are detailed in both LB and NoLB mice with an emphasis put upon the changes in power band frequencies.

Understanding if sleep disorders may serve experimentally as a surrogate marker of neurodegeneration or pathology progression could provide a way of early detection and lead to new therapeutic strategies to slow down its progression.

Implication of vitamin A in neuroprotection of dopaminergic neurons in a rat model of Parkinson's disease.

Anaïs Marie, Julien Leroy, Morgane Darricau, Serge Alfos, Véronique Desmedt-Peyrusse, Véronique Pallet, Sylvie Vancassel, Clémentine Bosch-Bouju
NutriNeuro, INRA, Nutrition et Neurobiologie Intégrée, UMR 1286, 33076 Bordeaux, France

Parkinson's disease is caused by a loss of dopaminergic neurons from the substantia nigra *pars compacta* (SNc) projecting to the striatum, leading to strong motor impairments. Vitamin A, or retinol, through the action of its active metabolite, retinoic acid, is involved in the development, differentiation and neuroprotection of these SNc dopaminergic neurons. Additionally, retinoic acid controls the expression of retinaldehyde dehydrogenase (RALDH), an enzyme responsible for the cellular detoxification of these neurons. **However, the cerebral bioavailability of retinoic acid decreases with aging, which reduces RALDH expression**. This may precipitate the neurodegenerative processes observed in Parkinson's diseases.

Here we hypothesize that nutritional supplementation with vitamin A normalizes brain levels of retinoic acid and thus RALDH, which exhibit a neuroprotective effect on dopaminergic neurons.

To test our hypothesis, we modeled Parkinson's disease with unilateral injection of 6-hydroxydopamine (6-OHDA) a toxin that selectively impairs dopaminergic neurons, into rats' striatum. Rats were supplemented or not with dietary vitamin A (20 UI/g) for 5 weeks before the lesion.

Level of dopaminergic lesion was assessed in the striatum with western-blot of tyrosine hydroxylase (TH), the production enzyme of dopamine. The impact of supplementation was measured with plasmatic dosage of retinol. Motor impairments induced by 6-OHDA and protective effect of vitamin A were quantified with the step test, cylinder test and rotarod. To evaluate the functionality of the dopaminergic system we quantified levels of dopamine and its metabolites production in different brain structures by HPLC. To refine the analysis and focus on the possible involvement of RALDH enzyme in neuroprotection of dopamine neurons we performed western-blot analysis of RALDH.

Altogether, this study provides new knowledge on the role of vitamin A in the pathophysiology of Parkinson's disease.

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

Hugo Martin[1], Sébastien Bullich[2], Fabien Ducrocq[1], Pierre Trifilieff[1], Sophie Layé[1], Bruno Guiard[2], Xavier Fioramonti[1].

[1]*Univ. Bordeaux, INRA, Bordeaux INP, NutriNeuro, UMR 1286, F-33000, Bordeaux, France*
[2]*Centre de Recherches sur la Cognition Animale, UMR5169 CNRS, Toulouse, France.*

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.

Title: Role of glucocorticoids in emotional alterations associated with type 2 diabetes in Goto-Kakizaki rats

Author: Mathilde Henry

A large literature documents the co-occurrence of type 2 diabetes (T2D) with psychiatric disorders such as anxiety disorders and depression; however, the nature of this co-morbidity remains unclear. Both T2D and depression involve chronic hyperactivity of hypothalamic-pituitary-adrenal axis, but the role of glucocorticoids in the emotional alterations associated with T2D remains under-explored. The Goto-Kakizaki (GK) line rat is a well-established non obese model of T2D. We recently demonstrated that GK rats showed depressive-like-behavior and hyperanxiety associated with high plasma corticosterone levels in basal and stress conditions. The aim of our project is to unravel the role of glucocorticoids in the emotional deficits reported in GK rats. GK rats exhibited an up-regulation of the expression of several glucocorticoids-related genes such as REDD1 (regulated in development and DNA damage responses 1) and SGK1 (Serum and Glucocorticoid-regulated Kinase 1) specifically in the medial prefrontal cortex (mPFC), a brain area sensitive to stress and affected in depression. The gene expression of the glucocorticoid-regenerating enzyme 11βHSD1 (11β-hydroxysteroid dehydrogenase type 1) was also increased in the mPFC of the GK rats. Finally, in response to an acute stress, GK rats exhibited a reduced EGR1 (early growth response 1) immunostaining in the mPFC associated with higher $EGR1^{+}$ cells in the paraventricular nucleus of hypothalamus and in the amygdala. We then tested whether GK emotional phenotype may be attenuated by lowering plasma corticosterone. Adrenalectomy partially restored stress-induced hyperglycaemia in GK rats but had no effect on their emotional disturbances. Further studies targeting brain glucocorticoid levels or glucocorticoid signaling (using pharmacological or viral approaches), especially in the mPFC will be conducted to determine the potential role of central glucocorticoids in the behavioral deficits associated with T2D.

Implication of nucleus accumbens dopaminergic and glutamatergic receptor heteromers in goal-directed behavior

Anna Petitbon, Roman Walle, Andry Andrianarivelo, Véronique De Smedt Peyrusse, Peter Vanhoutte, Pierre Trifilieff

The nucleus accumbens (NAc) is a main brain structure involved in the modulation of reward processing and motivation. It is mainly composed by medium spiny neurons (MSN) that express either the dopamine D1 or D2 receptors. Activity of MSNs is strongly regulated by the convergence of glutamatergic and dopaminergic inputs, however the molecular and cellular mechanisms underlying such signal integration are unclear. Heteromers formed by the physical interaction between dopaminergic and glutamatergic receptors recently emerged as molecular coincidence detectors of glutamate and dopamine transmissions. More specifically, heteromers formed by dopamine D1 receptor with GluN1 subunit of NMDA receptor and D2 receptor with GluN2B subunit of NMDA receptor enhance and decrease the activity of D1-MSN and D2-MSN, respectively. Recent findings demonstrate that both heteromers are involved in cocaine-induced behavioral adaptations. However, their implication in physiological reward processing remains unknown. Using operant conditioning tasks, we evaluated the expression of heteromers in the striatum of operant learner and naïve mice with Proximity Ligation Assay, a method allowing for the detection of specific antigen proximity on brain slices. As opposed to cocaine exposure, we did not observe any change after operant learning in any of the structure studied. In order to assess the role of D1/GluN1 and D2/GluN2B heteromers in reward processing, we will prevent the heteromerization process through the local, inducible expression of interfering peptide via viral gene transfer. Thanks to this approach, we will assess the consequence of heteromer blockade in the NAc on operant learning as well as incentive processes. Moreover, because such heteromers are also expressed in the prefrontal cortex, we will explore the consequence of heteromer blockade in this brain area on executive functions which highly depend on the integrity of the medial prefrontal cortex.

Role of hippocampal CB1 receptors in obesogenic diet-induced memory impairment

Ducourneau E-G

Obesity, one of the most serious health issues of this century, is associated with cardiovascular and metabolic diseases, but also with brain dysfunctions including learning and memory impairments. The growing prevalence of juvenile obesity is particularly alarming since adolescence is a developmental period critical for the maturation of brain structures essential for memory processing such as the hippocampus. Interestingly our group recently showed that the endocannabinoid system, which is overactive in obesity and regulates memory processes, contributes to hippocampal-dependent memory impairment induced by obesogenic high-fat diet (HFD) consumption throughout adolescence. Indeed, we showed that impairment of long-term object recognition memory (ORM) is associated with increased hippocampal endocannabinoid levels after ORM training in HFD-fed mice. Furthermore, partial hippocampal deletion of the main cannabinoid receptor (CB1R) rescued long-term ORM impairments, indicating that hippocampal CB1R over-activation after training is involved in memory deficits in HFD-fed mice. **However, the cell-type, cell-compartment and hippocampal part underlying those CB1R-dependent cognitive deficits are unknown.**
To address this question we will use CB1-flox mice and, thanks to the Cre-lox system we will first perform cell-type specific deletion of hippocampal CB1R through viral approaches allowing to express the Cre recombinase under specific promoter for either glutamatergic or GABAergic neurons. Secondly, we will determine whether HFD impairments are mediated by CB1R located at the plasma or the mitochondrial membrane by combining cell-type specific CB1R deletion with Cre-dependent re-expression of CB1R, either in the whole cell or restricted to the plasma membrane. Then we will identify which hippocampal part is more particularly underlying the memory deficits by restricting the viral approach to either the dorsal or the ventral region. Finally, we will determine whether HFD-induced memory deficits similarly involve cell-specific hippocampal CB1R in males and females.

Impact of n-3 PUFA deficiency on executive control: likely implication of cortical dopaminoceptive signal.

Andrea Contini, Chloé Arrondeau, Roman Walle, Veronique De Smedt-Peyrusse, Etienne Coutureau, Guillaume Ferreira, Fabien Ducrocq, Pierre Trifilieff

In the last decades several clinical studies have highlighted a link between a deficit in the levels of n-3 long chain polyunsaturated fatty acids and some psychiatric conditions such as schizophrenia and bipolar disorder. However, preclinical studies providing mechanistic evidence on the origin of this link are lacking, and whether or not n-3 PUFA deficiency is directly implicated in the symptomatology of these disorders is still unknown. Among the main symptoms of the aforementioned disorders, cognitive dysfunctions are the most predictive of relapse and therapy discontinuation, and are often associated to lower functional outcome. From a neurobiological point of view, a reduced tone of dopaminergic signal in cortical regions is thought to be critical for the maturation of these symptoms.

In order to evaluate whether a reduced accrual of n-3 PUFAs could be involved in the etiology of psychiatric endophenotypes, we employed a developmental mouse model of n-3 PUFA deficiency and assessed the effect on various neurochemical and behavioral parameters. We found that decreasing n-3 PUFA biostatus across development leads to reduced dopamine release in the medial prefrontal cortex (mPFC) that correlates with a perturbation in the ability of mice to display goal-directed actions, which is indicative of maladaptive behavior and poor executive control.

In order to further investigate the role of cortical dopaminergic transmission in executive functions, we employed a chemogenetic approach to selectively manipulate the activity of the two main populations of cortical dopaminoceptive neurons during a sensory-specific outcome devaluation task. We found that lowering the activity of either dopamine D1 or D2 receptor-expressing neurons impairs the ability of mice to emit goal-directed actions.

Altogether these findings suggest that n-3 PUFA deficiency could lead to impaired executive functions through a perturbation of dopamine transmission in the mPFC and support its causal implication in the symptomatology of psychiatric symptoms.

Deciphering the role of hippocampal and amygdala efferent pathways in memory changes induced by obesogenic diet intake throughout adolescence.

Ioannis Bakoyiannis[1,2], Etienne Coutureau[1,3], Gustavo Pacheco-Lopez[4], Guillaume Ferreira[1,2].
[1]Université de Bordeaux, 33077 Bordeaux, France.
[2]INRA, NutriNeuro, UMR 1286, 33077 Bordeaux, France.
[3]CNRS, INCIA, UMR 5287, 33077 Bordeaux, France.
[4]Department of Health Sciences, Metropolitan Autonomous University (UAM), Lerma, Mexico.

Abstract
Obesity epidemic is currently reaching an alarming level, with the prevalence increasing dramatically in youth. Obesity is associated with numerous comorbidities such as neurocognitive dysfunctions, specifically those affecting learning and memory function. This is particularly worrisome since childhood and adolescence are crucial periods for the maturation of certain brain structures, including the hippocampus (HPC) and the basolateral amygdala (BLA), necessary for shaping cognitive function for life duration. Our previous studies in animal models have shown that obesogenic high-fat diet (HFD) intake throughout adolescence is associated with opposite effects on HPC- and BLA-dependent memory systems, impairing HPC-dependent object and spatial memory and enhancing BLA-dependent cue-based aversive memory. We recently showed that chemogenetic silencing of ventral HPC projecting neurons, but not the BLA, was able to restore HFD-induced long-term memory deficits of object recognition. Inversely, chemogenetic silencing of BLA projecting neurons, but not the ventral HPC, normalized the enhanced long-term memory of odour aversion in HFD-fed group. We are currently characterising which projections of the ventral HPC and the BLA are mediating these effects. We further plan to examine whether neuromodulatory systems that are able to control the aforementioned projections, such as the endocannabinoid system, are involved in these memory effects.

Role of microglia in sleep/wake cycles

Picard K[1, 2], Decoeur F[2], Persillet M[3], Tremblay ME[1] and Nadjar A[2]
[1]Axe neurosciences, Centre de recherche du CHU de Québec-Université Laval, Québec, QC, Canada
[2]Nutrition et Neurobiologie Intégrée, UMR 1286, Institut National de la Recherche Agronomique, Université de Bordeaux, Bordeaux, France
[3]Institut des Maladies Neurodégénératives, CNRS UMR 5293, Université de Bordeaux, Bordeaux, France.

During sleep, the brain accomplishes various processes to allow consolidation of information acquired during the previous wake period, through the formation and elimination of synapses, a process called synaptic plasticity. Microglia, the resident immune cells of the central nervous system (CNS), are known as essential contributors to synaptic plasticity, which suggests they may have a predominant role in sleep. However, the implication of such a change in microglial function according to the various stages of wakefulness and sleep is unknown. Thus, we hypothesized that microglia interact with synapses differently between the states of sleep and wakefulness and that their activities at synapses exert a key role in the regulation of sleep. To test this hypothesis, we first determined the importance of microglia in the regulation of sleep/wake cycle. We exposed young adult mice (C57BL/6), males and females, to spontaneous sleep/wake cycle. A second group of mice was depleted in microglia by oral gavage of plexidartinib (PLX3397) which inhibits the receptor CSF1R (colony-stimulating factor 1 receptor) involved in microglia maintenance in the CNS. We recorded the mice neuronal activity by electroencephalography coupled with electromyography to visualize the different stages of the sleep-wake cycle. We quantified the time spent in the different phases of sleep and wakefulness, as well as the quality of sleep. Mice were also recorded 4 weeks after the end of PLX3397 treatment, when microglia have repopulated the brain, to determine whether this new microglial population can restore a normal sleep/wake cycle. We observed that mice depleted in microglia had more NREM sleep in the active phase. Moreover, only females had a reduction in their sleep pressure, which suggests a sexual dimorphism. This project will help uncover the involvement of microglia in the regulation of sleep, and therefore advance knowledge on the role of microglia in health conditions.

Role of PUFAs in microglia-oligodendrocyte interactions during brain development

Decoeur F, Leyrolle Q, Layé S, Nadjar A
INRA, Nutrition et Neurobiologie Intégrée, UMR 1286, 33076 Bordeaux, France
Univ. Bordeaux, Nutrition et Neurobiologie Intégrée, UMR 1286, 33076 Bordeaux, France

Westernization of dietary habits has led to a progressive reduction in n-3 polyunsaturated fatty acids (n-3 PUFAs) dietary intake. Our previous results showed that perinatal n-3 PUFA deficiency disrupts oligodendrocytes maturation and myelination process. This has long-term deleterious consequences on white matter structure, functional connectivity and behavior at adulthood. However, the mechanisms through which n-3 PUFA deficiency disrupts white matter integrity remain unclear. Several evidence point towards a disruption of microglia-oligodendrocytes interactions. Indeed, the expression levels *cd11c* and *igf-1* are severely decreased in microglia from juvenile n-3 PUFA deficient mice. These two genes were recently described as markers of a novel subset of microglia ($CD11c^+$) that promote oligodendrocyte differentiation and subsequent myelination in pups. Hence, we hypothesize that **n-3 PUFA deficiency decreases the density of CD11c-positive microglia, leading to decrease in oligodendrocyte maturation and subsequent deficits in myelination.** To test this, we first quantified the number of total microglia and plan to quantify CD11c-positive microglia, oligodendrocytes maturation markers and myelination across brain development (time course study). Our results revealed that n-3 PUFA deficiency decreases microglia number in the corpus callosum of male mice at P10 and P15. In a second series of experiments, and to test the causal link between low myelination and defects in brain connectivity, we injected n-3 deficient mice with clemastine (a booster of myelination) and assessed behavior and myelination features. No clear conclusion can be drawn from these experiments yet. Altogether, our study will provide new evidence on the role of PUFAs on microglia-oligodendrocyte interactions during brain development.

Moïra Rossitto

Title

Essential omega-3 acids tune microglial phagocytosis of synaptic elements in the developing brain

Auteurs

C. Madore, Q. Leyrolle, L. Morel, J.C. Delpech, A.D. Greenhalgh, C. Lacabanne, C. Bosch-Bouju, J. Bourel, A. Thomazeau, K.E. Hopperton, S. Beccari, A. Sere, A. Aubert, V. De Smedt-Peyrusse, C. Lecours, K. Bisht, L. Fourgeaud, S. Gregoire, L. Bretillon, N.J. Grant, J. Badaut, P. Gressens, A. Sierra, O. Butovsky, M.E. Tremblay, R.P. Bazinet, C. Joffre, A. Nadjar, S. Layé

Abstract

Omega-3 fatty acids (n-3 polyunsaturated fatty acids; n-3 PUFAs) are essential for the functional maturation of the brain. Westernization of dietary habits in both developed and developing countries is accompanied by a progressive reduction in dietary intake of n-3 PUFAs. Low maternal intake of n-3 PUFAs has been linked to neurodevelopmental diseases in epidemiological studies, but the mechanisms by which a n-3 PUFA dietary imbalance affects CNS development are poorly understood. Active microglial engulfment of synaptic elements is an important process for normal brain development and altered synapse refinement is a hallmark of several neurodevelopmental disorders. We identify a molecular mechanism for detrimental effects of low maternal n-3 PUFA intake on hippocampal development. Our results show that maternal dietary n-3 PUFA deficiency increases microglial phagocytosis of synaptic elements in the developing hippocampus, through the activation of 12/15-lipoxygenase (LOX)/12-HETE signaling, which alters neuronal morphology and affects cognition in the postnatal offspring.

Impact of marine-derived products on age-related cognitive decline prevention.

CHATAIGNER Mathilde, MORTESSAGNE Pierre, DINEL Anne-Laure, PALLET Véronique, LAYE Sophie, MEHAIGNERIE Alexis, BOUVRET Elodie, JOFFRE Corinne.

Brain aging is accompanied by a physiological decline in cognitive function. This alteration in memory and learning abilities is associated with chronic low-grade inflammation, characterized in the brain by increased activation of the immunocompetent microglial cells. Moreover, this neuroinflammation is associated to the development of anxiety disorders that affects 3.8% of the elderly, representing an increased risk factor for accelerated cognitive decline. Therefore, finding solutions to prevent or slow down these processes remains a real public health challenge.

Nutrition is an innovative strategy to prevent age-related cognitive impairment. Among the nutrients, marine by-products appear as a valuable source of valorisation since they contain DHA and low molecular weight peptides that have immunomodulatory, promnesic and anxiolytic properties. The objective of this study is to demonstrate the effectiveness of the association of DHA and low molecular weight peptides (BrainBooster) from the valorisation of marine by-products on the prevention of age-related cognitive decline and understand the mechanisms involved.

Mice aged of 7 weeks and 12 months were fed with a control diet for 12 weeks and then supplemented or not for 6 weeks with BrainBooster. Spatial learning and memory have been assessed with the Y-maze and the Morris water maze and stress reactivity was studied following restraint protocol. Microglial activation markers Iba1 and CD11b were quantified in mice hippocampus.

This study showed that aged mice have short-term and long-term hippocampal dependent memory deficits associated with increased CD11b expression and Iba1 positive cells as well as anxiety disorders, in basal conditions and acute stress. BrainBooster supplementation prevented short-term, but not long-term, memory deficits observed during aging. In addition, BrainBooster reduced microglial activation, and restored a stress response similar to that of young animals. BrainBooster is therefore promising thanks to its anti-inflammatory and anxiolytic properties. It would represent a strategy of choice in the prevention of age-related cognitive decline.