8th EDITION

NUTRINEURO ANNUAL MEETING

FEBRUARY 1st 2019

SCIENTIFIC PROGRAM

9h00 WELCOMING OF PARTICIPANTS

9h30-10h50 Nutrition and cellular function (Chair: Zoé, Hugo, Mathieu, Andrea)

. Lydie Morel: Dietary PUFAs immunomodulatory properties shape the neuronal network during development

. Roman Walle: Respective roles of the distinct populations of Medium Spiny Neurons of the Nucleus Accumbens in reward processing: From pharmacogenetic manipulation to disruption of dopamine/glutamate receptor heteromers

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

. Julien Artinian: Role of hippocampal CB1 receptors in obesogenic diet-induced memory impairment: cell type culprit and synaptic mechanisms involved

10h50-11h10 COFFEE BREAK

11h10-12h30 Nutrition and behaviour – part 1 (Chair: Anaïs, Pierre, Mathilde H)

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

. Ioannis Bakoyiannis: Are memory alterations induced by obesogenic diet consumption during adolescence related to changes in amygdalo-hippocampal pathway?

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

12h30 - 13h45 LUNCH

13h45-14h00 2019 Presentation of Master 2 students

14h00-15h00 Nutrition and brain circuits (Chair: Lydie, Roman, Fanny, Julien, Mathilde C)

. Zoé Husson: Role of the POMC-ventral striatal neurocircuit in the development of diet-induced obesity

. Hugo Martin: Unravelling the role of brain insulin-resistance in diabetes-related depression

. Mathieu Di Miceli: Role of DHEA, an omega-3 derivative, in synaptic plasticity.

. Andrea Contini: Impact of a deficiency in n-3 long-chain polyunsaturated fatty acids on cortical dependent behavior

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

15h15-16h15 Nutrition and behaviour – part 2 (Chair: Ines, Ioannis, Camille)

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

. Pierre Cardinal: The role of brain IDO in the resistance to Fluoxetine treatment

. Mathilde Henry: Role of HPA axis hyperactivity and inflammation in emotional disorders associated to type 2 diabetes in a non obese rat model

16h15-23h FESTIVITIES (organized by students and post-docs)

Amphi Ellul, 35 place Pey-Berland

Tram A and B – arrêt Pey-Berland Université de Bordeaux

ABSTRACTS

Dietary PUFAs immunomodulatory properties shape the neuronal network during development

Lydie Morel, Quentin Leyrolle, Agnès Aubert, Alexandra Sere, Véronique DeSmedt-Peyrusse, Corine Joffre, Agnès Nadjar, Sophie Layé

During development, the many cells of the central nervous system (CNS) interact to allow the maturation of a functional network. Amongst the necessary remodeling events is the synaptic pruning, during which certain synaptic terminals are removed to guaranty the efficiency of the neuronal signaling. This elimination activity is performed by microglia, the innate immune cell of the brain which is capable of phagocytosis. Polyunsaturated fatty acids (PUFAs) are immunomodulators and key regulators of brain innate immune system processes. Our group showed that by changing the ratio of n-3/n-6 PUFAs in the diet, their levels in the brain and in the composition of the microglia membrane were altered. Functional analyses and high-resolution imaging revealed that microglia-dependent synaptic pruning is inversely correlated to the n-3/n-6 PUFA ratio. Additionally, data obtained by protein and RNA quantification suggested a role of the complement system in the effect of microglial inflammation on the shaping of the neuronal network. The deleterious effect of dietary n-3/n-6 PUFA was inhibited by blocking microglial CR3 a key component of the complement pathway. This part of the study uses in vitro and ex-vivo models to better understand the mechanisms linking PUFAs and microglia inflammation. We present here new experiments investigating the implications of the C3/CD11b component as well as a pathway linking the PUFAs composition of the diet to the inflammatory status of microglia. Indeed, quantifications of the PUFAs derivatives in the microglia of animals fed with the low n-3/n-6 ratio have provided us with target lipids that were screened in vitro. We have identified a pro-phagocytic derivative of arachidonic acid (AA) : 12HETE. This mediator is synthesised from AA by the 12Lox enzyme. By modulating 12Lox enzymatic activity we chain the link between n-3 PUFA deficient diet and increased microglia inflammation during this key developmental period for the CNS.

Respective roles of the distinct populations of Medium Spiny Neurons of the Nucleus Accumbens in reward processing: From pharmacogenetic manipulation to disruption of dopamine/glutamate receptor heteromers

Roman Walle[1], Fabien Ducrocq[1], Anna Petitbon[1], Giulia Fois[5], Asma Oummadi[1], Véronique De Smedt-Peyrusse[1], Peter Vanhoutte[2, 3,4], François Georges[5], Pierre Trifilieff[1]

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The nucleus accumbens (NAc) is a main structure involved in reward processing. It is largely composed of GABAergic Medium Spiny Neurons (MSN) that are divided into two subpopulations, those expressing the dopamine D1 receptor (dMSNs), and those expressing the D2 receptor (iMSNs). Based on the model of the dorsal striatum, it has been proposed that dMSNs and iMSNs of the NAc play antagonistic effects on reward processing, but their respective roles are still largely debated. Functionally, the activity of MSNs is modulated by the convergence of glutamatergic signals arising from the cortex and thalamus and the reward-related signals encoded by dopaminergic inputs. Recent findings suggest that the detection of such convergent inputs at the synaptic level could be mediated by heteromers formed by dopamine and glutamate NMDA receptors, however, the implication of such mechanisms in reward processing is unknown.

The broad goal of this project is to determine how the two populations of MSNs in the NAc regulate reward-related processes. The main objectives are 1) to unravel the respective roles of dMSNs and iMSNs and 2) how they detect the convergence of dopamine and glutamate inputs to modulate reward processing.

Using operant conditioning tasks coupled with pharmacogenetic approaches, we showed that, whereas the activation of iMSNs decreases motivation to obtain a food reward but increases food consumption, their inhibition had the opposite effects. Surprisingly, both the inhibition and activation of dMSNs led to a strong decrease in motivation to obtain a food reward, notably related to anorexigenic effects.

Using a proximity ligation assay (PLA) we mapped the expression of D1R/GluN1 heteromers throughout the striatum and showed that operant learning has no effect on their expression. We are currently validating viral vectors that allow the conditional expression of interfering peptide to evaluate the implication of NMDA/Dopamine receptors heteromers in reward processing.

Role of PUFAs in microglia-oligodendrocyte interactions during brain development

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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. Moreover, previous reports showed that iron uptake is necessary for oligodendrocyte maturation and myelination and that microglia might be the iron-providers during neurodevelopment. In line with these observations, juvenile n-3 PUFA deficient mice display a decrease in total iron content in the white matter, as compared to n-3 balanced animals. Hence, we hypothesize that **n-3 PUFA deficiency decreases the density of iron-providing CD11c-positive microglia, leading to decrease in oligodendrocyte maturation and subsequent deficits in myelination.** To test this, we will first quantify the number of CD11c-positive cells, iron content, oligodendrocytes maturation markers and myelination across brain development (time course study). We will then provide iron to n-3 deficient mice on one hand, and specifically knock out CD11c-positive microglia in n-3 balanced animals on the other hand and assess oligodendrocyte maturation and myelination in both situations. Finally, to test the causal link between low myelination and defects in brain connectivity, we will inject n-3 deficient mice with clemastine (a booster of myelination) and assess cognitive and mood-related behavior. Altogether, our study will provide new evidence on the role of PUFAs on microglia-oligodendrocyte interactions during brain development.

Role of hippocampal CB1 receptors in obesogenic diet-induced memory impairment: cell type culprit and synaptic mechanisms involved

Artinian J, Janthakhin Y, Ferreira G

Obesity is associated with adverse cognitive outcomes. Its growing prevalence during adolescence is alarming since it is a developmental period of neurocognitive shaping particularly vulnerable to the effects of obesogenic high-fat diet (HFD) on hippocampus-dependent memory. Interestingly our group recently showed that the endocannabinoid system, which participates in obesity and regulates memory processes, mediates HFD-induced memory impairment. Indeed, we showed that long-term object recognition memory (ORM) impairment is associated with increased hippocampal endocannabinoid levels (specifically anandamide) after ORM training in HFD-fed mice. Furthermore, hippocampal deletion of the main cannabinoid receptor (CB1R) rescued long-term ORM impairments indicating that **hippocampal CB1R over-activation after training impairs ORM in HFD-fed mice. However, the cell type and the synaptic mechanisms underlying these cognitive deficits remain elusive.**
We will first determine which hippocampal cell type carrying CB1R (astrocytes, glutamatergic or GABAergic neurons) is responsible for HFD-induced ORM impairment. We will use the Cre-lox system to perform cell-type specific deletion of hippocampal CB1R. HFD-fed CB1-flox mice will receive hippocampal microinjection of viral vector expressing the Cre recombinase under a promoter specific to astrocytes (GFAP), glutamatergic neurons (CaMKII□) or all neurons (synapsin; as no effective GABAergic promoter is yet available) and their memory performance will be assessed 3-4 weeks later. Second, we will use *ex vivo* electrophysiology and pharmacology (CB1R agonist or antagonist) to decipher the impact of adolescent HFD on hippocampal synaptic mechanisms. More specifically, we will examine excitatory/inhibitory synaptic transmission, intrinsic excitability and synaptic plasticity of CA1 pyramidal cells. We will focus on well characterized CB1R-dependent long-term depression of excitation and inhibition and their impact onto long-term potentiation, an important cellular substrate of learning and memory. The results of these experiments will help to understand the synaptic mechanisms underlying HFD-induced memory deficits within hippocampal networks.

IMPACT OF MARINE-DERIVED PRODUCTS ON AGE-RELATED COGNITIVE DECLINE PREVENTION.

Mathilde CHATAIGNER
Supervisors: Corinne JOFFRE and Anne-Laure DINEL

Physiological brain aging leads to the decline of cognitive functions which can result in the development of neurodegenerative pathologies. It is associated with well-defined characteristics such as low-grade chronic inflammation, neuronal alterations, decrease of docosahexaenoic acid (DHA) content as well as cognitive alterations. Furthermore, 10% of the elderly present anxiety disorders thus representing a target for an accelerated cognitive decline.

Nutrition represents an innovative strategy to prevent age-related cognitive decline. Actually, two studies have shown a synergistic effect of DHA and bioactive peptides on cognitive impairment although the action mechanism remains unknown. DHA has immunomodulatory properties reducing the production of inflammatory cytokines. Bioactive peptides present anxiolytic properties through the modulation of the HPA axis. Therefore, due to their individual or synergistic effects, these compounds could contribute to a healthier aging. The aim of this project is to study the effects of combined DHA and peptides (BrainBooster product) on cognitive decline and the mechanisms involved.

Mice of 7 weeks-old and 12 months-old were fed with n-3 PUFA deficient diet during 12 weeks and were then supplemented with BrainBooster or not for 8 weeks. Cognitive capacities were evaluated through the object location and the Morris Water Maze tests. Our data showed memory impairments in aged mice which could be attributed to an increase in neuroinflammation. However, these alterations are not protected by BrainBooster despite the n-3 PUFA enrichment and the decreased n-6 PUFA content in the cortex of mice. Interestingly, our data show that dietary supplementation with BrainBooster promote a pro-resolving oxylipin profile in the brain. Our data suggest that BrainBooster supplementation may be a good regulator of brain, and potentially peripheral, cytokine production during aging which plays a key role in the age-related cognitive decline. Other studies are underway to evaluate the effects of BrainBooster supplementation on anxiety as well as neuroprotection.

Are memory alterations induced by obesogenic diet consumption during adolescence related to changes in amygdalo-hippocampal pathway?

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Obesity epidemic is currently reaching an alarming level, with the prevalence and severity of overweight also increasing dramatically in youth and persisting even in adulthood. Obesity is associated with numerous comorbidities such as neurocognitive dysfunctions, specifically those affecting learning and memory function. This is particularly interesting since childhood and adolescence are crucial periods for the maturation of certain brain structures, including the hippocampus (HPC) and the amygdala, necessary for shaping cognitive function for life duration. In this context, previous studies in the laboratory have shown that high-fat diet (HFD)-induced obesity covering adolescence is associated with bidirectional changes in the HPC and the basolateral amygdala (BLA): adolescent HFD intake impaired HPC plasticity and HPC-dependent recognition memory and enhanced BLA plasticity and BLA-dependent aversive memory. As amygdala-hippocampal connectivity establishes during adolescence this bidirectional effect of HFD may be related to changes in BLA-HPC pathway. The aim of the current study is, therefore, to examine the effects of adolescent HFD on the amygdalo-hippocampal pathway and to evaluate the contribution of this pathway to the memory changes observed in adolescent HFD-fed rats. To this purpose, we aim to 1) characterise the impact of adolescent HFD on reciprocal projections between BLA and HPC via a neuroanatomical approach at different post-weaning time points and 2) specifically manipulate BLA-to-HPC projections using advanced chemogenetic tools to restore memory dysfunction. We expect that the BLA-HPC pathway will be altered in adolescent HFD rats (anatomically and/or functionally) and also that the inactivation of the BLA-HPC pathway will normalise memory performance in HFD-fed rats. Results obtained from this study will be beneficial in context of adolescent obesity impact on brain structure and function at a cognitive level.

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

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Mood disorders (depression, anxiety) represent a major public health concern. Their prevalence is continuously rising, notably in patients exposed to chronic stress or suffering from medical conditions associated with low-grade chronic inflammation, including obesity. These patients also often display increased resistance to conventional antidepressants (AD). Interestingly, recent findings suggest that inflammatory processes may contribute to this therapeutic resistance. For example, it has been recently reported that an anti-inflammatory treatment significantly improves the therapeutic response in resistant depressive patients (Raison et al., 2013). It is therefore important to deeply characterize the inflammatory processes contributing to such a resistance to AD in order to identify strategies aiming to improve management and treatment of mood disorders. Among available strategies, nutritional approaches are particularly promising because of the immunomodulatory properties displayed by some nutrients. In this context, saffron, whose beneficial effects on health have already been reported in the literature, is a prime candidate.
This thesis will first aim to characterize the mechanisms contributing to AD resistance, in particular those linked to inflammation, by comparing the AD response in murine models of depression either associated with chronic activation of inflammatory processes (obesity models) or independent of any inflammation (models of stress-induced depression). The second aim will be to assess the impact of nutritional interventions with known immunomodulatory properties on those mechanisms and related therapeutic resistance. This work will be mainly performed using behavioural and neurobiological (PCR, western, neurochemistry…) measures, together with approaches of targeted nutritional supplementation.

Key words: Mood disorders, Therapeutic response, Nutritional interventions, Inflammation, Saffron

Role of the POMC-ventral striatal neurocircuit in the development of diet-induced obesity

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Eating is a process essential for life. Thus, powerful brain mechanisms have evolved to allow not only the matching of the organism's energy needs with energy intake, but also the recognition of food rich in calories so to guarantee survival under variable environmental food sources. To control food intake, neuronal circuits classically aiming at integrating information about the organism's energy status must somehow interact with circuits underlying "liking" and "wanting" signals. We have hypothesized that such interaction involves hypothalamic pro-opiomelanocortin (POMC) neurons, which are typically recognized as the mediators of hunger/satiety in response to metabolic and hormonal changes, and medium spiny neurons (MSNs) of the nucleus accumbens (NAc) in the ventral striatum, which decode reward and motivation.
When mice are fasted and then allowed to refeed for 2 hours on either normal or palatable food, we showed that NAc MSNs synaptic activities and intrinsic electrophysiological properties are differentially modulated depending on the nature of food, indicating that diet can impact NAc MSN functions.
In POMC-Cre mice injected in the hypothalamus with floxed viruses, we showed that direct POMC projections are present in the ventral striatum. Moreover, during electrophysiological recordings in NAc acute slices, selective optogenetic activation of POMC neuronal afferences affect MSNs excitability. These preliminary results suggest that POMC neurons are able to modulate the activity of NAC neurons, and thus might control motivation for food and food hedonic responses.
By using a multidisciplinary approach involving original genetic models, neuroanatomical, electrophysiological, behavioral and metabolic studies, we expect to unveil the exact link among exposure to excessive caloric sources, change in brain function and obesity physiopathology. We propose that the POMC-NAc circuit may be critical for food intake and especially for the overconsumption of palatable food and ensuing weight gain.

UNRAVELLING THE ROLE OF BRAIN INSULIN-RESISTANCE IN DIABETES-RELATED DEPRESSION

Hugo Martin & Xavier Fioramonti

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 health outcome. However, the mechanisms linking these two pathologies remain largely unknown. Knowing the role of the serotonin (5-HT) network in the pathophysiology of depression, we hypothesized that T2D affects this brain network. In support of this hypothesis, we recently demonstrated that naïve mice fed a high-fat/high-sucrose diet (HFD) which harbour metabolic abnormalities reminiscent of T2D accompanied by expression of hallmarks of anxiety- and depression-like behaviours present an impairment in serotoninergic neurotransmission. Nevertheless, the impact of T2D on the electrical properties of 5-HT neurons from the dorsal raphe nucleurs (DRN) has never been investigated. Thus, the aim of the study is to determine whether HFD-induced T2D alters the electrical properties of DRN 5-HT neurons.

To this end, we used patch clamp electrophysiology to study electrical activity of DRN 5-HT neurons using Pet-1-cre-mcherry mice to visualize specifically 5-HT neurons. T2D-associated mood disorders was modelling by feeding mice with HFD diet for 16 weeks. In conclusion, these results show that 16 weeks of HFD diet induce an alteration of the intrinsic electrical properties of DRN 5-HT neurons. These results help understanding previous data showing that release of 5-HT in the hippocampus is decreased in mouse model of T2D-associated mood disorders. We are currently performing recordings to highlight the conductance involved in the HFD-induced 5-HT neurons decreased input resistance. Moreover, we are also investigating the effect of insulin on 5-HT neurons in STD and HFD fed mice to determine 1/ whether insulin modulates the electrical activity of these neurons and 2/ whether an insulin resistance is present at the level of 5-HT neurons and could explain T2D-associated mood disorders.

Role of DHEA, an omega-3 derivative, in synaptic plasticity.

Mathieu Di Miceli, Maud Martinat, Louisa Linders, Renee Clausing, Vicky Nicolas, Clémentine Bosch-Bouju & Sophie Layé.

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. Recently, the role of n-3 polyunsaturated fatty acids (PUFAs) in the pathophysiology of mood disorders have been investigated. 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. The general purpose of our research is to examine the role of n-3 PUFAs in the prevention of depressive symptoms, in mice models. First, we examined how diets enriched in n-3 PUFAs could affect emotional behaviour in a mouse model of depression, together with synaptic activity measurements. Since n-3 PUFAs-rich diets contain DHA (docosahexaenoic acid), we are also focusing on the role of a DHA derivative, DHEA (docosahexaenoyl ethanolamide), in synaptic plasticity, as well as other endocannabinoids. Our preliminary results suggest that depression-induced loss of endocannabinoid plasticity could be prevented by n-3 PUFAs enriched diets, an effect that may arise from the *in vivo* conversion of DHA into DHEA, thus restoring synaptic plasticity through a shift towards other neuroplasticity mechanisms. This project will therefore provide a further understanding of the link between n-3 PUFAs, depressive behaviour and synaptic functions.

Impact of a deficiency in n-3 long-chain polyunsaturated fatty acids on cortical dependent behavior

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

Reward related dysfunctions and cognitive alterations represent the first cause of therapy discontinuation in patients with major depression disorders and schizophrenia, and pharmacological interventions employed to treat these symptoms are often of limited efficacy and poor tolerability in the long-term treatment. Recently, several lines of clinical evidence have highlighted a link between a reduced level of long-chain polyunsaturated fatty acids (PUFAs), and specifically of n-3 PUFAs, and the aforementioned psychiatric conditions. However, the implication of the lipids in the etiology of cognitive and reward related dysfunctions has still to be clarified. In the last years, our group has demonstrated in mice, that a reduced accrual of n-3 PUFAs across development leads to an impairment in reward related functions that are causally inked to an alteration in the activity of medium spiny neurons (MSNs), especially dopamine D2 receptor-expressing MSNs, in the nucleus accumbens (NAc). From a neuroanatomical point of view, the NAc represents a limbic interface between cortical and subcortical regions, and together with prefrontal cortex (PFC), constitutes the cortico-striatal pathway, aka the reward system. Dopaminergic neurotransmission in this pathway is critical for the expression of cognitive and reward related processes, and abnormal dopamine transmission at this level is considered playing a major role in the impairment of these functions in psychiatric patients. In order to expand the evidence gathered by the group, I evaluated whether n-3 PUFA deficiency entailed some perturbations of dopaminergic neurotransmission in the cortico-striatal pathway using multi-site brain microdialysis. Furthermore, I've investigated whether the reward related deficits displayed by n-3 PUFA deficient mice correlated with an impairment in cognitive functions. My experiments showed that while n-3 PUFA deficiency does not impair dopaminergic neurotransmission in the NAc, it profoundly affects that of the PFC. Furthermore, I found that these neurochemical alterations correlated with an inability of mice to perform goal-directed actions in a outcome-devaluation paradigm.

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

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Parkinson's disease (PD) is caused by a loss of dopaminergic neurons in the substantia nigra *pars compacta* (SNc), leading to strong motor impairments. Dopaminergic neurons from the SNc project to the striatum which allow the control of voluntary movements. Vitamin A, through the action of its active metabolite, retinoic acid (RA), is involved in the development, differentiation and neuroprotection of SNc dopaminergic neurons. Additionally, retinaldehyde dehydrogenase (RALDH), the synthesis enzyme of RA, is involved in cellular detoxification. However, the cerebral bioavailability of RA decreases during life, which reduces RALDH expression. This could precipitate neurodegenerative processes such as those observed in PD. Here we hypothesize that nutritional supplementation with vitamin A normalizes brain levels of RA and thus RALDH, which exhibit a neuroprotective effect on dopaminergic neurons. To test our hypothesis, we will model PD with unilateral injection of 6-hydroxydopamine (6-OHDA) toxin into rats' striatum supplemented or not with vitamin A (20 UI/g) for 5 weeks before lesion. Locomotor activity will be assessed with step test, cylinder test and rotarod. To evaluate the functionality of the dopaminergic system we will quantify levels of dopamine and its metabolites production in different brain structures by HPLC. The degeneration of dopaminergic neurons and their projections will be assessed in the striatum and SNc with immunostaining of tyrosine hydroxylase (TH), the production enzyme of dopamine. To refine the analysis and focus on the possible involvement of RALDH enzyme in neuroprotection of dopamine neurons, co-immunostaining of TH and RALDH will be realized.
Altogether, our study will provide new evidence on the role of vitamin A in the pathophysiology of PD and would possibly lead to new therapeutic strategies to prevent neurodegeneration.

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

Ines Delgado[a,b], Sandra Dexpert[a,b], Julie Sauvant[a,b], Lucile Capuron[a,b]

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Poor dietary habits are associated with an increased risk of neuropsychiatric symptoms, including alterations in cognitive function. The stress response system has been suggested to be involved in this association. Not only stress reactivity and diet are closely interrelated, but also stress is notorious for representing a potent modulator of cognitive function. However, the direct effect of diet on stress reactivity and its relationship with cognitive function has not been systematically assessed in experimental studies. The present study, performed in the frame of the AMBROSIAC JPI project, aims at investigating the impact of diet on stress-induced cognitive alterations in a group of healthy adult subjects.

Fifty healthy adult volunteers were recruited. Participants were stratified on the basis of their nutritional habits, i.e., healthy (balanced diet) versus unhealthy (unbalanced diet group), according to adherence to the French nutritional recommendations, assessed by the PNNS. Cognitive function was evaluated through performance in 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 a psychological stressor, the Trier Social Stress Test (TSST). Stress response was evaluated by salivary cortisol and blood pressure, measured at different time points.

The TSST produced a significant endocrine and autonomic stress response in all participants, regardless of dietary habits. Preliminary results show that cognitive performance improved in the second session for all tests, except for VRM. However, this improvement, notably on the PAL test, was more mitigated in participants with an unbalanced diet. Further analyses are being conducted to confirm these results.

The role of brain IDO in the resistance to Fluoxetine treatment

P. Cardinal, Monchaux C., Sauvant J., Vancassel S., Castanon N., Capuron L.

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 an increased vulnerability to depressive comorbidities urge for new treatment therapies. Accordingly, better knowledge on the pathophysiology of depression and mechanisms underlying depressive comorbidities in chronic medical conditions are urgently needed, in order to help in the development of targeted therapeutic strategies. There is strong evidence for a role of inflammation in the development of depression and increasing data suggests also its involvement in AD treatment resistance. One mechanism likely to contribute to this effect relies on the activation, by inflammatory factors, of the enzyme indoleamine-2,3-dioxygenase (IDO). The peripheral and brain activation of IDO leads to a shift in tryptophan metabolism from serotonin synthesis to the kynurenine pathway, which is believed to potentially participate to AD treatment resistance by both depleting 5HT function and generating neurotoxic metabolites.

In the present study, we propose to evaluate the role of IDO in AD treatment resistance in an acute model of inflammation (lipopolysaccharide, LPS)-induced depressive-like symptoms. Mice will be administered with fluoxetine concomitantly (or not) with 1 methyl tryptophan (1-MT), a selective inhibitor of IDO, after LPS administration. Depressive-like behavior will be evaluated using different behavioral paradigms, including the Forced swim test and tail suspension test. Immunological status will be evaluated, as well as inflammation in brain regions of interest such as the hippocampus, striatum or the prefrontal cortex. Based on our hypotheses, blockade of IDO by 1 MT should contribute to improve AD response in mice afflicted with LPS-induced depressive behavior.

Role of HPA axis hyperactivity and inflammation in emotional disorders associated to type 2 diabetes in a non obese rat model

Mathilde Henry, Muriel Darnaudéry

A large literature documents the co-occurrence of type 2 diabetes (T2D) with psychiatric disorders such as anxiety and depression; however the nature of this co-morbidity remains unclear. T2D and depression share pathophysiological origins as chronic activation of the innate immune system and hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis. Currently, obese animal models do not adequately reflect the full human T2D clinical context since T2D is not always associated with obesity and may occur at young age. The Goto-Kakizaki (GK) line rat is a spontaneous, non obese model of T2D established by inbreeding Wistar rats selected at the upper limit of normal glucose tolerance. GK rats are not diabetic at birth and mild hyperglycemia develops at 4 weeks of age.
GK exhibit a marked inflammation in the peripheral tissues including pancreatic islets and liver. We recently demonstrated that GK displayed hyperanxiety and reduced social interaction associated with high plasma corticosterone levels both in basal and post-stress conditions. We also reported an increase of IL-6 expression in the medial prefrontal cortex (mPFC) of GK. Our project aims to unravel the mechanisms underlying the link between T2D and emotional disorders in GK rats. We will answer to the following questions 1) What is the role of diabetes in the emergence of an anxious-depressive phenotype in GK rats? 2) What is the contribution of HPA axis dysfunctions and/ or inflammation in this phenotype? We will examine the behavioral alterations (anxiety, depressive-like behavior, memory) of GK before and after the appearance of T2D. To explore the causal role of HPA axis dysfunctions on GK phenotype, we will examined behavior after adrenalectomy or chronic administration of a corticosterone synthesis inhibitor. Finally, to explore the role of inflammation, we will test whether an anti-inflammatory treatment administered at the periphery or central level into the mPFC will attenuate the behavioural alterations in GK. The overall impact of this project will be to improve our understanding of emotional disorders related to T2D.