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Circadian clocks and feeding behavior

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Biological functions display daily rhythms, including feeding/lipogenesis during the active period and fasting/lipolysis during the resting period. Such a temporal organization is controlled by a circadian timing system made of interconnected endogenous clocks and oscillators. The master circadian clock, located in the suprachiasmatic nuclei of the hypothalamus, is mainly reset by light and synchronizes peripheral oscillations. The secondary clocks/oscillators, present in many brain regions and peripheral organs (e.g. liver and white adipose tissue), can be shifted by meal timing, as modulated by temporal restricted feeding, while the suprachiasmatic clock is relatively impervious to the impact of meal time. However, timed calorie restriction (i.e. when only a hypocaloric diet is given every day) is able to modify the suprachiasmatic clockwork and to modulate synchronisation to light, via increased phase-shifting effects of light. High-fat feeding also affects the suprachiasmatic clockwork and modulates synchronisation to light, via reduced shifting effects of light.

Secondary clocks in the brain outside the suprachiasmatic nuclei are differentially influenced by meal timing. Circadian oscillations can be either highly sensitive to feeding cues (i.e. their phase is shifted according to meal schedule) in some structures (e.g. paraventricular hypothalamic nuclei and cerebellum) or hardly affected in others (e.g. hippocampus). Furthermore, the circadian anticipation of meal time relies on cerebellum integrity.

These data indicate that feeding cues can markedly modulate the timing of the circadian system, not only at the periphery, but also within the brain. The light-entrainable clock in the suprachiasmatic nuclei, which drives the sleep-wake cycle, is only sensitive to nutritional cues associated with metabolically challenging conditions. The cerebral clocks sensitive to meal time, such as those in the metabolic hypothalamus and cerebellum, define a network of coupled meal-entrainable oscillators controlling the feeding cycle.

Numerous metabolic processes, like adipogenesis, are regulated by transcriptional networks shared by circadian clocks. Obesity and diabetes are associated with circadian alterations. Conversely, circadian dysfunctions, either due to impaired clockwork (e.g. knock-out of clock genes) or impaired synchronisation (e.g. chronic jet-lag or shift-work), are associated with increased metabolic risks. A chronic desynchronisation can trigger fat overload, leading to a so-called 'chronobesity'.

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Morbidly obese patients and drug: the clinical pharmacologist's view

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Drug lipophilicity, organ blood flow, tissue binding, drug plasma protein binding and the ionization state are the ABCs of pharmacokineticists. Most of us will consider that a lipophilic drug administered to an obese patient will lead to an increase of the peripheral distribution and perhaps to a tissue accumulation. However, we have to admit that few studies are performed in obese patients and even more rarely on morbidly obese. Meanwhile we all teach these concepts hoping that they are generally true. Science is hard and unsympathetic with us and reading the results of studies should encourage us to be more circumspect. Indeed, even if lipophilicity could be an important determinant for some drugs, others are less well predicted by this physicochemical property. Obesity is linked to a number of co-morbidities (i.e. heart insufficiency, hypertension) or to modification of the way of life (decrease in exercise), which could also affect pharmacokinetic parameters. The volume of distribution changes in the obese as well as clearance is drug-specific. So, should we have to recommend performing pharmacokinetic studies in obese patients for all drug development? This question has to be discussed as well as which design should be used, full profile and non-compartmental analysis or population pharmacokinetic modeling? Furthermore, which metric should be used, body weight, body mass index, body surface area...? All these issues will be addressed but all should not be definitively settled.

Is obesity a disease or only an adaptation?

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Obesity is increasing all around the world at an epidemic rate. Although France is not the most affected country, the last OBEPI study shows that 14.5% of the population was obese and 31.9% overweight. In fact, only 50% of the population has a normal body weight.

Increasing body weight is an adaptation to the large changes in life-style that are occurring with a decrease in physical activity and the development of sedentary behaviours as well as changes in food habits patterns. This leads to a positive energy balance and the body has no other solution than to increase fat mass. The increase in obesity prevalence is problematic, as this condition is associated with health complications such as diabetes and cardiovascular diseases, more particularly when the excess body fat is stored in the deep abdominal region. Cut-off values for obesity, defined as a body mass index (BMI, kg m^{-2}) >30 come from the epidemiological observations of the large increase in mortality risk above this level. However, we can find some people with large obesity and lacking of

metabolic alteration usually associated to obesity (obese metabolically normal), subjects only prone to mechanical complications of obesity. On the other hand, patients with total lack of fat, as seen in lipotrophic diabetes, have also important metabolic complications. Understanding the underlying mechanisms leading to ectopic fat accumulation are of major importance to detect subjects for whom weight gain will be particularly deleterious. However on a Public Health perspective, labelling obesity as a disease is a necessary step in a campaign to combat obesity. Prevention by deep changes in lifestyle is mandatory as many of chronic diseases such as diabetes, cardio-vascular diseases, cancer could be prevented by better management of body weight.

Mechanisms and consequences of human adipose tissue inflammation

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Obesity, defined as an excess of white adipose tissue mass, is considered a sterile and chronic inflammatory state, characterized by increased circulating levels of inflammatory factors as cytokines and chemokines. It is now widely recognized that the adipose tissue itself is a site of inflammation in obesity. In this talk, I will provide examples to show how transcriptomic analysis increased our knowledge of obesity-linked adipose tissue pathology. Our initial studies detected major alterations in inflammation-related genes, including increased expression of macrophage markers, in obese adipose tissue. Macrophage accumulation was confirmed by immunohistochemistry, with a more marked effect of obesity in visceral than subcutaneous fat depot. A positive relationship between the number of macrophages in visceral fat and the severity of non-alcoholic hepatic histopathology was found in a large population of obese subjects (Tordjman et al. *J Hepatol*, 2009; 51: 354–62). This suggests that macrophage accumulation contributes to the well-known association between abdominal obesity and metabolic complications. The mechanisms relating immune cell infiltration in hypertrophied adipose tissue are the focus of intense research. We contributed to show the importance of chemokines, including CCL5/RANTES, which promote monocyte diapedesis and macrophage survival (Keophipath et al. *Arterioscler Thromb Vasc Biol*, 2010; 30: 39–45). Further evaluation of transcriptomic interactions characterizing human adipose tissue showed a strong relationship linking inflammation to extracellular matrix components. Indeed, the obese adipose tissue displays large fibrotic areas, with distinct pattern and composition according to tissue anatomic location (Divoux et al. *Diabetes*, 2010; 59: 2817–25). Various cell types, including macrophages, mast cells and pre-adipocytes were detected in fibrotic bundles. Isolated human pre-adipocytes acquire a pro-fibrotic phenotype when cultured with activated macrophage conditioned media (Keophipath et al. *Mol Endocrinol*, 2009; 23:11–24) suggesting their contribution to fibrosis deposition in the inflammatory microenvironment of obese adipose tissue. Thus, the inflamed adipose tissue undergoes complex and interrelated alterations in obesity. The challenging task of determining their causes and consequences is a prerequisite for new therapeutic approaches targeting adipose tissue homeostasis.

Obesity and cancer: therapeutics aspects

S Hamza, B Guiu, P Hillon

The knowledge of the mechanisms involved in the relationship between obesity and cancer may help us to better understand the therapeutic aspects in cancer prevention and treatment in overweight patients. The mechanisms involved in carcinogenesis related to obesity are for a large part in connection with an excess of visceral fat. Visceral fat is responsible not only for an increased risk of cancer but also for a worsened severity and in some cases for loss of drug efficacy. These deleterious effects are essentially due to dysfunctional visceral adipose tissue. Changes in the physiological functions of adipose tissue lead to insulin resistance, chronic inflammation and altered secretion of adipokines.

Insulin resistance due to inflammation and free fatty acid excess contributes to the increased risk of cancer in obese people. Insulin resistance induces insulin secretion by pancreatic beta-cells and increases bio-availability of IGF-1, responsible for cellular growth and decreased apoptosis. The role of Insulin resistance explains the protective effect of drugs increasing insulin sensitivity like metformin, against hepatocellular carcinoma risk.

Altered secretion of adipokines in obese patients results from pro-inflammatory cytokines, leptin, VEGF and plasminogen activator inhibitor-1 (PAI-1) hypersecretion, and decreased adiponectin secretion. Adipokine abnormalities are involved in different carcinogenesis steps: cellular proliferation and apoptosis, angiogenesis, and extracellular alterations through the activation of matrix metalloproteinases leading to tumour growth, progression, and metastasis. Some of these mechanisms will be potential therapeutic targets in Human cancer in the future. They should explain the decreased efficacy of anti-angiogenic drugs described in high visceral fat volume patients suffering from metastatic colorectal and renal cancer.

The fight against visceral fat excess is based on nutritional recommendations and physical activity. In the future, some new antiangiogenic agents specifically inhibiting angiogenic receptors of visceral adipose tissue, could take a predominant place in obesity treatment. These drugs that are effective on weight loss in obese animals, are currently evaluated in patients suffering from metastatic prostate cancer whose severity seems to be strongly related to visceral obesity.

Discussion: Present results highlight the role of NR1 and nNOS activation in ventilatory adaptation to chronic anemia in Epo-TAg^h mice. However, NO response to acute hypoxia after acclimatization in Epo-TAg^h mice seems to be independent of the NR1 pathway and could imply others neuromediators.

25-P098

Combination of cigarette smoke extract (cse) and lipopolysaccharide (lps) induced cytokine release from epithelial cells by jak/stat and jnk signaling pathways

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Cigarette smoke is a major cause chronic obstructive pulmonary disease (COPD). Airway inflammation is a hallmark of COPD and is currently associated with a migration of inflammatory cells, oxidative stress production, parenchymal destruction or recurrent infection which play a crucial role in the progression of the disease. Nevertheless, the early mechanism of activation of epithelial cells by CSE associated with LPS is unclear. We investigated the effect of combination of CSE and very low concentrations of LPS in A549 epithelial cells activation.

CSE was prepared from Kentucky 2R1 cigarette smoke in contact with 20 mL RPMI medium. Alveolar epithelial type II cells A549 were treated with CSE (2% and 4%) alone or with LPS (0.1 µg/mL). Production of interleukin (IL)-8/CXCL-8, CCL2/MCP-1 and CXCL1/GRO-α were determined by ELISA. Activation of JNK and JAK/STAT pathways were determined by protein phosphorylation by Western blotting and Phospho-kinase array.

CSE did not induce production of IL-8/CXCL-8 (78 ± 12 pg/mL vs. control 62 ± 8 pg/mL) and VEGF (131 ± 11 pg/mL vs. control 45 ± 3 pg/mL) from A549 cells, but increased production of CCL2/MCP-1 (1417 ± 33 pg/mL vs. control 498 ± 83 pg/mL) and CXCL-1/GROα (445 ± 42 pg/mL vs. control 332 ± 62 pg/mL). LPS (0.1 µg/mL) was not able to induce the production of cytokines. However the combination of LPS (0.1 µg/mL) with CSE induced an important production of IL-8/CXCL-8 (242 ± 22 pg/mL), CCL2/MCP-1 (1666 ± 328 pg/mL), CXCL-1/GROα (820 ± 204 pg/mL) and VEGF (185 ± 4 pg/mL). This combination also induced activation of JAK/STAT signaling pathway and transient peak activation of JNK after 5 min.

Combination of CSE with LPS resulted in strong production of several cytokines. We also showed that the increased production of cytokines, involved JAK/STAT JNK signaling pathway. This also demonstrates the important role of combined activation of LPS during recurrent infections with cigarette smoke in the inflammatory process in COPD.

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The role of the basal ganglia in behavioral disorders: experimental studies in monkey

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There are growing evidences supporting the implication of the Basal Ganglia in a large spectrum of behavioral disorders: like obsessive-compulsive disorders (OCD), attention deficit/hyperactivity disorder (AD/HD), anxiety disorders, depression and apathy. However, experimental results from animal models and specifically on monkey are required to determine the involvement of specific territories within the Basal Ganglia. As it was demonstrated that movement disorders could be obtained by microinjections of bicuculline in the sensorimotor territory of the external Globus Pallidus (GPe), the purpose of our study was to assess the consequences of such injections in the associative and limbic GPe. Spontaneous behavior and performances in a simple-choice task were monitored. Effectively, two types of behavioral disorders were obtained, dependant of the injection site into the GPe. These behavioral effects shared similar features with AD/HD and compulsive disorders observed in human. Anatomical study of input and output projections related to the sites which induced the most striking effects was done. The production of AD/HD was linked to the associative territories of the basal ganglia and the production of compulsive behavior was linked to the limbic territories. In a last study, we showed that the same approach, applied to the associative and limbic territories of the striatum, induced a larger spectrum of behavioral disorders, including impulsive disorder, anxiety disorder and apathy. In conclusion, our results support the idea that the associative and limbic territories of the basal ganglia are involved in large spectrum of behavioral disorders and could be the site for new therapeutic approaches like deep brain stimulation in some psychiatric disorders.

26-O051

Early effects of high-fat diet on hypothalamic cell proliferation

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The hypothalamus is one of the main brain structure involved in the control of energy homeostasis. Recent reports indicate that hypothalamus exhibits neuroproliferative potency in adult. Moreover, it has been found that hypothalamic cell proliferation could be modulated by numerous intrinsic factors such as CNTF, IGF-1, bFGF and EGF, and by external and internal conditions such as dehydration, variation in ambient temperature and during ovarian cycle. Interestingly, experimental manipulation of neurogenesis can affect body weight. However, whether nutritional conditions could influence hypothalamic cell proliferation and thereby modify energy homeostasis is still unknown. To address this question, mice were subjected to a high fat diet (HFD) for 1 week and hypothalamic cell renewal was assessed through central chronic infusion of Bromodeoxy-Uridine (BrdU). Using this approach, we report that hypothalamus constitutively exhibits ≈2000 BrdU-positive neo-formed cells per day. This proliferative rate was significantly higher in

hypothalamus 3 days after the onset of HFD (+60%) but decreased by 50% on day 5. To determine whether these HFD-induced modifications of cell renewal were linked to change in cell proliferation, we counted Ki67 immunoreactive cells. We found 1937 Ki67 immunoreactive cells in hypothalamus from mice fed with standard chow. However, the number of such cell was significantly higher in mice fed with HFD for 1 and 3 days (+30% and 50%, respectively), and returned to basal value after 5 days. In order to evaluate the role of newborn cells, HFD fed mice were treated with the anti-mitotic arabinoside cytosine (AraC) for 30 days. Results show that AraC treatment increased HFD-induced body weight gain, suggesting that newborn HFD-induced cells produce anorectic function. Altogether these data demonstrate that a change in diet induces cell proliferation in the hypothalamus which might be involved in the control of long-term energy homeostasis.

26-O052

Weight gain following deep brain stimulation: a pet study

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Objective: Several hypotheses have been proposed to explain weight gain (WG) following deep brain stimulation (DBS) in Parkinson's disease (PD) but none fully succeed to clarify this common adverse effect that may have prejudicial health consequences. The aim of this study was to analyze the correlation between changes in cerebral metabolism and WG following bilateral DBS in patients with PD.

Methods: Body Mass Index (BMI) was calculated and cerebral activity prospectively measured using FDG (2-deoxy-2[18F]fluoro-D-glucose) 3 months before and 3 months after subthalamic (STN) DBS in 23 PD patients and pallidal (GPi) DBS in 19 PD patients.

Results: Mean [SD] increase in BMI was similar in both groups: +0.8 [1.5] in the STN group and +0.6 [1.7] in the GPi group. In contrast, group comparison revealed a dramatically different pattern of correlation between WG and changes in cerebral metabolism. Positive correlations were clearly marked in limbic and associative areas in the STN group, including both lateral and medial parts of the temporal lobe, right Brodmann Area (BA) 20, left BA21, BA22 and BA37, and the dorsal anterior cingulate cortex (BA32). In the GPi group, positive correlations were observed in sensori-motor areas, mainly in the prefrontal cortex (left and right BA6, left BA8, right BA9 and right BA46) and the right parietal cortex (BA7).

Discussion: These findings confirm a previous clinical study from our group suggesting that WG following DBS in PD is linked to improvement in motor dysfunction following GPi DBS and to change in limbic processes following STN DBS. This study also confirms that the STN is a key structure of the basal ganglia in limbic circuitry.

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26-O053

Severity disease biomarkers in patients with Spinocerebellar ataxia type 7 (SCA7)

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SCA7 is an autosomal dominant neurodegenerative disease that belongs to polyglutamine disorders. Patients present progressive cerebellar ataxia and the disease is usually fatal after 10–30 years of evolution. Age at onset and clinical severity are highly inconstant between patients and are not predictable. Because the causal gene SCA7 code ataxin-7 that is a transcriptional factor, we hypothesized that ataxin-7 interacts with transcriptional machinery and that transcriptomic alterations may partly explain this variability.

Objective: To identify biomarkers of disease severity in SCA7.

Methods: Twenty-four SCA7 patients and 23 healthy controls matched for age and gender were recruited at the Pitié-Salpêtrière Hospital. A trained neurologist performed clinical assessments using a specific severity scale and blood samples were collected at the same time. RNA from lymphocytes was extracted, amplified and hybridized on Illumina HT-12 arrays. Expression profiles of 48 804 probes were generated, and we performed statistical analysis using BRB-array Tools. Significant genes were confirmed by real time RT PCR.

Results: We found 1498 genes differentially expressed between patients and controls ($P < 0.01$, FDR<0.05), thus revealing a molecular signature of SCA7 disease (DNA catabolic process ($P = 0.009$, FE = 2.2), leucocyte chemotaxis ($P = 0.01$, FE = 2.8), regulation of defense response to virus ($P = 0.01$, FE = 3.0), biogenic amine metabolic process ($P = 0.01$, FE = 2.1), neuron apoptosis ($P = 0.02$, FE = 3.5), regulation of cell shape ($P = 0.05$, FE = 2.27), proteoglycan metabolic process ($P = 0.05$, FE = 2.8)). Among those deregulated genes, the expression of ATG12, a regulator gene of autophagy, was the most correlated with the severity of the disease (correlation coefficient = 0.64, $P = 0.0009$). We then looked at the autophagic pathway and discovered that 14 genes of this pathway (17%) were deregulated among SCA7 patients ($P < 0.01$, FDR<0.10).