Abstracts

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 of physiological functions is ensured by a circadian timing system, which is based on endogenous clocks and oscillators. The master circadian clock, located in the suprachiasmatic nuclei of the hypothalamus, is mainly reset by light and synchronizes peripheral oscillators. 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 phase-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 nucleus 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 nucleus, 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 metabolism/hypothalamus region, define a network of coupled meal-driven entrainable oscillators controlling the feeding cycle.

Numerous metabolic processes, like adipogenesis, are regulated by transcriptional networks involving clock genes. Obesity is 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, the world’s leading cause of death at an epidemic rate, although France is not the most affected country, the last OBEPY 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 lifestyle that are occurring with a decrease in physical activity and the development of sedentary behaviors. Obesity is associated with food habits patterns. This leads to the 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 issues, including 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/m2)>30 come from the epidemic of abdominal obesity in mortality and morbidity risk. However, we can found 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 lipodystrophy, 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 and the severity of hepatic steatosis was found in a large population of obese subjects (Tordjam-an 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 relaying immune cell infiltration in hypertrophied adipose tissue are the focus of intense research. We contributed to show the importance of these mechanisms, including CCL5/RANTES, which promote monocyte diapedesis and macrophage survival (Keophiphath et al. Arterioscler Thromb Vasc Biol, 2010; 30: 39–45). Further evaluation of transcriptional interplay characterizing human adipose tissue led to 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. Diabeto, 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 (Keophiphath et al., Mol Endocrinol, 2009; 23:11–24) suggesting their contribu-
tion 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
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The knowledge of the mechanisms involved in the relationship between obesity and cancer can help us to better understand the role of cancer in obesity 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. In fact, the visceral fat cell is the most inflammatory adipocyte type, linked 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 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. The 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 steric, cellular proliferation and apoptosis, angiogenesis, histopathology was found in a large population of obese subjects (Tordjam-an 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 relaying immune cell infiltration in hypertrophied adipose tissue are the focus of intense research. We contributed to show the importance of these mechanisms, including CCL5/RANTES, which promote monocyte diapedesis and macrophage survival (Keophiphath et al. Arterioscler Thromb Vasc Biol, 2010; 30: 39–45). Further evaluation of transcriptional interplay characterizing human adipose tissue led to 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. Diabeto, 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 (Keophiphath et al., Mol Endocrinol, 2009; 23:11–24) suggesting their contribu-
tion 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.

The fight against visceral fat excess is based on nutritional recommendations and physical activity. In the future, some new antiangiogenic agents specifically inhibiting angiogenesis and 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 prostatic cancer whose severity seems to be strongly related to visceral obesity.
Discussion: Present results highlight the role of NR1 and nNOS activation in ventilatory response to hyperoxia. Genetic and pharmacological approaches to acute hyperoxia after acclimatization in Epo-Tg mice seems to be independent of the NR1 pathway and could imply other neuromodulators.

25-P098 Combination of cigarette smoke extracts (CSE) and lipopolysaccharide (LPS) induce cell proliferation in hypothalamus: role of Jak/Stat and JAK2/STAT 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 diseases. We investigated the effect of combination of CSE and LPS in hypothalamus cell proliferation. In hypothalamic cells isolated from adult rats, LPS (100 ng/mL) induced cell proliferation which was significantly higher (P<0.01) compared to control. This effect was not modified by the addition of CSE (2% and 4% in organic solvent). However, the combination of CSE (2% and 4%) and LPS (100 ng/mL) induced a significant increase (P<0.01) in cell proliferation compared to control. The proliferative effect of the combination of CSE and LPS was inhibited by the addition of dexamethasone (1 μM). In conclusion, our results suggest that CSE and LPS induce cell proliferation in hypothalamus, a finding that may play a role in the development of obesity.

59-P121 The hypothalamus expresses the alamone hypothalmin (HPL) that regulates energy homeostasis

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Hypothalmine is a neuropeptide that is expressed in hypothalamus and that may play a role in the regulation of energy homeostasis. Recent studies have shown that hypothalmin regulates energy homeostasis in rodents. In this study, we investigated the expression of hypothalmin in hypothalamus of mice fed with a high fat diet (HFD) or a standard chow for 10 days. Mice were killed by decapitation and hypothalmin was measured in hypothalamus using ELISA. Results showed that hypothalmin expression in hypothalamus of mice fed with HFD was significantly higher (P<0.01) compared to control. This effect was not modified by the addition of dexamethasone (1 μM). In conclusion, our results suggest that hypothalmin may play a role in the regulation of energy homeostasis. This finding may have implications for the development of obesity, a disease that is associated with the expression of hypothalmin.

26-O052 Weight gain following deep brain stimulation: a pet study

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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 profound 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) PET/CT in 23 PD patients and pallidal (GPi) DBS for 3 months after subthalamic (STN) DBS in 23 PD patients and pallidal (GPi) DBS in 19 PD patients.

Results: Baseline BMI (19.2 ± 2.8) 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. Proinflammatory cytokines (IL-8/CXCL-8, CXCL-1/GRO) were significantly increased in STN group whereas inflammatory proteins (CCL2/MCP-1, CCL2/1GRO-α) were increased in GPi group. These findings confirm a previous clinical study on weight gain in PD patients. A group comparison suggesting that WG following DBS in PD is linked to motor dysfunction following GPi DBS and to change in limbic processes following STN DBS in PD patients was also observed in this study. This study also confirms that the STN is a key structure of the basal ganglia limbic circuitry.