

## The central nervous system at the core of the regulation of energy homeostasis

Serge Luquet<sup>1</sup>, Christophe Magnan<sup>2</sup>

<sup>1,2</sup> University Paris Diderot-Paris 7-Unit of Functional and Adaptive Biology (BFA) affiliated with CNRS

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### 1. ABSTRACT

Energy homeostasis is kept through a complex interplay of nutritional, neuronal and hormonal inputs that are integrated at the level of the central nervous system (CNS). A disruption of this regulation gives rise to life-threatening conditions that include obesity and type-2 diabetes, pathologies that are strongly linked epidemiologically and experimentally. The hypothalamus is a key integrator of nutrient-induced signals of hunger and satiety, crucial for processing information regarding energy stores and food availability. Much effort has been focused on the identification of hypothalamic pathways that control food intake but, until now, little attention has been given to a potential role for the hypothalamus in direct control of glucose homeostasis. Recent studies have cast a new light on the role of the CNS in regulating peripheral glucose via a hypothalamic lipid-sensing device that detects nutrient availability and relays, through the autonomic nervous system, a negative feedback signal on food intake, insulin sensitivity and insulin secretion. This review aims to summarize recent discoveries that highlight the brain as a potential target for anti-diabetic strategies.

### 2. INTRODUCTION

The twentieth century has witnessed a pandemic expansion of obesity-related disorders including atherosclerosis, hypertension, coronary diseases and diabetes mellitus in both developing and developed countries (1). This constellation of pathophysiologies as a whole defines the metabolic syndrome or syndrome X. Although genetic factors account for some cases of obesity, it is evident that a drastic change in lifestyle is definitively to be responsible. Indeed, the abundance of inexpensive, energy-rich diets combined with the reduced energy costs required to procure food has led to the widespread thermodynamic imbalance of excessive caloric intake and reduced energy expenditure.

This change in feeding habits is one of the main causes for the prevalence of obesity and is also driving the corollary epidemic in type-2 diabetes (T2D) since both pathophysiologies are strongly associated (2, 3). T2D is the most common form of diabetes accounting for ~ 90% of diabetics worldwide and is mainly characterized by the progressive loss of peripheral insulin sensitivity in target tissue such as muscle and liver (4, 5). The decrease in insulin-induced glucose transport in muscle and the failure

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of insulin to inhibit liver glucose production result in elevated blood glucose in diabetic patients. During the dynamic phase of diabetes, peripheral insulin resistance is compensated by the ability of pancreatic beta cell to enhance nutrient-induced insulin secretion. Fasting hyperglycemia, the key endocrine parameter that defines the diabetic stage *per se* occurs when  $\beta$  cells can no longer sustain high insulin demands. During the later stage of the pathology, the severity of hyperglycemia is mostly determined by an inappropriate increase in hepatic glucose production.

The urge to find a cure for T2D has promoted a frantic race for the discovery of a molecular link between obesity and T2D. This has left the scientific community with a broad variety of sophisticated genetic tools, including many spontaneous or genetically engineered rodent models of obesity consisting of single gene mutations. Mutations in the signaling pathway engaged by the adipocytokine leptin are striking examples of obese and diabetic models (respectively *ob/ob* or *db/db*) that, through extensive studies, have provided a solid foundation for the role of the CNS in the regulation of energy balance. Unfortunately, the monogenic basis of such models only partially encompasses the polygenic essence of the metabolic syndrome and leaves open the question of which organ (e.g., liver, adipose tissue, pancreas and muscles) is the “primary target” of insulin resistance and where the “primary defect” takes place.

With increasing body weight, triglyceride accumulation occurs not only in adipose stores, but in other organs as well. The deleterious effect of extra adipose lipid deposition in target organs may account for many of the features of the metabolic syndrome and defines the idea of “lipotoxicity”. A popular concept is that ectopic lipid storage in liver and muscle, secondary to adipose tissue anabolic ability, inhibits insulin-induced signaling pathways and result in insulin resistance. Recent studies provide an alternate way to comprehend the link between obesity and diabetes. These studies posit that specific brain centers fail to provide a proper adaptive response. This initial central defect will affect metabolic rate, food intake and glucose homeostasis and will translate into a secondary defect in the energy fluxes and communication between organs (6) promoting the progression of the pathology. The symptoms of the metabolic syndrome can therefore be viewed as the result, rather than the cause of the pathology; leaving the CNS as the source of the “primary defect” the crucial target of a comprehensive anti-diabetic strategy.

### 3. THE CENTRAL ANATOMY OF ENERGY-RELATED NERONAL NETWORK

#### 3.1. The hypothalamus

In the early 1940s experiments using electrical stimulation and lesioning allowed for the identification of functional nuclei in the mediobasal hypothalamus (MH) that had specific actions on energy homeostasis (7, 8). The ventromedial hypothalamus (VMH) was considered a “satiety area” because its destruction resulted in hyperphagia and obesity. In addition, when nuclei in the

VMH were electrically stimulated, food intake and body weight decreased. Conversely, the lateral hypothalamus (LH) was determined to be a “feeding center” because lesioning that region left animals aphagic, while electrical stimulation caused hyperphagia and obesity. In subsequent decades, this simple view of a “satiety center” that keeps a “feeding center” in check was largely abandoned because of the realization that the LH lesions disrupted dopaminergic nerve tracts passing through the hypothalamus that were essential for normal feeding and movement, and that the VMH lesions had a major impact on autonomic output (9). During the last decade, a growing number of sophisticated genetic and pharmacologic tools have profoundly changed our view on the homeostatic and non-homeostatic regulation of energy balance. Central feeding-related signals like, neuropeptide Y (NPY), agouti-related peptide (AgRP), orexins,  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH), and endocannabinoids, together with peripheral signals such as leptin, ghrelin, glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), oxyntomodulin (OXM) and oleylethanolamine (OEA) (Figure 1 and table 1) have been characterized in animal models, and are part of the central neuronal network that control energy balance.

#### 3.2. The Arcuate nucleus and the melanocortin pathway

Several observations led to the identification of the arcuate nucleus (ARC) of the hypothalamus as “a major integration site for inputs related to energy homeostasis,” and importantly, ARC neurons project to the paraventricular nucleus (PVN) and the LH, both of which are implicated in the control of appetite (10). ARC neurons are located at the bottom of the hypothalamus around the third ventricle. They are called “first order neurons” because they are in close vicinity to circulating satiety and hunger factors such as insulin, leptin and ghrelin. The ARC is uniquely suited to this task due to its anatomical proximity to the median eminence (ME) where the brain blood barrier (BBB) is more prone to exchange circulating signals.

The ARC contains at least two populations of neurons that are antagonistically regulated by circulating signals of hunger and satiety and exert opposite effects on energy balance (Figure 2). Activation of neurons making pro-opiomelanocortin (POMC) and cocaine-and amphetamine-related transcript (CART) decrease food intake and increase energy expenditure by releasing  $\alpha$ MSH, which activates melanocortin receptors. The neurons containing the orexigenic neuropeptides, agouti-related protein (AgRP) and neuropeptide Y (NPY) (NPY/AgRP neurons) also make gamma aminobutyric acid (GABA) (11), and exert their anabolic/orexigenic action primarily by opposing the anorexigenic action of the neighboring neurons containing POMC peptide and CART (Figure 2). Melanocortin peptides derived from posttranslational processing of POMC include adrenocorticotrophic hormone (ACTH) and  $\alpha$ ,  $\beta$  and  $\gamma$ -melanocyte-stimulating hormone (MSH). MSH bind to the melanocortin receptors, a family of five G-protein coupled melanocortin receptors that are widely distributed throughout the body (12, 13) with MC3R and MC4R being expressed in numerous places throughout the CNS.

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**Table 1.** Central and peripheral signals involved in energy balance regulation

<b>Molecules that stimulate feeding and reduce energy expenditure</b>	<b>Molecules that inhibits feeding and increase energy expenditure</b>
Neuropeptide Y (NPY)	$\alpha$ -Melanocyte Stimulating Hormone ( $\alpha$ -MSH)
Agouti-Related Protein (AgRP)	Cocaine & Amphetamine Related transcript (CART)
Melanin-Concentrating Hormone (MCH)	Urocortin
Galanin	Corticotropin-releasing factor (CRF)
Norepinephrine	Thyrotropin-releasing hormone (TRH)
Orexin A et B (or hypocretins)	Neurotensin
Opioids	Serotonin
Endocannabinoids	oxytocin
$\beta$ -endorphin	<i>Leptin</i>
<i>Ghrelin</i>	<i>Insulin</i>
	<i>Glucagon-Like Peptide-1 (GLP-1)</i>
	<i>Peptide YY<sub>3-36</sub> (PYY<sub>3-36</sub>)</i>
	<i>Oxytomodulin</i>
	<i>Cholecystokinin (CCK)</i>
	<i>Oleoylethanolamide (OEA)</i>
	<i>N-acylethanolamine (NAPE)</i>

Central signals (bold) and circulating signals (italic) involved in feeding behavior and energy expenditure regulation.

Mutation in the melanocortin signaling pathway including MC3R or MC4R-null mutants (14), Agouti yellow ( $A^y$ ) mice that result from ectopic expression of MCR antagonist agouti (15), and partial or total loss melanocortin peptide synthesis or action, result in hyperphagia, hypometabolism, hyperinsulinemia, and hyperglycemia in both rodents and humans (16, 17). The release of  $\alpha$ -MSH by POMC neurons and its binding to the Gs-coupled MCR initiates the central anorexic signaling pathway that result in decreased food intake and increased energy expenditure. AgRP is a natural inverse agonist of the melanocortin receptor (MC3R/MC4R) and exerts its orexigenic action partly by blocking the binding of  $\alpha$ -MSH to its receptor therefore inhibiting the  $\alpha$ -MSH-induced anorexic pathway. A noteworthy recent study demonstrated a role for AgRP in the regulation of glutamatergic neurons in the VMH through a melanocortin-independent pathway (18). NPY/AgRP neurons synapse directly onto POMC neurons on which they exert a GABAergic inhibitory tone (19, 20). In addition, POMC neurons express a NPY receptor (NPY-Y1), activation of which leads to post-synaptic inhibition of POMC neurons via Y1 receptor activation. POMC and AgRP neurons also express leptin receptors and insulin receptors and send dense projections to 'second order neurons' in the PVN, VMH, dorsomedial hypothalamus (DMH) and LH which, in turn, project to other brain areas essential for the long-term regulation of energy homeostasis such as the nucleus of the solitary tract (NTS) (Figure 2). The critical role of both populations in energy balance was definitively established by showing that NPY/AgRP neuron ablation leads to life-threatening anorexia (21, 24) whereas ablation of POMC neurons gives rise to hyperphagia (22).

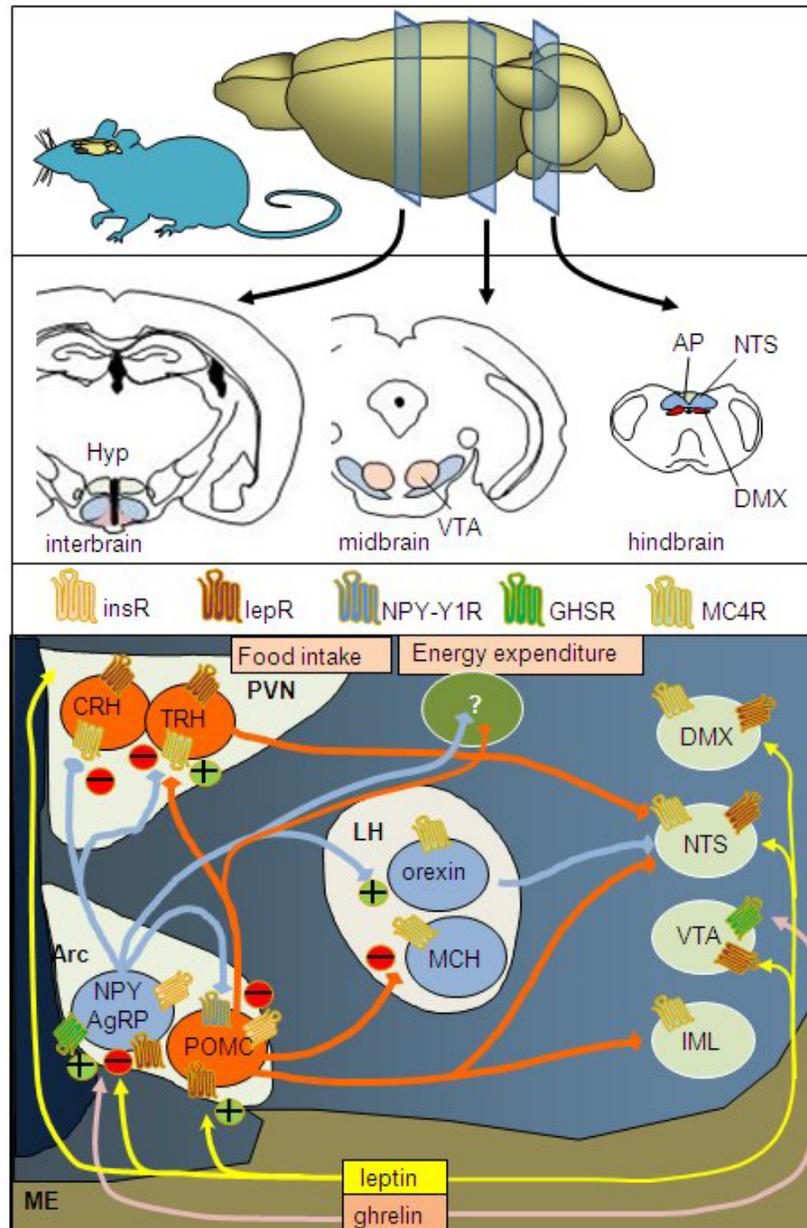
### 3.3. Second order target downstream the ARC

$\alpha$ -MSH and NPY/AgRP-containing fibers arising from hypothalamic neurons project densely to second-order

nuclei within and outside the hypothalamus (25). For instance, oxytocin, corticotropin-releasing hormone (CRH), and thyrotropin-releasing hormone-synthesizing neurons (TRH) are located in the PVN and express MC4R (26). The binding of  $\alpha$ -MSH to MC4R activates the hypothalamic-pituitary-thyroid (HPT) axis and hypothalamic-corticotropic axis (HPA). During fasting, increased release of AgRP by NPY/AgRP neurons is a key mechanism for fasting-induced down regulation of the HPT axis and the consequent adaptations during negative energy balance (27, 28). Arcuate neurons also project to PVN-autonomic preganglionic neurons, and a subset of POMC neurons project to the intermediolateral nucleus of the spinal cord (IML) where sympathetic preganglionic cholinergic neurons express MC4R. Additionally, cholinergic cells located in the dorsal motor nucleus of the vagus nerve (DMX) express MC4R. These observations support a role for MCR in autonomic regulation and predict that both direct ARC-IML and ARC-PVN-IML networks might account for the autonomic and metabolic effects of melanocortin signaling molecules.

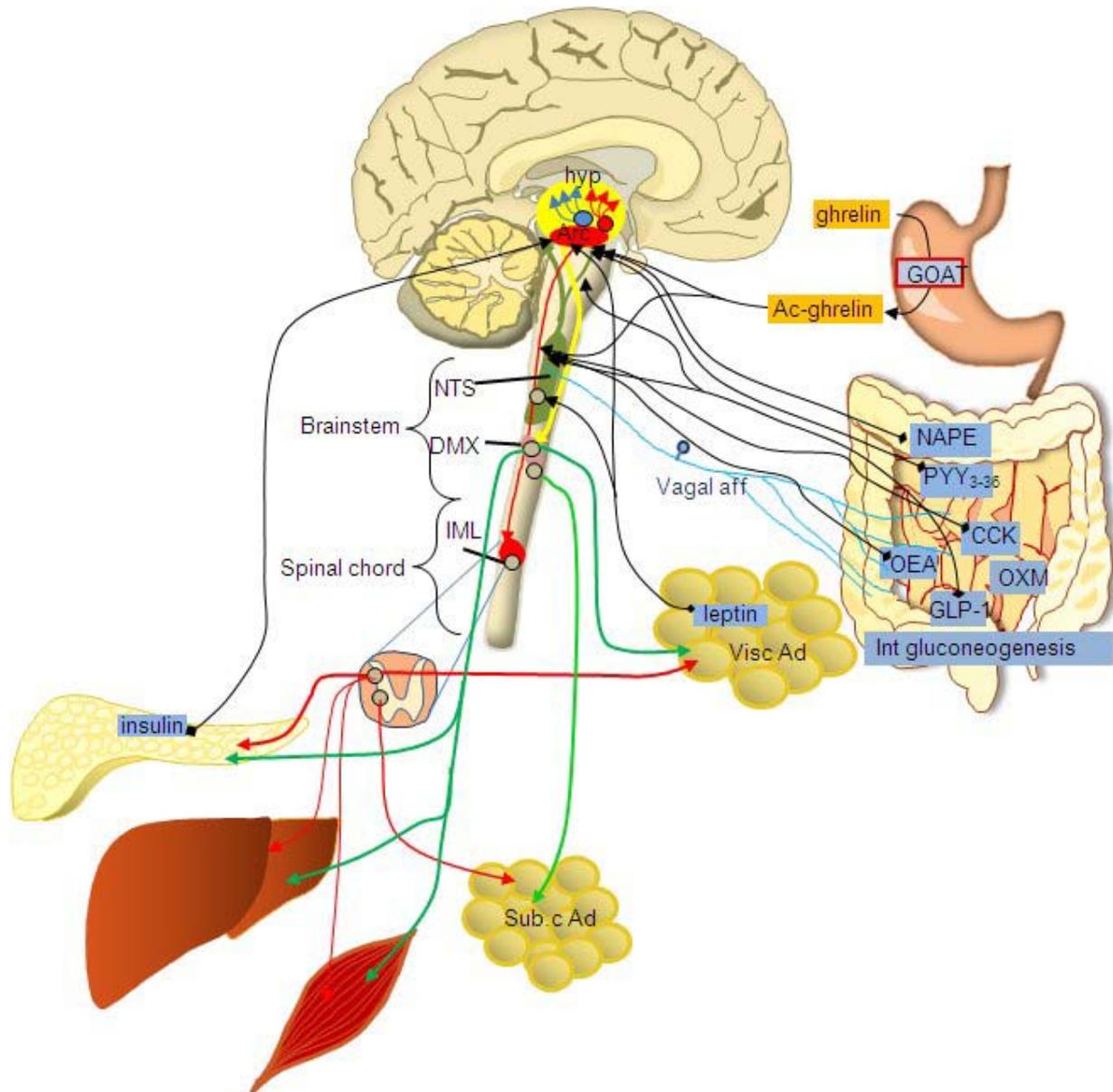
The LH contains two neuronal populations that produce orexins A and B (also called hypocretins) and melanin-concentrating hormone (MCH) (Figure 1). The LH receives both NPY- and  $\alpha$ -MSH-containing projections from the ARC and the LH exerts a GABAergic inhibitory tone onto VMH neurons. Inhibition of the anorexic VMH signal through the increase of LH-initiated GABAergic tone partly account for LH orexigenic's action (29). The LH orexin B-producing neurons project to the dopamine-producing neurons in the ventral tegmental area (VTA), a key structure of reward acquisition and goal-directed behavior (30). Moreover a GABAergic inhibitory tone exerted onto LH neurons is acutely removed via the activation of the nucleus accumbens (31). The complex

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**Figure 1.** Model depicting central neuronal network of energy homeostasis regulation. Interbrain, midbrain and hindbrain coronal (middle panel) section of the mouse brain (upper panel) showing some of the key neuroanatomic structures engaged in energy balance regulation i.e the hypothalamus (Hyp), the Ventral tegmental Area (VTA) and the Nucleus tractus solitarii (NTS) and dorsal motor nucleus of the vagus (DMX). Arcuate nucleus (ARC) neurons that make Neuropeptide Y (NPY) Agouti-related protein (AgRP) are also GABAergic and exert an inhibitory tone onto anorexic Pro-opiomelanocortin neurons (POMC). Both populations bear leptin receptor (lepR) and insulin receptor (insR) and project to second order neurons located in the paraventricular nucleus of the hypothalamus (PVN) including corticotrophin-releasing factor (CRF)- and Tyrotropin releasing hormone (TRH)-producing neurons, ventromedial (VMH)(not shown) and lateral hypothalamus (LH) that contains orexinic orexin- and Melanin concentrating hormone (MCH)-producing neurons. NPY/AgRP neurons increase food intake by increasing GABAergic inhibitory tone neighboring POMC neurons, by antagonizing  $\alpha$ MSH binding onto MC4-R through AgRP release and by NPY-mediated inhibition of POMC neurons via Gi-coupled NPY-Y1 receptor activation. Food intake regulation requires PVN expression of MC4-R, whereas energy expenditure engages a MC4-R bearing structure that resides elsewhere. Leptin and ghrelin have extra-hypothalamic targets in the NTS, DMX and onto mesolimbic dopaminergic neurons located in the VTA. In addition, POMC neurons exert control onto the sympathetic nervous system by projecting directly to preganglionic neurons of the intermediolateral cell column (IML).

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**Figure 2.** Central integration of peripheral nervous and hormonal inputs results in energy balance regulation. Gut-derived input involving short-term acting satiety signal like cholecystokinin (CCK), PYY<sub>3-36</sub>, or glucagon-like peptide 1 (GLP-1) come in addition to vagal afferent and target the brainstem nucleus tractus solitarius (NTS) and may have also hypothalamic target. Nutrient-regulated satiety signals initiated by fat ingestion like the lipid-derived satiety factor oleoylethanolamide (OEA) that acts by means of the vagus nerve or the N-acylphosphoethanolamine (NAPE) which acts directly onto hypothalamic NPY/AgRP neurons, or by protein diet such as intestinal gluconeogenesis also undergo vagal pathway to regulate feeding. Acyl-ghrelin (ac-ghrelin), the active form of the stomach-derived ghrelin is acylated through the action of Ghrelin-O acyl transferase (GOAT). The orexigenic action of Ac-ghrelin is mediated by arcuate (ARC) NPY/AgRP neurons. Long-term acting satiety such as the pancreatic-derived insulin and the adipocytokine leptin have target in the ARC where they initiate the melanocortin anorexigenic pathway through concerted activation of POMC neurons (red) and inhibition of NPY/AgRP neurons (blue). Hypothalamic integration of these inputs influences NTS and dorsal motor nucleus of the vagus (DMX) integration of peripheral signals. Autonomic nervous system (ANS) regulation of energy expenditure is mediated via direct action on skeletal muscle, liver, adipose tissue and pancreas biology via sympathetic and parasympathetic outflow. Sympathetic preganglionic neurons in the intermediolateral cell column (IML) are direct target of POMC neurons and both dorsal motor nucleus of the vagus (DMX) and IML are influenced by hypothalamic integrative processes that results from NTS-hypothalamus dialogue. Intraabdominal organs (visceral adipose tissue, liver, and pancreas) and subcutaneous adipose tissue have different pre-autonomic organization with different vagal motor neurons and sympathetic preganglionic neurons.

interplay of MCR-bearing neuronal subpopulations of the ARC, PVN, VMH, and LH defines the so-called melanocortin-signaling pathway and is a key neuro-circuit for the regulation of energy balance (32, 33) (Figure 2). Recent studies using sophisticated genetic tools provided an even more detailed dissection of the melanocortin signaling pathway. Using Cre-recombinase dependant reactivation of the allele, Balthasar and al. showed that restoration of melanocortin signaling specifically to the PVN and a subpopulation of amygdala neurons, is sufficient to normalize feeding behavior in otherwise hyperphagic animals, but had no effect on energy expenditure. This result adds further complexity to the central neuronal network governing energy balance by assigning the control of food intake and energy expenditure to separate neuro-anatomic structures (34, 35) (Figure 2), but suggests that pharmacologic strategies may be independently tailored to different aspects of obesity treatment such as overfeeding or hypometabolism.

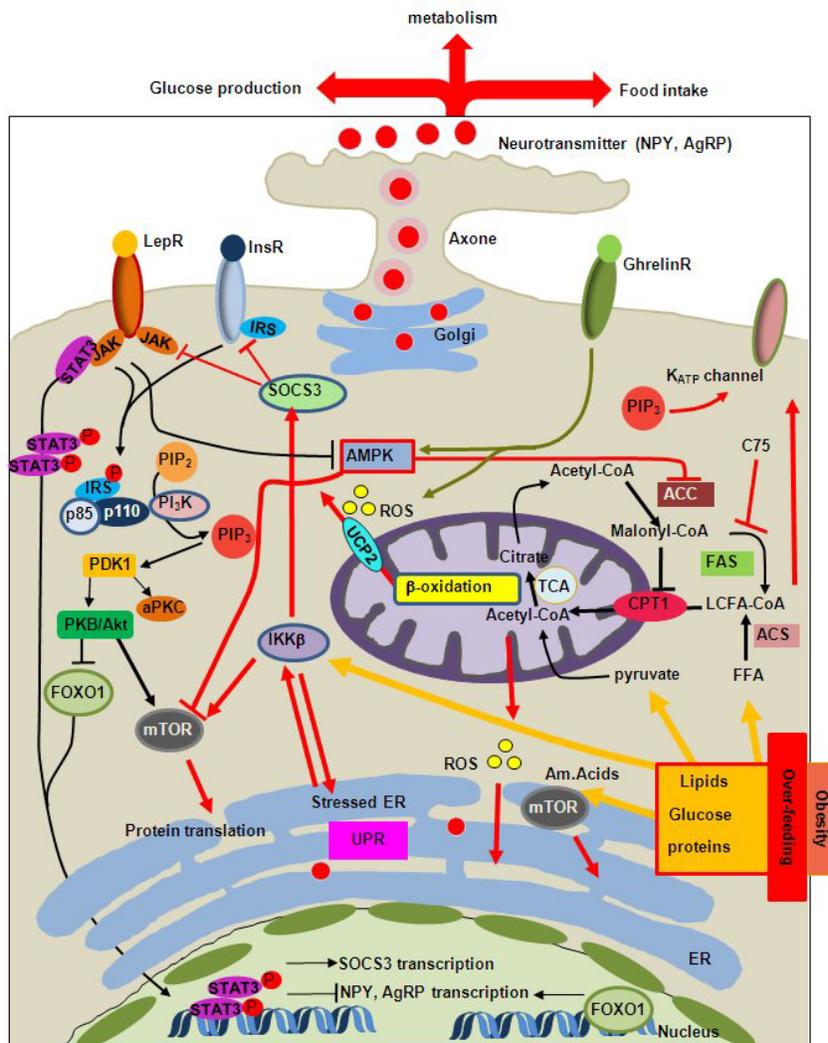
The brainstem is another key brain region involved in regulation of energy balance. It is classically viewed as a viscerosensitive relay because cranial nerves, especially the vagus nerve, carry information from the digestive tract to the brainstem. Vagal afferents synapse onto and stimulate neurons in the brainstem nucleus tractus solitarius (NTS). Food taste and texture, gathered by sensory neurons innervating the oral cavity, together with a gastric distension signal and gut-initiated satiety molecules such as cholecystokinin (CCK) are routed to the NTS primarily by the afferent portion of the vagus nerve. Vagal inputs are integrated within individual vagal sensory neurons before being transmitted to the NTS (36-39). Viscerosensitive, gustatory and meal-initiated signal integration participates in the short-term regulation of feeding. NTS neurons express the CCK-A receptor (40) and a sub-population expresses GLP1 and the GLP1 receptor (41). The NTS is in constant communication with the ARC metabolic sensor, and is itself sensitive to circulating energy-related signals such as leptin, ghrelin and insulin (19). Restoration of leptin signaling in the ARC rescues CCK-induced satiety in leptin-receptor-deficient rats (42) and leptin injection directly in the NTS is sufficient to reduce food intake (43) suggesting that homeostatic signals may directly modulate the short-term regulation of feeding through a direct effect onto NTS neurons.

#### 4. THE LEPTIN SIGNALING PATHWAY

The discovery that the mouse *obese* gene encodes a hormone, leptin, which is produced primarily by adipose tissue initiated a new era in the understanding of the central networks that govern energy balance regulation (44). Circulating leptin levels rise and fall in direct proportion to adipose tissue mass and are relatively insensitive to daily changes in food intake. Food deprivation causes leptin levels to drop as energy stores are utilized, and this decline promotes endocrine and behavioral alterations that result in increased appetite and decreased energy expenditure. These actions of leptin are mediated by the CNS; however, leptin

also acts directly on peripheral tissues (45, 46). Mice lacking leptin (*ob/ob*) become morbidly obese as a consequence of metabolic disturbances and hyperphagia; they are also cold intolerant, diabetic and infertile (9, 47). The *diabetic* mouse (*db/db*) has a phenotype similar to that of the *obese* mouse and it was shown that the mutated gene encodes a leptin receptor which is a single-pass transmembrane protein of the gp130 cytokine receptor family (48). Several forms of this receptor are synthesized from a single gene by alternative splicing (49). Only the long form of the leptin receptor, which is expressed abundantly in the ARC and VMH regions of the hypothalamus, is able to regulate gene transcription through the activation of the Janus Kinase-Signal transducer and activator of transcription (JAK-STAT) pathway (50) (Figure 3). Leptin receptor activation engages the phosphorylation of STAT3 by JAK2 at tyrosine residues, and phospho-STAT3 dimers enter the nucleus to regulate gene transcription (51) (Figure 3). The suppressor of cytokine signaling-3 (SOCS3) is a target of the leptin-mediated STAT cascade and SOCS3 is a potent inhibitor of both leptin- and insulin receptor signaling (52) (Figure 3). In the hypothalamus, leptin receptors are present in several hypothalamic nuclei including both POMC/CART and NPY/AgRP neurons in the ARC and in the VMH (53) (Figure 2). Extra hypothalamic targets include the NTS (43, 54) and the VTA dopamine neurons. VTA dopamine neurons project to the nucleus accumbens and a lack of sensitization to repeated amphetamine injection observed in *ob/ob* mice can be restored by leptin replacement (55). These results suggest that adipose derived hormone can also influence the brain circuitry that control reward and goal-directed behavior. It was recently shown that leptin injection in human patients with genetic leptin deficiency resulted in the neural activation of striatal structure and was able to specifically modify food reward perception (56). In the NTS, leptin appears to potentiate the action of short-term satiety signals such as CCK (43, 54). Sophisticated genetic tools are being used to dissect leptin-sensitive neurocircuitry that differentially regulates food intake, body weight and glucose homeostasis. Transgene-directed expression of the leptin receptor in the hypothalamus is sufficient to correct obesity, diabetes and infertility in the *db/db* model (57) whereas genetic ablation of the leptin receptor specifically onto POMC neurons results in mild obesity, suggesting that leptin signaling pathways outside of the ARC are critically involved in leptin's actions (58). Virus-mediated restoration of leptin signaling restricted to the ARC leads to a modest decrease in food intake and body weight in the *db/db*, but has a remarkable impact on hyperinsulinemia and blood glucose which were equivalent to control, non-diabetic, animals within a few months after the manipulation (59). This striking result provides some insight in to the mechanism linking obesity and diabetes by showing that leptin-sensitive networks controlling glucose homeostasis or food intake could be separately manipulated. One likely candidate for mediating glucose homeostasis is the melanocortin pathway because MC4Rs are expressed in several autonomic control structures including the PVN, DMX, NTS, and IML preganglionic neurons of the spinal cord.

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**Figure 3.** Hormonal and Nutritional signals integrated at the level of hypothalamic neurons. Binding of leptin and insulin on their respective receptors both activates the IRS- PI<sub>3</sub>K signaling cascade. Insulin receptor activation and JAK2 activation are both able to induce phosphorylation of IRS and the consequent activation of PI<sub>3</sub>K. Converting PIP<sub>2</sub> into PIP<sub>3</sub> following PI<sub>3</sub>K activation leads to PDK1 activation and the downstream target including PKB/Akt and atypical PKC. Leptin receptor-induced activation of JAK2 leads to STAT3 phosphorylation and dimerisation. STAT3 dimers and FOXO1, which is negatively regulated through PKB/Akt phosphorylation, enter the nucleus exert opposite action onto *AgRP* mRNA expression. SOCS3 is also a target of STAT3 transcriptional regulation. Ghrelin receptor activation increases NPY/AgRP neurons electric activity via the enhancement of mitochondrial proliferation/beta-oxidation mediated by increased AMPK activity and the consequent increased in long-chain fatty-acyl CoA (LCFA-CoA) intracellular level following ACC inactivation. Increased ROS levels are scavenged by UCP2. Raised LCFA-CoA activates K<sub>ATP</sub> channels leading to neuronal depolarization. Nutrients exposure activates hypothalamic sensing pathway through multiple mechanism involving direct entry into the tricarboxylic acid cycle (TCA cycle), amino-acids mediated activation of mTOR and increased β-oxidation. Free fatty acids (FFA) are activated into acyl-CoA through acyl-CoA synthase (ACS), LCFA-CoA can also be endogenously produced by the Fatty Acid Synthase (FAS) the latter being a target for C75 inhibitor. Overfeeding induces IKKβ /NF-κB pathway that results in hypothalamic leptin and insulin resistance partly mediated by SOCS3-directed inhibition of leptin and insulin receptor activity. Obesity and IKKβ can also engage the ER stress and the Unfolded Protein Response (UPR) and impairs leptin and insulin resistance. Constitutive activation of mTOR leads to ER stress and IKKβ mediated activation of mTOR is a potential mechanism by which nutrient excess can induce ER stress. Note that mTOR is directly controlled by AMPK activity which is under the positive regulation of ghrelin receptor activation negatively regulated by leptin and insulin receptor signaling. Modulation of hypothalamic neurons activity following hormonal and nutritional signals integration will translate into food intake modulation and endocrine and autonomic regulation of glucose production and metabolism.

## 5. SEROTONIN AND THE CONTROL OF PERIPHERAL GLUCOSE HOMEOSTASIS

Serotonin (5-hydroxytryptamine, 5-HT) analogues have anorexic properties and are widely used as anti-obesity treatments. Serotonin receptors are widely expressed in the CNS and peripheral nervous system, but 5-HT<sub>2C</sub> and 5-HT<sub>2B</sub> are thought to mediate most of the weight-loss actions of 5-HT agonists. Activation of the melanocortin signaling pathway is critically involved in serotonin's anorexic action (60, 61) and disruption of the 5-HT<sub>2C</sub> receptor leads to obesity and diabetes (62). Surprisingly, the possibility of a direct role for serotonin in the pathophysiology of T2D was largely neglected until a recent study from the Elmquist group which provided evidence that the effects of 5-HT<sub>2C</sub> receptor activation on peripheral glucose homeostasis could be separated from its effect on food intake. They showed that 5-HT<sub>2C</sub> agonist administration at doses that do not affect food intake improved glucose homeostasis by enhancing peripheral insulin sensitivity and increasing fasting plasma insulin without altering blood glucose or body weight. This action requires MC4R, but not MC3R, and was partly mediated by neural activation MC4R-positive sympathetic preganglionic cholinergic located in the IML (63) (Figure 2). These observations further substantiate the concept of separated central network that control feeding behavior and peripheral glucose homeostasis.

## 6. THE INSULIN SIGNALING PATHWAY IN THE CNS

Nutrient-induced release of insulin by beta cells of the pancreas is well known as a key mechanism of peripheral glucose handling by liver, muscle and adipose tissue. Recent observations provided evidence that, although brain glucose metabolism is not dependant on insulin level, insulin has a prominent action in the CNS where it modulates feeding behavior and peripheral metabolism. Insulin receptors are concentrated onto several hypothalamic nuclei important to the regulation of food intake and autonomic function (64). Insulin binding to its receptor initiates the recruitment of numerous second messengers including the insulin receptor substrate (IRS) which is tyrosine phosphorylated following insulin receptor activation (Figure 3). Phosphorylated IRS will in turn activate the phosphatidylinositol-3-OH kinase (PI<sub>3</sub>K) leading to the transformation of phosphatidylinositol-4,5-bisphosphate (PIP<sub>2</sub>) into phosphatidylinositol-3,4,5-triphosphate (PIP<sub>3</sub>). PIP<sub>3</sub> activation of the Phosphoinositide-dependent Kinase-1 (PDK-1) leads to activation of protein kinase B (PKB)/Akt together with the atypical PKC family members (65). The mammalian target of rapamycin (mTOR) and the forkhead box O1 transcription factor (FOXO1), which is specifically inhibited through PKB-mediated phosphorylation, are among the targets of activated PKB. A biochemical convergence exists between leptin and insulin signaling pathways since both insulin receptor and JAK2 are able to trigger IRS phosphorylation (66).

Intracerebroventricular (ICV) infusion of insulin was demonstrated to decrease food intake (67) and brain-

specific knock-out of the *insulin receptor* results in increased food intake and susceptibility to diet-induced obesity (68). This effect requires intact insulin receptor expression in hypothalamic nuclei (69). ICV infusion of insulin affects peripheral glucose production and central antagonism of insulin signaling blocks the ability of circulating insulin to inhibit hepatic glucose production measured in hyperinsulinemic-euglycemic clamp studies (69). K<sub>ATP</sub> channels play a pivotal role in insulin's action in the CNS because blockade of these ATP-sensitive ion channels abolishes the central effects of insulin and blunts insulin's systemic action on liver glucose output. These effects can also be mimicked by surgical removal of the hepatic branch of the vagal nerve (70). It has also been recently shown that deletion of the insulin-receptor specifically from NPY/AgRP neurons results in a perturbation of the overall insulin sensitivity measured in euglycemic-hyperinsulinemic clamp studies without altering feeding behavior (71). These results support the concept that alteration of insulin signaling within the CNS contributes to diabetic hyperglycaemia.

## 7. CENTRAL INTEGRATION OF NUTRITIONAL SIGNALS

### 7.1. Lipid sensing

The possibility that plasma fatty acids (FA) might act on the brain was neglected for a long time because they were not thought to cross the BBB. However, a growing amount of data attest that cerebral lipids come from both local synthesis and plasma origin (72). Furthermore, the structure and function of the BBB within hypothalamus - especially the ME and associated circumventricular organs (CVO)- is quite different from other parts of the brain (reviewed in (73)). In particular, CVO are characterized by their small size, high permeability and fenestrated capillaries (73). Thus, substances that do not cross BBB in other part of the brain may reach the hypothalamus. Indeed, it has been demonstrated using brain uptake index (BUI) method that palmitate uptake in hypothalamus is about 10 to 15% compared to <2% in other brain areas (74). There is now growing evidence that "hypothalamic FA sensing" is involved in the control of feeding behavior, hepatic glucose production and insulin secretion.

The physiological relevance of this FA sensing is demonstrated by various studies. For example, a local increase in FA in brain triggers changes in insulin secretion and action (particularly hepatic glucose output), with or without food intake modifications (75-77). This change appears to be due, at least in part, to modifications of the sympathetic/parasympathetic tone (78). The group of L. Rossetti group has demonstrated that 6 hours of oleic acid ICV infusion triggers a diminished hepatic glucose production (HGP) and decreased food intake (77). Octanoic acid had no effect within this protocol, suggesting that FA actions are related to their chain length or degree of saturation (77). These effects on food intake and HGP were also obtained by inhibiting hypothalamic FA oxidation without any FA infusion (79). Indeed the authors reported an increased intracellular pool of acyl-CoA following Carnitine Palmitoyl Transferase -1 inhibition (CPT1, the

enzyme allowing medium- and long-chain FA to enter the mitochondria where they undergo  $\beta$  oxidation) (79) and demonstrate that this increased acyl-CoA intracellular pool would be the “final” satiety signal rather than the FA by themselves (reviewed in (80)).

Deregulation of FA sensing could partly lead to metabolic diseases in predisposed subjects exposed to a chronic lipid overload. Such impairment of central effects of FA could be involved in the etiology of obesity and T2D (81, 82). Indeed, data show that excessive lipid load towards brain may alter nervous control of glucose and lipids homeostasis through changes of autonomic nervous system activity. First, a lipid overload due to high-fat diet has been demonstrated to modify of CNS activity in rats (83, 84). In humans, obesity is often associated with an altered sympathetic tone (85, 86) suggesting a relationship between lipids and ANS control centers in the brain. In addition, numerous studies from Pima Indians, a population displaying high prevalence for obesity and diabetes, showed that a decreased sympathetic tone is a predictive feature of further metabolic dysfunction (87).

The cellular and molecular effects of FA are being intensely investigated. As already evidenced, FA metabolism appears necessary to relay FA action. It is now established that the main enzymes involved in FA metabolism, such as fatty acid synthase (FAS), CPT1 or acetyl-CoA carboxylase (ACC) are expressed in both the hypothalamic neurons and glial cells. Evidence suggests that malonyl-CoA could be a key actor of hypothalamic FA sensing (88, 89). Indeed, when the supply of glucose and FA is increased, malonyl-CoA levels increase in keeping with a decreased need for fatty acid oxidation, and fatty acids are preferentially esterified to produce diacylglycerol and triglycerides. This increase in malonyl-CoA and acyl-CoA levels produces a strong signal of satiety (90). Central administration of C75, a potent inhibitor of FAS, also increases malonyl-CoA concentration in the hypothalamus, suppresses food intake and leads to profound weight loss (91)(Figure 3). It has been proposed that FAS inhibition alters the expression profiles of feeding-related neuropeptides (such as NPY), generally by inhibiting the expression of orexigenic peptides (91). C75 also increases energy consumption and therefore contributes to weight loss. It is still unclear if this action is mediated by a peripheral or a central mechanism. *In vitro* and *in vivo* studies demonstrate that at least part of C75's effects are mediated by the modulation of the energy-sensing kinase AMP kinase (AMPK)(Figure 3)(92). Indeed, ICV administration of AICAR (5-aminoimidazole-4-carboxamide ribonucleoside), a 5'-AMP kinase activator, rapidly lowers hypothalamic malonyl-CoA concentration and increases food intake (90). These effects correlate closely with the phosphorylation and thus inactivation of ACC, an established target of AMPK. Collectively, these data suggest a role for fatty acid metabolism in the perception and regulation of energy balance (93). Thus, dysfunction of these FA-sensitive neurons could be, at least in part, one of the early mechanisms leading to the impairment of the nervous control of energy homeostasis, obesity and T2D in predisposed subjects (82).

## 7.2. Glucose sensing

Similar to FA sensing, the presence of neurons sensitive to variations in extracellular glucose levels has been clearly demonstrated in the brain and particularly the hypothalamus (94, 95). Since the first works of Oomura and colleagues in 1975, two populations of glucosensing neurons have been observed that are either excited (GE) or inhibited (GI) as local glucose levels rise (94). Such neurons have mainly been characterized in the VMH and the arcuate nucleus. The mechanisms underlying such glucose-dependent activity in neurons of the brain are still poorly understood. It has been proposed that GE neurons use the same glucose ‘sensor’ as  $\beta$ -cells of the islet of Langerhans. In these cells, the sensor mainly involves Glut2, glucokinase and specific  $K_{ATP}$  channels (94). Transport of glucose through Glut2 and glucokinase leads to activation of hexokinase, a low affinity glucose sensor that is sensitive to glucose levels as low as 5 mM. Glut2 and glucokinase are present in some cells in the brain. In addition to these proteins, GLP1 receptor has been shown to be expressed in the human brain (96). Using calcium imaging to identify GE and GI neurons, Kang *et al.* confirmed the presence of glucokinase and  $K_{ATP}$  channels in some glucosensitive neurons in the VMH (97). Finally, the functional role of glucokinase has been evidenced by Kang *et al.*, who showed that the loss of glucokinase expression is associated with a striking decrease in the number of GE and GI neurons (98). However, whether astrocytes or neurons are the main glucose sensor is still matter of debate. An elegant study clearly demonstrated the existence of central glucose sensors requiring Glut2 expression in glial cells (99). In this study, the authors showed that genetic inactivation of Glut2 impaired glucagon secretion in response to hypoglycemia. When Glut2 was re-expressed by transgenesis, in glial cells, but not in neurons, physiological responses were restored (99). This work demonstrates that Glut2 in glial cells is involved in sensing hypoglycemia. The involvement of astrocytes as primary cells in glucose sensing implies crosstalk between these cells and neurons. Lactate may be one of the linking molecules. In agreement with the astrocyte–neuron lactate shuttle hypothesis, a recent study demonstrated that the effect of glucose on neuronal activity requires its conversion to lactate followed by stimulation of pyruvate metabolism (100). Indeed, ICV (or intra-DMH) infusion of either lactate or glucose is sufficient to lower blood glucose by inducing a rapid change in liver metabolism (100).

## 8. SIGNALS OF THE GUT-BRAIN AXIS

### 8.1 Peptidic signals

#### 8.1.2. Cholecystokinin (CCK)

CCK is a prototypal intestinal satiety molecule. It is produced by duodenal and jejuna mucosa in addition to neurons of the enteric and central nervous systems. CCK is secreted in response to luminal nutrients, particularly lipids and proteins. CCK interacts with two receptors expressed in the gut and brain, CCK-R1 in digestive tract and CCK-R2 in the CNS. Peripheral injection of CCK decreases meal size in a dose-dependent manner. CCK is a typical short-term acting gut-derived molecule and its effect is mediated by vagal inputs since both sub-diaphragmatic vagotomy

and vagal deafferentation abolishes CCK satiety action (Figure 2) (101).

### 8.1.3. Peptide Y<sub>3-36</sub> (PYY<sub>3-36</sub>)

PYY<sub>3-36</sub> is a peptide secreted during the post-prandial phase of digestion by entero-endocrine cells. Plasma level of PYY<sub>3-36</sub> is correlated to calories ingested and is maintained at a high level for several hours after meal termination. Perfusion of PYY<sub>3-36</sub> in lean and obese human subject leads to a prolonged satiation and induces body weight loss when administered chronically to rodents (102, 103). The anorectic action of PYY<sub>3-36</sub> involves a direct inhibition of orexigenic NPY/AgRP through activation of presynaptic NPY-Y2 receptor (102) and by the consequent decrease of the GABAergic inhibitory tone exerted by NPY/AgRP neurons onto POMC neurons. Feeding behavior is a composite output of both homeostatic, energy related regulation, and non-homeostatic, emotionally-driven food consumption. Using functional magnetic resonance imaging Batterham *et al.* recently showed that under conditions of high plasma PYY<sub>3-36</sub> levels, resembling the fed state, there is a high correlation between neural activity in the orbital frontal cortex and feeding behavior; whereas when PYY<sub>3-36</sub> are low, food intake correlates with hypothalamic neuronal activity (103). These results give new insights in to the role of PYY<sub>3-36</sub> and, in general, to circulating satiety signals as the central switch of feeding regulation from a homeostatic to a hedonic neural circuitry.

### 8.1.4. Ghrelin

Ghrelin is a 28 amino-acid peptide hormone primarily secreted by the stomach and the upper part of the gut. Some of its metabolic and endocrine actions require ghrelin to be acylated by a 8-carbon octanoate on residue serine 3. The endogenous target of ghrelin includes the growth-hormone secretagogue receptor 1 (GHS-R) (104). In both human and rodent, ghrelin administration leads to increased body weight and food intake together with increased gastric motility and acid secretion (105). Ghrelin release is initiated shortly before a meal and falls after meal termination (105). Ghrelin is the only known circulating hormone with orexigenic properties. NPY/AgRP neurons relay the effect of ghrelin on food intake because NPY/AgRP double knockout mice or ablation of NPY/AgRP neurons, abolishes ghrelin-induced feeding (107, 108). It was recently shown that ghrelin-mediated activation of NPY/AgRP involves intracellular increases in mitochondrial fatty-acid oxidation involving the AMP-Kinase, carnitine-palmitoyl transferase 1 (CPT1) and uncoupling protein 2 (UCP2) scavenging of radical oxygen species (ROS) (109) (Figure 3). Ghrelin has also numerous extra-hypothalamic effects, including the dopamine neurons in the VTA, where direct infusion induced robust feeding (110) and promotes synaptic re-organization together with striatal dopamine release (111). A recent advance in the ghrelin story was provided by the group of J. L. Goldstein who identified and biochemically characterized the enzyme responsible for ghrelin octanoylation required for its activation: the Ghrelin-O-Acyltransferase (GOAT) (112). GOAT is expressed in ghrelin-secreting tissues and provides a potential target for the development of anti-

obesity strategies based on the inhibition of ghrelin activation (112) (Figure 1 and Figure 2).

## 8.2. Nutrient-induced signals in the gut brain axis

### 8.2.1. lipid-derived signals

#### 8.2.1.1. Oleoylethanolamide (OEA)

The anorectic lipid mediator OEA is structurally related but pharmacologically distinct from the endocannabinoid family, it shares enzymes involved in cannabinoid biosynthesis including the N-Acylphosphatidylethanolamine phospholipase D (NAPE-PLD) and is likewise made "on demand" from phospholipids of the lipid membrane (113). Importantly, unlike anandamide and congeners that binds to the cannabinoid receptors 1 and 2 (CB1, CB2) to mediate potent orexigenic effect, OEA does not bind to CB1 nor CB2 but instead mediates its anorectic action through genomic and non-genomic activation by selective activation of the lipid-activated transcription factor proliferator-activated receptors-alpha (PPAR-alpha). OEA is synthesized in the small-intestinal mucosa cells in response to fat ingestion and exerts its satiety action by decreasing meal frequency, presumably by targeting the NTS through vagal input since its action is abolished when peripheral sensory fibers are removed (114, 115). OEA acts differently from CCK in that OEA increases the inter-meal interval whereas CCK preferentially reduces meal size. OEA was recently identified as a molecular link between the quality of dietary lipids ingested and satiety. Intra-duodenal infusion of oleic-acid results in a dose-dependent mobilization of OEA by the small intestine (Figure 2). The transport of oleic acid to the proximal part of the intestine requires the fatty acid translocase CD36, which provides the precursor of OEA synthesis allowing the OEA-satiety signal to be correlated to the amount and quality of fat ingested and therefore is reflective of meal fat content (115).

#### 8.2.1.2. N-Acylphosphoethanolamine (NAPE)

N-acylphosphatidylethanolamines (NAPEs) are abundant plasma lipids and their physiological role was elusive until a recent study from Gillum *et al.* demonstrated that NAPE are, like OEA, potent satiety molecules that are synthesized by the small intestine in response to fat ingestion. Systemic injection of NAPE decreases food intake with no sign of taste aversion and, unlike OEA's effect which is mediated by the vagal nerve, vagotomy does not alter the satiety action of peripherally injected NAPE. ICV injection of NAPE at nanomolar concentration reduces food intake and decreases fasting-induced activation of c-fos in the orexigenic NPY/AgRP neurons and peripheral NAPE enters the brain where it accumulates in the hypothalamus. Thus, NAPE seems to act directly on ARC neurons of the hypothalamus to reduce food intake. Interestingly, the postprandial increase in circulating NAPE concentration in response to fat ingestion is abolished in animals fed a high-fat diet (HFD) for several weeks, but unlike leptin resistance that occurs rapidly during diet-induced obesity NAPE retains its ability to inhibit food intake when administered to obese animals (116). This discovery adds to the wide spectrum of nutrient-induced signaling molecules in the gut-brain axis. Importantly both

NAPE and OEA, through different mechanisms, provide a crucial molecular signal linking the quantity and quality in dietary fat ingestion and the regulation of feeding behaviour.

### 8.3. Protein diet

It has been recently shown that the satiety effects of protein-enriched diets involve intestinal gluconeogenesis through the gut/brain axis (117, 118). Indeed, the expression of key gluconeogenic genes has been demonstrated in both rodents and in the human small intestine (reviewed in (118)). Mithieux *et al* demonstrated that protein-enriched diet led to decreased food intake by increasing portal vein glucose levels, mainly from intestinal gluconeogenesis (from glutamine). The decrease in food intake was mimicked when glucose was directly infused into the portal vein (without any change in systemic glycemia). Finally the satiety signal produced by protein-enriched diet or glucose portal infusion was lost in vagotomized rats (117). Another recent study highlighted that intestinal gluconeogenesis was a key factor for early metabolic changes after gastric bypass (especially hepatic insulin sensitivity) but not after gastric lap-band in mice (119). Moreover, there is some evidence that the circulating level of leucine also impacted food intake. Indeed, leucine has been shown to modulate the activity of the energy and nutrient sensor pathways controlled by AMPK and mTOR in the hypothalamus (120). Taken together, all these data support a crucial role of gut/brain axis as a key modulator of feeding behavior.

## 9. CENTRAL ER STRESS AND INTEGRATION OF METABOLIC SIGNALS

Obesity is characterized by the chronic activation of inflammatory pathways which in turn contribute to tissue insulin resistance and type-2 diabetes. In metabolic tissues, this low-grade inflammatory state engages several biochemical events of the immune system that interfere with insulin signaling and leads to a cluster of chronic metabolic disorders, including T2D and cardiovascular disease (121). The etiology of this inflammation has been mostly studied in peripheral organs such as liver and adipose tissue. However, recent work from Zhang *et al.* provides important insight into the core mechanism that links hypothalamic nutrient sensing, central insulin and leptin signaling cascades, and the activation of inflammatory and endoplasmic reticulum (ER) stress pathways (122). The authors show that the IKK $\beta$ /NF- $\kappa$ B complex, a master regulator of innate immunity, is crucially implicated in the central integration, by hypothalamic neurons, of nutrients and hormonal signals. IKK $\beta$ /NF- $\kappa$ B is abundantly expressed in the MH where it remains inactive, but when animals are fed a HFD the activity of the NF- $\kappa$ B is up-regulated; and the same applies in genetic obesity and hyperphagia in *ob/ob* mice. Central nutrient overload achieved by ICV injection of lipid or glucose also activates the IKK $\beta$ /NF- $\kappa$ B pathway. Over-expression of a constitutively active form of IKK $\beta$  in the vicinity of the hypothalamus increased food intake and body weight whereas expression of a dominant-negative form, or genetic deletion of IKK $\beta$  in the brain (or specifically in NPY/AgRP

neurons), resulted in decreased feeding and prevented HFD-induced obesity and diabetes. They also demonstrate that hypothalamic ER stress mediates the effect of nutrient excess onto IKK $\beta$ /NF- $\kappa$ B activation notably by showing that hypothalamic activation of NF- $\kappa$ B can be negated by ICV injection of a ER stress inhibitor. Finally, nutrient-excess induces central leptin and insulin resistance through the transcriptional regulation of SOCS3 by nutrient-activated IKK $\beta$ /NF- $\kappa$ B. In turn SOCS3 prevents leptin and insulin initiated signaling cascades (Figure 3) (122). By pinpointing the causal role of hypothalamic inflammation in the process of diet-induced leptin and central insulin resistance, Zhang and colleagues unraveled a crucial mechanism involved in the development of the metabolic syndrome. Central nutrient toxicity could be the starting point of a central defect that will translate into the perturbation of the central control of feeding behavior, autonomic glucose and metabolism. In this view, the CNS is at the core of energy balance regulation and needs to be considered as a primary target for anti-obesity and/or anti-diabetes strategies (122) (Figure 3).

## 10. AUTONOMIC CONTROL OF ENERGY HOMEOSTASIS

As mentioned above peripheral signals originating from gut or bloodstream continually inform the CNS of energetic status (i.e., fed or fasted, rested or exercised) which in turn monitors the status of both peripheral glucose stores and ongoing fuel availability matching glucose production to glucose utilization; thus allowing maintenance of glycemia in a physiological range of 0.8-1.2 mg/dl regardless of the situation. This implies a precise innervations of target organs such as liver, adipose tissue and endocrine pancreas by autonomic nervous system fibers (123). In the liver, many nerve terminals contain classical neurotransmitters (norepinephrine, serotonin, and acetylcholine) and neuropeptides (substance P, calcitonin gene-related peptide, NPY, vasoactive intestinal polypeptide, somatostatin, glucagon, glucagon-like peptide 1, neurotensin, and galanin). Sympathetic hepatic nerves can physiologically increase hepatic glucose output. It has been recently shown that ICV administration of NPY acutely induces insulin resistance, inhibiting endogenous glucose production via activation of sympathetic output to the liver (124). However, sympathetic innervations appear to contribute relatively little to the stimulation of hepatic glucose output under physiological conditions. Parasympathetic hepatic nerves potentiate insulin-dependent hepatic glucose extraction when the portal glucose sensor detects prandial glucose delivery from the gut (123). In addition, they might coordinate the hepatic and extrahepatic glucose utilization to prevent hypoglycemia and, at the same time, warrant efficient disposal of excess glucose. This crosstalk between brain and liver articulates central nutrient sensing to peripheral nutrient production and its disruption may lead to hyperglycemia (125). In parallel to direct neural connections, the hypothalamus can affect metabolic functions by neuroendocrine connections such as the hypothalamus-pancreas axis, the hypothalamus-adrenal axis, and the hypothalamus-pituitary axis (123). In the

hypothalamus-pancreas axis, autonomic nerves control the release of glucagon and insulin, which directly enter the liver and affect liver metabolism. In the hypothalamus-adrenal axis, autonomic nerves stimulate the release of catecholamine such as epinephrine and noradrenalin from the adrenal medulla, which also effects liver metabolism. In the hypothalamus-pituitary axis, release of glucocorticoids and thyroid hormones is stimulated by pituitary hormones. Both groups of hormones modulate hepatic metabolism. Finally, an interesting study recently demonstrated that neuronal signals from the liver may contribute to the regulation of pancreatic beta cell mass, thus highlighting inter-organ metabolic relay as informative signals (126). The pancreatic islets by themselves are richly innervated by parasympathetic, sympathetic and sensory nerves (127). The neuropeptides, vasoactive intestinal polypeptide, pituitary adenylate cyclase activating polypeptide and gastrin releasing peptide are constituents of "classical" acetylcholine-containing parasympathetic nerves; whereas the neuropeptides galanin and NPY are localized to sympathetic nerve terminals with noradrenalin. Stimulation of the autonomic nerves and treatment with neurotransmitters affect islet hormone secretion. Thus, insulin secretion is stimulated by parasympathetic nerves and inhibited by sympathetic nerves. It has been evidenced that autonomic innervations of the islet are of physiological importance in mediating the cephalic phase of insulin secretion allowing the synchronization of the  $\beta$ -cells into one functional islet with a regular oscillation in hormone secretion. This mechanism insures an optimized islet hormone secretion during metabolic stress, e.g. hypoglycemia and neuroglucopenia. The autonomic nerves could also be involved in islet adaptation to insulin resistance (78) with possible implications for the development of glucose intolerance and T2D (127).

Regarding white adipose tissue (WAT), the sympathetic innervations is the principal initiator of lipid mobilization not only in rodents, but in all mammals including humans. Sympathetic nerve fibers stimulate lipolysis, leading to the release of glycerol and free fatty acids. In addition, recent research in rats has clearly shown functional parasympathetic innervations of WAT (128). Distinct somatotopy within the parasympathetic nuclei define a separate sets of autonomic neurons in the brainstem that innervate either the visceral or the subcutaneous fat compartments (128). Parasympathectomy induces insulin resistance with respect to glucose and fatty acid uptake in the innervated fat depot and has selective effects on local synthesis of adipokines by WAT and the modulation of fat cell number. Altogether it could be hypothesized that shifting the equilibrium between the sympathetic/parasympathetic activity onto WAT could participate in the development of visceral depot and metabolic syndrome (129)(Figure 1).

### 11. CONCLUSIONS AND PERSPECTIVES

The physiological bases of the metabolic syndrome are certainly legions and the conventional wisdom often envisioned T2D as a consequence of obesity by virtue of extra-adipose storage of TG arising from an

excess in body fat. The Randle hypothesis states that the "primary defect" of insulin resistance lies in excess of free fatty acids for oxidation by muscles and other tissues leading to the impairment of carbohydrate oxidation and glucose intolerance as is seen in obesity and obese diabetics (130). An emerging view in the field of diabetes research has rekindled this debate over the link between diabetes and obesity by providing strong evidence that integrative processes of hormonal, nutritional and nervous inputs in key hypothalamic nuclei could be causally involved not only in aberrant feeding behavior but also in impaired peripheral insulin sensitivity and glucose metabolism. Indeed, in addition to leptin, ghrelin or gut-derived peptide inputs, the hypothalamus retains the ability to finely tune neural output in response to nutrient signals and an excess of nutrients can lead to hypothalamic inflammation, resulting in central insulin and leptin resistance (112). In turn hypothalamic defects in melanocortin signaling translates into both neuro-endocrine deregulation and modified sympathetic/parasympathetic inputs on metabolically active tissue. The disintegration of signal coordination affects most tissues usually incriminated in the establishment and progression of T2D: the pancreas, by loss of proper autonomic control of insulin secretion, the liver by deregulated gluconeogenesis and the adipose tissue by impaired lipolysis. In this neurocentric model the "primary defect" lies in CNS sensing - and the metabolic syndrome could be viewed as the result of this defect rather than the cause. A growing number of studies are adding support to this concept of central cause of diabetes (82); for instance, by unraveling the networks that are recruited by central leptin, insulin or nutrient sensing that specifically affect glucose metabolism without affecting feeding behavior (131).

There can now be little question that the CNS is at the core of the regulation of energy homeostasis. However, nowadays there is no market drug specifically targeting the central nervous system to control glucose homeostasis and diabetes. The only available molecules target appetite and body weight, especially through modulation of serotonergic pathway. It has been also demonstrated that antagonism of CB1 pathway could be a potent anti-obesity strategy. However, the first drug available on the market has been recently withdrawn and such target will be probably given up.

Regarding diabetes it has been proposed that GLP-1 could act through CNS, at least for modulation of food intake. It cannot be excluded that some anti-diabetic GLP-1 effect may be also related to its CNS action. Development of new therapeutic drugs implies to clearly identify target specifically expressed within hypothalamus. However, most of putative mechanisms are also described in peripheral tissues (AMPK, CPT1...) and the main challenge awaiting brain-directed pharmacology resides in the design of molecules that specifically target a subset of neuronal population and will not have adverse effect in the periphery. To that aim we need a greater understanding the intimate properties of the BBB together and to further elucidate molecular signature of the neuronal pathway that orchestrate body weight and glucose homeostasis

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regulation and whose failure leads to the establishment of diabetes. Accomplishing this will allow us to pharmacologically target components of this central circuitry and provide new strategies for anti-diabetic treatments.

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**Abbreviations:** CNS: central nervous system, T2D: type 2 diabetes, MH: mediobasal hypothalamus, VMH: ventromedial hypothalamus, LH: lateral hypothalamus, NPY: Neuropeptide Y, AgRP: Agouti related peptide,  $\alpha$ -MSH:  $\alpha$ -melanocyte stimulating hormone, GLP-1: Glucagon-like peptide 1, CCK: cholecystokinin, OXM: oxyntomodulin, OEA: oleoylethanolamine, ARC: arcuate nucleus, PVN: paraventricular nucleus, ME: Median Eminence, BBB: Brain Blood Barrier, POMC: pro-opiomelanocortin, CART: amphetamine-related transcript, GABA: gamma aminobutyric acid, ACTH: adrenocorticotrophic hormone, MCR: melanocortin receptors, A<sup>y</sup>: Agouti yellow, DMH: dorsomedial hypothalamus, NTS: Nucleus of the Solitary Tract, CRH: corticotropin-releasing hormone, TRH: thyrotropin-releasing hormone-synthesizing neurons, HPT: hypothalamic-pituitary-thyroid, HPA: hypothalamic-corticotrophic axis, DMX: dorsal motor nucleus of the vagus nerves, IML: intermediolateral cell column, LeptR: leptin receptor, InsR: insulin receptor, GLP-1: glucagon-like peptide 1, GOAT: Ghrelin-O acyl transferase, IRS: insulin receptor substrate, PI<sub>3</sub>K: phosphatidylinositol-3-OH kinase, PIP<sub>3</sub>: phosphatidylinositol-3,4,5-triphosphate, PDK-1: Phosphoinositide-dependent Kinase-1, (PKB)/Akt: protein kinase B, mTOR: mammalian target of rapamycin, FOXO1: forkhead box O1 transcription factor, CVO: circumventricular organs, CPT1: Carnitine Palmitoyl Transferase -1 inhibition, ACC: acetyl-CoA carboxylase, AICAR: 5-aminoimidazole-4-carboxamide ribonucleoside, WAT: white adipose tissue, JAK-STAT: Janus Kinase-Signal transducer and activator of transcription, SOCS3: suppressor of cytokine signaling-3, VTA: ventral tegmental area, LCFA-CoA: long-chain fatty-acyl CoA

**Key Words:** Type 2 Diabetes, Leptin, Insulin, Hypothalamic Nutrient Sensing, Obesity, Metabolism, Melanocortin, Review

**Send correspondence to:** Christophe Magnan, University Paris Diderot-Paris 7-Unit of Functional and Adaptive Biology (BFA) affiliated with CNRS, PO BOX 7126, 4 rue Lagroua Weill Halle, 75205 Paris Cedex 13, France, Tel: 33-1-5727-7793, Fax: 33-1-5727-7796, E-mail: christophe.magnan@univ-paris-diderot.fr

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