Central orchestration of peripheral nutrient partitioning and substrate utilization: Implications for the metabolic syndrome

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Abstract

Energy homeostasis is maintained through a complex interplay of nutrient intake and energy expenditure. The central nervous system is an essential component of this regulation, as it integrates circulating signals of hunger and satiety to develop adaptive responses at the behavioural and metabolic levels, while the hypothalamus is regarded as a particularly crucial structure in the brain in terms of energy homeostasis. The arcuate nucleus (ARC) of the hypothalamus contains at least two intermingled neuronal populations: the neurons that produce neuropeptide Y (NPY); and the Agouti-related protein (AgRP) produced by AgRP/NPY neurons situated below the third ventricle in close proximity to proopiomelanocortin (POMC)-producing neurons. POMC neurons exert their catabolic and anorectic actions by releasing α-melanocyte-stimulating hormone (α-MSH), while AgRP neurons oppose this action by exerting tonic GABAergic inhibition of POMC neurons and releasing the melanocortin receptor inverse agonist AgRP. The release of neurotransmitters and neuropeptides by second-order AgRP neurons appears to take place on a multiple time scale, thereby allowing neuromodulation of preganglionic neuronal activity and subsequent control of nutrient partitioning – in other words, the coordinated regulation of conversion, storage and utilization of carbohydrates vs. lipids. This suggests that the function of AgRP neurons extends beyond the strict regulation of feeding to the regulation of effector organ activity, such that AgRP neurons may now be viewed as an important bridge between central detection of nutrient availability and peripheral nutrient partitioning, thus providing a mechanistic link between obesity and obesity-related disorders.

Keywords: Obesity; Diabetes; Nutrient partitioning; Hypothalamus; Agouti-related peptide

1. Introduction

The current abundance of energy-rich foods combined with a shift to more sedentary lifestyles has led to thermodynamic imbalance. As a consequence, excess calorie intake and reduced energy expenditure are now the main causes behind the prevalence of obesity as well as obesity-related diseases such as atherosclerosis, hypertension, dyslipidaemia, coronary diseases and diabetes in both developing and developed countries [1]. This constellation of pathophysiology has been dubbed ‘the metabolic syndrome’ or ‘syndrome X’ and, although genetic factors account for some cases of obesity, it is evident that drastic environmental changes in combination with both inherited and acquired susceptibility are instrumental in its pandemic development. In particular, a drastic change in eating habits is now emerging as one of the main causes of the prevalence of obesity, and this is also driving the concomitant epidemic of type 2 diabetes (T2D) as both are pathophysiologically intimately associated [2,3].

The World Health Organization (WHO; www.who.int/mediacentre/factsheets/fs311/en/) has highlighted the fact that obesity worldwide has more than doubled since 1980. In 2008, 1.5 billion adults aged 20 and older were overweight. The French Healthcare System may now also consider obesity an epidemic. A recent report from the French Sénat (Senate) has highlighted the dramatic progression of obesity in France (www.senat.fr/rap/r10-158/r10-1580.html#toc0), leading to the launch in 2011 of an obesity plan (plan obésité) backed by the highest authorities. According to the WHO, the fundamental
cause of obesity and overweight is an energy imbalance between calories consumed and calories expended.

Other than rare cases of monogenic obesity, it has become evident that obesity as well as the physiological mechanism linking it to obesity-related pathologies are multifactorial and encompass a wide spectrum of interactions at molecular, cellular and integrated levels. For this reason, obesity-related metabolic complications can no longer be solely attributed to excess nutrient intakes, but most likely also involve the inappropriate conversion, storage and utilization of nutrients, an integrated process referred to as ‘nutrient partitioning’. Orchestrating the fate of a nutrient once ingested requires coordinated dialogues between organs, including postprandial insulin release from the pancreas, nutrient conversion and storage in the liver and adipose tissue, and glucose/lipid utilization in muscle. Nutrient partitioning is an active phenomenon that takes place at both physiological and cellular levels. At the integrated level, appropriate nutrient partitioning relies on the ability of the brain to orchestrate peripheral organ activity through, in particular, modulation of autonomic nervous system (ANS) output, but it also requires peripheral inputs that convey ‘readouts’ of energy states. Indeed, the central nervous system (CNS) has a central role in the control of energy balance. Food intake and energy expenditure are complex behavioural and metabolic adaptive responses that result from the integration of circulating signals of hunger and satiety at the level of highly differentiated central neural substrates (Fig. 1). An emerging view sees the links between obesity and obesity-related diseases such as diabetes and dyslipidaemia as the result of a primary disabling dysfunction of the brain to orchestrate activity in the peripheral tissues [4]. The present review aims to provide a novel framework in which arcuate nucleus (ARC) hunger-activated neurons of the hypothalamus not only regulate feeding, but also feeding-independent processes, including nutrient partitioning.

1.1. The old age of hypothalamic feeding centres and the new age of leptin signalling

In the CNS, the hypothalamus is regarded as a key integrative structure in the regulation of energy balance. The hypothalamus contains a population comprising a wide variety of highly differentiated neurons involved in the homoeostatic control of several physiological systems, including reproduction, salt and water intakes, wake/sleep circadian rhythm and body temperature.

The hypothalamus has long been recognized as the primary integrator of circulating signals of hunger and satiety and, thus, has been extensively studied for its intimate involvement in whole-body energy balance. In the early 1940s, experiments using electrical stimulation and lesions allowed the identification of functional nuclei in the mediobasal hypothalamus (MBH) with specific actions on energy homoeostasis [5,6]. The ventromedial hypothalamus (VMH) was first considered a satiety area because destruction of the medial hypothalamus (MH) resulted in hyperphagia and obesity, whereas electrical stimulation of the VMH decreased food intake and body weight. On the other hand, damage to the lateral hypothalamus (LH) led to anorexia whereas LH stimulation caused voracious feeding and obesity. However, the overall conceptual framework that emerged from these observations wherein the ‘satiety centre’ kept the ‘feeding centre’ in check was then largely abandoned when it was realized that LH lesions disrupted the dopaminergic nerve tracts passing through the hypothalamus that were essential for normal feeding and movement, whereas VMH lesions had a major impact on autonomic output [7]. Indeed, over the past decade a growing number of sophisticated genetic and pharmacological tools have profoundly changed our view of homoeostatic and non-homoeostatic regulation of energy balance.

The study of naturally obese (ob/ob) and diabetic (db/db) mice promoted the idea of a circulating factor linking fat stores with food intake. In 1994, a breakthrough was made with the discovery of the mouse obese gene encoding a 16-kDa protein called leptin (Lept), which was mostly produced by adipose tissue [8]. Circulating leptin levels rise and fall in direct proportion to adipose tissue mass, but are relatively insensitive to daily changes in food intake. Food deprivation causes leptin levels to fall as energy stores are utilized, and the decrease promotes
endocrine and behavioural alterations that result in increased appetite and reduced energy expenditure. Leptin targets are primarily found in the CNS, but are also present in peripheral tissues [9,10]. Mice lacking leptin (ob/ob) become morbidly obese as a consequence of metabolic disturbances and hyperphagia; they are also cold-intolerant, diabetic and infertile [7,11]. Later, the discovery of the leptin receptor – a single-pass transmembrane protein of the gp130 cytokine receptor family [12], the mutation of which is responsible for the db/db phenotype Lep<sup>db</sup> [13] – generated a massive effort by pharmaceutical companies to develop a therapy based on leptin treatment to cure obesity. Unfortunately, it was quickly discovered that genetic obesity involving mutation of the leptin receptor was responsible for only a small percentage of human obesity [14]. Nevertheless, the momentum triggered by the identification of the leptin signalling pathway led to a new era of feeding and obesity research and the identification of hypothalamic targets in the CNS that are direct targets of the leptin signalling pathway [15].

1.2. Arcuate AgRP and POMC neurons: Two opposing branches of the melanocortin system

Neuropeptide Y (NPY) was first characterized by Tatemoto et al. [16] and later described as a highly potent feeding stimulator [17]. The dominant obesity associated with Agouti yellow (Ay) mice was found to result from ectopic expression of the agouti gene and tonic inhibition of the melanocortin receptor signalling pathway [18]. Agouti-related protein (AgRP) was revealed to be the endogenously released neuropeptide that acts as an inverse agonist for melanocortin receptors [19–21]. Soon after, both neuropeptides were found to colocalize in the hunger-activated neurons of the hypothalamus [22] and to be associated in most processes arising from those neurons. In addition, those neurons were shown to release gamma-aminobutyric acid (GABA) as the main neurotransmitter, thus further establishing the inhibitory actions of NPY/AgRP neurons [23]. In the CNS, as AgRP is solely produced by these neurons, they are now commonly referred to as ‘AgRP neurons’. AgRP neurons are located close to a circumventricular organ dubbed the ‘median eminence’ (ME), where the blood–brain barrier (BBB) has been specifically designed to regulate any exchanges with circulating signals (Fig. 1). This anatomical feature allows ARC neurons to rapidly engage in electrophysiological changes in response to the entry of circulating hormones and satiety hormones, hence their appellation as ‘first-order’ neurons (Fig. 1). The neurons that make proopiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) are also located in the ARC in close proximity to AgRP neurons. POMC neurons have a mixed excitatory and inhibitory nature, and release the neurotransmitters glutamate and GABA [24] as well as post-translational products of POMC peptide, such as the α-, β-, γ-melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH). POMC and AgRP neurons have reciprocal antagonistic actions, and GABAergic inputs are projected by AgRP neurons to POMC neurons [25–29]. In addition, the release of NPY by AgRP neurons leads to activation of the G-protein-coupled NPY Y<sub>1</sub> receptor located on POMC neurons. Both neuron populations share the same ‘second-order’ CNS targets found within the paraventricular (PVN), VMH, dorsomedial (DMH) and LH nuclei of the hypothalamus, as well as extrahypothalamic targets such as the nucleus of tractus solitarius (NTS), the parabrachial nucleus (PBN) [30] and the intermediolateral cell column (Fig. 1) [31]. In these structures the release of α-MSH by POMC neurons initiates the anorectic/catabolic melanocortin signalling cascade by binding α-MSH to the G protein-coupled melanocortin receptor (MCR). Of the five G protein-coupled MCR (MCR<sub>1</sub> to MCR<sub>5</sub>) distributed throughout the body, MCR<sub>3</sub> and MCR<sub>4</sub> have their expression restricted to the CNS [32,33]. However, during energy deprivation, electrophysiological AgRP neurons are increased, leading to an enhanced release of AgRP, which opposes α-MSH binding to postsynaptic targets [34]. For example, oxytocin, corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH) synthesizing neurons may be found in the PVN expressed by MCR<sub>4</sub> [32]. In this case, the competition between α-MSH and AgRP signalling has direct repercussions on energy conservation during times of energy paucity. The α-MSH-initiated cascade will then positively regulate both the hypothalamic–pituitary–thyroid (HPT) axis and hypothalamic–corticotropic axis (HPA), whereas the fasting-mediated increases in AgRP release are instrumental for adaptive responses of the HPA and HPT during negative energy balances [35,36]. POMC and AgRP neurons may thus be considered the two opposing branches of the ‘melanocortin system’, so demonstrating a paradigmatic ‘yin/yang’ type of energy homeostasis regulation. Changes to the melanocortin signalling pathway such as by MCR<sub>3</sub>R or MCR<sub>4</sub>R null mutations [37], or any enzyme involved in the processing of melanocortin peptide, together with ectopic expression of the MCR agonist agouti yellow (A<sup>y</sup>) [18] thus result in increased feeding and decreased energy expenditure and, invariably, morbid obesity in both humans and mice [38,39]. These observations may be said to have established the general framework that sees AgRP neurons as the natural opponents of POMC activity mostly through their antagonistic action on the melanocortin signalling pathway. Only recently has their integrated role been extended to other functions, including the encoding of goal-directed behaviour and peripheral nutrient partitioning.

1.3. Role for AgRP neurons beyond melanocortin antagonistic actions: Lighting up the hunger pathway

Definitive confirmation of the crucial importance of AgRP neurons in the maintenance of feeding comes from several studies using selective ablation of these neurons. While the methodology differed, the overall conclusion was that acute depletion of AgRP neurons leads to profound anorexia [40–42]. Initially, it was suspected that this behavioural response was the result of unopposed melanocortin signalling, but the same result was obtained when AgRP neurons are ablated in Ay mice [43], a model in which the melanocortin signalling pathway is already opposed by ectopic expression of the natural agouti receptor antagonist [18]. The same group provided strong evidence that, of the postsynaptic targets in which c-fos staining...
reveals hyperactivity as a consequence of AgRP neuron ablation [43], it was the pharmacological replacement of GABA in the pontine structure PBN that prevented weight loss. This study demonstrated that GABA made by AgRP neurons was a critical requirement for mediating their activity in a melanocortin-independent manner [44,45]. Wu et al. [46] went on to show that GABAergic tone from AgRP neurons was indeed necessary for maintaining balance between glutamatergic inputs from a subpopulation of viscerosensitive NTS neurons. Given the integrative role of the NTS as a functional hub for food-related cues gathered by sensory neurons innervating the oral cavity, for cognitive and emotional processing centres such as the insula and prefrontal cortex and central nucleus of the amygdala (CeA), and for vagus-borne viscerosensitive information from the gut, the study by Wu et al. [46] suggested a direct role for AgRP neurons in the modulation of brain stem ability to relay reward and aversion information while integrating cognitive and emotional feedback. A formal demonstration was recently provided by another group [47], which demonstrated that calcitonin gene-related peptide-expressing neurons in the outer external lateral subdivision of the PBN project into the amygdala and integrated parts of the inhibitory input from ARC AgRP neurons to form a functionally important circuit for maintaining appetite.

These new observations have cast new light on the independent action of POMC and AgRP neurons in structures that might not express melanocortin receptors or where GABAergic input from AgRP neurons are the physiological relevant signal [48–50]. This work has also confirmed a role for AgRP neurons independent of the melanocortin pathway, as was strongly suggested by studies showing that AgRP-mediated feeding responses remain in the genetic background of MCR4 knockout mice [35].

Subsequently, sophisticated genetic tools allowing for the manipulation of AgRP neurons in vivo have revealed that this neuronal network is also able to initiate the full sequence leading to food ingestion. Chemical- and light-mediated activation of AgRP neurons in vivo was achieved through the forced expression of designer receptors exclusively activated by designer drugs (designer receptors exclusively activated by designer drugs, or DREADDs) or by photo-activated channelrhodopsin-2 (ChR2) allowing light absorption [51,52]. These two studies provided complementary demonstrations that activation of AgRP neurons is sufficient to orchestrate the complex sequence of ingestion behaviour [52,53], while acute inhibition of AgRP neurons was found to diminish feeding [52]. More important, the use of optogenetic techniques by the Scott Sternson Lab confirmed that AgRP neurons evoked GABAergic currents that impinged on POMC neurons, thereby supporting the observations of Wu et al. [44,45], who found that light-mediated activation of AgRP neurons promoted feeding in AQ mice [54] and thus proposed an in-depth neuroanatomical mechanism by showing that photo-activation of AgRP neurons or axons located in the PVN could elicit robust feeding solely with the combination of NPY and GABA-mediated inhibition of PVN oxytocin (OT) neurons. Interestingly, they also found that, unlike the PWN, light activation of ChR2-expressing AgRP axons in the PBN was inefficient at promoting feeding [54].

Integrating the notion of time-resolved release of neurotransmitter and the projection of a segregated population of AgRP neurons preferentially to different second-order structures can reconcile this discrepancy. Indeed, the immediate need for food encoded by rapid neurotransmission might engage the ARC–PVN axis, while input to the pontine PBN might be critical for maintaining balance in gut-derived inputs (aversion, for instance). AgRP input to the PBN could convey an acute hunger-activated feeding response, whereas AgRP inputs to the PBN could be of a more tonic nature and involve longer-lasting microcurrents, thus ensuring a proper excitatory balance in the PBN. ARC–PVN and ARC–PBN circuitry might each work according to a different time scale to modulate gut-mediated aversion inputs and acute energy needs. In this case, the promotion of feeding and prevention of starvation – albeit two faces of the same coin – would have different neuroanatomical supports. In fact, Atasoy et al. [54] have reported some peculiar features of the AgRP synaptic connection to the PVN. They found that, after light excitation, the PBN received prolonged asynchronous GABA release at the AgRP synapse that sustained inhibition for hundreds of milliseconds after action-potential-mediated inhibitory postsynaptic currents (IPSCs) occurred. This time scale is usually associated with neuromodulation, but was in this case fully recapitulated by biphasic GABA release.

Thus, AgRP neurons that synapse with the PBN can modulate postsynaptic activity for two orders of magnitude longer after the occurrence of action potentials [54]. In addition, it is possible that delays in fast- and slow-acting neurotransmitters initiated by changes in AgRP neuronal activity may occur, but at different time scales and in different postsynaptic structures. A recent study by Krashes et al. [55] has now definitively established that AgRP release by AgRP neurons is sufficient to induce feeding for a prolonged period of time while GABA and NPY co-release is crucial for inducing rapid feeding events.

Taken altogether, this body of work casts new light on AgRP neurons by demonstrating how they might operate by different time scales and with the combined use of slow- and fast-acting chemicals in melanocortin-dependent and -independent ways to induce subtle and drastic adaptive changes.

1.4. Central orchestration of peripheral nutrient partitioning: Consequences for the metabolic syndrome

Every metabolically active tissue (pancreas, liver, visceral adipose tissue) receives neural input from the ANS [4,56]. From the study of adipose lipolysis, brown adipose tissue thermogenesis, muscle contraction and substrate selection, liver neoglucogenesis/lipogenesis and pancreatic insulin release, it has become evident that ANS modulation of effenter organ activity is a crucial component in an integrated adaptive response initiated in the brain as a result of the integration of hormonal and neural afferent inputs.

Pre-autonomic hypothalamic neurons have distinctive organization according to their effenter organs [4], and both POMC and AgRP neurons project dense synaptic inputs to preganglionic structures such as the PBN. It is therefore possible to envision a role for ARC neurons in addition to the
acute regulation of feeding in the modulation of efferent organ activity through ANS output regulation. AgRP neurons also exhibit pacemaker activity [57], suggesting that their actions extend beyond the starvation period (which rarely occurs under normal conditions) and into the intermeal period. During this period, the coordinated input from AgRP neurons to preganglionic structures could be instrumental in the determination of peripheral carbohydrate handling independent of nutrient intake. The fact that AgRP neurons can modulate postsynaptic activity in the PVN for two orders of magnitude longer after action potentials have occurred [54] is a strong argument in favour of this hypothesis.

In addition, recent studies have demonstrated a role for melanocortin signalling in peripheral lipid metabolism independent of food intake [58–60]. These effects have also been observed in pair-fed animals [58] and were mediated by the sympathetic nervous system. The POMC and AgRP neuronal populations could therefore independently affect peripheral nutrient partitioning (carbohydrate vs. fat) in a coordinated and not necessarily opposing manner. In fact, using an animal model with selective neonatal ablation of AgRP neurons [42,61], our group was able to definitively substantiate this hypothesis by showing that mice lacking AgRP neurons displayed drastic changes in ANS output to peripheral tissues, characterized by decreased norepinephrine turnover rates (an indirect reflection of sympathetic outflow) in the pancreas, liver and ‘white’ glycolytic muscle, and increased norepinephrine turnover rates in oxidative fat-burning muscle (Fig. 2). When fed a regular chow (carbohydrate-rich) diet, feeding efficiency was dramatically increased and accompanied with hyperinsulinemia and late-onset obesity that was not due to increased caloric intake, but instead involved a shift in substrate utilization due to simultaneous metabolic changes in a number of peripheral tissues. Indeed, the respiratory quotient (RQ = VCO2/VO2), which reflects the nature of the substrate being used by an organism – for example, RQ = 1 for glucose utilization and RQ = 0.7 for lipid utilization – revealed a change in substrate utilization towards lipid oxidation correlating with enhanced carbohydrate conversion in the liver associated with increased triglyceride (TG) synthesis and export [49] (Fig. 2). In addition, a shift towards a lipid substrate preference was evidenced by both increased peripheral lipid handling and soleus muscle mitochondrial respiration. This change in RQ profile was seen at the beginning of the dark period, when AgRP neurons should be activated by nutrient deprivation. It was therefore hypothesized that these metabolic changes coordinated by the ANS would favour fat vs. carbohydrate oxidation. Indeed, when switched to a high-fat diet, AgRP-neuron-ablated mice normalized their feeding efficiency and showed both a paradoxical improvement in glucose tolerance and reduction of body weight gain compared with control mice [50,62]. These data demonstrate that AgRP neurons play a role that extends beyond the regulation of feeding to the control of ANS output and peripheral nutrient partitioning (Fig. 2). The present observations are in line with other recent work showing that selective impairment of AgRP neuron activity leads to impaired metabolic plasticity [63]. It was also found that part of the phenotype as well as RQ could be selectively

Fig. 2. AgRP neurons, a central switch for peripheral nutrient partitioning. Neonatal ablation of AgRP neurons affects food intake and promotes changes in autonomic nervous system (ANS) output to peripheral tissues, with decreased outflow to the pancreas, liver and white glucose-using extensor digitorum longum (EDL) muscle, but increased outflow to oxidative lipid-burning soleus muscle, while parasympathetic nervous system (PNS) output is decreased in the liver. These changes are associated with an increase in liver lipid production together with increases in sterol regulatory element-binding protein-1c (SREBP1c), glucokinase (GK) and stearoyl-CoA desaturase-1 (SCD1) mRNA to support an enhanced lipogenic programme; liver triglyceride (TG) export is also increased along with peripheral TG catabolic activity. These global changes lead to increased transformation of carbohydrates into lipids and increased lipid oxidation. The metabolic set point is more adapted to high-fat feeding, and mice lacking AgRP neurons display greater feeding efficiency and obesity when fed a carbohydrate diet, but reduced body weight gain and improved glucose tolerance with a high-fat diet. L-PK: t-pyruvate kinase; G6P: glucose-6-phosphate; PEP: phosphoenolpyruvate; VLDL: very-low-density lipoprotein; Ox: oxidative; Glyc: glycolytic.

normalized through GABAA receptor agonist treatment, suggesting that AgRP-neuron-mediated ANS control presumably involves both rapid and long-lasting GABA inputs.

The present results are consistent with studies suggesting that GABA may be a crucial signalling molecule by which AgRP neurons control peripheral nutrient partitioning. It is highly likely that the control of ANS output by AgRP neurons relies more prominently on the slower, tonic GABAergic inputs that are longer-lasting currents compatible with the nutrient
partitioning that occurs after the meal during post-ingestion processes. This suggests that beyond their well-described involvement in the acute regulation of food intake, AgRP neurons may also directly regulate the fate of nutrients once ingested through the orchestration of a coordinated dialogue between organs, including pancreatic postprandial insulin release, nutrient conversion and storage in liver and adipose tissue, and glucose/lipid utilization in muscle (Fig. 2) [58,59,64].

The present work suggests that AgRP neurons are a central switching point between peripheral substrate utilization and optimization of carbohydrate vs. lipid oxidation [50]. Even obese mice lacking AgRP neurons retain the ability to expand their adipose tissue mass and show improved glucose tolerance and insulin sensitivity with high-fat feeding. This counterintuitive observation can be resolved by considering the role of AgRP neurons beyond feeding as a central switch that maintains the metabolic balance between carbohydrate and lipid utilization, while the lack of AgRP neurons translates to better adaptation to a high-fat diet (Fig. 2). In this case, the line between healthy obesity and obesity associated with concomitant diseases could be the result of a defective central switch, with aberrant ANS outputs and nutrient partitioning. This hypothesis is consistent with early observations associating defective sympathetic tone and obesity-related complications [65] and support an emerging concept in which the metabolic syndrome may be viewed as a brain disorder involving aberrant peripheral energy fluxes [4,66].

Disclosure of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdiabett.2013.11.002.

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