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Review

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

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Abstract

Energy homoeostasis 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 homoeostasis. 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 efferent 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 susceptibly 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

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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 as to '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.

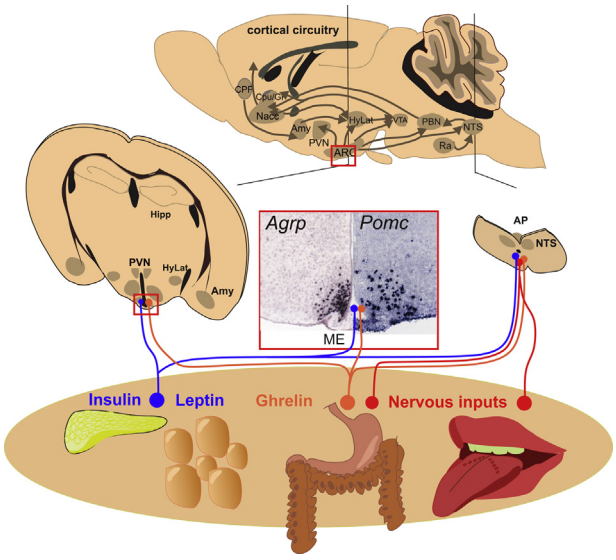

Fig. 1. Arcuate nucleus (ARC) and integration of metabolic signals. Sagittal section of a mouse brain (upper) shows the interconnectivity of brain nuclei involved in the control of homoeostatic and non-homeostatic energy balance. ARC neurons are projected to second-order targets such as the paraventricular nucleus (PVN), lateral hypothalamus (HyLat), parabrachial nucleus (PBN) and dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain. VTA dopaminergic neurons in the nucleus accumbens (Nacc) process the reward and motivational aspects of feeding, while taste-related cues from the oral cavity and gut-initiated viscerosensitive information are routed to the nucleus tractus solitarius (NTS). The NTS targets the PBN and also receives serotonergic input from raphe (Ra) such as the raphe obscurus (ROb) and raphe magnus (RMg), and exerts anorectic action through glutamatergic excitation of the PBN. The *Agrp* and *Pomc* are located close to the median eminence (ME), a circumventricular organ that allows peripheral signals to enter the blood–brain barrier: these include anorectic/catabolic leptin, synthesized primarily by adipose tissue; and the orexigenic signals of ghrelin, produced by the stomach. First-order AgRP and POMC neurons integrate metabolic inputs and have direct connections to brain regions processing reward and motivation together with food-related cues such as palatability and aversion. The central in-situ hybridization photos were downloaded from the *Allen mouse brain atlas* (Seattle, WA: Allen Institute for Brain Science, 2009; online at http://mouse.brain-map.org).

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 (Lep^{ob}), 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