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Commentary

Targeting AgRP neurons to maintain energy balance: Lessons from animal models

Sebastián Zagmutt[a], Paula Mera[a], M. Carmen Soler-Vázquez[a], Laura Herrero[a,b], Dolors Serra[a,b,*]

[a] Department of Biochemistry and Physiology, School of Pharmacy and Food Sciences, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, E-08028 Barcelona, Spain

[b] Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, E-28029 Madrid, Spain

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ABSTRACT

The current obesity epidemic is a major worldwide health and economic burden. In the modern environment, an increase in the intake of high-fat and high-sugar foods plays a crucial role in the development of obesity by disrupting the mechanisms governing food intake and energy balance. Food intake and whole-body energy balance are regulated by the central nervous system through a sophisticated neuronal network located mostly in the hypothalamus. In particular, the hypothalamic arcuate nucleus (ARC) is a fundamental center that senses hormonal and nutrient-related signals informing about the energy state of the organism. The ARC contains two small, defined populations of neurons with opposite functions: anorexigenic proopiomelanocortin (POMC)-expressing neurons and orexigenic Agouti-related protein (AgRP)-expressing neurons. AgRP neurons, which also co-produce neuropeptide Y (NPY) and γ-Aminobutyric acid (GABA), are involved in an increase in hunger and a decrease in energy expenditure. In this review, we summarize the key findings from the most common animal models targeting AgRP neurons and the tools used to discern the role of this specific neuronal population in the control of peripheral metabolism, appetite, feeding-related behavior, and other complex behaviors. We also discuss how knowledge gained from these studies has revealed new pathways and key proteins that could be potential therapeutic targets to reduce appetite and food addictions in obesity and other diseases.

1. Introduction

The hypothalamus is a region of the diencephalon located below the thalamus on each side of the third ventricle. It is composed of many small neuronal nuclei that integrate endocrine, nutritional and sensory signals, which culminate in the generation of precise neuroendocrine, behavioral, and autonomic responses aimed at controlling body homeostasis. Anatomically, the hypothalamus extends from the anterior commissure, lamina terminalis, and optic chiasm to the caudal limit of the mammillary bodies. Within these anatomical limits, hypothalamic nuclei are organized into the following zones and regions: preoptic area, composed of the medial and lateral preoptic nuclei; lateral zone, includes the lateral hypothalamic nucleus (LHA), and the tuberal nuclei; and the medial zone, subdivided into the anterior (or supraoptic) region, which contains supraoptic, paraventricular (PVH), suprachiasmatic, and anterior nuclei; the tuberal region, which contains ventromedial nuclei (VHM), the dorsomedial hypothalamic nucleus, and the arcuate nucleus (ARC); and finally the third region or mammillary part, which consists of the medial, intermediate, and lateral mammillary and posterior hypothalamic nuclei.

The first experiments connecting the hypothalamus with the regulation of energy balance and food intake were done by Hetherington and Ranson over 70 years ago. Their studies reported that lesions in the VHM nuclei of rats caused hyperphagia and obesity [1]. Later, Anand and Brobeck demonstrated in 1951 that bilateral destruction of the lateral portion of the LHA causes complete inhibition of food intake [2].

Abbreviations: ARC, arcuate nucleus; POMC, proopiomelanocortin; GABA, γ-aminobutyric acid; LHA, lateral hypothalamic nucleus; VHA, ventromedial nuclei; PVH, paraventricular; PBN, parabrachial nuclei; MSH, melanocyte-stimulating hormone; CART, amphetamine-stimulating hormone transcript; ChR, channelrhodopsin; DREADDs, designer receptor exclusively activated by designer drugs; CNO, clozapine; PI3K, phosphoinositide 3-kinase; PIP_3, phosphatidylinositol-3,4,5-triphosphate; FOXO1, forkhead box O1; BSX, brain specific homeobox; BAT, brown adipose tissue; ICV, intracerebroventricular; FAs, fatty acids; AMPK, AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; CPT1, carnitine palmitoyltransferase 1; FAS, fatty acid synthase; MCD, malonyl-CoA decarboxylase; SNS, sympathetic nervous system; WAT, white adipose tissue; ATF4, activating transcription factor 4; UCP1, uncoupling protein 1

* Corresponding author at: Department of Biochemistry and Physiology, School of Pharmacy and Food Sciences, Universitat de Barcelona, E-08028 Barcelona, Spain.

E-mail address: dserra@ub.edu (D. Serra).

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These results gave rise to the “dual-center hypothesis”, which suggests that VHM and LHA are the hypothalamic centers that regulate satiety and appetite respectively [3]. Nonetheless, following studies have further established that ARC nuclei play a more crucial role in the regulation of food intake and energy balance.

The relevance of the ARC was identified with the discovery of the melanocortin system, which plays a key role in a number of homeostatic processes [4,5], and reviewed elsewhere [6,7] The melanocortin system consists of 1) melanocortin peptides (α-, β-, and γ-melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone) derived from the precursor proopiomelanocortin (POMC); 2) five melanocortin receptors (MCRs, MC1R-MC5R, MC3R and MC4R are particularly involved in food intake energy balance regulation), which are widely expressed in the hypothalamus; and 3) the endogenous melanocortin antagonist (AgRP). All these components are expressed mainly in two populations of hypothalamic neurons: neurons that co-produce AgRP, NPY, and GABA (AgRP/NPY neurons) [8,9] and neurons that co-produce POMC and cocaine and amphetamine-stimulating hormone transcript (CART) (POMC/CART neurons) [10] Both are located at the base of the hypothalamus in close proximity to fenestrated capillaries. POMC/CART neurons and AgRP/NPY neurons exert opposite functions and are reciprocally regulated (Fig. 1). While POMC/CART neurons express anorexigenic peptides and have appetite-suppressing functions, AgRP/NPY neurons express orexigenic peptides and have an appetite-stimulating role. NPY acts as a neurotransmitter in the brain and is thought to have several functions besides food intake, including regulation of fat storage [11]. The appetite-stimulating response to NPY is mediated by multiple NPY receptor subtypes, which are all Gi protein-coupled receptors. There are six identified NPY receptors, but the Y1 and Y5 isoforms are most strongly associated with the effect of NPY on feeding revised in [12]. Furthermore, AgRP/NPY neurons also release AgRP neuropeptide, a melanocortin antagonist that prevents the binding of α-MSH onto MC3R and MC4R, thus activating hunger [13]. AgRP/NPY neurons also release GABA. GABA is an inhibitory neurotransmitter, and may exert its orexigenic action through GABAergic-mediated inhibition of POMC/CART neurons [14].

In recent decades, many animal models have been used to establish the relevance of this system in food intake and energy balance regulation. In this review, we analyze the techniques and approaches used to generate these animal models and their contribution to dissecting the molecular mechanisms and specific roles of AgRP/NPY neurons (thereafter AgRP neurons) on the modulation of peripheral glucose and lipid metabolism, thermogenesis, food intake, feeding behaviors, and other complex behaviors beyond feeding. We believe that this comprehensive review will help researchers in the field in search of specific pharmacological strategies to fight against excessive eating, obesity, and derived diseases.

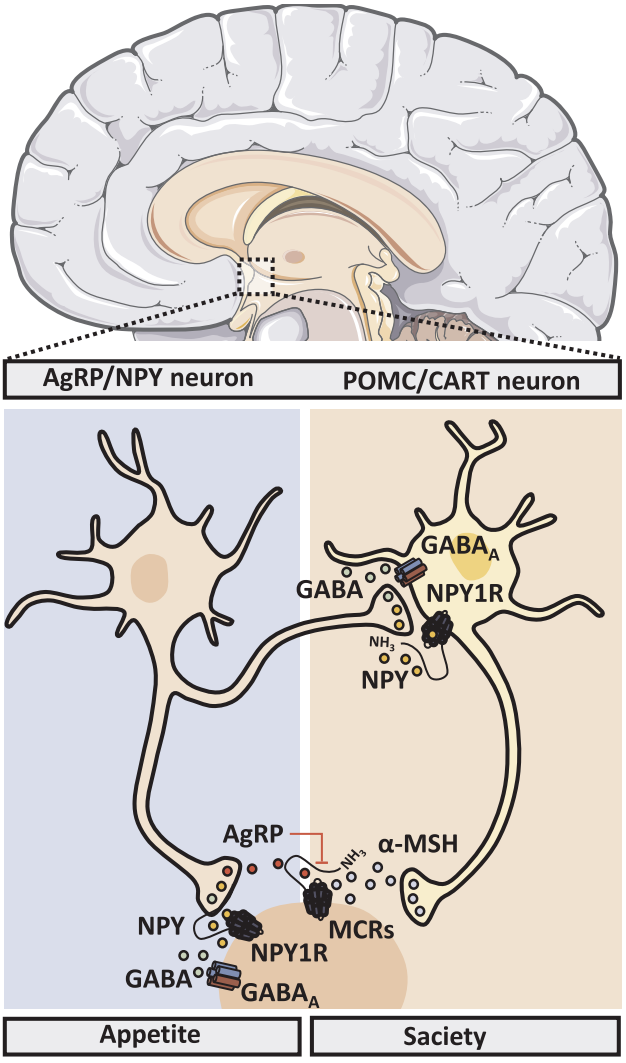

Fig. 1. Melanocortin system. AgRP/NPY and POMC/CART neurons are located at the base of the hypothalamus in close proximity to fenestrated capillaries. POMC neurons exert an anorexigenic function and increase energy expenditure through the expression of the post-transcriptional product of the POMC gene, including α-melanocyte-stimulating hormone (α-MSH), β-MSH, γ-MSH that binds to the melanocortin receptor (MCR), an anorexigenic target. NPY/AgRP neurons increase food intake and decrease energy expenditure through the release of neuropeptide Y (NPY), γ- amino-butyric acid (GABA), and agouti-related protein (AgRP). NPY act through NPY1R and NPY5R, while AgRP antagonize α-MSH action and GABA is an inhibitory neurotransmitter that exerts orexigenic action through GABAergic-mediated inhibition of POMC neurons.

2. Animal models targeting the activity of AgRP neurons

One of the oldest genetic models that demonstrated the involvement of the agouti protein in energy balance regulation is the lethal yellow A^y mouse, which expresses the agouti protein in all tissues [15]. This mouse develops an obesogenic phenotype characterized by excessive food intake, hyperinsulinemia, and increased body weight. The study of A^y mice also showed that the agouti protein acts as an antagonist at MC1R and MC4R. Subsequently, using knock-out techniques, the genetic deletion of MC4R (MC4R-KO) further contributed to the understanding of the melanocortin system and its role in energy homeostasis. MC4R-KO mice also display hyperphagia and obesity under free-feeding conditions [16,17]. Despite this, AgRP-deficient mice show normal food intake, body weight, and energy expenditure, and only a significant impairment in the regulation of body weight during aging [18]. Furthermore using the Cre-loxP system, a large number of genes have been deleted from AgRP neurons in an effort to dissect the molecular mechanisms involved in the main physiological roles of this set of neurons [14,19,20]. Taken together, these studies suggested that the various components of the melanocortin system and specific AgRP genes might contribute differently to the regulation of food intake and energy balance, and thus motivated additional studies in the field.

In recent years, several biotechnological tools have been developed and applied to study the physiological role of AgRP neurons. The optogenetic approach combines genetic and optical methods to control and monitor the activity of single neurons in living tissues [21,22]. This groundbreaking technique is based on the expression of microbial opsins, such as channelrhodopsin (ChR) or halorhodopsin, which are light-gated proteins that directly regulate the flow of ions across the plasma membrane. Thus, in mice expressing opsins, light stimulation might inhibit or stimulate the activity of specific neuronal populations. The analogous pharmacosynthetic chemogenetic approach, known as the designer receptor exclusively activated by designer drugs (DREADDs), has also been used to control the activity of a single