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Review

Neural melanocortin receptors in obesity and related metabolic disorders ☆

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ABSTRACT

Obesity is a global health issue, as it is associated with increased risk of developing chronic conditions associated with disorders of metabolism such as type 2 diabetes and cardiovascular disease. A better understanding of how excessive fat accumulation develops and causes diseases of the metabolic syndrome is urgently needed. The hypothalamic melanocortin system is an important point of convergence connecting signals of metabolic status with the neural circuitry that governs appetite and the autonomic and neuroendocrine system controling metabolism. This system has a critical role in the defense of body weight and maintenance of homeostasis. Two neural melanocortin receptors, melanocortin 3 and 4 receptors (MC3R and MC4R), play crucial roles in the regulation of energy balance. Mutations in the *MC4R* gene are the most common cause of monogenic obesity in humans, and a large literature indicates a role in regulating both energy intake through the control of satiety and energy expenditure. In contrast, MC3Rs have a more subtle role in energy homeostasis. Results from our lab indicate an important role for MC3Rs in synchronizing rhythms in foraging behavior with caloric cues and maintaining metabolic homeostasis during periods of nutrient scarcity. However, while deletion of the *Mc3r* gene in mice alters nutrient partitioning to favor accumulation of fat mass no obvious role for *MC3R* haploinsufficiency in human obesity has been reported. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

1. Introduction

Obesity is one of the major health issues faced by society in the 21st century [1–3]. Over the last three decades, the number of persons categorized as obese (body mass index of >30 kg/m^2) has risen dramatically in high-income countries and is now also increasing in developing nations. The World Health Organization reported that more people die as a result of conditions resulting from obesity compared to those associated with malnutrition and being underweight. Obesity alters the body's ability to regulate homeostasis and is almost invariably associated with hyperinsulinemia indicating insulin resistance. Obesity is also associated with increased risk of hyperlipidemia and hypertension [4]. Collectively, these conditions are associated with increased prevalence of type 2 diabetes and cardiovascular disease [5]. Strategies for preventing as well as attenuating obesity and its comorbidities are urgently needed.

Simply stated, preventing weight gain requires coordinating calorie intake with energy requirements over time. The homeostatic control of adiposity involves both peripheral and central mechanisms acting in concert [6,7]. For historical reasons, the examination of pathways in the central nervous system initially focused on the hypothalamus. Lesions in the paraventricular (PVN), arcuate (ARC) or ventromedial nuclei of the hypothalamus (VMH) had been observed nearly a century ago to cause hyperphagia and obesity [8,9]. Mouse genetics had the key role in providing leads in the identification of specific neural substrates involved. This review focuses on the central nervous melanocortin system. An abundant literature has developed describing how this system regulates energy balance. First order melanocortin neurons situated primarily in the arcuate nucleus of the hypothalamus (ARC) are regulated by many signals of metabolic status. The transmission of this information about the energy status acts on target neurons expressing two members of the melanocortin receptor family.

This review begins by providing an overview of the melanocortin system and its integration in the neural network involved in the regulation of body weight and metabolic homeostasis. It will then focus on the current understanding of the role of neural melanocortin receptors, the well-known MC4R and the poorly understood MC3R in preventing obesity. Discussions on how the melanocortin system integrates signals from the periphery have been provided in several recent reviews on the regulation of melanocortin neurons that release the endogenous ligands for the melanocortin receptors [10,11].

2. Overview of the melanocortin system

2.1. The melanocortin family: six endogenous ligands and five receptors

The melanocortin receptors are members of the G protein coupled receptor (GPCR) family. Stimulation by melanocortin agonists is associated

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with increased accumulation of cAMP by increased activation of adenylyl cyclase. The five receptors (MC1R to MC5R) were named in order of their cloning [12–24]. The melanocortin receptors have a broad distribution, being expressed throughout the body. MC3R and MC4R are referred as the neural MCRs due to their high expression in the brain, although they also exhibit expression in peripheral tissues [14,25,26].

The melanocortin ligands are produced by proopiomelanocortin (POMC), a preprohormone post-translationally processed by pro-hormone convertases (PC1/PC2) to produce the melanocortins, β-endorphin (β-END), and β- and γ-lipotropin (LPH; Fig. 1). POMC is expressed in the brain, anterior and intermediate lobes of the pituitary, skin and many peripheral organs. The post-translational processing of POMC varies between tissues. Adrenocorticotrophic hormone (ACTH) is produced in the anterior lobe of the pituitary. In the central nervous system, only the melanocyte stimulating hormones (MSH), α-MSH, β-MSH and γ –MSH, are produced with an exception in rodents that lack the N-terminal cleavage site for β-MSH [27].

ACTH, α-MSH, β-MSH, and γ-MSH exhibit agonist activity, albeit with variable degrees of specificity. When agonism is defined as stimulation of cAMP accumulation in cell-based assays, α-, β- and γ-MSH all exhibit agonist activity in cell lines expressing MC1R, MC3R, MC4R and MC5R. However, the MC2R is unique in showing affinity only for ACTH. While γ-MSH exhibits modest selectivity for MC3R, it is still a functional agonist for the other MCRs (Fig. 1) [28,29]. There are three different isoforms of γ-MSH (γ1-, γ2- and γ3-MSH) which may have variable biological activity [30].

The melanocortin receptors are unique when compared to other members of this family in that endogenous antagonists were also identified soon after their cloning. Agouti and Agouti related peptide (AgRP) interact with specific melanocortin receptors to inhibit the activity of MSH. The expression of agouti in mouse is primarily found in the skin, in the cells of the dermal papilla [31] consistent with its role in the regulation of hair-pigment production by melanocyte, but it is also present in testis [32]. The human homolog, agouti signaling protein (ASIP), has been reported to be also expressed in the adipose tissue [33]. AgRP is expressed in the brain, adrenal gland, testis, lung and kidney [34].

Both agouti and AgRP were initially described to function as selective competitive antagonists. Agouti was reported to act as an antagonist for the MC1R and MC4R, while AgRP was reported to function as an antagonist for the MC3R and MC4R [35]. While it is true that agouti and AgRP act as competitive antagonists that prevent binding of MSH, subsequent studies indicated that binding of these peptides to melanocortin receptors results in activation of signaling pathways. Soon after its identification, AgRP was reported to exhibit inverse agonist properties inhibiting the high level of basal activity of MC4Rs [36,37] and MC3Rs [38] in the absence of α-MSH. More recently, it was reported that AgRP could stimulate coupling of MC4R expressed in a hypothalamic neuronal cell line (GT1-7) to the Gi/o subunit [39]. Interestingly, the electrophysiological characterization of the response of neurons to AgRP in the ventromedial hypothalamus has also indicated the involvement of Gi/o-dependent pathways [40]. The relevance of *in vivo* inverse agonism of AgRP is supported by results showing that central administration of AgRP to neuronal specific POMC deficient mice induces a delayed increase in food intake and reduction in oxygen consumption [41]. However, this finding has been questioned with no difference in the obese phenotype of double *Pomc*−/−; *Agrp*−/− mice compared with *Pomc*−/− mice [42,43]. Inverse agonism by agouti at the MC1R has also been suggested to have a functional relevance as it is responsible for the yellow coat color of obese A^y/a mice [44,45].

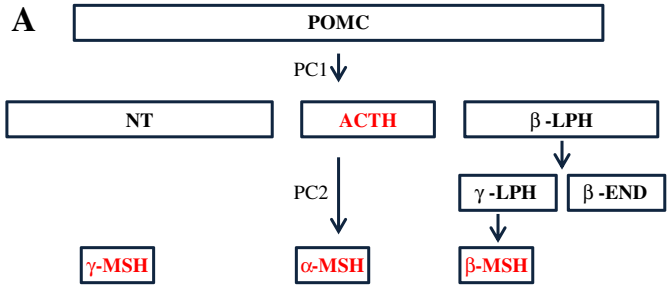
A common feature of several GPCRs is the observation that agonist binding promotes receptor internalization following the recruitment of β-arrestins. The recruitment of β-arrestins and the consecutive internalization of the neural MCRS are observed following binding of either AgRP or α-MSH [46]. Collectively, these findings suggest that MSH and AgRP function as biased agonists and that the regulation of the coupling of MC4R involves both stimulatory or inhibitory G proteins [39,40,47]. It has also been proposed that melanocortin effect on energy expenditure is mediated via Gs, whereas action on food intake involves other signaling [48].

The development of resonance energy transfer techniques has enabled the visualization of GPCR interactions. Much has been learnt on GPCR dimerization/oligomerization, and this is now increasingly accepted as a general phenomenon that results in changes in the biochemical characteristics of GPCRs. Both neural melanocortin receptors have been reported to form heterodimers with other GPCRs [49–53].

2.2. Anatomy of the central melanocortin system

The hypothalamic melanocortin system is a point of intersection in the neurocircuitry connecting appetite and the autonomic and neuroendocrine control of metabolism with signals of metabolic status to defend body weight. Within the brain, two different neuronal populations expressing POMC have been distinguished by their anatomical site. The largest population is located in the hypothalamus, and more specifically in the lateral part of the ARC. This population coexpresses the cocaine amphetamine-related transcript (CART) [54]. A second smaller population is located in the brainstem, in the nucleus of tractus solitarii (NTS). The neuronal population expressing AgRP is restricted to the medial ARC and co-expresses neuropeptide Y (NPY) [55,56]. The pattern of the distribution of AgRP and POMC neuronal projections is similar in the forebrain, however only POMC neurons may send projections to the brainstem [57].

The two distinct neuronal populations described above are considered to have opposite effects on energy homeostasis. POMC neurons via release of MSH inhibit food intake, while AgRP neurons promote food intake. The development of new techniques allowing remote control of neuronal activity either via light-activated ion channels (optogenetic) or via stimulation of "designer" GPCRs (DREADD, Designer Receptors Exclusively Activated by Designer Drug) have helped to clearly establish that acute stimulation of AgRP neurons is sufficient to initiate feeding [58,59]. On the other hand, photic stimulation of channel rhodopsin expressed by POMC neurons decreases food intake [58]. Mice lacking *Pomc* gene products are hyperphagic and obese [60–63]. AgRP over-expressing mice are a mouse model of obesity [35,64]. Unexpectedly, neonatal deletion of AgRP did not produce a lean phenotype [65].



B

Receptor	Ligand affinity at receptor
MC1R	α-MSH =ACTH>β-MSH>γ-MSH
MC2R	ACTH
MC3R	γ-MSH>α-MSH=β-MSH>ACTH
MC4R	α-MSH =β-MSH>ACTH>>γ-MSH
MC5R	α-MSH >ACTH>β-MSH>γ-MSH

Fig. 1. The melanocortin peptides and their receptors. Structure and processing of POMC hormone precursor (A). Affinity of MCRs for the melanocortins (B).