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Review

Melanocortins and body weight regulation: Glucocorticoids, Agouti-related protein and beyond

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ABSTRACT

In the intervening three decades since Panksepp observed for the first time that centrally administered α-melanocyte stimulating hormone decreased food intake (Panksepp and Meeker, 1976), a wealth of data have accrued to firmly establish melanocortin signaling as a central regulator of food intake and fat mass. Advances in molecular biology have not only allowed detailed studies of spontaneously occurring obese mice with altered melanocortin signaling to be undertaken but also permitted the generation of a plethora of mouse models with precise perturbations at critical steps in the melanocortin system to finesse further the cellular and molecular architecture of relevant pathways. In this article we focus in upon a number of these mouse models which continue to help us tease apart the complexities of this critical system. Further, we review data on the important interaction between pro-opiomelanocortin derived peptides and the adrenal system and the relationship between agonist and antagonist peptides acting at central melanocortin receptors.

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1. Introduction

1.1. Pro-opiomelanocortin (POMC)

Pro-opiomelanocortin (POMC) is the archetypal polypeptide precursor. *In toto* it is functionally inert but requires extensive, tissue-specific post-translation modification to generate a range of smaller, biologically active peptides. These include adrenocorticotrophic hormone (ACTH) and α-, β- and γ-melanocyte stimulating hormone (MSH), collectively known as the melanocortins. The action

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of the melanocortin peptides is mediated by a family of five G protein-coupled seven transmembrane domain receptors, known as melanocortin receptors type 1 to type 5 (melanocortin MC_1 receptor to melanocortin MC_5 receptor). Melanocortin MC_1 receptor is expressed on melanocytes, melanocortin MC_2 receptor is expressed in the adrenal cortex and is the target for pituitary-derived ACTH whilst melanocortin MC_5 receptor is found in sebaceous glands. However, the melanocortin MC_3 and MC_4 receptors are both highly expressed in regions of the brain known to be involved in the control of food intake and energy balance (Cone, 1999).

1.2. The central melanocortin system

The hypothalamus acts as a primary sensor of alterations in energy stores by receiving and integrating neural, metabolic and humoral signals from the periphery. Within the arcuate nucleus of the hypothalamus are two separate populations of neurons which express either POMC or both neuropeptide Y and Agouti-related protein (AgRP) (Schwartz et al., 2000). A unique feature of the central melanocortin system is that in addition to the range of POMC-derived ligands, there exists a second peptide produced in the hypothalamus that has biological activity at melanocortin receptors. Thus, whereas POMC-derived melanocortins α- and β-MSH are agonists, AgRP is a potent melanocortin antagonist at the melanocortin MC_3 and MC_4 receptors (see below for further exploration of the role of AgRP). From the arcuate nucleus, these two populations of neurons project to other brain areas that are involved in energy homeostasis. These include other hypothalamic regions such as the paraventricular nucleus, lateral hypothalamus and the dorsomedial nucleus. In addition to the hypothalamus, POMC neurons are also found in the brainstem, in particular within the nucleus of the solitary tract. The nucleus of the solitary tract is the primary site for innervation by vagal afferents from the gut (Schwartz, 2000) and it may be that the melanocortin system within the nucleus of the solitary tract may also be important in integrating short-term gut-derived satiety signals (Fan et al., 2004). Indeed, there do appear to be some intriguing and important differences between POMC neurons in the nucleus of the solitary tract and the arcuate nucleus. A study from Bjorbaek's group demonstrated that although fasting induced a fall in POMC mRNA in both regions, in contrast to the arcuate nucleus, this reduction was not reversed by leptin administration (Huo et al., 2006). Furthermore, again in sharp contrast to the arcuate nucleus, leptin did not cause STAT-3 phosphorylation or c-fos activation within nucleus of the solitary tract POMC neurons, suggesting therefore that leptin signaling via POMC-derived peptides in the central nervous system (CNS) occurs entirely via hypothalamic POMC neurons.

2. POMC deficiency

The first report of the phenotype of two children congenitally lacking POMC gene products appeared in 1998. As a result of ACTH deficiency, both subjects presented in early childhood with the metabolic consequences of hypocortisolemia and went on to develop severe, early-onset obesity associated with hyperphagia, due to reduced hypothalamic melanocortinergic signaling. Both probands also had pale skin and red hair because of reduced signaling through melanocortin MC_1 receptor on melanocytes in skin and hair follicles. Three additional children with an identical phenotype have subsequently been reported by the same group. More recently, however, colleagues in Cambridge have reported a child of Turkish origin with severe obesity and hypoadrenalism due to POMC deficiency who does not have red hair (Farooqi et al., 2006). The retention of dark, eumelanin-rich hair in this child indicates that eumelanin synthesis in humans has no absolute requirement for melanocortin peptides and indicates that, just as in mice, additional genetic factors are likely to contribute to how the index monogenic defect is reflected in the final phenotype (Smart and Low, 2003).

This aside, the first report of a mouse model with disruption of both alleles of the POMC gene (Yaswen et al., 1999) essentially recapitulated the phenotype seen in humans, indicating that melanocortin pathways in humans and rodents subserve very similar physiological functions. We have also extensively studied a second, independent line of mice lacking all POMC-derived peptides that are also markedly obese, hyperphagic and have both altered pigmentation and adrenal insufficiency (Fig. 1). This increase in weight is as a result of an increase in both fat and lean mass. Additionally, Pomc null ($Pomc^{-/-}$) mice have a lower basal metabolic rate than their wild type litter mates, which may be due in part to reduced activity of the hypothalamic-pituitary-thyroid axis. More recently, Xu et al. have generated a further corticosterone-deficient mouse model of POMC deficiency by deletion of the critical mitochondrial transcription factor, Tfam, from POMC expressing cells (Xu et al., 2005). These mice exhibited a progressive adult-onset obesity with an increase in both fat and lean mass.

3. POMC and dietary fat

We have used *Pomc* null mice to determine how *Pomc* haploinsufficiency might interact with changes in dietary composition. On standard chow, only homozygous mutant mice became obese, with mice heterozygous for the mutant allele ($Pomc^{+/-}$) achieving an adult weight similar to that of wild type mice. However, with high fat feeding (45% fat), $Pomc^{+/-}$ mice also became obese. At 6 months of age they weighed 20% more than wild type littermates, who failed to develop obesity on high fat diet. The development of obesity in heterozygous mice was the result of increased energy intake, with $Pomc^{-/-}$ and $Pomc^{+/-}$ eating 40% and 18% more than wild type mice, respectively. Thus under certain environmental conditions, a single functional copy of the Pomc gene is not sufficient to maintain normal energy homeostasis. Additional evidence for this hypothesis comes from the findings that none of the 10 adults heterozygous for *POMC* mutations reported by Krude et al. had a low-normal BMI value, with body weight in heterozygous mutation carriers shifted to the high-normal +1 BMI-SDS or even overweight range of +2 BMI-SDS (Krude et al., 2003). The availability of a large extended pedigree related to the Turkish *POMC* null proband highlighted above provided the opportunity to address whether loss of one copy of the POMC gene was sufficient to alter obesity risk. Twelve relatives were heterozygous for the mutation and 7 were wild type. Of the 12 heterozygotes, 11 were obese or overweight compared with only 1 of the 7 wild type relatives. The mean BMI SD score was 1.7 ± 0.5 in heterozygotes and 0.4 ± 0.4 in the wild type relatives (Farooqi et al., 2006). Thus *POMC* haploinsufficiency may indeed shift the individual body weight to higher normal or mildly obese level.

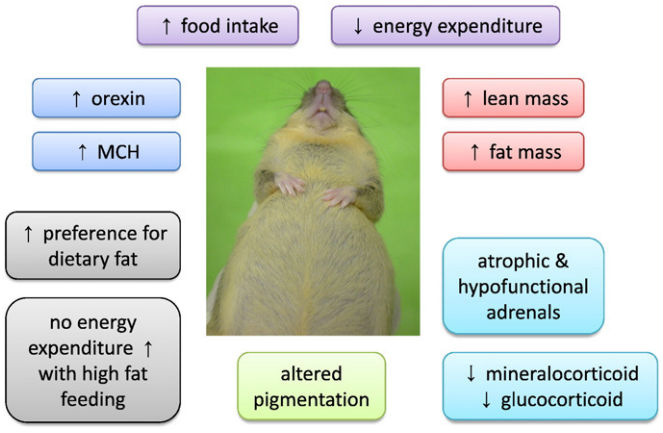

Fig. 1. Consequences of POMC deficiency.