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Review

Role of melanocortin in the long-term regulation of energy balance: Lessons from a seasonal model

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Abbreviations:
α-MSH, α-melanocyte stimulating hormone
AGRP, Agouti-related protein
ARC, arcuate nucleus
CART, cocaine- and amphetamine-regulated transcript
CRF, corticotrophin-releasing factor
icv, intracerebroventricular
LHA, lateral hypothalamus
MC3-R, melanocortin-3 receptor
MC4-R, melanocortin-4 receptor
MCH, melanin-concentrating hormone
MSG, monosodium glutamate
MTII, Melanotan-II

ABSTRACT

Siberian hamsters express photoperiod-regulated seasonal cycles of body weight and food intake, providing an opportunity to study the role of melanocortin systems in regulating long-term adaptive changes in energy metabolism. These hamsters accumulate intraperitoneal fat reserves when kept in long summer photoperiods, but show a profound long-term decrease in food intake and body weight when exposed to a short winter photoperiod. Icv administration of a MC3/4-R agonist (MTII) potently suppresses food intake in hamsters in both the obese and lean state, indicating the potential for melanocortin systems to regulate energy metabolism in the hypothalamus of the Siberian hamster. Icv treatment with the melanocortin antagonist SHU9119 increases food intake in both seasonal states. Moreover, hamsters bearing neurotoxic lesions, which destroy the majority of POMC expressing neurons in the arcuate nucleus are still able to show seasonal regulation of body weight. These studies in a seasonal model substantiate the view that endogenous melanocortin systems exert a tonic inhibition of food intake in mammals. The observations that this melanocortin tone occurs to a similar extent in both an anabolic state induced by a long day photoperiod, and in a catabolic state induced by a short day photoperiod, suggests that alterations in endogenous melanocortin tone are not the primary cause of the lipolysis, weight-loss and hypophagia which characterize the establishment of the short day-induced overwintering state.

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NPY, neuropeptide Y
OB-Rb, leptin receptor
POMC, pro-opiomelanocortin
PVN, paraventricular nucleus
PYY, peptide YY
SOCS3, cytokine signaling-3
STAT, signal transducer and activator of transcription

Contents

1. Introduction

It is widely accepted that the melanocortin system plays a role in the central regulation of food intake and energy balance ([48] for review). Genetic mutations in melanocortin-4 receptors (MC4-R) or its associated signaling pathways have been found in some cases of morbid obesity in humans [63,21], and a variety of experimental approaches that have been carried out in laboratory rats and mice substantiate a role for melanocortin receptors in the regulation of energy balance. For example, neuroanatomical studies confirm that MC4-R mRNA is detected in the paraventricular nuclei of the hypothalamus, dorsomedial hypothalamus and the lateral hypothalamic area, all structures previously implicated in the control of feeding behavior [43]. MC4-R deficient transgenic mice are hyperphagic and obese [29] suggesting that this receptor has a role in the control of feeding, and targeted mutation the melanocortin-3 receptor (MC3-R) also results in increased adiposity [10,11]. Pharmacological studies also provide evidence for a role for melanocortins in the regulation of food intake. A major cleavage product of pro-opiomelanocortin (POMC), α-melanocyte stimulating hormone (α-MSH) or Melanotan-II (MTII), a synthetic MC3/4-R agonist, potently inhibit food intake in mice and rats [9,20,27,30,61]. Correspondingly, in both mice and rats, intracerebroventricular (icv) injections of the MC3/4-R antagonist SHU9119 [28] elicit an increase of food intake [20,25,58].

Collectively, these acute pharmacological or transgenic approaches in rodents demonstrate the potential for melanocortin pathways to be important homeostatic regulators of energy balance. What is not yet clear is whether chronic alterations in melanocortin signaling might contribute to the increasing prevalence in obesity, which is apparent in modern human culture [45,65]. This may be better addressed by studying the function of melanocortin pathways in rodents in which energy balance is chronically altered. Several groups have developed models of dietary induction of obesity in mice [8] or rats [16,37] for this purpose; we have investigated whether the function of melanocortin systems changes in mammals which show profound long-term annual cycles in adiposity and body weight. Annual cycles in body weight are relatively common in mammals, which have evolved strategies to survive in seasonal environments where changes in both energy supply and energy expenditure are anticipated [41]. In general, such species can accumulate caloric reserves stored as fat depots in seasons (spring–summer) when food supply is abundant, then catabolize these energy reserves as part of a winter survival strategy. Although small rodents including Siberian [36] and Syrian hamsters [31], and bank voles [46] have been popular models for experimental studies of such seasonal cycles, several commercially important larger mammals such as sheep also display such seasonal trends and significant inroads into the actions of melanocortin systems have been made in these species [15].

2. The Siberian hamster: a seasonal rodent

Our studies have focused on the Siberian hamster (*Phodopus sungorus*) because it is readily maintained in conventional animal husbandry units, has a wide range of seasonal cycles which can be synchronized and regulated solely by ambient daylength, and most importantly, shows a very striking seasonal change in body weight (Fig. 1). Under increasing or long summer photoperiod, the Siberian hamster reaches its maximum body weight, but under decreasing or short winter photoperiod, it enters a profound catabolic state, decreases its food intake and gradually loses body weight [19,39,59], mainly through a loss of intraperitoneal fat stores [6]. The reduction in body weight takes approximately 12–16 weeks to reach the maximum weight-loss of up to 40% of initial weight (Fig. 1) [40,49,50,59]. These seasonal changes in energy metabolism