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Animals models of MCH function and what they can tell us about its role in energy balance

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Abstract

Melanin-concentrating hormone (MCH) has attracted considerable attention because of its effects on food intake and body weight and the MCH receptor (MCHR1) remains one of the viable targets for obesity therapy. This review summarizes the literature examining the effects of MCH on body weight, food intake and energy expenditure in rodent models, and the central sites where MCH acts in regulating energy homeostasis. Emphasis is given on the discrepancies between the genetic and pharmacologic models of MCHR1 inactivation. We propose some solutions to resolve these discrepancies and discuss some future directions in MCH research.

Introduction

Melanin-concentrating hormone (MCH) is a peptide originally isolated from fish as a regulator of skin color [22]. The mammalian melanin-concentrating hormone (MCH) is a 19 amino acid cyclic peptide selectively expressed in lateral hypothalamic neurons. MCH neurons project widely throughout the central nervous system from the olfactory bulb to the spinal cord [6]. MCH acts through two G-protein coupled receptors MCHR1 and -2 in humans, dogs and ferrets but rodents express only MCHR1 [58]. The position of the MCH neurons in the lateral hypothalamic area, the widespread projections of the MCH neurons and the broad expression of the MCHR receptors suggested that this peptide might regulate various functions such as arousal, sensorimotor integration and motivated behaviors [37]. Several recent reviews summarize the various functions of MCH [40] [38,45]. In this manuscript, we focus on the regulation of appetite and energy expenditure by MCH.

Genetic manipulation of MCH expression

The first mouse model of MCH deletion published by the Maratos-Flier lab [51] demonstrated the role of MCH in energy balance with decreased body weight and resistance to diet induced obesity (DIO). Lower food intake and increased energy expenditure were proposed to account for the body weight phenotype. The mice in this study were on a mixed background (129SvJXC57BL6) and crossing of this mouse model to different backgrounds produced slightly different phenotypes, albeit both DIO resistant. MCH-KO mice on C57BL/6 background increased their activity and energy expenditure but MCH-KO on the 129/SvEv background were actually hyperphagic with increased energy expenditure accounting for their leanness [24]. The reduced adiposity of MCH-KO mice persists at least for 19 months with significantly improved glucose homeostasis [21].

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The Maratos-Flier group has also reported an overexpression model of MCH [28]. Approximately a 2-fold increase in MCH expression was adequate to cause moderate obesity and increase food intake in mice. High-fat diet feeding was required to reveal the obese phenotype on the FVB background but the obesity prone C57BL/6 background revealed the obese phenotype even on the low-fat chow diet. It was noted that the hyperinsulinemia in this background was disproportionate to the degree of obesity, suggesting an effect of MCH on the islet independent of obesity [28]. Later studies showed that MCH has direct effects on the beta cells, suggesting that MCH might have peripheral actions in addition to central effects in regulating glucose metabolism [56] [42].

Recently, a mouse model expressing the ataxin-3 toxin in MCH neurons has been reported [2]. Approximately 60–70% of MCH-expressing neurons progressively degenerate in the first few weeks in life leading to late onset leanness, hypophagia and increased energy expenditure. Crossing of the MCH/ataxin-3 mouse with the ob/ob mouse resulted in decreased body weight and significantly reduced blood glucose. The MCH/ataxin-3 mouse essentially recapitulates the MCH-KO mouse phenotype. This finding suggests that MCH is the main peptide in these neurons regulating energy homeostasis, although the contribution of other peptides (NGE, NEI, CART) and classical neurotransmitters (GABA) encoded by these neurons cannot be excluded. Perhaps significantly, this mouse model shows hypophagia, which is consistent with the action of MCH as an orexigenic peptide. This finding contrasts to the other models of MCH or MCHR1 deletion (see below), which show either no changes in food intake or hyperphagia. Although the MCH neurons express other neurotransmitters in addition to MCH, it is tempting to speculate that the relatively late onset deletion of MCH neurons limits the compensatory response of the central nervous system to MCH absence, revealing the orexigenic function of MCH in this model.

Genetic inactivation of MCHR1 expression

Mice have one G-protein coupled receptor with high affinity for MCH (MCHR1) expressed widely in the central nervous system [4,11,26,46,52]. The MCHR1 was genetically ablated independently by several groups [3,12,32]. All studies consistently show increased leanness (decreased adiposity) in MCHR1-KO mice on chow diet and more prominently on a high fat diet. The major mechanism behind the leanness appears to be increased energy expenditure, with likely contribution from increased locomotor activity and from increased resting energy expenditure. The increase in the resting energy expenditure appears to be at least in part through the increase in sympathetic activity in MCHR1-KO mice and likely through the brainstem projections of MCH neurons [3]. Paradoxically, MCHR1-KO mice show significant hyperphagia and also hyperactivity. Since treatment with MCHR1 antagonists do not increase but rather decrease food intake in rodents (see below), the observed hyperphagia in MCHR1-KO mice has been interpreted as a compensatory response of the MCHR1-KO mice to the decreased adiposity or as a developmental aberration of unclear physiological significance caused by the absence MCHR1 signaling during development. The hyperactivity phenotype has also been followed up with several studies showing increased sensitivity of the mesolimbic dopamine system in the MCHR1-KO and MCH-KO mice [41,53,54,60,62]. In contrast, treatment of rodents with MCH or MCHR1 antagonists does not change their locomotor activity [17,50]. This discrepancy makes the role of MCH in regulating locomotor activity unclear, but it points out to an important region of MCH actions outside the hypothalamus (nucleus accumbens) involved in reward to food.

Effect of MCH deletion in leptin-deficient background

Both MCH-KO and MCHR1-KO mice have been crossed with the leptin-deficient ob/ob mice. Crossing the MCH-KO mice to the leptin-deficient background caused a significant reduction

in body weight of the double null mice with improved glucose homeostasis. The weight loss occurred despite similar food intake of the double knockout mouse to the ob/ob mouse suggesting that increased energy expenditure (app. 25%) and 3-fold increased locomotor activity (3-fold) accounted for the leanness in this model [49]. When exposed to cold, the double knockout mice maintained their temperature better than the ob/ob mice. Evidence for increased thermogenesis in this model was also supported by the increased UCP-1 expression in the brown adipose tissue [49].

Some differences between the two models emerged when MCHR1-KO were crossed to the leptin-deficient background. The mice did not have decreased body weight compared to ob/ob mice, but adiposity decreased and glucose homeostasis improved in the double knockout mice [7]. Improved core body temperature was also noted but UCP-1 levels were not changed. The absence of weight loss contrasts with the phenotype of the MCH ob/ob double knockout mice, which are significantly leaner. One hypothetical explanation for the discrepancy between the peptide and the receptor knockouts could be the activity of other neuropeptides encoded by the proMCH gene, NEI or NGE, which are deleted in the MCH-KO but present in the MCHR1-KO mice. Although NEI has been reported to have locomotor and behavioral effects in rodents [48] its role if any in body weight regulation will need to be resolved by additional experiments.

Central effects of MCH on energy balance

The first report of the orexigenic effect of MCH in rats was published by in 1996 by the Maratos-Flier lab and stimulated the interest in the action of this peptide. The effect is transient, it lasts for 2–4 hours and results in 2–3 fold increase in cumulative food intake [43,44]. In comparison to NPY, the prototypical orexigenic peptide, the effect of MCH on food intake is similar in duration with that of NPY but more modest in magnitude (MCH 2–3 fold vs NPY 8-fold) [27,55]. The effect of MCH administration is not limited to food as it also increases sucrose and alcohol intake [15,47]. Water intake is also increased by MCH independently of food intake [13,36]. Several studies examined the effect of chronic MCH infusion on food intake and body weight in mice and rats [14,17,50]. Chronic infusion of peptide MCH agonist in rats increased cumulative food intake and body weight gain on a moderately high fat diet by 38% compared to a control group [50]. Increased caloric efficiency with MCH infusion was also noted, suggesting that MCH infusion promotes not only the accumulation of calories though increasing food intake but also promotes their storage in the adipose tissue [50]. Similarly, chronic infusion in mice increased food intake and body weight gain. The effect of MCH was apparent even on chow diet but was exaggerated by a moderately high fat diet [17]. Increased food intake appears to account for most of the observed increase in body weight because pair-feeding the MCH-infused groups normalized the body and fat pad weight [20]. However, increased lipogenesis in the liver and white adipose tissue were not normalized by pair-feeding suggesting that MCH might affect peripheral lipid metabolism independent of its effects on food intake and body weight [20]. A recent study also supports this observation [18]. The precise sites of MCH actions in affecting peripheral substrate utilization are only now being investigated and should provide important insight into the metabolic effects of MCH.

Effects of MCHR1 antagonists on energy balance

Several peptidic antagonists for the MCHR1 have been synthesized in an attempt to decrease body weight by pharmacological manipulation of the MCHR1 signaling [5]. Acute injections of MCHR1 antagonists do not produce a significant decrease in food intake but, as expected, block the orexigenic effect of MCH [33,36,50]. On the other hand, central nervous system infusions of peptidic MCHR1 antagonists over 14 days reduced food intake by 16% and body weight gain by 35% in rats [50]. Similar results are also seen with mice. Chronic infusion of MCHR1 antagonists over a 4-week period also completely prevented the body weight increase

in mice fed a high fat diet. It decreased the adiposity, fat pad weight and improved the hepatosteatosis of MCHR1 antagonist infused group. Blood glucose, insulin and cholesterol were also improved [33]. Importantly, the same antagonist is ineffective in reducing food intake and body weight in MCHR1-KO mice, demonstrating that the selective manipulation of the MCH system is responsible for the observed changes [33]. No changes in locomotor activity were observed in the studies with either the peptidic agonists or antagonists of MCHR1, suggesting that the locomotor phenotype is unique to the genetic models of MCH or MCHR1 inactivation.

Pharmaceutical companies have devoted a considerable effort in the development of small molecule antagonists for the MCHR1. Several structurally distinct small molecule antagonists have been synthesized and tested in cell-based assays for their selectivity and affinity and for potency in rodents. Comprehensive review of these experiments is outside the scope of this review. For examples of the hurdles the pharmaceuticals companies face in achieving the desired selectivity and efficacy of MCHR1 antagonists interested readers should consult some recent reviews [30,34]. In agreement with the peptide infusions described above, the small molecule antagonists of MCHR1 consistently reduce body weight and protect against DIO. The first reports in 2002 demonstrated that small molecules MCHR1 antagonists are a viable approach for obesity therapy [9,57]. The first orally active MCHR1 antagonist was published by Takeda and was effective in reducing food intake stimulated by icv injection of MCH in rats [57]. Another compound, SNAP-7491 (Synaptic) was also effective in blocking MCH-induced increase in food intake. Daily administration of SNAP-7491 reduced body weight gain in lean rats. The compound was also effective in reducing the weight of DIO rats by 26% after 4 weeks of treatment [9]. Several other small molecule MCHR1 antagonists have been synthesized by pharmaceuticals companies and many studies show their effectiveness in reducing food intake and body weight in rodents. It is unclear what the relative contribution of energy expenditure and reduced food intake is in producing weight loss with these compounds, as most of these studies do not report data on energy expenditure, for examples see [25,31,59].

Although most of these compounds are screened for specificity, some affinity towards others receptors (e.g. serotonin receptors) has been observed with some classes of MCHR1 antagonists [30]. Therefore the contribution of others receptors in reducing food intake cannot be excluded and ideally these compounds should be evaluated in MCHR1-KO mice. A recent publication by Gehlert et al, is a good example of a carefully done study, which used MCHR1-KO mice as a negative control for the small molecule MCHR1 antagonist GW803430 to show that the reduction in body weight and food intake are specific through antagonism of the MCHR1. The authors also describe anxiolytic and antidepressant effects, which have been noticed with other MCHR1 antagonists as well. Anxiolytic and antidepressant effects of MCHR1 antagonists would certainly be desirable in treating obese populations. The behavioral actions of MCH not related to energy balance are described elsewhere in this issue.

Central sites of MCHR1 signaling regulating energy homeostasis

The widespread expression of the MCHR1 in the CNS complicates considerably the investigation of the sites MCH acts in regulating energy homeostasis. The sites of MCH action regulating energy metabolism have been addressed by a few studies. The hypothalamus was the first site of MCH actions to be investigated. All the information has been derived from site-specific injections of MCH or MCHR1 antagonists, as conditional deletions of MCHR1 from specific hypothalamic nuclei have not been reported to date to provide genetic evidence of site-specific MCH actions. Pharmacological doses of MCH significantly stimulate food intake in rats when injected into the dorsomedial, the arcuate and the paraventricular nucleus of the hypothalamus [1]. Although these results suggest the potential sites of MCH action in the

hypothalamus, further experiments will be required to test if they are the physiologically relevant sites of MCH action.

The phenotype of the MCH-KO and MCHR1-KO mice, suggested that MCH might also act outside the hypothalamus and this notion is supported by the strong expression of MCHR1 outside the hypothalamus [19]. Both knockout models exhibit hyperactivity and sensitivity to psychostimulants, which has been interpreted as MCH acting in the mesolimbic dopamine system and more specifically in the medial shell of the nucleus accumbens, which strongly expresses MCHR1 receptors. Although, the effects on locomotor activity are not reproduced with MCH or MCHR1 antagonists, injections of MCH into this nucleus increase food intake but not substrate oxidation [16,18]. The increase in food intake after MCH administration is consistent with the inhibitory nature of MCHR1 signaling as injections of muscimol (GABA receptor agonist) into the shell of the nucleus accumbens also potently stimulate food intake.

On the other hand, caudal projections of MCH neurons to the dorsal vagal complex-NTS of the brainstem might be expected regulate autonomic responses but not feeding. This notion has been supported by injections of MCH into the 4th ventricle, which decrease core body temperature but do not affect food intake [61]. Central infusions of MCH or injections into the medial NTS decrease blood pressure and heart rate in rats [10,35]. Genetic mouse models also support the autonomic effects of MCH. MCHR1-KO mice have increased sympathetic activity and increased heart rate [3]. Deletion of MCH from leptin-deficient mice increases their cold tolerance and expression of UCP-1 in brown adipose tissue and MCH knockdown using antisense oligonucleotides has similar effects in the rat [39]. Additional effects of MCH on energy balance might be mediated through its effects on neuroendocrine systems as MCH suppresses the hypothalamic-pituitary-thyroid axis [23].

Discrepancies between the genetic and the pharmacological models of MCH function

All rodent models consistently show that acute or chronic MCH infusion increases appetite and body weight. On the other hand, inactivation of the MCHR1 results in body weight loss and/or decreased adiposity (Table 1 summarizes the phenotypes discussed in this manuscript). However, some discrepancy is apparent between the models regarding the mechanisms by which MCH regulates body weight. The pharmacological models point to the regulation of food intake as the major factor with some contributions from changes in energy expenditure. On the other hand, the genetic models of MCH or MCHR1 inactivation suggest that the increased energy expenditure is the major mechanism underlying their leanness. Food intake in these models is either not changed or in some actually increased and in contrast to the orexigenic actions of MCH. The same models also show increased locomotor activity not seen with pharmacological infusions of MCH or MCHR1 antagonists. Some of the differences could be due to the use of different models, mice versus rats, different genetic background, diets and other experimental details. However it is unlikely that methodological differences can account for all the discrepancies. A more plausible and worrying explanation is that the knockout models suffer from developmental adaptations due to absence of MCH signaling and emerge with phenotypes not representative of MCH functions in the adults. For example, the hyperphagia of the MCHR1-KO mice has been interpreted as a compensatory adaptation to the decreased adiposity but chronic (weeks) pharmacological blockade of MCHR1 receptor in mice decreases both food intake and body weight. Although it is in principle possible that a longer blockade of the MCHR1 in adult animals could eventually reach a point where compensatory pathways would negate the effects of MCHR1 antagonists on food intake, it seems unlikely that the animals would actually become hyperphagic like the MCHR1-KO mice and such an outcome remains to be demonstrated. The problem of developmental compensations is of course a much larger issue affecting neuroscience research in general.

With regard to the hypothalamic regulation of feeding, perhaps the most compelling evidence on the plasticity of the hypothalamus has been provided by the elegant study from the Palmiter group. In this study, the diphtheria toxin was used to selectively ablate the NPY/AGRP neurons of the arcuate nucleus of the hypothalamus. When the ablation of the NPY/AGRP neurons occurred during the early postnatal life, feeding was minimally disrupted. In contrast, ablation later in life caused death from starvation [29].

Although the knockout models are invaluable in studying the function of specific genes, the capacity of the central nervous system for adaptation can also limit their usefulness in studying complex behaviors. One way of potentially eliminating these artifacts would be the use of conditional and inducible knockouts [8], which would provide site specificity and temporal control over MCH actions and would be expected to decrease any compensatory artifacts.

Concluding Remarks

Significant progress has been made towards our understanding of MCH actions in regulating appetite and energy balance. However several challenges remain. For example, the pathways through which MCH affects peripheral energy and substrate utilization need to be more thoroughly investigated. The interaction of MCH neurons with other circuits such as the mesolimbic dopamine system and the sleep circuitry are other exciting areas of research. The function of the second MCH receptor MCHR2 in energy balance is unknown and it will require the use of other animal models such as ferrets and dogs. Perhaps more importantly, the MCH actions need to be placed in a physiological context. Very little is known about the activity of MCH neurons under various conditions such as feeding and fasting, high fat-low fat diets and obesity. Addressing these questions might require the development of new tools but it will keep the MCH research active and fruitful for years to come.

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Table 1

Metabolic phenotypes of animal models of MCH function.

	MCH	MCH-OE	MCHRI antagonist	MCH-KO	MCHRI-KO
Body weight	↗	→ ↗ ^{a,b}	↘	↘	→ ↘ ^b
Adipose tissue mass	↗	↗	↘	↘	↘
Food intake	↗	↗	↘	↗ ↘ → ^a	↗
Energy expenditure	↘?	n.d.	↗?	↗	↗
Locomotor activity	→ ↗ ^{a,b}	n.d.	→	↗	↗

^a strain dependent;
^b diet dependent;
? weak effect, not adequately studied;
n.d.: not defined