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Enhanced running wheel activity of both Mch1r- and Pmch-deficient mice

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Abstract

Mch1r-deficient (*Mch1r*$^{-/-}$) mice are hyperphagic, hyperactive, lean, and resistant to diet-induced obesity. To examine whether the MCH1R is involved in regulating activity-based energy expenditure, we investigated voluntary wheel running (WR) activity of wild-type (WT) and *Mch1r*$^{-/-}$ mice basally, in response to diets with different caloric density and with different feeding schedules. We also evaluated WR activity of mice with ablation of the prepro-MCH gene (*Pmch*$^{-/-}$ mice). Dark cycle WR activity of *Mch1r*$^{-/-}$ mice fed low fat (LF) chow was increased significantly relative to WT mice. Transition to moderate high-fat (MHF) diet was associated with an increase in nocturnal WR activity in both genotypes. Both *Mch1r*$^{-/-}$ and WT mice exhibited food anticipatory activity (FAA) before the daily scheduled feeding time, indicating that MCH1R is not required for FAA. Naloxone (3 mg/kg, i.p.) suppressed WR activity of both genotypes, suggesting opioid regulation of locomotor activity. WR increased nocturnal dynorphin mRNA levels in *Mch1r*$^{-/-}$ brain. Importantly, Pmch-deficient mice had significantly enhanced WR activity relative to WT controls. These results suggest that endogenous MCH plays an inhibitory role in regulating locomotor activity. In summary, we demonstrated enhanced WR activities in mice lacking either MCH or its cognate receptor.
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1. Introduction

Melanin-concentrating hormone (MCH) was first described and isolated from salmon pituitary, has 17 amino acids, and has direct effects on salmon pigmentation [1]. In contrast, rat MCH is comprised of 19 amino acids and is involved in other functions [2,3]. In the mammalian brain, MCH-producing neurons are located predominantly in the lateral hypothalamus and rostromedial zona incerta and project widely in the neuraxis [3]. MCH is one of several neuropeptides in the brain that stimulate feeding in rodents [4,5]. Mice with targeted deletion of the *Mch* gene have reduced body weight, suppressed appetite, and increased metabolic rate [6], while transgenic mice with chronic overexpression of MCH are obese and insulin-resistant [7]. Chronic infusions of MCH produced hyperphagia and obesity in rats [8] and mice [9].

Two G-protein coupled MCH receptors have been identified in humans, MCH1R and MCH2R; however, only MCH1R is found in rodents [10–14]. MCH1R is distributed in the cerebral cortex, caudate putamen, ventral, and dorsal medial hypothalamus [10,15]. Expression of MCH1R mRNA is up-regulated by fasting or genetic leptin deficiency [16]. Treatment with MCH1R selective antagonists suppresses food intake and decreases body weight gain in rats [17–19]. *Mch1r*$^{-/-}$ mice are hyperphagic, lean, less susceptible to diet-induced obesity, and resistant to centrally administered MCH [20,21], indicating that MCH1R is involved in mediating the effects of MCH on energy homeostasis in rodents. Interestingly, targeted disruption of *Mch1r* in mice results in increased locomotor activity [21]. However, the voluntary wheel running (WR) activity and feed patterning behavior of *Mch1r*$^{-/-}$ mice have not been described.

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Daily feeding schedules can entrain circadian rhythms of food-anticipatory activity (FAA) in mammals [22–24]. Restricted access to food during daytime leads to a marked increase in locomotor activity during the hours preceding feeding time. The site of the circadian oscillator(s) that drive food-entrained rhythms (i.e., food-entrainable oscillator, FEO) is unknown [25] and believed to be distinct from the light-entrained oscillators of the suprachiasmatic nucleus (SCN) because food-entrained rhythms persist in SCN-lesioned animals [26,27]. MCH-containing neurons in the lateral hypothalamus regulate feeding, energy metabolism, and arousal state, raising the possibility that they may also participate in the entrainment of activity rhythms by a daily mealtime. To examine this, the locomotor activity of *Mch1r*$^{-/-}$ and WT mice was evaluated in response to scheduled feeding.

Voluntary WR has been shown to be rewarding to rodents via activation of the endogenous opioid system [28–32]. Both WR and cocaine treatment up-regulate dynorphin mRNA levels in the medial caudate putamen of rats [30]. The opiate receptor antagonist naloxone suppresses voluntary WR behavior [31] and conditioned place preference induced by WR [32] in Sprague–Dawley rats. We explored whether endogenous opioid systems mediate WR behavior in *Mch1r*$^{-/-}$ and WT mice. To this end, we examined the effects of WR on dynorphin gene expression and the effects of acute naloxone administration on WR activity in *Mch1r*$^{-/-}$ and WT mice.

The purpose of these studies was to examine whether the MCH1R is involved in regulating activity-based energy expenditure by evaluating (1) WR activity and feed patterning of *Mch1r*$^{-/-}$ and WT mice and to further mechanistically address the hyperactive phenotype of *Mch1r*$^{-/-}$ mice by determining (2) plasma hormone levels of *Mch1r*$^{-/-}$ and WT mice with and without running wheels, (3) gene expression in brains of *Mch1r*$^{-/-}$ and WT mice with and without running wheels, (4) food-anticipatory activity of *Mch1r*$^{-/-}$ and WT mice in response to scheduled feeding during the daytime, and (5) effects of the opioid receptor antagonist naloxone on WR activity of *Mch1r*$^{-/-}$ and WT mice. It was reported that mice with ablation of the prepro-MCH gene (*Pmch*$^{-/-}$) had similar activity levels as WT mice as indicated by an open-field locomotion test [6]. Since Mch1r-deficient mice are hyperactive [21], we evaluated the WR activities of Pmch-deficient and WT mice to further investigate the role of MCH in the control of locomotor behavior and arousal in mice.

2. Materials and methods

2.1. Animals

All testing protocols used in this study were reviewed and approved by the Merck Research Laboratories Institutional Animals Care and Use Committee in Rahway, NJ. Male Mch1r- and Pmch-deficient mice were generated as previously described [6,21]. All *Mch1r* mice were F3 generation littermates on a C57BL/6J×129SvEv (50%/50%) mixed genetic background and derived from heterozygous×heterozygous crosses. *Pmch* mice were back-crossed for seven generations (N7) onto a C57BL/6N genetic background and derived from time-matched wild-type×wild-type and homozygous×homozygous crosses. Male *Mch1r* and *Pmch* mice were 6–8 months of age when studied. Mice were housed in either Nalgene metabolic mouse cages or cages equipped with running wheels according to the study requirements. Mice housed in running wheel cages had unlimited access to running wheels during the study period. Mice were given 5–7 days of acclimation before data collection or drug treatments were initiated. Mice were maintained at 22±2 °C with 12:12 h light/dark cycle (lights off at 1700 h) and fed either a standard rodent (low fat; LF) chow (Harlan Teklad Diet 7012, Madison, WI, 13.4 kcal from fat, 3.75 kcal/g) or a moderate high-fat (MHF) diet (D12266B, Research Diets, New Brunswick, NJ, 32% kcal from fat, 4.4 kcal/g).

2.2. Drug administration

Naloxone was purchased from Tocris Cookson (Ellisville, MO) and was dissolved in 0.9% saline on the day of dosing. Naloxone (3 mg/kg) and saline were administered via intraperitoneal injection (i.p.) in a volume of 0.1 ml/animal. All treatments started 1 h before the onset of the dark cycle.

2.3. Food and water intake measurements

Mice were separated into individual microisolator cages for a minimum of 7 days before measuring food intake. We provided milled standard (LF) rodent chow or MHF diet in a food hopper attached to the side of the cage and weighed the hopper daily. Food intake was determined by measuring the weight of the food remaining in the food cup overnight (18 h) and 24 h after drug administration (in the naloxone study). The difference between these measurements indicated daytime food intake. We measured the duration and frequency of feeding with an automated food intake system (Mini-Mitter, Sunriver, OR). Feeding frequency was reported as the number of times an animal broke the photobeam to approach the food hopper, and feeding duration was reported as the length of time the photobeam was interrupted. In some instances, an animal would have its head in the food hopper, but it was not actively eating. These measurements were used as an index of food-seeking behavior. Water intake was measured by weighing the water bottle of each animal daily. Body weights of the mice were determined daily on the morning of each study.

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