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Research report

Amphetamine reward in food restricted mice lacking the melanin-concentrating hormone receptor-1

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HIGHLIGHTS

- Food restriction increases the rewarding potency of drugs.
- The MCH pathway is well located to influence reward.
- CPP induced by amphetamine is not enhanced by food restriction in MCHR1-KO mice.
- The MCH signaling might play a role in the effect of food restriction on drug reward.

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ABSTRACT

Chronic food restriction (FR) and maintenance of low body weight have long been known to increase the rewarding and motor-activating effects of addictive drugs. However, the neurobiological mechanisms through which FR potentiates drug reward remain largely unknown. Melanin-concentrating hormone (MCH) signaling could be one of these mechanisms since this peptide is involved in energy homeostasis and modulates mesolimbic dopaminergic transmission. The purpose of the present study was to test this hypothesis by investigating the impact of FR on amphetamine reward in wild-type (WT) and knock-out mice lacking the melanin-concentrating hormone receptor-1 (MCHR1-KO). The rewarding effects of amphetamine (0.75–2.25 mg/kg, i.p.) were measured with the conditioned place preference (CPP) technique. The food of the mice was restricted to maintain their body weight at 80–85% of their free-feeding (FF) weight throughout the entire CPP experiment. Locomotor activity of the animals was recorded during the conditioning sessions. Our results show that locomotion of all the food-restricted mice treated with saline or amphetamine increased over the sessions whatever the genotype. On the place preference test, the amplitude of CPP induced by 0.75 mg/kg amphetamine was higher in food restricted WT mice than in free-fed WT mice and food restricted MCHR1-KO mice. However, FR did not affect amphetamine reward in MCHR1-KO mice. The present results indicate that MCH signaling could be involved in the ability of FR to increase amphetamine-induced CPP.

1. Introduction

The melanin-concentrating hormone (MCH) is a cyclic 19-amino acid peptide produced by neurons located exclusively in the lateral hypothalamus (LH) area and the zona incerta. MCH neurons project their fibers to almost all brain areas including those involved in drug addiction such as the nucleus accumbens (NAc) [1]. In the mouse brain, the actions of MCH are mediated through melanin-concentrating hormone receptor-1 (MCHR1) that is highly expressed in the shell of the NAc [2,3]. Based on these observations, it has been suggested that the MCH system plays an important role to regulate responses to rewarding stimuli [4]. On one hand, the shell of the NAc is involved in mediating the motivational properties of food and drugs and is a terminal area of the mesolimbic dopamine system [5,6]. On the other hand, the LH area is also implicated in motivated behaviors that are modulated by food and drug administration [7]. For example, pioneer brain self-stimulation experiments found that the electrical

Abbreviations: CPP, conditioned place preference; D_1R, dopamine D_1 receptor; D_2R, dopamine D_2 receptor; FF, free feeding; FR, food restriction; LH, lateral hypothalamus; MCH, melanin concentrating hormone; MCHR1, melanin concentrating hormone receptor-1; MCHR1-KO, melanin concentrating hormone receptor-1 knockout; WT, wild-type.

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stimulation of this region is highly reinforcing [7,8]. When electrodes are implanted in the LH of rodents, they will robustly self-administer electrical currents in this region, a behavior referred to as LH self-stimulation [8]. Both food restriction (FR) and addictive drugs can facilitate LH self-stimulation [9,10].

Several studies have investigated the role of MCH signaling in the stimulant and rewarding effects of psychostimulants. However, conflicting results have been obtained. Smith and colleagues [11] found that MCHR1 knockout mice (MCHR1-KO) are more sensitive to the locomotor stimulant effects of amphetamine than wild-type mice. In addition, the development of sensitization to the stimulant effects of amphetamine is facilitated in MCHR1-KO mice [12]. In our laboratory, we also found that MCHR1-KO mice are more sensitive to the acute motor stimulatory effects of amphetamine when compared to their wild-type (WT) counterparts. However, the development of behavioral sensitization to the stimulant effects of amphetamine was similar in both genotypes [13]. Chung and colleagues [14] have demonstrated that the intracerebroventricular (i.c.v.) administration of MCH potentiates cocaine-induced hyperactivity in mice. Additionally, behavioral sensitization to the stimulant effects of cocaine and cocaine-induced conditioned place preference (CPP) were lower in MCHR1-KO mice than in WT mice. In our previous studies, we have demonstrated that MCHR1-KO mice, unlike WT mice, do not develop behavioral sensitization to the stimulant effects of cocaine. In contrast, the acute motor effects of cocaine were not altered in MCHR1-KO mice [15]. Furthermore, the amplitude of CPP for amphetamine and cocaine was not changed in MCHR1-KO mice when compared with their WT counterparts [16].

MCH neurons play an essential role in the control of food intake [17] and there are numerous data demonstrating that food and drugs activate similar neuronal reward pathways [5,6]. It is well established that the feeding regimen and FR can interfere with central reward processes and modify the rewarding properties of drugs. For example, chronic FR facilitates LH self-stimulation [9] and increases the rewarding effects of cocaine and amphetamine [18]. In addition, fasting and chronic FR upregulate MCH mRNA expression and activate the MCH system [19–23]. It is thus possible that MCH transmission is involved in the ability of FR to increase the rewarding properties of drugs. Therefore, the purpose of the present study was to investigate whether FR differentially affects the rewarding effects of amphetamine in MCHR1-KO and WT mice. Mice from both genotypes were food restricted to maintain their body weight at 80–85% of free-feeding (FF) weight. While being food restricted, they underwent a biased conditioning procedure for amphetamine-induced CPP. In order to also investigate the impact of FR on amphetamine-induced locomotion, activity of the mice was recorded during the conditioning sessions. We expected that FR would increase amphetamine reward only in WT mice.

2. Materials and methods

2.1. Animals and housing

Mice lacking a functional MCHR1 have been previously described [24] and were maintained on a mixed genetic background (129SvJ × C57BL/6J) for 5–6 generations. Heterozygote breeding pairs were used to generate WT and homozygous MCHR1-KO mice. Males were single housed and maintained on a 12 h light/dark cycle with access to food and water *ad libitum* unless noted otherwise. Mice were between 12 and 15 weeks old at the time of the experiments. In every experiment, both genotypes were age matched and evaluated simultaneously. The genotype of the mice was verified using polymerase chain reaction of tail-tip DNA as described previously [24]. All experimental procedures were carried out in accordance with the standards of care and use of laboratory animals laid down by the European Communities Council (Directive N° 86/609/EEC, 24 November 1986). Protocols were reviewed and approved by the Animal Care Committee of the University of Liège.

2.2. Pharmacological treatments

D-Amphetamine sulphate (amphetamine) purchased from Federa (Louvain-La-Neuve, Belgium) was dissolved in an isotonic saline solution (0.9% NaCl) and was always administered at a volume of 0.01 ml/g body weight *via* the intraperitoneal (i.p.) route. The control treatment consisted of an equal volume of saline solution.

2.3. Behavioral apparatus

We utilized a battery of eight place-preference devices purchased from Technical & Scientific Equipment, Bad Homburg, Germany (TSE Place Preference System, model 257000-MAU) described in [25]. Each chamber was composed of three different compartments with distinct visual and tactile cues: two large equally sized outer compartments (16.5 cm × 15 cm × 20 cm) separated by a smaller central compartment (6.5 cm × 15 cm × 20 cm). During place-preference sessions, the separating walls used during conditioning (during which the mouse was confined in one of the outer compartment) were exchanged for walls containing an arched gateway (3.5 cm × 4 cm), allowing free movements through the entire apparatus. The central compartment served as a starting point for place preference tests. All compartments were made of removable opaque PVC tablets. One of the outer compartments was colored white, and the other was colored with alternate black and white 2.5-cm vertical stripes, the inside of the central compartment being gray. To provide tactile cues, removable clear acrylic resin tablets whose upper surface was markedly textured were placed on the floor of each outer compartment. The tablet placed in the left compartment (striped walls) presented a relatively thinly embossed texture with 2 mm^2 punches, whereas that inserted in the right compartment (white walls) was textured with larger 4 mm^2 punches. The central area (gray walls) was provided with a smooth floor. Entrance into and movements within the compartments were automatically recorded *via* an array of infrared detectors mounted every 28 mm along the entire length of the walls. The infrared detectors allowed the calculation of the time spent (s) in each compartment and the monitoring of locomotor activity that was measured in terms of the total distance traveled (cm). One computer operated the eight devices simultaneously. To insure some degree of visual and acoustical isolation, the CPP devices were individually enclosed in white melamine cubicles (60 cm × 40 cm × 40 cm).

2.4. Experimental procedure

Five days before the beginning of the CPP experiments, mice of each genotype were divided into two groups and assigned to the food-restricted condition or the *ad libitum*-fed condition. In the food-restricted condition, food of the mice was restricted until their body weight reached ~85% of their initial weight. The FR was maintained during the entire behavioral experiment. Mice of each condition were re-divided into three subgroups ($n = 16$), each corresponding to a pharmacological treatment (saline, 0.75 mg/kg and 2.25 mg/kg amphetamine).

On the first day, the pre-conditioning session, all mice were injected with saline and placed into the apparatus with free access to all compartments for 45 min, the time spent in each compartment being used as a measure for spontaneous preference for one of the outer sides. The conditioning phase started 24 h after the pre-conditioning session. During the conditioning phase,