Psychoneuroendocrinology (2015) 56, 79—87

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/psyneuen

Dopamine release in the lateral hypothalamus is stimulated by α-MSH in both the anticipatory and consummatory phases of feeding

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Received 31 October 2014; received in revised form 24 February 2015; accepted 24 February 2015

KEYWORDS
Dopamine;
Neuropeptides;
α-MSH;
Melanocortin;
Eating disorders;
Anorexia nervosa

Summary α-Melanocyte-stimulating hormone (α-MSH), is a hypothalamic neuropeptide signaling satiation, but it is not known if α-MSH may stimulate dopamine release in a feeding control brain region of the lateral hypothalamic area (LHA), during the anticipatory and consummatory phases of feeding behavior. To address these questions, dynamics of dopamine release were measured in 15 min microdialysis samples simultaneously from the LHA and the nucleus accumbens (NAc) during consecutive exposure and provision of food and 1% sucrose in Wistar rats after overnight food deprivation. α-MSH was infused via the microdialysis probe either into the LHA or NAc starting before food exposure. Food, sucrose and water intakes were automatically monitored and analyzed concomitantly with microdialysis samples. We found that LHA-α-MSH-infused rats stopped eating earlier and consumed less food and sucrose as compared to control and NAc-α-MSH-infused rats. Exposure to food produced a peak of LHA dopamine in both LHA-α-MSH and NAc-α-MSH-infused rats but not in the controls. During food provision, LHA dopamine levels were strongly elevated in LHA-α-MSH infused rats, while delivery of α-MSH into the NAc induced a less intense increase of dopamine in both NAc and LHA. In all rats, LHA dopamine levels correlated inversely with sucrose intake. In conclusion, our study showed that α-MSH stimulates dopamine release in the LHA during both the anticipatory and consummatory phases of feeding, decreases food intake and inhibits sucrose intake. These data suggest that LHA dopamine release can be involved in α-MSH anorexigenic effects.

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http://dx.doi.org/10.1016/j.psyneuen.2015.02.020
0306-4530/

1. Introduction

Interactions between peptide hormones/neuropeptides signaling hunger and satiety with the brain mesolimbic dopamine system may underlie the coordinated regulation of the homeostatic and hedonic components of feeding behavior (Hoebel et al., 1994; Berthoud, 2011; van Zessen et al., 2012). The central melanocortin system constitutes the final common pathway signaling satiation, whereas α-melanocyte-stimulating hormone (α-MSH), produced by the proopiomelanocortin (POMC) neurons of the hypothalamic arcuate nucleus, activates melanocortin receptors type 4 (MC4R) (Cone, 2005). MC4R are highly expressed in the hypothalamus, including the paraventricular nucleus and the lateral hypothalamic area (LHA) as well as in the striatum and nucleus accumbens (NAc) (Mountjoy et al., 1994; Kishi et al., 2003; Hsu et al., 2005), the brain regions rich in dopaminergic nerve terminals (Fuxe, 1965).

It is, hence, likely that the mechanisms underlying α-MSH effects on feeding behavior may involve modulation of dopamine release in these brain regions. Indeed, earlier works showed that intracerebroventricular or ventral tegmental area (VTA) administrations of α-MSH were followed by increased dopamine release in the NAc (Torre and Celis, 1988; Florijn et al., 1993; Lindblom et al., 2001). However, it is not known if α-MSH may stimulate dopamine release locally in the LHA, a brain region controlling energy metabolism (Berthoud and Münzberg, 2011), and if such release can be associated with feeding behavior.

Clarification of α-MSH effects on hypothalamic dopamine may help to better understand the molecular mechanisms of psychiatric conditions of altered appetite, such as anorexia nervosa and bulimia (Friederich et al., 2013). Implication of altered α-MSH signaling in eating disorders is supported by data showing that psychopathological traits in patients with anorexia nervosa and bulimia are associated with plasma levels of α-MSH-reactive autoantibodies (Fetissov et al., 2005b). Such antibodies in rats were shown to modify food intake and anxiety (Hamze Sinno et al., 2009), most likely affecting the MC4R activation (Lucas et al., 2014). Patients with anorexia nervosa are characterized by preoccupation with food (Blechert et al., 2011) which is, paradoxically, not followed by normal food intake, indicating a disruption of the physiological mechanism of transition from the anticipatory to consummatory phases of feeding behavior (Ikemoto and Panksepp, 1996). The mesolimbic dopamine system in the rostral forebrain has been implicated in the motivational aspects of feeding behavior (Avena et al., 2008; Berridge et al., 2010), as a general feature of motivated behavior (Salamone and Correa, 2012), including signaling of the appetitive motivation, pleasure and reinforcement (Salamone and Correa, 2013), but the contribution of the hypothalamic dopamine system to such functions is less clear.

Although earlier works named the LHA as a ''pleasure center'' (Olds and Milner, 1954), the later studies indicated that the LHA contribution to pleasure signaling involves activation of fibers of passage toward the VTA dopamine neurons releasing dopamine mainly in the NAc and other rostral brain sites (Wise, 2013). Nevertheless, the microdialysis studies showed that dopamine release in the LHA during feeding is proportional to meal size (Meguid et al., 1995) and that basal LHA dopamine levels are elevated in fed vs. fasted state (Fetissov et al., 2000). Furthermore, dopamine acute and chronic administrations into the LHA produce anorexigenic effects (Leibowitz and Rossakis, 1979; Yang et al., 1997), supporting a local action of LHA dopamine in the regulation of feeding behavior (Chen et al., 2014). Thus, it is possible that α-MSH in the LHA may stimulate dopamine release locally as well as distantly in the NAc during the anticipatory and/or consummatory phases of feeding behavior and that such release may be associated with the homeostatic and/or hedonic aspects of α-MSH anorexigenic effects.

To address these questions, in the present work, we used microdialysis in free moving rats to study effects of local LHA α-MSH delivery on dopamine release in both the LHA and NAc during food exposure and food provision, corresponding to the anticipatory and consummatory phases of feeding behavior, respectively. To study if these effects are preferentially related to the hedonic or homeostatic satiety, rats that previously developed preference for drinking 1% sucrose, were provided during the microdialysis experiment with the standard rat chow, 1% sucrose and water which intakes were measured. Furthermore, to compare the LHA and NAc for the α-MSH-induced dopamine release in relation to feeding behavior, we also studied effects of α-MSH infusion in the NAc.

2. Material and methods

2.1. Animals

Three month-old male Wistar rats ($n = 24$) were obtained from Janvier Labs (L'Arbresle, France) and housed for 1—3 weeks in standard holding cages (3 rats per cage) to acclimatize them to a specialized 24 °C air-conditioned animal facility with 12-h light—dark cycle, light phase between 0700 h and 1900 h. Animal care and experimentation were in accordance with guidelines of European Community (Decree 86/609/EEC) and the study was approved by the Regional Ethical Committee (N/07-11-12/30/11-15). Rats were fed ad libitum with standard pelleted rodent chow (RM1 diet, SDS, Essex, UK) with drinking water always available.

2.2. Surgery

For implantation of the microdialysis guides, rats were anaesthetized by an intraperitoneal injection of ketamine (75 mg/kg)/xylazine (5 mg/kg) mixture (3:1 vol — 0.1 mL/100 g body weight) and placed into a New Standard Stereotaxic Instrument for Rats and Mice (Stoelting Europe, Dublin, Ireland). Microdialysis CMA 11 guide cannulas (CMA Microdialysis AB, Kista, Sweden) were implanted under an operating microscope (Carl Zeiss, Jena, Germany) into the left LHA (posterior: −2.8 mm from Bregma, lateral: +1.0 mm from the midline, and ventral: 7.5 mm from the dura mater) and right NAc (anterior: +1.5 mm from Bregma, lateral: −2.8 mm from midline, and ventral: 5.4 mm from the dura mater with a 10° angle toward midline), with the incisor bar set at −3.3 mm (Swanson, 1998). The guide cannulas were fixed to the scull using dental cement supported by the anchor screws. After awaking, rats were kept individually in the metabolism cages (Tecniplast, Lyon, France) for 1