

Research Report

Orexin A in the nucleus accumbens stimulates feeding and locomotor activity

A.J. Thorpe^{c,d}, C.M. Kotz^{a,b,c,e,*}^aVeterans Affairs Medical Center, One Veterans Drive, Minneapolis, MN 55417, USA^bMinnesota Obesity Center, One Veterans Drive, Minneapolis, MN 55417, USA^cDepartment of Neuroscience, University of Minnesota, 1334 Eckles Avenue, Saint Paul, MN 55108, USA^dMinnesota Craniofacial Training Program, University of Minnesota, 1334 Eckles Avenue, Saint Paul, MN 55108, USA^eFood Science and Nutrition, University of Minnesota, 1334 Eckles Avenue, Saint Paul, MN 55108, USA

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Abstract

Due to the nature of processing within the accumbens shell (AccSh) and the presence of orexin receptors and varicosities within the AccSh, we hypothesized that orexin A may partly regulate feeding behavior and locomotor activity via signaling in this site. To test this hypothesis, male Sprague–Dawley rats were implanted with guide cannulae directed to the medial portion of the AccSh. Orexin A (0, 100, 500, and 1000 pmol, in 0.5 μ l artificial cerebrospinal fluid) was infused into the AccSh and feeding behavior and locomotor activity were monitored. The effect of pretreatment with an orexin 1 receptor antagonist (SB334867A) on orexin A-induced feeding and locomotor activity was assessed. Orexin A augmented feeding in the 0–1 h and 1–2 h post-infusion interval ($P = 0.0058$ and $P = 0.025$, respectively) and stimulated locomotor activity in the 30–60 min, 60–90 min, and 90–120 min post-infusion intervals ($P \leq 0.0001$, $P = 0.0056$ and $P = 0.046$, respectively). Orexin A-induced feeding was significantly attenuated by preadministration of SB334867A in the 0–1 h post-infusion time interval ($P = 0.03$). Orexin A-induced locomotor activity was not affected by SB334867A. These data support the hypothesis that the AccSh is a site of orexin A modulation of feeding behavior and locomotor activity.

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1. Introduction

The orexin peptides (A and B, also known as hypocretin 1 and 2) are produced by neurons in the caudal aspect of the lateral hypothalamic area, including the perifornical and dorsomedial aspects of the hypothalamus [8,31]. The diffuse efferent projection pattern of the orexin neurons, and the widespread expression of the g-protein coupled orexin receptors (OX1R and OX2R), predict orexins to be

important regulators of homeostatic functions (for review see [43]). Among these, one of the first proposed actions of orexin was the regulation of appetite; hence its name from the Greek word for appetite (orexis). Orexin A delivered intraventricularly or into various hypothalamic nuclei results in a feeding response in rodents [10,11,37].

Orexins also have important roles in the regulation of arousal and sleep thresholds. This is exemplified by the fact that the human condition of narcolepsy may be caused by loss of orexin neurons and subsequent loss of their modulatory control, and that the canine condition of narcolepsy is due to a mutation in the gene encoding the orexin 2 receptor [20,39]. Orexin receptors are densely expressed in nuclei central to maintaining arousal, and

* Corresponding author. Veterans Affairs Medical Center, One Veterans Drive, Research Route 151, Minneapolis, MN 55417, USA. Fax: +1 612 725 2084.

E-mail address: kotzx004@umn.edu (C.M. Kotz).

intracerebroventricular administration of orexin A results in suppressed REM and increased locomotor activity [1,4,7,12,41,42].

Orexin neurons project to the nucleus accumbens and to the ventral tegmental area (VTA), both of which are known to contribute to processing of reinforced behaviors, including feeding [5,7,27]. Additionally, neurons in the nucleus accumbens express orexin receptors and are inhibited by orexin A, and mesolimbic neurons located in the VTA, involved in the regulation of reward, are activated by orexin A [7,24,26]. Preference for a high fat diet involves the mesolimbic dopaminergic system and opioid system [13]. Opioids in the nucleus accumbens may “modulate the hedonic impact of food reward” [13]. Since intraventricular orexin A may selectively enhance intake of highly palatable diets [6], the orexins may act within the AccSh to modulate feeding behavior [38].

Based on the convergence of neuroanatomical and behavioral data, we postulate that the AccSh may be a site modulated by orexin A. To test this hypothesis, orexin A was infused intra-AccSh, and subsequent effects on feeding and locomotor activity were examined. Additionally, to determine whether these effects were mediated by the orexin 1 receptor, the orexin 1 receptor antagonist SB334867A was administered prior to orexin A in a separate set of experiments.

2. Methods

2.1. Surgery

One week after arrival, male Sprague–Dawley rats (Harlan, Madison Wisconsin) weighing 250 g at time of arrival, underwent stereotaxic surgery for implantation of a permanent guide cannula (8.0 mm, 26 gauge, Plastics One, Roanoke, Virginia) directed to the shell of the nucleus accumbens (medial portion) using the following coordinates: anterior/posterior (+3.0 mm), medial/lateral (+1.0 mm), dorsal/ventral (−6.0 mm); with the incisor bar set at +5.0 mm. A combination of Ketamine (90 mg/kg) and Xylazine (15 mg/kg) was used as an anesthetic, and Flunixin (2.5 mg/kg) was administered as a postoperative analgesic. Animals were housed in individual hanging wire cages in a temperature (22 °C) and light (12 h/12 h) controlled room. Rat chow (Harlan Teklad 8604) and water (tap) were available ad libitum. Animals were handled daily and subject to at least 3 mock injections, to habituate animals to the injection procedure. Drugs were delivered via injector cannulae (33 gauge, Plastics One, Roanoke, VA) that extended 2.0 mm beyond the tip of the guide cannulae. Infusions took place over 30 s with the injector left in place for an additional 15 s to allow for complete drug extrusion. In all experiments, drugs were prepared immediately prior to administration. All experiments received local Institutional Animal Care and Use Committee approval.

2.2. Experiment 1a

Orexin A (American Peptides, Sunnyvale, CA: 0, 100, 500, 1000 pmol in 0.5 μ l artificial cerebrospinal fluid, aCSF) was administered intra-AccSh in a counter balanced Latin square design 6 h into the light phase ($n = 10$). With this design, each possible treatment was represented during each session and each animal received all the possible treatments with at least 48 h between treatments. Chow intake was monitored 1, 2, 4 and 24 h after AccSh infusion by manually weighing food hoppers and adjusting for spillage.

2.3. Experiment 1b

In a separate group of animals ($n = 13$), vehicle_{sterile H₂O} or SB334867A (gift from GlaxoSmithKline: 1, 3 or 6 ng) was administered intra-AccSh 10 min prior to vehicle_{aCSF} or orexin A (500 pmol) in a counter balanced Latin square design 6 h into the light phase. Only the high dose (6 ng) of SB334867A was administered in conjunction with vehicle_{aCSF}. Chow intake was monitored 1, 2 and 4 h after AccSh infusions by manually weighing food hoppers and adjusting for spillage. SB334867A, shown to be an effective OX1R antagonist, was dissolved in 2% cyclodextran in sterile water [33].

2.4. Experiment 2a

In a separate group of animals ($n = 10$), locomotor activity was monitored with 43.2 cm $\times$ 43.2 cm open field chamber activity monitors (ENV-515 Test Environment; Med Associates, St, Albans Vermont) equipped with three 16 beam infrared arrays to detect movement in the x , y and z coordinates. “Activity Monitor” (Med Associates, St, Albans VT) software was used for collection and processing of raw activity data. Prior to experimental manipulations, animals were placed in the activity chambers at least 3 times, for 2 h, to habituate animals to this environment. During experimental manipulations, animals were removed from their home cage, infused intra-AccSh with orexin A (0, 100, 500, 1000 pmol in 0.5 μ l aCSF) in a counterbalanced Latin square design 6 h into the light phase, and placed in the activity chambers for locomotor assessment for 2 h. No food or water was available during locomotor assessment. With this design, each possible treatment was represented during each session and each animal received all the possible treatments with at least 48 h between treatments.

2.5. Experiment 2b

After a 2 week washout period, the same animals ($n = 13$) from experiment 2a were used to test the effect of SB334867A on locomotor activity. This experiment was designed similarly to experiment 2a, except that vehicle_{sterile H₂O} or SB334867A (1, 3, or 6 ng) was administered intra-AccSh 10 min prior to vehicle_{aCSF} or orexin A (500 pmol) in a counter balanced

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