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MECHANISMS UNDERLYING OBESITY RESISTANCE ASSOCIATED WITH HIGH SPONTANEOUS PHYSICAL ACTIVITY

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Abstract—Obesity resistance due to elevated orexin signaling is accompanied by high levels of spontaneous physical activity (SPA). The behavioral and neural mechanisms underlying this observation have not been fully worked out. We determined the contribution of hypothalamic orexin receptors (OXRs) to SPA stimulated by orexin A (OXA), whether OXA-stimulated SPA was secondary to arousal and whether voluntary wheel running led to compensations in 24-h SPA. We further tested whether orexin action on dopamine one receptors (DA1R) in the substantia nigra (SN) plays an important role in the generation of SPA. To test this, SPA response was determined in lean and obese rats with cannulae targeted toward the rostral lateral hypothalamus (rLH) or SN. Sleep/wake states were also measured in rats with rLH cannula and electroencephalogram/electromyogram radiotelemetry transmitters. SPA in lean rats was more sensitive to antagonism of the OX1R and in the early response to the orexin 2 agonist. OXA increased arousal equally in lean and obese rodents, which is discordant from the greater SPA response in lean rats. Obesity-resistant rats ran more and wheel running was directly related to 24-h SPA levels. The OX1R antagonist, SB-334867-A, and the DA1R antagonist, SCH3390, in SN more effectively reduced SPA stimulated by OXA in obesity-resistant rats. These data suggest OXA-stimulated SPA is not secondary to enhanced arousal, propensity for SPA parallels inclination to run and that orexin action on dopaminergic neurons in SN may participate in the mediation of SPA and running wheel activity. Published by Elsevier Ltd. on behalf of IBRO.

Key words: hypocretin, lateral hypothalamus, locomotor activity, diet-induced obesity, reward.

INTRODUCTION

Obesity resistance that is accompanied by elevated orexin signaling is also associated with high levels of spontaneous physical activity (SPA) (Kotz et al., 2012). Orexin A (OXA, also referred to as hypocretin 1), a neuropeptide synthesized in discrete areas within the lateral, perifornical, and dorsomedial hypothalamus (de Lecea et al., 1998; Sakurai et al., 1998), is crucial for normal energy homeostasis and arousal. SPA stimulated by central OXA infusion induces weight loss (Novak and Levine, 2009) while mice lacking OXA are obese and have lower physical activity despite lower energy intake compared to wild-type mice (Hara et al., 2001), highlighting the critical energy balance role of OXA-stimulated SPA. Central OXA infusion also stimulates arousal and lack of endogenous orexin or orexin receptors (OXRs) disrupts sleep/wake patterns, so it has been suggested that orexin-stimulated SPA may be secondary to arousal. SPA induced by orexin also increases energy expenditure, but the contribution of this and voluntary activity such as wheel running to total daily energy expenditure is unclear in rodents. Thus whether the SPA increase translates into an overall daily increase in energy output remains to be determined since there is the possibility of compensation in one physical activity compartment for changes in another.

It is clear that activation of OXRs (OX1R and OX2R) modulates SPA, but the pathway linking orexin neuronal action to SPA remains relatively undefined. The selective OX1R antagonist, SB-334867-A, reduces OXA-stimulated increases in energy expenditure (Kiwaki et al., 2004) and several types of physical activity (Duxon et al., 2001; Jones et al., 2001; Rodgers et al., 2001; Kiwaki et al., 2004). Antagonism of both OXRs reduces overall physical activity (Brisbare-Roch et al., 2007; Whitman et al., 2009; Winrow et al., 2011), oxygen consumption (Li and Nattie, 2010) as well as orexin B- and amphetamine-stimulated physical activity (Bergman et al., 2008; Winrow et al., 2010). In addition, it has been found that dopamine receptor antagonists

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Abbreviations: ANOVA, analysis of variance; AW, active wake; DA1R, dopamine one receptor; EEG, electroencephalogram; EMG, electromyogram; OP, obesity prone; OR, obesity resistant; OXA, orexin A; OXR, orexin receptor; REM, rapid eye movement; rLH, rostral lateral hypothalamus; SN, substantia nigra; SPA, spontaneous physical activity; SWS, slow wave sleep.

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reduce OXA-stimulated physical activity (Nakamura et al., 2000; Matsuzaki et al., 2002; Kotz et al., 2006), and a large body of work has revealed differences in dopamine neurotransmission between obese and lean rodents (Levin et al., 1986; Yang and Meguid, 1995; Fetissov et al., 2002; Geiger et al., 2008; Waters et al., 2008; Rada et al., 2010; Garland et al., 2011). The sites of action for orexin on dopaminergic neurons have not been fully established, but one possible site is the substantia nigra (SN) (Kotz et al., 2006, 2008).

Based on our past work showing elevated 24-h SPA, OXA-stimulated SPA, OXR mRNA and protein levels in lean obesity-resistant (OR) rats (Novak et al., 2006; Teske et al., 2006; Kotz et al., 2012), we sought to investigate brain and behavior-related mechanisms underlying these results. We hypothesized that in OR rats (1) orexin antagonists in the hypothalamus would be more effective at blocking OXA-stimulated SPA; (2) orexin agonists would be more effective in stimulating SPA; (3) that OXA-stimulated arousal would be similar in lean and obese rats, while OXA stimulation of SPA would be greater in lean rats; (4) propensity to run would be greater in lean rats and directly proportional to 24-h SPA levels; and (5) OXA-stimulated SPA after infusion into SN would be greater in lean rats and that antagonism of orexin and dopamine receptors would block the induced SPA more effectively in lean rats.

EXPERIMENTAL PROCEDURES

Animals

Male Sprague–Dawley and selectively bred obesity-prone (OP) and OR rats (Charles River, Kingston, NY, USA) were housed individually in either wire-hanging cages or solid-bottom cages in corn-cob bedding with a 12-h light/12-h dark photo-cycle (lights on at 0600 h) in a temperature-controlled room (21–22 °C). Rodent chow (Harlan Teklad 8604) and water were allowed ad libitum. Studies were approved by the Institutional Animal Care and Use Committee at the Minneapolis VA Health Care System and the University of Minnesota. Four sets of rats were used. The first set of rats was used for studies one and two. A second set of rats was used for study three and the third for study four. A fourth set of rats was used for studies five and six.

Surgery

Animals were anesthetized with Ketamine (50 mg/kg) and Xylazine (15 mg/kg) and 26-gauge stainless steel unilateral cannulae (Plastics One, Roanoke, VA) were directed toward the rostral lateral hypothalamus (rLH) or SN as described previously (Kotz et al., 2006; Teske et al., 2006). Stereotaxic coordinates were determined from the rat brain atlas of Paxinos et al. (1985). The coordinates for the rLH and SN, respectively, were as follows: −2.2 and −5.3 mm posterior, 1.9 and 2.4 mm lateral to bregma, and 7.3 and 7.6 mm below the skull surface. For all cannulations, the incisor bar was set at 3.3 mm below the ear bars. A dummy stylet was placed in the guide cannula that extended to the tip of the cannula after surgery and between injections. Animals were allowed to recover from surgery for at least seven days before experimental trials began. One OP, one OR, and two Sprague–Dawley rats died of unknown cause after surgery.

In study three, animals were implanted with electroencephalogram (EEG) electrodes, electromyogram (EMG) electrodes and a transmitter (F40-EET, Data Sciences International, St Paul, MN, USA) to allow recording of sleep/wake states by radiotelemetry in addition to the rLH cannula as described previously (Mavanji et al., 2010). After cannula implantation, bilateral surface EEG electrodes (3.1 mm posterior and 1.5 mm lateral to bregma) (Paxinos et al., 1985) were secured through bur holes to contact the dura to record future cortical EEG. Then two leads were secured in the nuchal muscles to record EMG. The transmitter was placed in a blunt dissected channel across the animals hindlimb. Animals were returned to plastic solid-bottom cages with corn-cob rodent bedding after surgery and remained in the solid-bottom cages throughout the duration of this study.

Drugs

OXA (American Peptides, Sunnyvale, CA, USA), the selective OX2R agonist (Ala^{11}, D-Leu^{15}-Orexin B (Asahi et al., 2003) (Tocris, Ellisville, MO, USA), and the selective dopamine one receptor (DA1R) antagonist (SCH3390) (Sigma, St. Louis, MO, USA) were dissolved in artificial cerebrospinal fluid. The selective OX1R antagonist (SB-334867-A) was provided as a gift by GlaxoSmithKline and was dissolved in 5% dimethyl sulfoxide in sterile water. Artificial cerebrospinal fluid was used as the vehicle control for studies with OXA and SCH3390. Five percent dimethyl sulfoxide in sterile water was used as the vehicle control for studies with SB-334867-A. All drugs were stored at 4 °C for less than 48 h.

Injections

A volume of 0.5 µl was injected slowly over 30 s with a 33-gauge injector (Plastics One, Roanoke, VA) that extended 1.0 mm beyond the tip of the guide cannula as described previously (Kotz et al., 2002, 2006; Teske et al., 2006). The injector was left in place an additional 10 s to ensure extrusion from the tip and to minimize distribution of the drug upward on the cannula tract. After injection, the injector was withdrawn and the stylet replaced. The first set of rats received 16 injections, the second set of rats received 16 injections, and the third set of rats received two injections in total. In previous studies, lack of extensive tissue damage after 50 repeated injections as measured by gliosis around the injection site and light microscopy at 100× was demonstrated (Picker et al., 1999). Cannula placement was verified physiologically based on the reported SPA response to 250 pmol/0.5 µl OXA in the rLH in OP, OR and Sprague–Dawley rats (Teske et al., 2006) and the SPA response to 500 pmol/0.5 µl OXA in the SN in Sprague–Dawley rats (Kotz et al., 2008). Rats in the

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