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Effects of oxytocin on nicotine withdrawal in rats

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ABSTRACT

Development of medications that attenuate symptoms of nicotine withdrawal may be useful for facilitating smoking cessation. The neuropeptide oxytocin (OXY) decreases withdrawal signs and other addiction-related effects of several drugs of abuse in animals, but has not been examined in a preclinical model of nicotine addiction. The goal of this study was to examine the effects of OXY on nicotine withdrawal in rats, measured as increases in somatic signs and elevations in intracranial self-stimulation (ICSS) thresholds (anhedonia-like behavior) during antagonist-precipitated withdrawal from a chronic nicotine infusion. Effects of OXY on baseline ICSS thresholds in non-dependent rats were also evaluated. OXY (0.06 – 1.0 mg/kg, i.p.) blocked withdrawal-induced elevations in somatic signs in nicotine-dependent rats without affecting somatic signs in non-dependent rats. In contrast, OXY did not affect nicotine withdrawal-induced elevations in ICSS thresholds. Relatively high doses of OXY (0.75 or 2.0 mg/kg) elevated baseline ICSS thresholds in non-dependent rats. These findings demonstrate that OXY blocks somatic signs but not elevations in ICSS thresholds during antagonist-precipitated nicotine withdrawal. The ability of higher OXY doses to elevate baseline ICSS thresholds in non-dependent rats may reflect an aversive and/or motoric effect. These data suggest that OXY-based medications may be useful for treating the somatic component of the nicotine withdrawal syndrome, but may not be effective in attenuating withdrawal-induced anhedonia.

1. Introduction

Tobacco smoking is the leading preventable cause of death in the United States and other industrialized countries (Benowitz, 2008; Mathers and Loncar, 2006). Cessation of tobacco use produces a nicotine withdrawal syndrome characterized by negative affective (emotional) symptoms (e.g., depression, anxiety), cognitive deficits, weight gain, and somatic symptoms (Hughes, 2007a,b; Kenny and Markou, 2001; Paolini and De Biasi, 2011). Avoidance of nicotine withdrawal symptoms is thought to play a critical role in maintaining tobacco use (Baker et al., 2004; Hughes, 2007a; Koob and Le Moal, 2008; Markou, 2008; Paolini and De Biasi, 2011; Watkins et al., 2000a). Development of medications that attenuate the nicotine withdrawal syndrome may therefore be useful for facilitating smoking cessation.

The neuropeptide oxytocin (OXY) is being evaluated as a potential treatment for a variety of behavioral disorders. While best known for its peripheral endocrine effects related to parturition and lactation, OXY also acts as a neurotransmitter/neuromodulator to influence social behaviors (e.g., pair bonding, maternal behavior) and other CNS effects including learning and memory, anxiety, and depression (for review, see Baskerville and Douglas, 2010; Lee et al., 2009; Neumann, 2008; Viero et al., 2010). OXY has also been implicated in drug addiction, which is mediated by similar neural substrates as social behavior (e.g., mesolimbic dopamine system) and is associated with social deficits (Baskerville and Douglas, 2010; Carson et al., 2013; McGregor and Bowen, 2012; McGregor et al., 2008). In preclinical studies, systemic administration of OXY attenuates the addiction-related behavioral effects (e.g., withdrawal, intravenous self-administration) of several drugs of abuse including opiates and methamphetamine (e.g., Carson et al., 2010a,b; Cui et al., 2001; Kovacs et al., 1985; Qi et al., 2009). The use of OXY or OXY-based medications for the treatment of drug addiction has been proposed (Kovacs et al., 1998; McGregor and Bowen, 2012; McGregor et al., 2008; Sarnyai, 2011), and an ongoing clinical trial is evaluating the ability of OXY nasal spray to attenuate alcohol withdrawal (ClinicalTrials.gov Identifier: NCT01212185).

The role of OXY in the behavioral effects of nicotine has not yet been investigated. To this end, the current study examined the effects of OXY on antagonist-precipitated nicotine withdrawal in rats. Because previous studies demonstrating effects of OXY on drug withdrawal have measured overt, physical withdrawal signs (Cui et al., 2001; Kovacs et al., 1998; Szabo et al., 1987), we initially examined the ability of

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OXY to attenuate somatic signs of nicotine withdrawal (e.g., gasping, shaking) (see Malin and Goyarzu, 2009; Malin et al., 1992). Following demonstration of efficacy of OXY in this model, we examined effects of OXY on nicotine withdrawal-induced elevations in intracranial self-stimulation (ICSS) thresholds. This measure is often considered analogous to the diminished interest or pleasure in otherwise reinforcing stimuli (anhedonia) associated with nicotine withdrawal (see Epping-Jordan et al., 1998; Watkins et al., 2000a,b). Elevations in somatic signs and ICSS thresholds during nicotine withdrawal have been dissociated in terms of their neural substrates (e.g., peripheral versus central mediation) and sensitivity to treatment drugs (e.g., Bruijnzeel et al., 2010; Epping-Jordan et al., 1998; Watkins et al., 2000a,b). In addition, only ICSS threshold elevations simulate the negative affective consequences of nicotine withdrawal that are thought to play a particularly important role in maintaining tobacco addiction (e.g., Baker et al., 2004; Kenny and Markou, 2001; Koob and Le Moal, 2005, 2008).

A secondary goal of this study was to determine the effects of OXY on baseline ICSS thresholds in non-dependent animals. It is well established that drugs with abuse liability reduce baseline ICSS thresholds, reflecting an enhancement of the reinforcing effects of the brain stimulation (e.g., Harrison et al., 2002; Wise, 1996). In contrast, acute injection of aversive drugs elevates baseline ICSS thresholds (Carlezon et al., 2006; Fowler et al., 2011). Evaluating effects of OXY on baseline ICSS thresholds therefore provided insights into potential side effects (abuse liability, aversion) of the use of OXY for treating drug addiction or other behavioral disorders (e.g., autism, social phobia, see Baskerville and Douglas, 2010).

2. Materials and methods

2.1. Animals

Experimentally naïve male Wistar rats (Charles River Laboratories, Wilmington, MA) weighing 275–300 g at arrival were individually housed in a temperature- and humidity-controlled colony room with unlimited access to food and water. Rats were housed under a reversed 12-h light/dark cycle and tested during the dark (active) phase. Animals were allowed a period of at least one week to acclimate to the experimental housing following arrival in the colony. Animal husbandry and experimental protocols were approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation in accordance with the 1996 NIH Guide for the Care and Use of Laboratory Animals and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2003).

2.2. Drugs

Nicotine bitartrate, mecamylamine hydrochloride (MEC), and oxytocin (OXY) (Sigma Chemical Co., St. Louis, MO) were each dissolved in sterile saline. The pH of the nicotine solution was adjusted to 7.4 with dilute NaOH. Nicotine doses are expressed as the base. Nicotine was administered s.c. via osmotic minipump (see below). Injections were administered s.c. (MEC) or i.p. (OXY) in a volume of 1.0 ml/kg, as is conventional in the literature (e.g., Carson et al., 2010a; Watkins et al., 2000b).

2.3. Osmotic minipump surgery

Rats were anesthetized with an isoflurane/oxygen vapor mixture (1–3% oxyflurane) and prepared with s.c. Alzet osmotic minipumps (model 2ML4; Durect Corporation, Cupertino, CA). Pumps were filled with either physiological saline or nicotine solution adjusted to deliver a nicotine dose of 3.2 mg/kg/day for 28 days. The surgical wound was closed with 9 mm stainless steel wound clips (Stoelting Co, Wood Dale, IL) and treated with povidone-iodine ointment (Aplicare, Meriden, CT). Rats received an injection of buprenorphine (0.1 mg/kg, s.c.) immediately following surgery and again ≈ 18 h later to ameliorate any post-operative pain. Rats also received daily i.m. injections of the antibiotic ceftriaxone (5.25 mg) for two days following surgery.

2.4. Assessment of somatic signs

During each test session, rats were placed in a clear plastic circular chamber and videotaped for 10 min. Tapes were later scored for somatic signs by a blinded, trained observer using a validated checklist (Harris et al., 2011, 2013; Malin et al., 1992). Withdrawal signs included abdominal constrictions (gasps and writhes), facial fasciculations (teeth chattering, cheek tremor, or chewing), blinks, and miscellaneous, less frequent signs (e.g., yawns, ptosis, shakes). Multiple successive counts of any sign required a distinct pause between episodes. If continuously present, facial fasciculations were recorded only once every 15 s, and ptosis only once per minute.

2.5. Intracranial self-stimulation (ICSS)

2.5.1. Equipment

Intracranial self-stimulation (ICSS) training and testing occurred in operant conditioning chambers (29 cm × 26 cm × 33 cm high) (Med Associates, St. Albans, VT) placed inside sound-attenuated cubicles. A 5-cm wide metal wheel manipulandum was fixed to the front wall. Brain stimulation was administered with constant-current stimulators (Model #PHM-152, Med-Associates). Rats were connected to the stimulation circuit through bipolar leads (Plastics One, Roanoke, VA) attached to gold-contact swivel commutators (Plastics One). MED-PC IV software was used to control stimulation parameters and for data collection.

2.5.2. Stereotaxic surgery

Animals were anesthetized with i.m. ketamine (75 mg/kg) and xylazine (7.5 mg/kg) and implanted with a bipolar stainless steel electrode (Model MS303/2: Plastics One) in the medial forebrain bundle at the level of the lateral hypothalamus [AP −0.5 and ML ± 1.7 mm from bregma, DV −8.3 mm from dura with the incisor bar set 5 mm above the inter-aural line (Pellegrino et al., 1979)]. The side of the brain in which the electrode was placed was alternated across subjects. Animals were allowed to recover for at least one week prior to ICSS training, during which time they were treated with buprenorphine and ceftriaxone as described for the osmotic minipump surgical procedure.

2.5.3. ICSS training procedure

Rats were trained on a modified version of the Kornetsky and Esposito (1979) discrete-trial current-threshold procedure as described previously (see Harris et al., 2010; Markou and Koob, 1992; Roiko et al., 2009). Each trial was initiated with presentation of a non-contingent stimulus (0.1 ms cathodal squarewave pulses at a frequency of 100 Hz for 500 ms) followed by a 7.5-s window during which a positive response on the wheel manipulandum produced a second, contingent stimulation identical to the first. Lack of responding in the 7.5-s time window was considered a negative response. Each positive or negative response was followed by a variable inter-trial interval averaging 10 s (range = 7.5 to 12.5 s), during which time additional responses delayed onset of the subsequent trial by 12.5 s. Stimulus intensities were presented in four alternating descending and ascending series (step size = 5 uA), with five trials presented at each current intensity step. The current threshold for each series was defined as the midpoint between two consecutive current intensity steps that yielded three or more positive responses and two consecutive current intensity steps that yielded three or more negative responses. The overall threshold for the approximately 45 min session was defined as the mean of the current thresholds from the four alternating series. To assess performance effects (e.g., motor disruption), response latencies (time between