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Oxytocin Acts in Nucleus Accumbens to Attenuate Methamphetamine Seeking and Demand

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ABSTRACT

BACKGROUND: Evidence indicates that oxytocin, an endogenous peptide well known for its role in social behaviors, childbirth, and lactation, is a promising addiction pharmacotherapy. We employed a within-session behavioral-economic (BE) procedure in rats to examine oxytocin as a pharmacotherapy for methamphetamine (meth) addiction. The BE paradigm was modeled after BE procedures used to assess motivation for drugs in humans with addiction. The same BE variables assessed across species have been shown to predict later relapse behavior. Thus, the translational potential of preclinical BE studies is particularly strong.

METHODS: We tested the effects of systemic and microinfused oxytocin on demand for self-administered intravenous meth and reinstatement of extinguished meth seeking in male and female rats using a BE paradigm. Correlations between meth demand and meth seeking were assessed.

RESULTS: Female rats showed greater demand (i.e., motivation) for meth compared with male rats. In both male and female rats, meth demand predicted reinstatement of meth seeking, and systemic oxytocin decreased demand for meth and attenuated reinstatement to meth seeking. Oxytocin was most effective at decreasing meth demand and seeking in rats with the strongest motivation for drug. Finally, these effects of systemic oxytocin were mediated by actions in the nucleus accumbens.

CONCLUSIONS: Oxytocin decreases meth demand and seeking in both sexes, and these effects depend on oxytocin signaling in the nucleus accumbens. Overall, these data indicate that development of oxytocin-based therapies may be a promising treatment approach for meth addiction in humans.

Keywords: Addiction, Behavioral economics, Methamphetamine, Oxytocin, Reinstatement, Self-administration

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Oxytocin, an endogenous neuropeptide well known for its role in social behaviors and childbirth, is a potential pharmacotherapy for addiction (1–9). Clinical and preclinical research has shown that oxytocin can decrease addiction-related behaviors, including drug cravings in humans (10,11) and self-administration and relapse-like behaviors in rodents (12–16). These effects of oxytocin may be caused by interactions within the mesocorticolimbic dopamine system, as this system mediates both social behaviors and addiction-like behaviors (17), including motivated drug seeking during relapse (18–24).

Behavioral-economic (BE) paradigms designed to assess addiction-like behaviors can be applied similarly in humans and animals, giving them high translational potential. In this approach, demand for a drug is measured under varying price (or effort) conditions, providing demand curves that allow estimates of free consumption (Q_0) and motivation (16,25). These analyses allow for direct comparison of the same BE variables across species or reinforcers (26,27). Importantly, the variables measured with this translational approach (particularly demand elasticity [α] and Q_0) have been shown to predict addiction behaviors in both humans (28–30) and animals (16,25,31,32) and may be an effective approach for developing and testing potential pharmacotherapies (16).

Previous methods to generate demand curves required subjects to stabilize responding at multiple different prices (number of lever presses per reward) over weeks of testing (31,33), limiting the ability to assess underlying brain mechanisms or possible pharmacotherapies. This limitation has recently been overcome with the design of a within-session BE procedure for cocaine self-administration (25,34,35). However, no comparable within-session paradigm exists for methamphetamine (meth) self-administration. We developed a new within-session BE method to accommodate the longer half-life of meth. We verified that demand curve variables (α and Q_0) obtained with our new method were similar to variables obtained in a conventional, multiday BE paradigm. This novel within-session paradigm permits construction of demand curves for meth (or other long-acting rewards) within a single 105-minute session.

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Using this BE procedure, we find that there is a close relationship between the economic demand for meth and reinstatement of extinguished meth seeking. We also show that in both male and female rats, oxytocin decreases motivation to seek meth and proportionally attenuates reinstatement behavior (16). Numerous studies have demonstrated a crucial role of the nucleus accumbens (NAc) core in mediating effects of oxytocin on reward-related behaviors (8,9,13,17,36–41). We show here that oxytocin decreased Fos activation in NAc core neurons associated with reinstated meth seeking and that oxytocin actions in NAc are both sufficient and necessary to decrease meth demand and seeking. Overall, this work indicates that oxytocin may be a promising treatment for meth addiction and highlights the NAc as a region of interest for further assessment of the mechanism of oxytocin in drug addiction.

METHODS AND MATERIALS

Subjects

Male and female Sprague Dawley rats (initial weight 200–275 g; Harlan Laboratories, Inc., Indianapolis, IN) were individually housed on a reversed 12-hour light/dark cycle in a temperature- and humidity-controlled vivarium. Water and food were available ad libitum. All experimental protocols were approved by the Institutional Animal Care and Use Committee and were in accordance with the *Guide for the Care and Use of Laboratory Animals* (42).

Meth Self-administration and BE Procedures

Rats acquired intravenous meth self-administration in daily 2-hour sessions (fixed ratio [FR] 1 schedule) for a minimum of five sessions (>20 infusions/session). The meth dose per infusion was adjusted for female rats (17.5 μg/50 μL) and male rats (20 μg/50 μL) to account for differences in average body weight (43,44). In subsequent sessions, FR values were increased (i.e., FR3, FR10, FR32, FR100), and rats self-administered meth at each FR value until they reached <15% variability in the last 2 days and were then switched to the within-session BE paradigm. Rats experienced the within-session procedure (minimum of five sessions) until demand elasticity was stable (i.e., α values within 25% of the mean of the last three sessions). All testing during BE sessions was performed in a within-subject, counterbalanced manner, with responding restabilized between each test.

After within-session BE tests, rats underwent a minimum of seven extinction sessions (2-hour/daily sessions) to a criterion of <25 active lever presses on 2 consecutive days. After reaching criterion, rats underwent cue-induced reinstatement testing where one meth-associated cue (light + tone) was presented at the beginning of the session, and subsequent responding on the active lever resulted in presentation of the cues along a FR1 schedule. Between all reinstatement tests, rats experienced a minimum of two extinction sessions or until criterion was met. See Supplemental Methods for surgery, drugs, standard self-administration procedures, estrous cycle monitoring, and statistical analysis.

Immunohistochemistry

Immediately after a final cue-induced reinstatement test or extinction, rats were sacrificed for Fos labeling. As the Fos protein takes 60 to 90 minutes to express, this analysis captured the first 30 minutes of the session and has been previously used to assess reinstatement-induced Fos (45). The total number of Fos-positive neurons was quantified in the NAc core. See Supplemental Methods for more specific immunohistochemical analysis.

Demand Curve Analysis

An exponential demand equation (25,27) was used to fit a demand curve to the results from each session to determine economic demand parameters for meth, as prevously described (25). Briefly, demand variables Q_0 (drug consumption at null cost) and α (rate of consumption decline with increasing price) were extracted from the demand curves and used in subsequent analyses. Price is defined here as the number of responses needed to obtain one meth infusion. The primary measure of "free consumption" was Q_0 (mg/kg/rat), corresponding to consumption at null effort. The primary measure of "motivation" to self-administer drug was demand elasticity, which corresponds to the rate at which consumption decreases with increasing effort (25). Importantly, demand elasticity scales inversely with motivation for meth. See Supplemental Methods and elsewhere (25,27) for specifics of demand curve analysis.

Intracerebroventricular Microinfusions

After rats were stabilized on the within-session BE procedure as described above, they received unilateral microinfusions of oxytocin into a lateral ventricle. An infusion pump delivered 1 μL/2 min; injectors were left in place for an additional 2 minutes. All rats received four microinfusions in a counterbalanced manner of desGly-NH_2,d$(CH_2)_5$[D-Tyr^2,Thr^4]OVT oxytocin antagonist (OXA; 2 μg/infusion) or artificial cerebrospinal fluid (aCSF) immediately followed by oxytocin (1 mg/kg intraperitoneal [i.p.]) or saline (sal) 30 minutes before testing. Responding was restabilized between tests.

NAc Core Microinfusions

On test days, rats received bilateral microinfusions (0.5 μL/side) over a 1-minute period, and injectors were left in place for 1 minute. To test whether oxytocin in the NAc core decreased meth seeking, rats received microinfusions of either oxytocin (0.6 μg/side) or aCSF vehicle (in a counterbalanced manner) 10 minutes before being tested on the BE paradigm and/or cue-induced reinstatement. To test if systemic oxytocin acted within the NAc to reduce meth seeking, rats received microinfusions of either OXA (1 μg/side) or aCSF vehicle into NAc immediately followed by a systemic injection of oxytocin (1 mg/kg) or saline 30 minutes before testing on the BE paradigm. Responding was restabilized between all tests. To show specificity of effect of oxytocin to NAc, a separate group of rats with cannula placements outside of the NAc was also assessed. Rats tested on cue-induced reinstatement received a maximum of two tests (oxytocin or vehicle, counterbalanced)