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Oxytocin reduces alcohol consumption in prairie voles

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ABSTRACT

Alcohol use disorder (AUD) negatively affects millions of people every year in the United States, and effective treatments for AUD are still needed. The neuropeptide oxytocin has shown promise for reducing alcohol drinking in mice and rats. Because oxytocin also plays a key role in complex prosocial behaviors like bonding and attachment, we tested the effect of oxytocin on alcohol drinking in prairie voles, a species that both consumes high amounts of alcohol and forms oxytocin dependent social bonds in a manner similar to humans. Oxytocin treatment (1.0, 3.0, and 10.0 mg/kg, i.p.) reduced alcohol consumption in male and female prairie voles in animals that had access to 15% ethanol vs water every other day for 12 alcohol drinking sessions. In animals with continuous access to 15% alcohol and water, oxytocin (3.0 mg/kg) reduced alcohol consumption only in the first hour of access after treatment, with no significant effects on consumption over the 24-hr period. In an open field locomotor test, oxytocin (1.0, 3.0, and 10.0 mg/kg, i.p.) did not affect overall locomotor activity; however, ethanol (2 g/kg, i.p.) increased locomotor activity in males and females, and produced anxiolytic effects (increased time in the center of an open field) in females only. Because prairie voles have been shown to match the alcohol consumption of their cage mate, we evaluated the relationship between cage mates' alcohol drinking. There was an overall pattern of social facilitation (consumption by one cage mate predicted consumption by the other cage mate); however, we found significant individual differences across cages in which many cages did not show significant matching, and, in some cases one cage mate's consumption negatively predicted the other cage mate's consumption. Overall, our data provide support for the potential of oxytocin as a treatment to reduce alcohol consumption.

1. Introduction

Oxytocin is a neuropeptide known to be involved in maternal, reproductive, and other types of social behavior. Recently oxytocin has been shown to have diverse and generally protective effects in multiple aspects of drug abuse, including alcohol abuse [7,28,31]. Alcohol use disorder (AUD) remains a major public health concern, with approximately 17 million adults suffering with AUD (niaaa.nih.gov), and yet the available treatments for AUD have offered only limited success [18]. Oxytocin has shown some promise in animal models of alcohol consumption and responses to alcohol.

Oxytocin has been shown to be generally effective at reducing alcohol consumption, as well as physiological and behavioral responses to alcohol. Oxytocin administration, both peripheral and ICV inhibited the development of tolerance to the hypothermic effects of high doses of ethanol in mice [43,44]. Additionally, ICV oxytocin administration reduced ethanol-induced sedation and ataxia in the wire-hanging, righting reflex, and open-field tests in rats [6]. Oxytocin administration reduced alcohol consumption in several studies. Low dose peripheral oxytocin administration reduced self-administration of an ethanol solution and ethanol gelatin in rats [30]. McGregor and Bowen [31] found an impressive 6-week decrease in consumption of a low alcohol sweet vodka drink compared to a sucrose solution following a single peripheral oxytocin administration in rats. Additionally, they found that 10 days of oxytocin administration prior to drinking reduced preference for the sweet alcohol drink. ICV oxytocin administration reduced alcohol consumption in rats with long-term chronic intermittent alcohol access [37]. Oxytocin administration also reduced two-bottle ethanol drinking in mice but with restrictions: oxytocin reduced alcohol drinking only when administered peripherally at a relatively high dose (10 mg/kg) in singly housed mice, not in mice subjected to chronic subordinate housing, and not when administered ICV [36]. Most

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recently, oxytocin administration reduced operant alcohol self-administration and breakpoints in a progressive ratio test, in addition to reducing alcohol consumption in the drinking in the dark method in mice [26]. Recent studies have illuminated aspects of the mechanism by which oxytocin can inhibit ethanol responses and reward, acting to block the accumbens dopamine response to both acute and chronic ethanol injections [37]. Oxytocin also acts directly on GABA receptors to reduce ethanol-induced GABA receptor activity [6]. Especially given data from a clinical trial in which oxytocin treatment reduced withdrawal severity and requests for Lorazepam in detoxing alcoholics [34], the literature to date suggests significant potential for treatments with oxytocin or drugs that can act via similar mechanisms.

Though studies of oxytocin and alcohol support a generally inhibitory role for oxytocin in alcohol consumption and responses, some inconsistencies are apparent. The duration and robustness of the effects of oxytocin seem to differ according to species, dose, route of administration, and method of alcohol administration [30,31,36,37]. Further studies of the effects of oxytocin on alcohol consumption and alcohol responses will benefit our understanding of oxytocin's potential for ameliorating AUD. Given the importance of oxytocin for social behavior, the use of an animal model that shares important social characteristics with humans is useful. Prairie voles and humans have in common complex social structures, social monogamy, biparental and alloparental behavior, and show devastating responses to isolation [12–15,32] and much is known about the function of oxytocin in these social behaviors in prairie voles. Furthermore, prairie voles are useful for alcohol studies because they voluntarily consume high levels of unsweetened alcohol without training [1,41]). Notable work has shown their alcohol consumption, like humans, is sensitive to complex social factors [1–4,23]. Finally, it is valuable to expand studies of potential AUD treatments to species beyond mice and rats, as these two species are closely related, are members of genetically closed populations, and have lost many of the behaviors of mice and rats in the wild [40]. Prairie voles, in contrast, are typically only a small number of generations removed from wild-caught animals, allowing for an understanding of the effects of oxytocin in a genetically diverse population. Finally, drug reward and social reward pathways are thought to overlap and include dopamine pathways that can be modulated by oxytocin [5,29,31,37,39]; therefore, understanding how oxytocin impacts alcohol reward in a species that, unlike mice and rats, displays lasting social bonds indicative of profound social reward in a manner similar to humans is valuable.

The purpose of this study was to determine the effects of oxytocin treatment on alcohol consumption in two different alcohol access methods (chronic intermittent and continuous alcohol access) in prairie voles, to assess the locomotor and anxiolytic effects of oxytocin and ethanol in prairie voles, and to investigate if oxytocin treatment could alter social facilitation of alcohol drinking in prairie voles. Sex differences in alcohol drinking, locomotor, and anxiolytic effects of oxytocin and ethanol were characterized.

2. Materials & methods

2.1. Subjects

Adult male and female prairie voles were bred and housed at Bucknell University. Animals were F3 generation descendants of prairie voles caught near Champagne-Urbana, Illinois, USA. Animals were pair-housed (except where specified) with a same-sex sibling in polycarbonate cages (19 cm × 29.2 cm × 12.7 cm, Ancare, Bellmore, NY, USA) with Harlan Teklad aspen sani-chip bedding (Envigo, Somerset, NJ, USA), and given ad libitum access to water and high fiber rabbit chow (Purina Mills, Inc., Gray Summit, MO, USA). Colony rooms were maintained on a 14:10 light cycle (lights on at 06:00) at approximately 70 °F. Animals were ages 8–27 weeks, and ages were counterbalanced across studies and treatment groups. All experiments and procedures were approved by the Bucknell University IACUC and conducted in accordance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research [46].

2.2. Drugs

Oxytocin acetate salt (Bachem, Torrence, CA, USA) dissolved in 0.9% saline was injected (i.p.; 1.0, 3.0, and 10.0 mg/kg). These doses were chosen based on their efficacy in other studies of alcohol consumption [30,31,36]. In the case of rat studies, the equivalent surface area dosage conversion [10] was used to estimate a dose range for prairie voles. Injection volumes for oxytocin and saline were 10 mL/kg. 95% ethyl alcohol was diluted to 15% alcohol in water for alcohol drinking experiments. For injection in locomotor studies, 95% ethyl alcohol was diluted to 20% in saline, then administered at a dose of 2 g/kg, i.p. The 2.0 g/kg dose of ethanol was chosen because it has previously been shown to induce acute locomotor activation in mice [42].

2.3. Procedure

2.3.1. Effect of oxytocin on chronic intermittent access alcohol drinking in male and female prairie voles

Adult male (n = 34) and female (n = 34) prairie voles were given access to 15% ethanol and water according to a chronic intermittent access two-bottle method [33]. A mesh divider made of galvanized steel hardware cloth with 0.5 in. square openings was inserted down the middle of the length of the cage, bisecting it such that each animal had access to half of the cage (approximately 8.9 cm × 29.2 cm). This allowed for measurement of individual fluid consumption, while still providing animals with visual, olfactory, and tactile contact with their cage mate. Dividers were only used on the first habituation day and on alcohol drinking days. On water days, dividers were removed when alcohol bottles were replaced with water bottles in order to limit any possible stress associated with having the divider in the cage, although no signs of stress were observed. Specifically, on day 1, dividers were inserted and each animal had access to two bottles of water to habituate them to two-bottle access. On day 2, dividers were removed and animals had access to all four water bottles that were in place on day 1. Day 3 was the first day of ethanol access: dividers were inserted and each animal had access to one bottle of 15% ethanol and one bottle of water. On day 4 dividers were removed, and animals had access to 4 bottles of water. The conditions for days 3 and 4 were repeated, such that animals had access to alcohol for 24 h every other day until they had completed 12 alcohol drinking days (25 days total). On all alcohol access days, the position (left-right) of the water and alcohol bottles was alternated relative to their last drinking session. Thirty minutes before alcohol drinking sessions 8, 9, 10, animals were injected with saline (i.p.) to habituate them to injection procedures. Vehicle (saline) or oxytocin (OT 1.0, 3.0, or 10.0 mg/kg, i.p.) treatment was administered 30-min before the start of sessions 11 and 12 (injections at 08:00, bottles on at 08:30). Animals in the same cage were given the same treatment. Each animal received a vehicle treatment and one dose of oxytocin, with the order counterbalanced across sessions 11 and 12. On vehicle and oxytocin treatment days, ethanol and water consumption were measured 1, 6, 12, and 24 h after alcohol and water bottles were put on each cage. Animals were weighed once per week at the start of a water drinking day.

2.3.2. Effect of oxytocin on continuous access alcohol drinking in male and female prairie voles

To determine if oxytocin would reduce drinking when animals had continuous access to alcohol, and to utilize the drinking method that has been used frequently in prairie voles, we tested the effect of oxytocin on alcohol consumption in 12 male and 14 female prairie voles with continuous access to 15% ethanol vs water for 13 days. The position of water and alcohol bottles was alternated each day. Divided