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Prosocial effects of oxytocin in two mouse models of autism spectrum disorders

Brian L. Teng [a,d,*], Randal J. Nonneman [a,c], Kara L. Agster [a,b], Viktoriya D. Nikolova [a,b], Tamara T. Davis [a,d], Natallia V. Riddick [a,b], Lorinda K. Baker [a], Cort A. Pedersen [a,b], Michael B. Jarstfer [a,d], Sheryl S. Moy [a,b]

[a] Carolina Institute for Developmental Disabilities, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA
[b] Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA
[c] Department of Genetics, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA
[d] UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA

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ABSTRACT

Clinical evidence suggests that oxytocin treatment improves social deficits and repetitive behavior in autism spectrum disorders (ASDs). However, the neuropeptide has a short plasma half-life and poor ability to penetrate the blood–brain barrier. In order to facilitate the development of more bioavailable oxytocinergic compounds as therapeutics to treat core ASD symptoms, small animal models must be validated for preclinical screens. This study examined the preclinical utility of two inbred mouse strains, BALB/cByJ and C58/J, that exhibit phenotypes relevant to core ASD symptoms. Mice from both strains were intraperitoneally administered oxytocin, using either acute or sub-chronic regimens. Acute oxytocin did not increase sociability in BALB/cByJ; however, sub-chronic oxytocin had significant prosocial effects in both BALB/cByJ and C58/J. Increased sociability was observed 24 h following the final oxytocin dose in BALB/cByJ, while prosocial effects of oxytocin emerged 1–2 weeks post-treatment in C58/J. Furthermore, acute oxytocin decreased motor stereotypy in C58/J and did not induce hypoactivity or anxiolytic-like effects in an open field test. This study demonstrates that oxytocin administration can attenuate social deficits and repetitive behavior in mouse models of ASD, dependent on dose regimen and genotype. These findings provide validation of the BALB/cByJ and C58/J models as useful platforms for screening novel drugs for intervention in ASDs and for elucidating the mechanisms contributing to the prosocial effects of oxytocin.

1. Introduction

Autism spectrum disorders (ASDs), which occur in approximately 1% of the population, are characterized by core deficits in sociability and communication skills, as well as abnormal restrictive and repetitive behaviors (CDC, 2012; Elsabbagh et al., 2012; Nazeer and Ghaziuddin, 2012). Although clinical evidence suggests that some medications may alleviate repetitive behavior in ASDs (e.g. atypical antipsychotics and selective serotonin reuptake inhibitors), these drugs have not proven to be consistently effective and have been associated with significant adverse side effects (Carrasco et al., 2012; McDougle et al., 2005; McPheeters et al., 2011; Stachnik and Nunn-Thompson, 2007). Furthermore, there are no pharmacological interventions for treating the social deficits associated with ASDs; however, the oxytocin signaling pathway is emerging as a promising avenue for ASD drug discovery efforts (Meyer-Lindenberg et al., 2011; Striepens et al., 2011).

Oxytocin is a neuropeptide hormone with a long recognized role in maternal responses, but there is increasing evidence that oxytocin mediates other aspects of social behavior, and that disruption of normal oxytocin function could lead to impaired sociability and affiliative interactions (Insel, 2010). In line with this premise, several reports indicate oxytocin signaling may be deficient in ASDs (Higashida et al., 2012; Striepens et al., 2011). Thus, pharmacological activation of central oxytocin receptors could have beneficial effects on core ASD symptoms, especially social deficits. This hypothesis is supported by studies that demonstrate acute high doses of oxytocin can improve social function and reduce repetitive behavior in individuals with ASD (Andari et al., 2010;

* Corresponding author. UNC Eshelman School of Pharmacy, Division of Chemical Biology and Medicinal Chemistry, University of North Carolina, 308 Beard Hall, Campus Box 7568, Chapel Hill, NC 27599-7568, USA. Tel.: +1 919 966 8654.
E-mail addresses: brianlteng@unc.edu, brianlteng@gmail.com (B.L. Teng).

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Guastella et al., 2010; Hollander et al., 2007, 2003). However, the clinical utility of oxytocin is limited by its short half-life, poor ability to cross the blood–brain barrier, and affinity for vasopressin receptors (Chini and Manning, 2007; Kang and Park, 2000; Morin et al., 2008; Schorscher-Petcu et al., 2010). These concerns underscore the need to explore the development of selective, non-peptide drugs to target the oxytocin pathway. To achieve this goal, appropriate small animal models are critical for preclinical efficacy testing of novel oxytocinergic compounds.

Previously, we screened multiple commercially-available inbred mouse strains for abnormal phenotypes relevant to core symptoms of human developmental disorders, and identified strains that could serve as appropriate behavioral models for ASDs (Moy et al., 2004, 2008, 2007). For example, we found that specific strains have deficient sociability in a three-chambered choice task, which measures the time a test mouse spends in proximity to a stranger mouse versus an empty cage (i.e. non-social object) (Moy et al., 2008, 2007; Nadler et al., 2004). One of these strains, BALB/cByJ, exhibited both a lack of social preference and high levels of anxiety-like behavior, which could reflect the comorbid anxiety frequently observed in ASDs (Brodkin, 2007). BALB/cJ, a related sub-strain, also has impaired sociability in a three-chambered choice task (Brodkin et al., 2004; Sankoorikal et al., 2006), as well as deficient ultrasonic vocalization during social interaction, which may be relevant to core communication deficits observed in ASDs (Kikusui et al., 2011; Panksepp et al., 2007).

C58/J is another inbred mouse strain that shows low sociability in the three-chambered choice task (Moy et al., 2008; Ryan et al., 2010). C58/J mice also have deficits in social transmission of food preference, a test used to model social communication, and exhibit overt, abnormal repetitive behavior (Ryan et al., 2010). At an early age, C58/J mice spontaneously develop motor stereotypies, which include backflipping, "jackhammer" jumping, and upright scrabbling (Ryan et al., 2010). These robust ASD-like phenotypes in social and repetitive behaviors make the C58/J strain an attractive model for the preclinical evaluation of drug candidates to treat autism. Thus far, one study has identified an agent (GRN-529, a negative allosteric modulator of the metabotropic glutamate receptor subtype 5) that has efficacy in reducing the repetitive behavior of C58/J mice, but the study did not examine drug effects on the lack of sociability in this strain (Silverman et al., 2012b).

Overall, the oxytocin receptor is among the most promising targets for intervention in ASDs, which highlights the need for translational models to assess the behavioral pharmacology of therapeutics targeting the oxytocin pathway (including oxytocin itself). In the present studies, we utilized BALB/cByJ and C58/J to evaluate the effects of oxytocin treatment on behavioral phenotypes relevant to core ASD symptoms. Using both inbred strains allowed the identification of prosocial oxytocin effects that were dependent on genetic background, and the ability to investigate oxytocin efficacy against aberrant repetitive behavior in C58/J.

2. Methods and materials

2.1. Animals

For the BALB/cByJ model, cohorts of male mice (3–4 weeks old, $n = 12–24$) were obtained from Jackson Laboratory (JAX; Bar Harbor, ME). For the C58/J model, mice were offspring of C58/J breeding pairs (JAX) weaned at postnatal day 21 and caged with same-sex littermates. Dams were fed ProLab RMH 2000 and all other mice were fed ProLab RMH 3000 ad libitum with free access to water. Mice were maintained in groups of 2–4 animals per polycarbonate mouse cage lined with Bed-o'Cobs bedding. For enrichment, each cage contained a small section of PVC pipe and two nestlet squares. Mice were housed in an animal facility at The University of North Carolina at Chapel Hill (UNC) in a room with a 12-h light/dark cycle (lights off at 7 pm). All animal care and procedures were conducted in strict compliance with the animal welfare policies set by the National Institutes of Health and UNC, and were approved by the UNC Institutional Animal Care and Use Committee.

2.2. Drug treatment

Oxytocin (Bachem, Torrance, CA) was dissolved in saline containing 0.002% acetic acid. For acute treatments, mice were given a single intraperitoneal (IP) injection of vehicle or 1.0 mg/kg oxytocin 50 min prior to testing for sociability (BALB/cByJ model; Fig. 1), or for repetitive behavior (C58/J model). For sub-chronic treatments (both models), mice were given four IP injections of vehicle or 1.0 mg/kg oxytocin across 8–9 days, with at least 48 h between each injection; behavioral tests

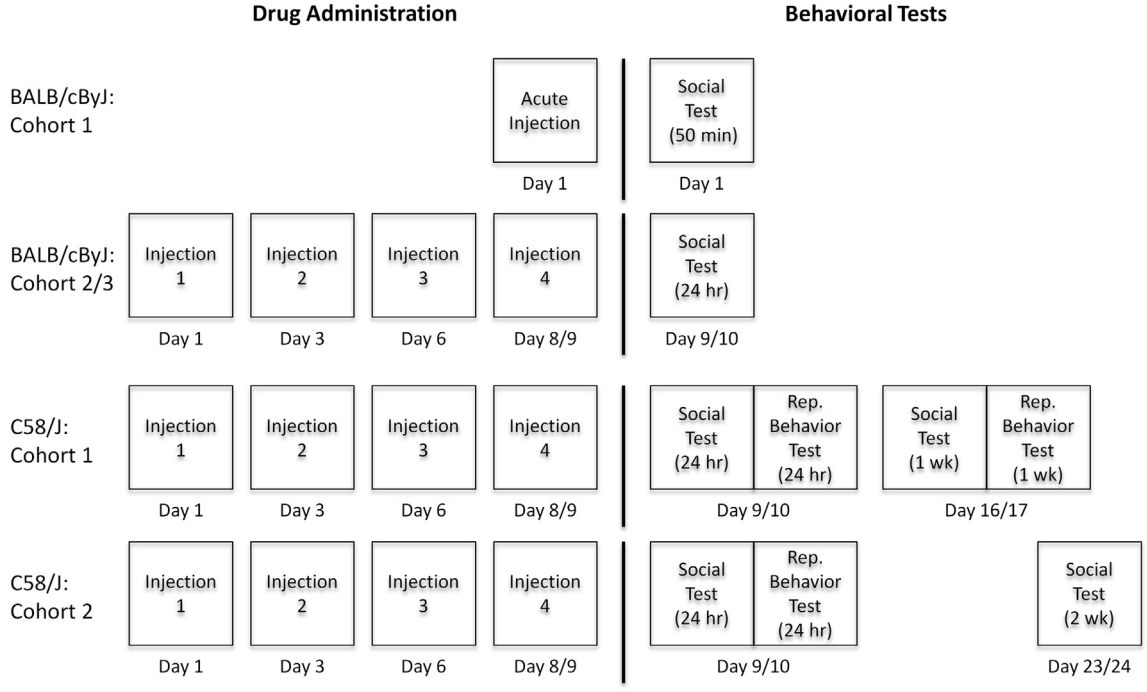

Fig. 1. Experimental timelines for the acute and sub-chronic oxytocin regimens, and behavioral tests in BALB/cByJ and C58/J mice. The acute regimen was a single-dose of vehicle or oxytocin (1.0 mg/kg) administered 50 min before behavioral testing. The sub-chronic regimen consisted of four doses of either vehicle or oxytocin (1.0 mg/kg) across an 8–9 day period, with at least 48 h between each IP injection. Sociability (Social) or repetitive (Rep.) behavior testing occurred on the indicated days. C58/J Cohorts 3 and 4 are not shown.