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Involvement of the oxytocin system in the nucleus accumbens in the regulation of juvenile social novelty-seeking behavior

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ABSTRACT

Exploration of novel environments, stimuli, and conspecifics is highly adaptive during the juvenile period, as individuals transition from immaturity to adulthood. We recently showed that juvenile rats prefer to interact with a novel individual over a familiar cage mate. However, the neural mechanisms underlying this juvenile social novelty-seeking behavior remain largely unknown. One potential candidate is the oxytocin (OXT) system, given its involvement in various motivated social behaviors. Here, we show that administration of the specific oxytocin receptor antagonist desGly-NH_2,d$(CH_2)_5$-[Tyr(Me)^2,Thr^4]OVT reduces social novelty seeking-behavior in juvenile male rats when injected into the nucleus accumbens (10 ng/0.5 μl/side). The same drug dose was ineffective at altering social novelty-seeking behavior when administered into the lateral septum or basolateral amygdala. These results are the first to suggest the involvement of the OXT system in the nucleus accumbens in the regulation of juvenile social novelty-seeking behavior.

1. Introduction

Across species, the juvenile period is characterized by heightened engagement in novelty-seeking behavior and increased social interaction with peers as compared to both younger and older ages (Spear, 2000). These behaviors are likely to be highly adaptive as individuals transition from immaturity to adulthood (Spear, 2000). However, a high novelty-seeking behavioral phenotype may predispose individuals to risk-taking and substance use (Dellu et al., 1996). Conversely, reduced social novelty-seeking is a characteristic of autism spectrum disorders (ASD) and may contribute to low social reciprocity and social interest in individuals with ASD (Anckarsäter et al., 2006; American Psychiatric Association, 2013). Thus, understanding the neural mechanisms underlying social novelty-seeking behavior may be a first step towards understanding how this behavior is disrupted in individuals diagnosed with substance use disorders or ASD.

To study social novelty-seeking behavior, we recently developed the 'social novelty preference test' in which juvenile rats showed a robust preference to interact with a novel over a familiar (cage mate) conspecific (Smith et al., 2015). Using a cage mate as the familiar stimulus makes this test distinct from other social preference tests such as the social discrimination test (Engelmann et al., 1995) and the three-chambered social preference test (Crawley, 2004; Moy et al., 2004; Nadler et al., 2004). Here, we aim to determine whether social novelty-seeking behavior is modulated by the brain oxytocin (OXT) system. OXT has been shown to regulate numerous social behaviors in various species via activation of the OXT receptor (OTR) in the brain (Anacker and Beery, 2013; Meyer-Lindenberg et al., 2011). However, most of this research has been conducted in adult animals and much less is known regarding the regulation of social behavior in juveniles. We focus here on the OXT system in the nucleus accumbens (NAc), lateral septum (LS) and basolateral amygdala (BLA), because these brain regions show higher OTR binding density in juvenile rats as compared to adult rats (Smith et al., 2017) and because the OXT system in these brain regions has been implicated in the regulation of various social behaviors (Guzmán et al., 2013, 2014; Lukas et al., 2013; Dölen et al., 2013; Chang et al., 2015). We hypothesize that OTR activation in either the NAc, LS, or BLA will facilitate social novelty-seeking behavior.

2. Methods

2.1. Animals

Male Wistar rats were obtained from Charles River Laboratories (Raleigh, NC) and housed in standard rat cages (26.7 × 48.3 × 20.3 cm) under standard laboratory conditions (12-h light/dark cycle, lights on at 7:00 am, food and water available ad libitum, 22 °C, 60% humidity). Experimental rats (23 days of age at arrival) were housed in same-sex pairs. Stimulus rats (22 days of age at arrival) were housed in same-sex groups of 3–4 and were one day younger than experimental rats

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to ensure that they were unrelated. All experiments were conducted in accordance with the NIH *Guide to the Care and Use of Laboratory Animals* and approved by the Boston College Institutional Animal Care and Use Committee (IACUC).

2.2. Cannulation and injection procedures

At 27 or 28 days of age, experimental rats were anesthetized with isoflurane (2–3%; Henry Schein, Dublin OH) and positioned into a stereotaxic frame with the incisor bar set at −4.5 mm. Throughout surgery, a heating pad was used to maintain body temperature. Coordinates were based on Paxinos and Watson (2007) and adapted for use in juveniles to hit target brain regions (see Fig. 1). Guide cannulae (22 gauge, Plastics One, Roanoke, VA) were implanted 2 mm dorsal to the target region, which was either the NAc (bilateral cannula implantation: 2.5 mm rostral to bregma, ±2.5 mm lateral to the midline, 4.6 mm ventral to the surface of the skull, angle of 10^0 from the midline), the LS (single cannula implantation aiming at the medial LS: 1.0 mm rostral to bregma, +1.0 mm lateral to the midline, −3.6 mm ventral to the surface of the skull, angle of 10^0 from the midline), or the BLA (bilateral cannula implantation: 2.7 mm caudal to bregma, ±4.3 mm lateral to the midline, 6.3 mm ventral to the surface of the skull). Guide cannulae were secured via stainless steel screws and dental acrylic adhesive and were closed with a dummy cannula (28 gauge; Plastics One). Experimental rats served both as subjects and as cage mate stimulus rats. Novel stimulus rats were exposed to sham surgeries in which all procedures were the same except that no guide cannula was implanted. Following surgery, rats were given an injection of Rimadyl analgesic (10 mg/kg; Henry Schein, Dublin OH) and singly housed for 1 h before rehousing with their cage mate.

Experimental rats were handled daily for four days prior to testing to habituate them to the injection procedure. Injection systems were composed of polyethylene tubing connected to an injector cannula and a 10 μl Hamilton syringe. The injector cannula (28 gauge; Plastics One)

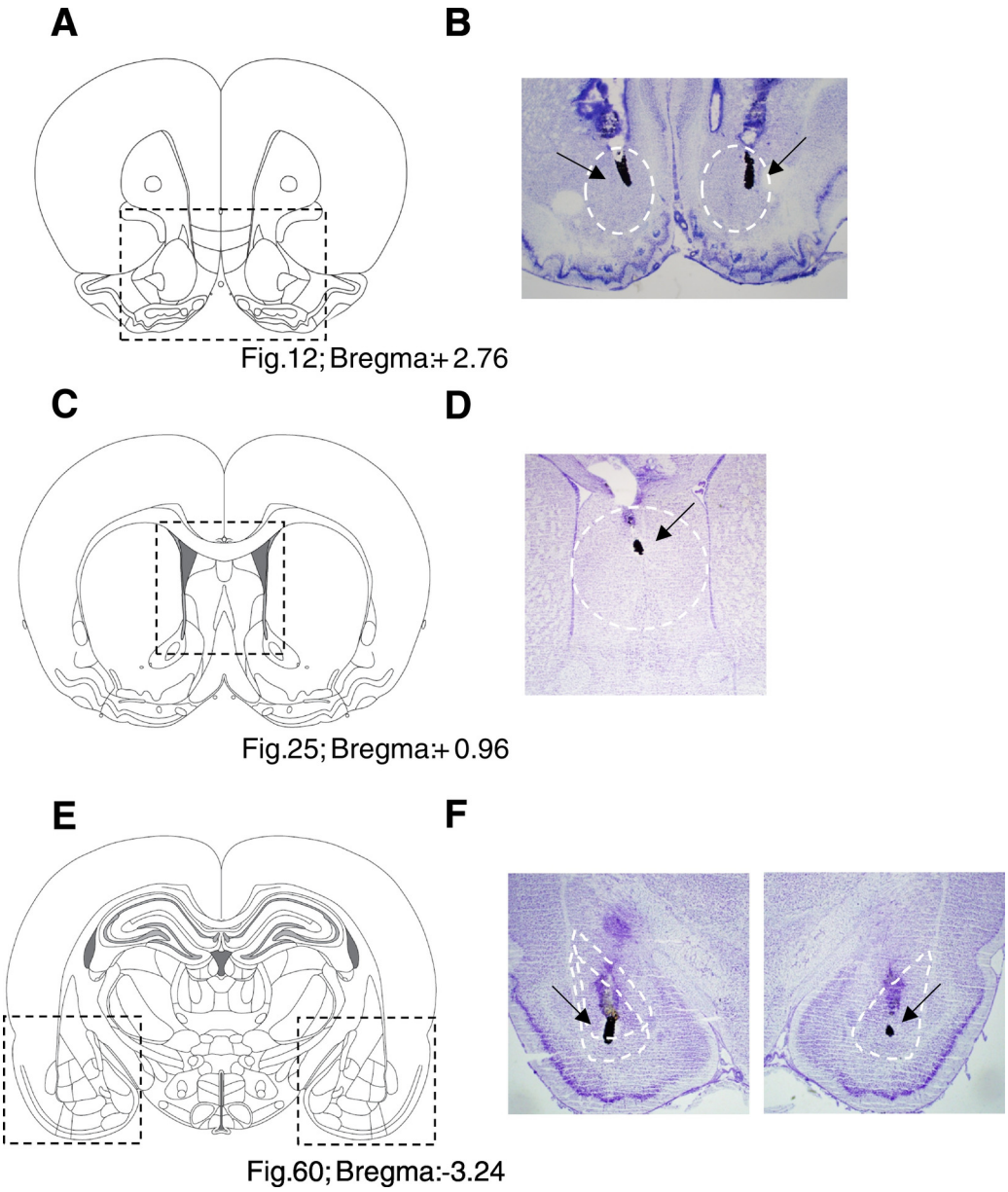

Fig. 1. Representative cannula placements in the NAc, LS, and BLA. Schematic drawings of the rat brain adapted from Paxinos and Watson (2007) illustrating the NAc (A), LS (C) and BLA (E), as well as Nissl-stained coronal brain sections indicating with arrows the location of microinjections using charcoal as a marker (B,D,F). Bilateral cannulae were implanted in the NAc and in the BLA, while one cannula was implanted in the center of the LS. Animals with incorrect cannula placements were excluded from analysis. Dashed squares in schematic drawings represent the area of enlargement in Nissl images; Dashed outlines represent target brain areas.