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Involvement of the oxytocin system in the bed nucleus of the stria terminalis in the sex-specific regulation of social recognition

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ABSTRACT

Sex differences in the oxytocin (OT) system in the brain may explain why OT often regulates social behaviors in sex-specific ways. However, a link between sex differences in the OT system and sex-specific regulation of social behavior has not been tested. Here, we determined whether sex differences in the OT receptor (OTR) or in OT release in the posterior bed nucleus of the stria terminalis (pBNST) mediates sex-specific regulation of social recognition in rats. We recently showed that, compared to female rats, male rats have a three-fold higher OTR binding density in the pBNST, a sexually dimorphic area implicated in the regulation of social behaviors. We now demonstrate that OTR antagonist (5 ng/0.5 μl/side) administration into the pBNST impairs social recognition in both sexes, while OT (100 pg/0.5 μl/side) administration into the pBNST prolongs the duration of social recognition in males only. These effects seem specific to social recognition, as neither treatment altered total social investigation time in either sex. Moreover, baseline OT release in the pBNST, as measured with in vivo microdialysis, did not differ between the sexes. However, males showed higher OT release in the pBNST during social recognition compared to females. These findings suggest a sex-specific role of the OT system in the pBNST in the regulation of social recognition.

1. Introduction

The neuropeptide oxytocin (OT) is synthesized mainly in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus (Buijs, 1978; Sofroniew, 1983), and regulates a wide variety of social behaviors in rodents and humans (Veenema and Neumann, 2008; Heinrichs et al., 2009; Ross and Young, 2009; Goodson and Thompson, 2010; Guastella and MacLeod, 2012). Importantly, OT has been shown to regulate some of these behaviors in sex-specific ways (reviewed in Dumais and Veenema, 2015, 2016). This may be due to sex differences in the OT system in the brain. Although OT mRNA expression is similar in the PVN and SON of male and female rats (Dumais et al., 2013), the OT receptor (OTR) is highly sexually dimorphic, with male rats showing higher OTR binding densities in many forebrain regions compared to female rats (Uhl-Bronner et al., 2005; Dumais et al., 2013).

The most robust sex difference in OTR binding density in the rat brain is found in the posterior bed nucleus of the stria terminalis (pBNST), in which males have a three-fold higher OTR binding density compared to females (Dumais et al., 2013). The pBNST has extensive connections with areas involved in social information processing (most notably the accessory olfactory bulb and medial amygdala; Scalia and Winans, 1975; Weller and Smith, 1982; Gu et al., 2003; Dong and Swanson, 2004) and is part of the social decision-making network (O'Connell and Hofmann, 2011). Indeed, the pBNST plays an essential role in transmitting chemosensory social information and modulating olfactory-guided social behaviors (Petrulis, 2013). For example, neuronal activation is increased in the pBNST in male Mandarin voles (He et al., 2014) and in female rats (Hosokawa and Chiba, 2007) in response to opposite-sex odors, and lesioning the pBNST impairs opposite-sex odor preference in male hamsters (Been and Petrulis, 2010). In addition, blocking OTR in the pBNST reduced male odor-induced vaginal marking in female hamsters (Martinez et al., 2010), suggesting a role for the OTR in the pBNST in social odor processing and/or olfactory-guided social behaviors. To the best of our knowledge, there are no comparative studies on the role of OTR in the pBNST in males and females.

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We hypothesized that the sex difference in OTR binding density in the pBNST is implicated in the sex-specific regulation of social behavior. To test this, we determined the effects of acute pharmacological manipulations of the OT system in the pBNST on social investigation (reflecting the motivation to approach a conspecific for the assessment of social cues) and social recognition (the ability to discriminate between familiar and unfamiliar conspecifics) in adult male and female rats. Social investigation and social recognition were chosen because these behaviors are modulated by the OT system (Gabor et al., 2012; Lukas et al., 2013; Dumais et al., 2013), require the processing of chemosensory social information, and can be tested with neutral social stimuli (i.e., juvenile rats), allowing focus on social odor processing without interference of sexual or aggressive behaviors.

We further hypothesized that the sex difference in OTR binding density in the pBNST corresponds with a sex difference in local OT release. Higher OTR binding density, as seen in males (Dumais et al., 2013), could be associated with higher OT release or could be a compensatory mechanism for lower OT release. To determine the relationship between sex differences in OTR binding density and OT release in the pBNST, we used in vivo microdialysis to measure extracellular OT release in the pBNST of male and female rats under baseline conditions and during exposure to the social recognition test.

2. Methods

2.1. Animals

Wistar rats were obtained from Charles River at 8–9 weeks of age (Wilmington, MA) and maintained on a 12 h light/dark cycle, lights on at 0700 h, and food and water were available ad libitum. Subjects were adult male and female rats housed in same-sex pairs in standard rat cages (26.7 × 48.3 × 20.3 cm) unless otherwise mentioned, and were given at least one week to acclimate to our facilities. Stimulus male and female rats were 22 days at arrival, were housed four per cage, and were used at 25–30 days of age. All experiments were conducted in accordance with the guidelines of the NIH and approved by the Boston College Institutional Animal Care and Use Committee (IACUC).

2.2. Stereotaxic surgery

2.2.1. Cannulation

After daily handling for one week to familiarize them with the injection procedure, experimental rats were anesthetized using isoflurane and mounted on a stereotaxic frame. A heating pad was used to regulate body temperature of rats while anesthetized. Guide cannulae (22 gauge; Plastics One, Roanoke, VA) were implanted bilaterally 2 mm dorsal to the pBNST (0.8 caudal to bregma, 1.5 and −1.5 lateral to midline, and 4.8 ventral to the skull surface; according to Paxinos and Watson, 1998). Guide cannulae were fixed to the skull with four stainless steel screws and acrylic glue and closed with dummy cannulae (26 gauge; Plastics One, Roanoke, VA). After surgery, rats were individually housed in standard rat cages (26.7 × 48.3 × 20.3 cm). Behavioral testing was performed 3 and 5 days after surgery.

2.2.2. Microdialysis probe placement

A separate set of rats was used for in vivo measurement of extracellular OT release. Handling and surgical procedures were similar to the procedures described above except for the placement of microdialysis probes instead of cannulae. Microdialysis probes (BrainLink, the Netherlands) were implanted unilaterally into the pBNST (0.8 caudal to bregma, −1.5 lateral to midline, and 7.0 ventral to the skull surface). Two inch pieces of polyethylene tubing were fixed to the ends of the microdialysis probes in order for attachment to the microinfusion pumps and eppendorf tubes for sample collection. After surgery, rats were individually housed in standard rat cages (26.7 × 48.3 × 20.3 cm). Microdialysis and behavioral testing were performed 2 days after surgery.

2.3. Behavioral testing

2.3.1. Social investigation test

To test for social investigation, the time rats spent investigating an unfamiliar same-sex juvenile rat was measured according to Dumais et al. (2013). A juvenile rat was used in order to assess general social approach of the experimental rat toward a social stimulus that does not elicit aggressive or sexual behaviors. Indeed, no aggressive or mounting behaviors were observed during the social investigation test. A juvenile rat was placed into the experimental rat's home cage for 4 min, and time spent investigating the juvenile was measured. Testing was performed during the light phase between 1200 h and 1700 h. Behaviors were video recorded and analyzed using JWatcher (http://www.jwatcher.ucla.edu) by an experimenter blind to treatment groups. Behavior was considered social investigation when the experimental rat was actively sniffing the juvenile, including sniffing the anogenital and head/neck regions.

2.3.2. Social recognition test

Social recognition was measured using the social discrimination paradigm, according to Veenema et al. (2012) and adapted from Engelmann et al. (1995). This paradigm consists of two trials. In the first trial (T1), the experimental rat is exposed in its home cage to an unfamiliar same-sex juvenile for 4 min (T1 is the same as the social investigation test described above). After a preset interval, the experimental rat undergoes a second trial (T2) in which the rat is exposed in its home cage to the same (familiar) juvenile along with an unfamiliar same-sex juvenile for 4 min (see Movie 1 in Supplementary material). To allow the experimenter to distinguish between the two juveniles, juveniles were marked on their backs with either red or black permanent marker 1 h prior to testing. The color of the marker was counterbalanced between novel and familiar juveniles. Using this social discrimination paradigm, previous studies found that adult rats show social recognition after a 1 h interval, but not after a 3 h interval (Veenema et al., 2012; Bernal-Mondragon et al., 2013; Lee et al., 2014). We hypothesized that OTR blockade may impair social recognition, while OT administration may prolong social recognition. Therefore, we used a 1 h interval for the OTR antagonist experiment, and a 3 h interval for the OT experiment. Testing was performed during the light phase between 1200 h and 1700 h. Behaviors were video recorded, and time spent investigating the juvenile rats was measured using JWatcher by an experimenter blind to treatment groups. As expected, no aggressive or mounting behaviors of the experimental rats toward the juvenile rats were observed during the test. The percentage of time investigating the novel juvenile (time investigating novel juvenile/time investigating familiar + novel juvenile × 100) during T2 was calculated as the measure of social recognition. The time spent investigating one juvenile in T1 and two juveniles in T2 was calculated as the measure of total social investigation time (in seconds) in T1 and T2, respectively.

2.4. Experimental procedures

2.4.1. Experiment 1: effect of OTR manipulations in the BNST on social investigation and social recognition

The effects of the OTR antagonist desGly-NH_2,d$(CH_2)_5$-[Tyr(Me)^2,Thr^4]OVT (Manning et al., 2008; 5 ng/0.5 μl/side) and synthetic OT (Sigma; 100 pg/0.5 μl/side) were each compared to