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Research article

Chronic central oxytocin infusion impairs sociability in mandarin voles

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ABSTRACT

Oxytocin (OT) has been reported to increase social contact, however some studies have related OT to reduced social contact, particularly with unfamiliar individuals. The underlying mechanisms of OT on social contact remain unclear. In this study, male mandarin vole (*Microtus mandarinus*), a socially monogamous rodent, was used as an animal model in which osmotic minipumps were used to intracerebroventricularly administer two dosages of OT or saline for 12 consecutive days. We examined the effect of long-term OT treatment on social behavior, anxiety levels, and levels of oxytocin, vasopressin (AVP) and dopamine (DA) receptors mRNA expression in the nucleus accumbens (NAcc), and medial amygdala (MeA). The data showed that chronic central OT infusion decreased social preference behavior (a reduction of preference for interacting with novel social stimulus relative to a novel object) concomitant to a reduction of OT receptors in the NAcc and MeA. We also found alterations in AVP and DA receptor levels in the NAcc and MeA after treatment with OT. Moreover, chronic central OT treatment did not affect levels of anxiety-related behavior in male voles. In conclusion, these results indicated that chronic OT treatment may differ from the treatment effects predicted in short-term studies, and significant dosage effects were observed.

1. Introduction

In many species, close social interactions are essential because they facilitate reproduction, increase survival, provide a sense of security, and reduce feelings of stress and anxiety (Coria-Avila et al., 2014). Living in social groups has clear benefits, resulting in increased survival, enhanced fitness of the group, and increased progression of brain development and cognitive abilities (Neumann, 2009). In a recent study, it was shown that the neuropeptide oxytocin (OT) was strongly implicated in social behavior, including social recognition (Gur et al., 2014), social approaches (Lukas et al., 2011), pair bonding (Williams et al., 1994), paternal care (Parker et al., 2001), and maternal behavior (Pedersen et al., 1982). Moreover, many neuropsychiatric diseases are characterized by impaired social behavior, such as social anxiety disorder, borderline personality disorder, autism spectrum disorders, and schizophrenia (Meyerlindenberg et al., 2011; Striepens et al., 2011). Thus, OT is a promising candidate for treatment of such disorders, which have the potential to require repeated or chronic treatment.

Like other peptides, OT can produce different effects based on different dosages, social condition, and duration of treatments (Ferguson et al., 2001; Huang et al., 2014; Peters et al., 2014). Although prosocial and emotional improvement effects of OT treatment have been emphasized (Beery and Zucker, 2010; Slattery and Neumann, 2010; Williams et al., 1994; Witt et al., 1992), the decreased or deterred social interaction and anxiogenic effects of OT have also been documented (Bales et al., 2013; Huang et al., 2014). For example, chronic infusion of OT for a duration of 7 days was found to selectively suppress aggression and enhance social exploration (Calcagnoli et al., 2014). However, chronic blockage of OT receptors (OTRs) increased aggressive behaviors in the early period of encounter when an intruder was introduced (Calcagnoli et al., 2014). Chronic intracerebroventricular (ICV) infusion of OT for 15 days at a high dose (10 ng/h), but not at low (1 ng/h) dose, induced an anxiogenic phenotype with a concomitant reduction of OT receptor (OTR) binding within the septum, the basolateral and medial amygdala, as well as the median raphe nucleus (Peters et al., 2014). In addition, Bales and colleagues reported that short-term intranasal administration of OT enhanced social contact between male cage-mates, whereas a daily intranasal OT application for 3 weeks impaired partner preference formation in male prairie voles (Bales et al., 2013). Repeated injections of OT to the central amygdala of female golden hamster dams increased aggression toward a male intruder (Ferris et al., 1992). The data above suggests that the duration of administration may be a key player in influencing the effects of OT on social behavior. The mechanisms underlying the differences found in the effect of OT on social

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behavior are not clear. One possibility may be that long-term administration desensitizes and down-regulates receptors or induces other habituation pathways (Beery, 2015; Insel et al., 1992). In none of these studies mentioned above, the impact of chronic OT infusion on the levels of central OTRs was investigated. This would be of particular importance if various psychopathological disorders were possibly treated by chronic use of OT.

Previous studies have shown that OT closely interacts with neural pathways that are responsible for processing motivationally relevant stimuli (Love, 2014). In particular, OT impacts the dopaminergic activity within the mesocorticolimbic dopamine (DA) system, which is crucial for reward and motivation behavior, but also for the expression of affiliative behavior (Love, 2014). For example, administration of OT into the ventral tegmental area (VTA), amygdala, and hippocampus stimulates the release of extracellular DA within the nucleus accumbens, which receives dopaminergic projections from the VTA (Baskerville et al., 2009; Succu et al., 2007). Chronic treatment with selective dopaminergic agonists, such as SKF-38393 and quinpirole, decreased the density of D2 receptors (Subramaniam et al., 1992). In addition, intra-striatal DA infusion increased the binding of D2-DA receptors in a 6-hydroxydopamine lesioned rat (Woiciechowsky et al., 1995). Thus, these data suggested that OT may impact the release of DA, subsequently leading to changes in the expression of DA receptors.

Although OT primarily binds to the OTR, it also has a weak affinity for vasopressin receptors (AVPR) (Donaldson and Young, 2008). The high sequence homology between AVP and OT, AVP and OT receptor subtypes, and the high degree of chemical similarity among these active ligands often results in overlap of selectivity profiles (Chini et al., 2008). Such similarities in the structure of receptors may influence ligand receptor recognition/activation. For example, in the lateral septum (LS), OT acts through vasopressin 1a receptors (V1aRs) to decrease partner preference (Anacker et al., 2016). Based on these findings, we hypothesized that long-lasting central infusion of OT changes AVP receptor levels.

OT, AVP, and DA are neurochemicals that play an important role in the regulation of sociability. These neurochemicals and their receptors, OTR, vasopressin receptor 1a (V1aR), and the dopamine receptor (DR) are highly expressed in the medial amygdala (MeA) and nucleus accumbens (NAcc), which play a role in social behavior (Arakawa et al., 2010; Holder et al., 2015; Kalivas and Nakamura, 1999; Ostrowski et al., 1994; Shapiro and Insel, 1992; Timmer et al., 2011). For example, the amygdala, a region of the brain that is strongly involved in social perception and emotional processing, has been implicated as one of the key regions involved in mediating neuronal actions of OT on social behavior in humans (Baumgartner et al., 2008; Gamer et al., 2010; Hurlemann et al., 2010) as well as in rodents (Choleris et al., 2007; Lee et al., 2007). More specifically, the MeA plays a central role in the vomeronasal pathway upstream of hypothalamic centers dedicated to defensive and social responses (Bergan et al., 2014). OT knockout mice exhibit social recognition impairments, however, these impairments can be reversed by OT infusion into the MeA, indicating a role of the amygdala in this process (Ferguson et al., 2001; Kavaliers et al., 2003). The NAcc also has been implicated in diverse aspects of social interaction, such as on social reward and motivation (Fareri et al., 2012; Fliessbach et al., 2007), as well as on reward processing. Thus, we predicted that chronic, central OT infusion affects social and emotional behavior via modifying the levels of OTR, V1aR, and DR in the MeA and NAcc.

Mandarin vole (*Microtus mandarinus*), a species of socially monogamous rodents widely distributed in China (Tai and Wang, 2001), is becoming an animal model for studies that focus on neurobiological mechanisms underlying social bonding (Jia et al., 2009; Yu et al., 2013). The mandarin vole is increasingly used for screening drugs that have therapeutic potential for the treatment of social disorders (Jia et al., 2008; Yu et al., 2016). Mandarin voles form enduring pair bonding and display high levels of bi-parental care (Jia et al., 2009). The high levels of sociability that are characterized by specific regions of the brain are evolutionarily shaped in mandarin voles but are lacking in traditional animal models (Wang et al., 2015).

Using mandarin voles, the major aims of the current study were to investigate whether chronic ICV infusion of OT using osmotic minipumps (OMP) affects emotion and social behaviors, and whether modifying these behaviors was associated with changes in the levels of OT, AVP, and DA receptors in the MeA and the NAcc. In the present study, a series of tests on social and anxiety behavior combined with RT-PCR analysis were used to investigate the long-term effects of chronic, central OT infusion by OMP. We hypothesized that the long-term effects of chronic OT treatment would alter social and emotional behavior, as well as the OT, AVP, and DA receptors in a dosage-dependent fashion.

2. Methods and materials

2.1. Subjects

F2 generation male mandarin voles (4 months old and average 30–34 g weight) originating from a wild population in Henan, China, were used as experimental subjects. Throughout the experimental period, animals were maintained under standard housing conditions (14:10 h light/dark period; lights on at 20:00 h; ambient temperature 25 ± 3 °C). All animals had unlimited access to food (carrots and rabbit chow) and water and were housed in polycarbonate cages (44 cm × 22 cm × 16 cm), containing cotton for nesting material. Mandarin voles are nocturnal animals and all behavioral tests were conducted during their active phase. All experimental and behavioral procedures were in accordance with the Guide for the Care and Use of Laboratory Animals of China, and were reviewed by the institutional animal care and use committee at Shaanxi Normal University.

2.2. Alzet minipump surgeries

Assessment of the effect of chronic OT infusion on anxiety-related and social behaviors was achieved via implantation of OMP (infusion rate: 0.25 μl/h for 14 days; Alzet; Model 1002; USA). Voles were anesthetized using isoflurane anesthesia (R.W.D. Life Science, Shenzhen, China) and cannulas were implanted stereotaxically. Animals were placed into a stereotaxic frame, and the ICV cannula (23 G, 3 mm length) was lowered into the right lateral ventricle (posterior 0.3 mm, lateral 0.8 mm, depth 0.25 mm). Pumps were filled with either saline (Ringer solution, pH 7.4, Xi'an Jingxi Shuanghe Pharmaceutical, Xi'an, China), or OT (Bachem Company, CA, USA) (10 ng/h, 1 ng/h). Animals were randomly assigned to one of the three experimental groups and were treated with either saline solution (n = 7), 1 ng/h OT (n = 6), or 10 ng/h OT (n = 8). The doses of OT were chosen based on the results of a previous study (Peters et al., 2014). Each OMP was implanted subcutaneously in the dorsal region of the vole. A 1-cm long skin incision was made at the neck of the voles, the OMP was implanted and connected with the ICV cannula by silicone tubing.

2.3. Behavioral testing

2.3.1. Light–dark box testing

Thirteen days after surgery, the effects of ICV chronic infusion of OT on anxiety-related behavior were assessed in a light–dark box (LDB) between 0800 h and 1100 h (Peters et al., 2013). The LDB consisted of a brightly lit (27 × 27 × 27 cm) and a dark (18 × 27 × 27 cm) compartment, separated by a portion wall containing a small opening (6 × 7 cm) at floor level. Voles were individually placed in the dark compartment to habituate (with the opening being closed). Thirty seconds after the opening between the light and the dark compartment was opened, voles were allowed to freely explore their environment for 5 min. The time spent in the light box (a measure of anxiety) and the