



Oxytocin in the medial preoptic area facilitates male sexual behavior in the rat

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ABSTRACT

Oxytocin (OT) is a versatile neuropeptide that is involved in a variety of mammalian behaviors, and its role in reproductive function and behavior has been well established. The majority of pharmacological studies of the effects of OT on male sexual behavior have focused on the paraventricular nucleus (PVN), ventral tegmental area (VTA), hippocampus, and amygdala. Less attention has been given to the medial preoptic area (MPOA), a major integrative site for male sexual behavior. The present study investigated the effects of intra-MPOA administration of OT and (d(CH₂)⁵1, Tyr(Me)², Thr⁴, Orn⁸, Tyr-NH²⁹)-vasotocin, an OT antagonist (OTA), on copulation in the male rat. The relationship between OT receptor (OTR) binding levels in the MPOA and sexual efficiency was also explored. Microinjection of OT into the MPOA facilitated copulation in sexually experienced male rats, whereas similar injections of an OTA inhibited certain aspects of copulation but had no significant effect on locomotor activity in an open field. Contrary to expectation, sexually efficient males had lower levels of OTR binding in the rostral MPOA compared to inefficient animals. The present data suggest that OT activity in the MPOA is not necessary for the expression of male sexual behavior but is sufficient to facilitate copulatory behaviors and improve sexual efficiency in sexually experienced male rats. These data also suggest that OTR activity in the MPOA stimulates anogenital investigation, facilitates the initiation of copulation, and plays a role in the sensitization effect of the first ejaculation on subsequent ejaculations.

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Introduction

Oxytocin (OT) belongs to a highly conserved family of peptides that regulate social and reproductive behaviors in vertebrates (Boyd, 1997; Mahlmann et al., 1994). OT promotes female rat sexual and maternal behaviors (Caldwell et al., 1989, 1994; Pedersen et al., 1982, 1994) and regulates male reproductive function. OT neurons in the male rat paraventricular nucleus of the hypothalamus (PVN) are activated (i.e., Fos-immunoreactive, -ir) following copulation (Witt and Insel, 1994) or *ex copula* non-contact erections (Baskerville et al., 2009). Infusion of nanogram (ng) amounts of OT into the lateral ventricles stimulates copulation in male rats (Argiolas and Gessa, 1991; Arletti et al., 1985); these effects are blocked by pretreatment with an OT receptor (OTR) antagonist (OTA) (Arletti et al., 1992). Intracerebroventricular (icv) administration of an OTA increases intromission and ejaculation latencies and decreases mounts and intromissions (Argiolas et al., 1988). In addition, OT binding sites and varicosities have been identified in thoracolumbar and lumbosacral

spinal segments that control penile erection in rats, and OTR is expressed in penile tissue in men (Veronneau-Longueville et al., 1999; Vignozzi et al., 2004). OT treatment (icv) induces *ex copula* penile erection in male rats (Argiolas et al., 1985); these effects are dependent, in part, on stimulation of OTRs in the PVN and CA1 region of the hippocampus (Melis et al., 1986). Male rats that fail to copulate to ejaculation have lower levels of OT mRNA in the PVN, compared to sexually vigorous males (Arletti et al., 1997). OT can also restore copulation in males whose copulatory behavior had been impaired by chronic fluoxetine (Cantor et al., 1999). Plasma concentrations of OT increase during the sexual response in rats and humans (Carmichael et al., 1987; Stoneham et al., 1985); and a link between sexual impotence and reduced central OT production has been established in the male rat (Arletti et al., 1997).

OT and the mesolimbic dopamine system interact to promote male rat sexual behavior. Microinjection of OT into the PVN, ventral tegmental area (VTA), ventral subiculum, or posteromedial cortical nucleus of the amygdala induces penile erection and increases dopamine levels in the nucleus accumbens (NAcc) (Melis et al., 2007, 2009; Succu et al., 2007, 2008). OTA treatment (icv) reduces non-contact erections in the presence of a receptive female (Melis et al., 1999), and intraperitoneal (ip) injections of OT stimulate the onset of copulation in aging (20-month old) male rats (Arletti et al., 1990, 1992). Taken together, the available data suggest that OT is involved in both the consummatory and appetitive phases of the sexual response in males.

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Most pharmacological studies of the effects of OT on male sexual behavior have used icv administration of OT or OTA; the relatively few researchers who tested site-specific effects focused primarily on the PVN, VTA, hippocampus, and amygdala. Less attention has been given to the medial preoptic area (MPOA), a major site of integration for male sexual behavior (reviewed in Hull et al., 2002 and Hull and Rodriguez-Manzo, 2009). OT-producing neurons and OT binding sites have been identified in the MPOA of male rats (Tribollet et al., 1992), and OT-containing MPOA neurons are activated (Fos-ir) by copulation (Baskerville et al., 2009). In female rats, a few OT-ir neurons in the MPOA project indirectly to the clitoris and vagina, suggesting a role for OT in the MPOA in the control of sexual function in females (Gelez et al., 2010). Thus, a major goal of the present study is to determine whether OT acts in the MPOA to facilitate male sexual behavior.

There is a great deal of variability in reproductive behavior of rodents. In female rats, levels of OTR binding are higher in high licking and grooming (LG) mothers than in low LG mothers (Francis et al., 2000). In addition, more maternally responsive females have higher levels of OTR binding in the amygdala, bed nucleus of the stria terminalis, and MPOA compared to mothers that are less responsive (Champagne et al., 2001). We wished to test whether differences in OT or OTR activity in the MPOA may be associated with differences in male sexual behavior.

Using factor analysis, Sachs (1978) condensed 10 measures of copulatory behavior into 4 factors. An *initiation factor* comprises latencies to the first mount and intromission. *Intromission count factor* corresponds to the number of intromissions required to elicit an ejaculation. *Hit rate factor* is the ratio of successful penile intromissions to total mount attempts. *Copulatory rate factor* includes the latency to the first ejaculation, latency to the resumption of copulation following an ejaculation, and average time interval between intromissions. Efficiency generally refers to the ability to accomplish a goal effectively, with minimal waste of time or resources. Therefore, we hypothesized that intra-MPOA injection of OT would improve sexual efficiency by facilitating one or more of the above factors—i.e., increase *hit rate factor* and decrease *initiation*, *copulatory rate*, and *intromission count factors*, whereas injection of an OTA was expected to inhibit one or more of these factors. We also hypothesized that sexual efficiency would be correlated with OTR binding in the MPOA of sexually experienced male rats.

Methods

Overview of experiments

This study comprises three experiments. Experiment 1 tested the effects of intra-MPOA injections of OT on copulatory behaviors in sexually experienced male rats. Experiment 2a tested the effects of intra-MPOA injections of an OTA on copulatory behaviors in sexually experienced males. In Experiment 2b, the effects of intra-MPOA injection of an OTA on locomotor activity were assessed. In Experiment 3, the relationship between sexual efficiency and OTR binding in the MPOA was explored.

Animals and surgery

Adult Long–Evans/Blue–Spruce rats (Harlan, Indianapolis, IN) were housed singly in large plastic cages in a climate-controlled room, with food and water available ad lib. The light:dark cycle was 14:10, with lights off at 11:00 AM and on at 9:00 PM. Stimulus females of the same strain were housed in a different room. All procedures were in accordance with the National Institutes of Health *Guidelines for the Use of Animals* and were approved by the University's Institutional Animal Care and Use Committee.

Stimulus females and ovariectomies (Experiments 1–3)

Females were ovariectomized, using bilateral flank incisions, under ketamine hydrochloride (75 mg/kg) and xylazine hydrochloride (10 mg/kg) anesthesia and allowed 2 weeks to recover. They were injected with 10 µg estradiol benzoate 48 h, and 500 µg progesterone 4 h, before a copulation test. Receptivity of the female was confirmed by allowing three intromissions by a stud male; only females that showed lordosis in response to the stud male were used for sexual experience sessions and behavioral testing.

Experimental males and stereotaxic surgeries (Experiments 1–2)

After becoming sexually experienced (i.e., achieving at least 4 ejaculations prior to behavioral testing), rats were anesthetized with ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (4 mg/kg) and then implanted with a 23 g stainless steel guide cannula ending 1 mm above the MPOA. Stereotaxic coordinates (from bregma, AP +2.1; ML +0.4; DV –0.65 from dura) used for the anterior MPOA were adapted from Pellegrino et al. (1979). The guide cannula was secured in place by stainless steel screws and dental acrylic. A stainless steel stylet was then inserted into the guide cannula to prevent obstruction of the lumen.

Behavioral testing

Sexual experience sessions (Experiments 1, 2a, and 3)

In Experiments 1 and 2a, males were paired with receptive females for a combined total of 4–6 h over a 2 week period; only males that ejaculated at least 4 times during this time period were included in the study. In Experiment 3, 25 male rats had 11 30-min copulation sessions in their home cages over a 6 week period.

Drug microinjections and copulation tests (Experiments 1 and 2a)

Behavioral tests started approximately one week after surgery and occurred between 12.00 and 17.00 h, once a week for 4 weeks (for a total of 4 copulation tests). Each male rat was first taken from the animal colony to another room. The stylet was removed from the guide cannula and replaced with an injection cannula, which was 1 mm longer than the guide cannula. Injections were administered at a rate of 0.5 µl/min using a Harvard infusion pump. After the injection of drug (OT or the OTA (d(CH₂)₅, Tyr(Me)₂, Thr⁴, Orn⁸, Tyr-NH₂⁹)-vasotocin, Bachem Americas, Inc.) or vehicle, the injection cannula was left in place for 1 min to allow for adequate diffusion of solution. The injection cannula was then replaced with the stylet, and the animal was returned to its home cage. The animal was then taken to a testing room, and a receptive stimulus female was introduced into the male's home cage approximately 5 min after the microinjection.

Each test lasted for 30 min after the male's first intromission, or for 30 min after introduction of the female if no intromission occurred. The following measures were recorded: frequency of anogenital investigation during the first 5 min of the 30-min copulation test (AGI), latency to first mount (ML), latency to first intromission (IL), latency from first intromission to first ejaculation (EL), postejaculatory interval (PEI, period of quiescence between first ejaculation and subsequent intromission), mount frequency preceding first ejaculation (MF1, first copulatory series), mount frequency preceding second ejaculation (MF2, second copulatory series), total mount frequency for 30-min test (MFT), intromission frequency preceding first ejaculation (IF1, first copulatory series), intromission frequency preceding second ejaculation (IF2, second copulatory series), total intromission frequency for 30-min test (IFT), intromission ratio for first copulatory series [IR1, IR1 = IF1/(IF1 + MF1)], intromission ratio for second copulatory series [IR2, IR2 = IF2/(IF2 + MF2)], intromission ratio for 30 min test [IRT,

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