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Neonatal manipulation of oxytocin influences female reproductive behavior and success

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Abstract

During early neonatal development, oxytocin (OT) may influence the expression of adult behavior and physiology. Here we test the prediction that early postnatal exposure to OT or an oxytocin antagonist (OTA) can affect the subsequent expression of sexual receptivity and reproductive success of females. To test this hypothesis, female prairie voles (*Microtus ochrogaster*) received one of four treatments within 24 h of birth. Three groups received an intraperitoneal injection of OT, OTA, or isotonic saline. A fourth group was handled, but not injected. Around 75 days of age, females were paired with sexually experienced males for 72 h and sexual activity was recorded. Treatment had no effect on the probability of mating. Injection, regardless of treatment, reduced latency to mate compared with handled controls. OT and OTA treatment decreased mating bout frequency compared to saline and handled controls, while OTA treatment increased reproductive success, probability of successfully producing a litter. The results suggest that neonatally OT, both endogenous and exogenous, can affect the expression of adult female reproductive activity and that blocking the effects of endogenous OT during neonatal development can affect female reproductive success. Finally, the results suggest that a number of aspects of reproduction are regulated by OT during the postnatal period, but that the mechanism of action may differ depending upon the reproductive activity.
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Keywords: Developmental effects; Microtus; Oxytocin; Oxytocin antagonist; Sexual receptivity; Reproductive success; Prairie vole

Introduction

Oxytocin (OT) plays an important role in regulating female reproduction, including mating behavior. In adult female rats, treatment of estrogen-primed ovariectomized females with OT facilitated mating, including lordosis and proceptive behaviors (Arletti and Bertolini, 1985; Caldwell et al., 1984, 1986; Gorzalka and Lester, 1987), while treatment with an OT antagonist (OTA) reduced or inhibited the expression of sexual behavior (Caldwell et al., 1990, 1994; McCarthy et al., 1994; Pedersen and Boccia, 2002; Witt and Insel, 1991). OT may influence the expression of sexual receptivity by regulating the effects of progesterone (Caldwell et al., 1994; Pedersen and Boccia, 2002; Schumacher et al., 1990) as well as stimulating the release of gonadotropins (Johnston et al., 1990; Robinson and Evans, 1990; Samson et al., 1992).

While most of the effects of OT, especially those related to reproduction, have been demonstrated in adults, it has been hypothesized that during neonatal development OT has an organizational effect on the central nervous systems (CNS) (Shaprio and Insel, 1989; Yoshimura et al., 1996). In rats, neonatal treatment with OT produced marked changes in weight and responses to pain (Uvnäs-Moberg et al., 1998) and placental and fetal growth during pregnancy as adults (Sohlström et al., 2002). In male prairie voles (*Microtus ochrogaster*), a single neonatal treatment with OT facilitated the onset of partner preferences (Bales and Carter, 2003a). In female

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prairie voles, neonatal treatment with OT produced an increase in aggression following exposure to a male (Bales and Carter, 2003b) and affected the number of ultrasound vocalizations in response to maternal separation (Kramer et al., 2003). Neonatal manipulation of OT effects neuronal activation, altering the expression of c-Fos (Cushing et al., 2003). Finally, there are indications that neonatal OT can directly affect female reproduction, as treatment with OT during neonatal days 1–7 delayed vaginal opening and the age of first estrus in Sprague–Dawley rats (Withuhn et al., 2003).

Many of the effects of OT are steroid-dependent, with estrogen (E) up-regulating the expression of OT receptors and perhaps the production of OT (Johnson, 1992). However, there also are indications that OT can influence the effects of E. Female prairie voles treated with OT were significantly more likely to display sexual receptivity when subsequently treated with a low dose of E than control females (Cushing and Carter, 1999), and OT modulates the expression of estrogen receptors in some cell lines (Cassoni et al., 2002). In rats, OT-treated females were significantly heavier after puberty and the increase was associated with fat depositions regulated by E (Uvnäs-Moberg et al., 1998). Taken together, these studies suggest the possibility that during early neonatal development OT may play a role in organizing female reproduction. Therefore, we tested the hypothesis that neonatal manipulation of OT can influence the subsequent expression of female reproductive activity, including reproductive success.

Prairie voles were used as the model system because there is extensive evidence that OT plays a major role in regulating their social and reproductive behaviors (Carter and Keverne, 2002; Cushing and Carter, 1999; Insel and Young, 2001; Williams et al., 1994; Witt et al., 1991). Prairie voles do not undergo a spontaneous estrous cycle. Sexually naïve females require exposure to a novel male that triggers an endocrine cascade, stimulated by chemical and tactile cues, that leads to the formation of social bonds and sexual receptivity (Carter et al., 1995; Morgan et al., 1997). This means that social interaction and the formation of pair bonds, which is stimulated by OT, precedes sexual activity. OT affects the response of females to E (Cushing and Carter, 1999), and finally, neonatal manipulation of OT has long-lasting effects on the expression of behavior and physiology in this species (Bales and Carter, 2003a, b; Kramer et al., 2003).

Materials and methods

Animals used in this study were laboratory-reared F_3 or F_4 generation prairie voles that originated from wild-stock trapped near Urbana, Illinois. On the day of birth, all pups were removed from the parents and placed on cotton bedding and a lamp was used to maintain temperature. Female pups received one of four treatments. Females were given a single intraperitoneal injection (50-μl volume) of isotonic saline (SAL), 3 μg OT/50 μl saline (OT), or 0.3 μg OT antagonist/50 μl saline (OTA, [d$(CH_2)_5$, Tyr(Me)^2, Orn^8]-Vasotocin-Peninsula Laboratories, Belmont, CA), while a fourth group was handled but not injected (HAN), with an n of 10–13 per treatment. The dosage of OT was approximately 1 μg/g body weight and for OTA, 0.1 μg/g body weight. The dose of OT and OTA were used because there is extensive literature indicating that during the neonatal period these doses can effect a variety of physiological and behavioral responses in both rats and voles (Bales and Carter, 2003a,b; Kramer et al., 2003; Sohlström et al., 2002; Uvnäs-Moberg et al., 1998; Withuhn et al., 2003; Yamamoto et al., 2004). A lower dose of OTA was used because the antagonist binds OTR more effectively than OT, with an affinity for OTR greater than 10 times that of the natural ligand (Barberis and Tribollet, 1996).

Pups were assigned to treatment groups randomly with the restriction that within each litter there was at least one control (SAL or HAN) and one experimental (OT or OTA) pup. No treatment was represented more than once per litter. Pups were returned as a group to the home cage within 10 min of removal, and reared by the mother and father. Leaving the sire with the dam and litter is standard husbandry for prairie voles, as they are monogamous and biparental care is the norm in this species. Females were weaned at 21 days of age and housed in same sex sibling pairs. Animals were maintained on a 14:10 light/dark cycle and provided Purina High Fiber Rabbit Chow and water ad libitum. Animals were housed in accordance with the USDA and NIH guidelines and prior to conducting any research all procedures were approved by the University of Illinois at Chicago Animal Care and Use Committee.

Sexual receptivity and litter production

At approximately 75 days of age, females participated in a 72-h mating test. The test was conducted for 72 h because sexually naïve female prairie voles require a prolonged exposure to a novel male to become sexually receptive (Carter et al., 1995). Additionally, during the formation of a pair bond, prairie voles mate for an extended period of time (Cushing and Carter, 1999; Roberts et al., 1998; Williams et al., 1992). Treated females were placed in a cage (12 × 18 × 28 cm) with a sexually experienced male between 1400 and 1500 h. Prior to being used in a test, males were placed with a sexually receptive stimulus female. Stimulus females were estrogen-primed, having received two subcutaneous injections, one per day, of 10 μg of estradiol benzoate, starting 48 h before testing. Previous studies have indicated that this treatment stimulates sexual receptivity in female prairie voles (Bowler et al., 2002; Cushing and Hite,

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