Pharmacology Biochemistry and Behavior, Vol. 43, pp. 855–861, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Enhanced Social Interactions in Rats Following Chronic, Centrally Infused Oxytocin

DIANE M. WITT,[1] JAMES T. WINSLOW AND THOMAS R. INSEL

Laboratory of Neurophysiology, National Institute of Mental Health, P.O. Box 289, Poolesville, MD 20837

Received 13 March 1992

WITT, D. M., J. T. WINSLOW AND T. R. INSEL. *Enhanced social interactions in rats following chronic, centrally infused oxytocin.* PHARMACOL BIOCHEM BEHAV **43**(3) 855–861, 1992.—Most studies investigating the behavioral effects of centrally administered oxytocin (OT) have been confined to single acute injections followed by brief behavioral observations lasting up to 90 min. The present study examines the behavioral effects of chronic, centrally administered OT in male rats observed continuously for prolonged periods of time. Either artificial cerebrospinal fluid or OT was centrally infused (via osmotic minipump) to gonadally intact male rats. Behavioral observations were made on males paired with either ovariectomized or estrous females during a 6-h time period. Most striking was the observation that durations of physical contact were doubled in pairs containing OT-infused males, even in the absence of sexual interactions. Also, OT-infused males showed significantly higher levels of anogenital sniffing of females and autogrooming; however, sexual interactions were unaffected by chronic OT. Chronic OT had no effect on body temperature, analgesia, or exploratory behavior in an open field. These findings suggest that chronic OT in male rats has behavioral effects that may significantly enhance adult social (nonsexual) interactions, possibly through alterations in olfactory and somatosensory information processing.

Chronic OT Social interactions Physical contact Autogrooming Analgesia Anxiety

COPULATORY behavior is a potent stimulus for the release of oxytocin (OT), with elevations observed in both cerebrospinal fluid (CSF) and plasma following ejaculation (5,23,26). Using a selective OT antagonist, Argiolas et al. (1) clearly showed deficits in male sexual behavior, thus suggesting a physiological role for OT in the expression of male copulatory behavior. However, behavioral studies of exogenous OT stimulation have been somewhat ambiguous. For example, Arletti et al. (2) showed that in sexually experienced males central administration of as little as 1 ng OT successfully facilitated the male's copulatory performance by shortening the ejaculatory latency and subsequent postejaculatory interval. Furthermore, Melis et al. (20) found that low levels of OT induced episodic penile erections, although these were observed ex copulo. In contrast, Stoneham et al. (26) showed that central administration of OT, at doses of 250–500 ng, increased latencies to the first mount and intromission and lengthened the postejaculatory interval, typically a measure of sexual satiety. Together, these studies suggest a physiological role for OT in male reproductive behavior, but they also indicate that differences in dosages could result in either potentiation or attenuation of male sexual responses.

The current studies were stimulated by chance observations of behavioral changes in male rats receiving chronic, central administration of OT during experiments on homologous regulation of brain OT receptors. The results of the receptor studies are reported elsewhere (14). Here, we describe effects of chronic OT on male sexual and social behavior during prolonged pairing with sexually receptive or nonreceptive females. Additional tests were performed to evaluate whether behavioral responses to chronic OT infusion were due to changes in thermoregulation, exploratory behavior, activity levels, or analgesia.

METHOD

Prior to surgery, male Sprague-Dawley rats (Taconic Farms, Germantown, NY) were sexually experienced by routine screening (two to three times per week) with estrous females. Subsequently, these males, weighing 450–700 g, were anesthetized with chloropent (0.3 ml/kg) and implanted with an in-dwelling stainless steel cannula (22 ga) aimed at the lateral ventricle. Each cannula was connected to a segment of polyethylene tubing (PE 60, approximately 4.5 mm in length, Clay-Adams, Parsippany, NJ) that was attached to an osmotic minipump (Alzet 2002, Palo Alto, CA) delivering either CSF or OT (100 ng/0.5 μl/h). All minipumps were preincubated in a 37°C saline bath overnight prior to surgical implantation.

The efficacy of each OT osmotic pump was verified by radioimmunoassay (RIA) of plasma levels and pump contents as previously described (14). Assay of pump contents revealed about 44% destruction of oxytocin over a 10-day in vivo time period (baseline concentration = 80.8 ng/μl; final concentration = 45.0 ng/μl). Despite this peptide decay (over approxi-

[1] To whom requests for reprints should be addressed.

mately 10 days), plasma OT levels were 7.8 ± 1.3 pg/ml in CSF controls and 70.0 ± 13.2 pg/ml in OT-infused males. From these data, it seems likely that OT concentrations in brain were significantly above physiological levels in OT-infused males.

Time-Lapse Videotaping

Behavioral testing was conducted in a semicircular arena measuring 40 cm in diameter with a Plexiglas front panel. Tapwater and rat chow were available continuously during the videotaping period (6 h). The arena was illuminated by a 100-W red light bulb because all videotaping occurred during the dark phase of the light cycle (between 1300–1900 h). Time-lapse videotaping (TLV) was conducted using a Sony CCD (HVM-200) low-light intensity videocamera and a Panasonic (wv-5470) monochrome video monitor connected to a JVC (BR-905OU) time-lapse videorecorder. This video system permitted 6 h of real time to be recorded onto tapes that were analyzed in 30 min. Behavioral responses during playback were recorded on a computerized event recorder system using a Macintosh computer by an observer naive to the pump contents. Behaviors were quantified and adjustments were made for taping speed.

Behavioral Testing (TLV)

Males were first videotaped approximately 48 h after pump implantation. Males were initially tested with an estradiol benzoate (EB)-primed female and videotaped for 6 h and then returned to their home cages for 24–48 h, after which time they were videotaped for 6 h with an ovariectomized (OVX) female. After a brief acclimation to the arena, test males were introduced to either an OVX or EB-primed female and videotaping commenced. The following behavioral measures were recorded: a) latency to the first mount (seconds); b) frequency of mounting; c) latency to first ejaculation; d) frequency of ejaculation (per hour); e) postejaculatory interval—time from ejaculation to subsequent mount (seconds). The resolution of TLV (in the absence of ventral viewing) did not permit the accurate determination of intromission behavior; therefore, these data were omitted from the analysis. The frequencies (per 6 h) and durations (min/6 h) were also recorded for the following: autogrooming of the f) upper body and g) genitals; h) direct physical contact (body surface contact during non-sexual interactions with the female); and i) male investigation (sniffing) of the female's anogenital region.

Rectal Temperatures/Analgesia Testing

Rectal temperatures and a tail withdrawal test (for assessment of OT-induced analgesia) preceded all open-field tests of exploratory behavior. Rectal temperatures were taken using a YSI Scanning Tele-Thermometer (Model 47). The analgesic effects of chronic OT infusion were evaluated by dipping the male rat's tail into 60°C tapwater. The mean latency to tail withdrawal was determined after three consecutive tail dips.

Exploratory Behavioral Testing

Our pilot studies, using TLV, suggested a marked increase in measures of physical contact between OT-treated males and females. To determine whether increased contact was due to decreased exploration, males were monitored in an open field for exploratory behavior. Males were tested in a white-walled arena (1 m in diameter) with a Plexiglas floor. The floor was divided into concentric squares of equal measurements for the quantification of exploratory behavior. Exploration of the inner area of the open field (those blocks not adjacent to the wall) is typically reduced in anxious rats (4,17). During these 5-min tests, the arena was illuminated by either a single photoflood (red light—100-W red bulb) or fluorescent (white light) overhead lights. Levels of general activity were assessed by tallying the number of times the male passed both front paws into a square on the arena floor. Frequency of rearing behavior and the presence of fecal boli were also noted. The open-field arena was cleaned with alcohol and air dried between tests. Males were tested on separate days, under white light or red light, in a counterbalanced manner.

Data Analysis

TLV behavioral data were grouped and analyzed separately according to the estrous status of the male's partner (OVX vs. EB-primed female). In all cases, behavioral responses as well as peptide and gonadal steroid levels were compared, between CSF controls and OT-infused males, using unpaired Student's t-test with $p < 0.05$ required for significance. Variance is expressed as the SEM throughout the analyses.

RESULTS

Physical Contact

The time spent in direct physical contact more than doubled in OT-infused males compared to CSF controls not only when males were paired with EB-primed females, $t(16) = 2$, $p = 0.05$ (Fig. 1b), but also when males had OVX female partners, $t(16) = 2.7$, $p = 0.02$. OT-infused males were in direct physical contact for approximately 50 min–1 h of the entire 6-h testing period. However, the frequencies of physical contact were significantly increased (doubled) only in OT males paired with OVX females, $t(11) = 3.2$, $p = 0.01$ (Fig. 1a).

Male Anogenital Sniffing

OT-infused males exhibited significantly longer durations in sniffing the anogenital regions of EB-primed females, $t(16) = 2.8$, $p = 0.01$, and OVX females, $t(11) = 2.4$, $p = 0.03$, than did CSF control males. However, the frequencies of anogenital sniffing were significantly greater than CSF controls only in OT-infused males paired with OVX partners, $t(11) = 2.2$, $p = 0.05$.

Autogrooming

Upper body autogrooming was profoundly affected by OT infusion. Males receiving chronic OT and paired with EB-primed females showed an approximate four fold increase in the duration of autogrooming when compared to CSF controls, $t(11) = 4.9$, $p = 0.0002$ (Fig. 2b). Furthermore, these males autogroomed at frequencies three times greater than CSF controls, $t(16) = 07.8$, $p = 0.0004$ (Fig. 2a). Similarly, when paired with OVX females OT-infused males exhibited upper-body autogrooming lasting two to three times longer than CSF controls, $t(11) = 4.2$, $p = 0.004$ (Fig. 2b). Also, upper-body autogrooming, when OVX females were present, was twice as frequent in OT-infused males than in CSF controls, $t(11) = 3.7$, $p = 0.004$.

When OVX females were present, genital autogrooming (latencies and frequencies), although nonsignificant due to variability, appeared to be enhanced with chronic OT infusion (Table 1, Fig. 2a). Clearly, when EB-primed females were

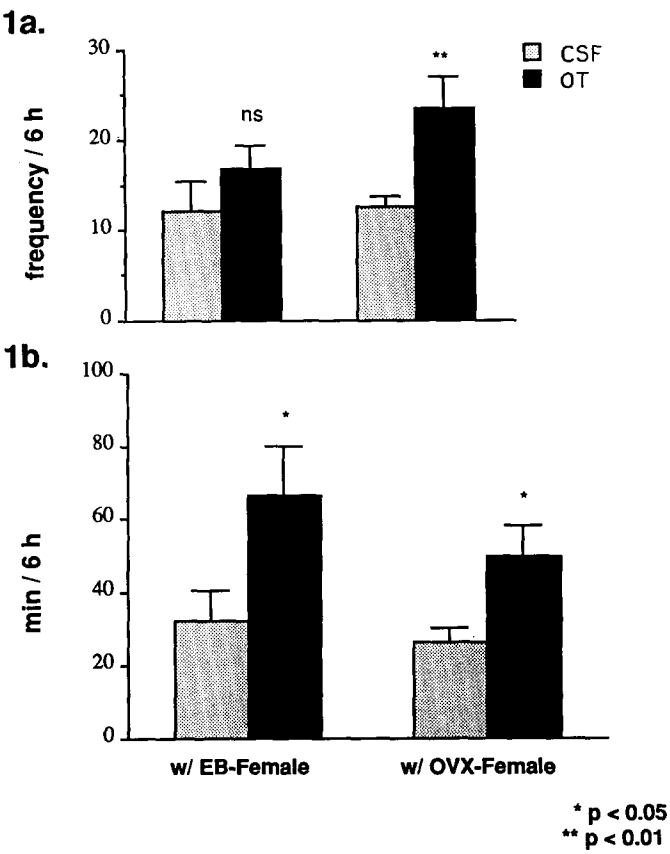

FIG. 1. Physical contact frequencies (a) and durations (b) during 6 h of time-lapse videotaping. Comparisons are made according to the estrous status of the male's partner [ovariectomized (OVX) vs. EB-primed female]. *Oxytocin (OT) data significantly different from cerebrospinal fluid (CSF) controls.

present genital autogrooming durations were twice as long for OT-infused males when compared to CSF controls, $t(16) = 2.8, p = 0.01$ (Fig. 2b).

Sexual Behaviors

Although mounting occasionally occurred in males paired with OVX females, there was no difference in the frequency of mounting between CSF- and OT-infused males. Ejaculations were never observed when males were paired with OVX females (Table 1). However, when males were paired with estrous females species-typical sexual interactions ensued. OT infusion had no effect on the latency to mount or frequency of mounting throughout the 6-h taping (Table 1). Similarly, ejaculation latencies and frequencies, as well as postejaculatory intervals, did not differ as a function of pump content.

Rectal Temperature/Exploratory Behavior/Analgesia

Rectal temperatures did not vary as a function of pump content (Table 2). Likewise, tail withdrawal tests for analgesia revealed no significant difference between OT-infused males and CSF controls. However, open-field tests for exploratory behavior revealed a significant increase in rearing frequencies in OT-infused males when compared to CSF controls under both white, $t(16) = 2.5, p = 0.02$, and red light, $t(16) = 2.7, p = 0.01$. Other open-field measures, such as inner and outer block crossings and boli deposition, did not vary as a function of pump content under either types of field illuminations.

DISCUSSION

The data presented here demonstrate that chronic OT exposure has prolonged effects on social interactions in rats. The amount of time spent in direct physical contact, as well as the duration of anogenital sniffing directed toward the female, was dramatically increased in males receiving chronic OT infusions. Also, autogrooming, particularly upper-body grooming, was significantly enhanced by chronic OT infusion. Surprisingly, chronic OT administration had no effect on male sexual behavior. In addition, measures of exploratory behavior, pain sensitivity, and thermoregulation were unaffected by chronic OT administration.

Social Interactions

Gonadally intact males show distinct preferences for estrous females (9), and males typically reduce sociability during copulatory refractory periods (22). However, this was not the case for OT-infused males in our study. These males spent as much as 20% of the entire observation period in direct physical contact with the female regardless of her estrous status. A significant increase in the frequency of contact with OVX females, which do not typically exhibit proceptive behaviors (3), suggests that increased contact was initiated by OT-infused males. An increased frequency in anogenital investigation of the female by OT-infused males provides further support for a direct action of OT on male social initiatives. Similarly, acute ICV OT injections increase social interactions in female rats (29) and male and female prairie voles (18,28).

Chronic OT infusion may have indirectly influenced social interactions among conspecifics. For example, social memory, based upon juvenile chemosignals, is impaired by OT injections (6 μg/kg) in adult males (7). In the current study, OT-mediated contact behaviors, anogenital sniffing, and upper-body autogrooming may be involved in the processing of information required for social memory formation between adult conspecifics.

Autogrooming and Arousal

Similar to acute ICV OT injections in mice (8) and rats (25), chronic OT infusion dramatically increased autogrooming in male rats. However, the pattern of OT-induced autogrooming differed from previous reports. The frequency and duration of upper-body autogrooming were both significantly increased by chronic OT infusion and appeared to be unrelated to the stimulus female's estrous status. In contrast, durations of genital autogrooming were increased in OT-infused males, but only in the presence of EB-primed females, and were probably associated with copulatory activity. The frequencies of genital autogrooming were not affected, suggesting that OT-enhanced autogrooming was reflected by a trend toward increased bout lengths. OT-infused males appeared to become engrossed in the autogrooming motor pattern once initiated. One explanation for this finding is that OT-infused males may lack sufficient somatosensory input from the genital area. Although we found no changes in pain sensitivities, as verified in the analgesia test, we cannot rule out more subtle changes in sensory function after chronic OT infusion. It is also possible that this increase in autogrooming reflects OT-induced perseveration of motor patterns. However, other ster-

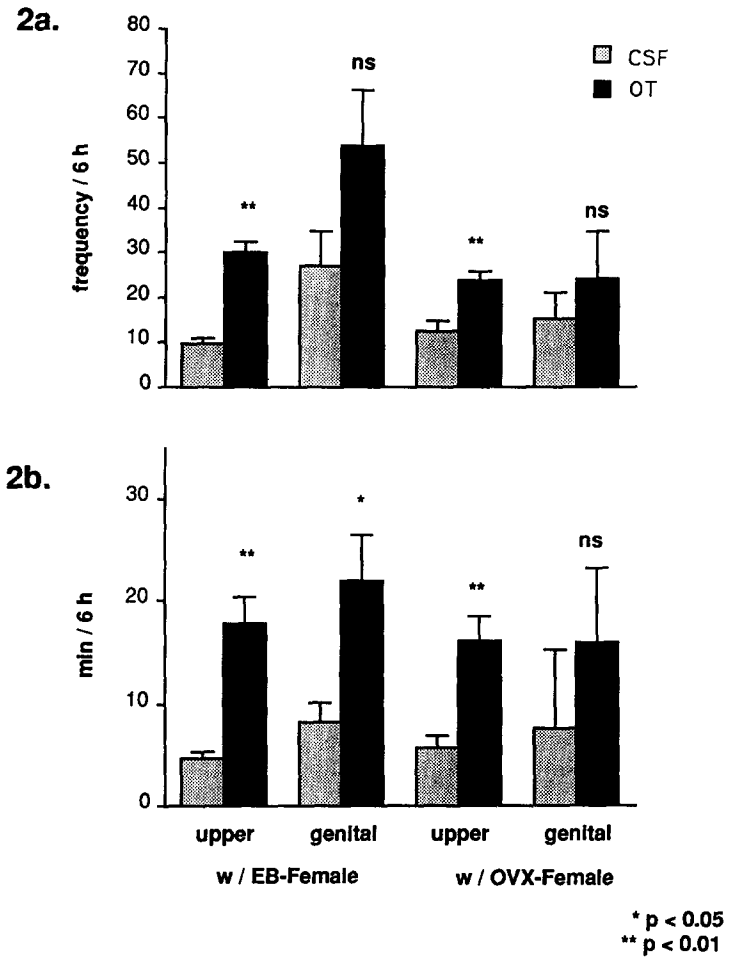

FIG. 2. Autogrooming frequencies (a) and durations (b) of upper-body and genital regions during 6 h of time-lapse videotaping. Comparisons are made according to the estrous status of the male's partner [ovariectomized (OVX) vs. EB-primed female]. *Oxytocin (OT) data significantly different from cerebrospinal fluid (CSF) controls.

eotypical motor patterns such as episodic penile erections (in the absence of sexual interactions), yawning, or barrel rotations (20,21), characteristic of acute OT injections (5 ng–10 μg), were also not observed. Although not specifically measured, hyperreactivity or emotionality, such as enhanced startle responses (16), was not apparent.

Certainly, increased autogrooming can occur in response to increased fear or arousal, and exogenous corticotropin (ACTH) fragments similarly produce marked elevations in autogrooming (12). Yet, in the present study anxiety-like behaviors, decrements in sexual responses, and distinct social preferences (estrous over anestrous females) (22), common to ACTH-stimulated animals, were not apparent with chronic OT infusion. Therefore, the pronounced autogrooming elicited by chronic OT infusion appears to differ significantly from reported ACTH-mediated behavioral responses. The presence of normal sexual interactions and exploratory behavior along with the absence of motor disturbances or analgesic or temperature effects suggests that the observed increases in social interaction were probably not secondary to nonspecific effects of peptide administration.

Sexual Behavior

The failure to detect changes in sexual behavior following chronic administration of OT was surprising. Chronic OT infusion did not affect mounting, ejaculation, or postejaculatory refractory periods. Previous reports have shown that acute OT injections significantly alter male sexual behavior (2,13) and may induce episodic penile erections and other disturbances in motor actions (20,21), all of which were absent with chronic OT infusions. The most probable explanation is that, in the current study, the initial OT effects on sexual behavior were overlooked because videotaping commenced approximately 48 h after the onset of OT infusion.

Another explanation for the absence of OT effects on sexual behavior may be due, in part, to the physiological effects that chronic OT infusion has on terminal fields within the brain. We (14) have shown that chronic OT infusions (100 ng/h) decreased OT receptor binding, as measured using in vitro autoradiography, by approximately 50% in both steroid-dependent and -independent OT receptor distributions. This OT effect appeared to be a genuine receptor down regulation,

TABLE 1

SEXUAL BEHAVIOR MEASURES IN MALES PAIRED WITH EITHER EB-TREATED (ESTROUS) OR OVARIECTOMIZED (ANESTROUS) FEMALES

	EB-Primed Female		OVX Female	
Male Paired With	CSF (n = 9)	OT (n = 9)	CSF (n = 7)	OT (n = 6)
Physical contact				
Duration (min/6 h)	32.1 ± 8.6	66.1 ± 13.8*	26.4 ± 3.8	49.7 ± 8.2*
Frequency/6 h	12.2 ± 3.3	16.9 ± 2.5	2.6 ± 1.1	23.5 ± 3.5†
Male anogenital sniff				
Duration (min/6 h)	8.7 ± 2.3	17.9 ± 2.4*	10.8 ± 1.6	24.1 ± 5.7*
Frequency/6 h	34.3 ± 9.4	72.1 ± 19.7	29.3 ± 5.8	69.5 ± 18.3*
Upper-body autogrooming				
Duration (min/6 h)	4.6 ± 0.8	17.9 ± 2.6†	5.7 ± 1.2	16.2 ± 2.3†
Frequency/6 h	9.7 ± 1.1	29.9 ± 2.3†	12.3 ± 2.4	23.7 ± 1.9†
Genital autogrooming				
Duration (min/6 h)	8.3 ± 1.9	22.0 ± 4.5*	7.6 ± 1.9	15.9 ± 7.2
Frequency/6 h	26.8 ± 8.1	53.7 ± 12.7	15.1 ± 5.9	24.3 ± 10.4
Mount				
Latency (seconds)	2.7 ± 1.5	0.7 ± 0.3	0.2 ± 0.1	1.5 ± 0.9
Frequency/6 h	67.6 ± 23.6	101.7 ± 27.5	26.3 ± 24.5	27.8 ± 16.2
Ejaculation				
Latency (seconds)	309.5 ± 33.5	418.1 ± 90.0	–	–
Frequency/h	2.6 ± 1.0	2.6 ± 0.6	–	–
Postejaculatory interval				
Duration (seconds)	240.9 ± 99.5	310.6 ± 65.8	–	–

Values are presented as means ± SEM for temperatures, latencies, and frequencies of behavioral responses.
*Group significantly different ($p < 0.05$) from CSF controls.
†Group significantly different ($p < 0.01$) from CSF controls.

not merely displacement by exogenous peptide, as receptor binding remained low even 24 h following pump removal. In that same study, acute injections of OT (1,000 ng) did not cause marked decreases in OT receptor binding. Therefore, the absence of an effect on sexual behavior with chronic OT administration may be due, in part, to a reduction in the number of OT receptors and concomitant desensitization of oxytocinergic neuronal activity.

TABLE 2

MEASURES OF RECTAL TEMPERATURES, TAIL WITHDRAWAL RESPONSES, AND EXPLORATORY BEHAVIOR (UNDER RED AND WHITE LIGHT)

	CSF	OT
Rectal temperatures (°C)	37.2 ± 0.3	37.3 ± 0.2
Tail withdrawal latency (seconds)	2.6 ± 0.3	2.8 ± 0.3
Exploratory behaviors (frequencies)		
Red light (5-min test)		
Inner squares	56.6 ± 13.0	63.9 ± 7.0
Outer squares	42.4 ± 4.0	48.4 ± 4.0
Rears	18.2 ± 2.0	26.2 ± 2.0*
Boli (5 min)	1.0 ± 0.4	0.3 ± 0.2
White light (5-min test)		
Inner squares	24.7 ± 9.0	32.7 ± 6.0
Outer squares	34.5 ± 5.0	43.3 ± 6.0
Rears	9.0 ± 1.0	14.0 ± 1.0†
Boli	1.9 ± 1.0	1.9 ± 0.6

Values are presented as means ± SEM for temperatures, latencies, and frequencies of behavioral responses.
*Group significantly different ($p < 0.05$) from CSF controls.
†Group significantly different ($p < 0.01$) from CSF controls.

In the present study, plasma testosterone concentrations did not differ as a function of OT infusion (14), and sexual behavior per se was unaffected by chronic OT. The finding that plasma testosterone concentrations did not differ as a function of OT infusion is consistent with physiological desensitization because previous studies in rats and monkeys have shown that acute OT injections may be associated with increased release of luteinizing hormone (15,24) and elevated gonadal steroid levels (27). Mitigating against the desensitization hypothesis is the finding that OT enhancement of autogrooming was preserved.

OT is closely related to the structurally similar peptide arginine vasopressin (AVP). Centrally administered vasopressin has been found to have potent behavioral effects, such as enhanced autogrooming (19,25) and flank marking (10). Also, AVP antagonism results in a reduction of intraspecific aggression behavior in male hamsters (11). In all likelihood, chronic OT infusion affected brain AVP receptors along with OT receptors and may have altered AVP receptor-mediated behavioral responses simultaneously. It is also known from acute OT injection studies that OT-enhanced autogrooming is mediated by dopaminergic and opioid neurotransmission because haloperidol blocks and naloxone attenuates OT-induced autogrooming (8,25). Clearly, OT affects neurotransmission in a number of distinct neuropeptides, all of which may have behavioral properties of their own.

The current study represents a condition rarely observed under natural or even pathologic conditions in rodents because OT is typically released in a reflexive or pulsatile manner (6) rather than continuously (as delivered by osmotic pump). However, chronic continuous infusions of synthetic OT are often used to facilitate normal labor or resolve hypotonic uterine dysfunction during labor and may have central effects in humans. The current findings demonstrate that prolonged, continuous administration of OT can have long-term effects on social behavior. In male rats, exposure to chemosignals through proximity and anogenital sniffing, followed by upper-body autogrooming, which would facilitate chemosignal delivery to the olfactory epithelium, all appear to be enhanced by chronic OT infusions. It is possible that chronic OT infusions may alter the gating of somatosensory and olfactory stimuli to make social interactions positively reinforcing for animals that would not otherwise be socially motivated. The current study may be the first to implicate OT in the enhancement of social interactions in male rats outside the confines of sexual interactions.

ACKNOWLEDGEMENTS

Gratitude is expressed to C. Ron Harbaugh for surgical expertise and C. Sue Carter for insightful discussions with the authors.

REFERENCES

1. Argiolas, A.; Melis, M. R.; Vargiu, L.; Gessa, G. L. d[CH_2)$_5$Tyr-(Me)-(Orn^8]vasotocin, a potent oxytocin antagonist, antagonizes penile erection and yawning induced by oxytocin and apomorphine, but not by ACTH-(1-24). Eur. J. Pharmacol. 134:221-224; 1987.
2. Arletti, R.; Bazzani, C.; Castelli, M.; Bertolini, A. Oxytocin improves male copulatory performance in rats. Horm. Behav. 19: 14-20; 1985.
3. Beach, F. Sexual attractivity, proceptivity, and receptivity in female mammals. Horm. Behav. 7:105-138; 1976.
4. Britton, D.; Koob, G. F.; Rivier, J.; Vale, W. Intraventricular corticotropin-releasing factor enhances behavioral effects of novelty. Life Sci. 31:363-367; 1982.
5. Carmichael, M. S.; Humbert, R.; Dixen, J.; Palmisano, G.; Greenleaf, W.; Davidson, J. M. Plasma oxytocin increases in the human sexual response. J. Clin. Endocrinol. Metab. 64:27-31; 1987.
6. Cunningham, E. T.; Sawchenko, P. E. Reflex control of magnocellular vasopressin and oxytocin secretion. Trends Neurosci. 14: 406-411; 1991.
7. Dantzer, R.; Bluthe, R.-M.; Koob, G. F.; Le Moal, M. Modulation of social memory in male rats by neurohypophyseal peptides. Psychopharmacology (Berl.) 91:363-368; 1987.
8. Drago, F.; Pedersen, C. A.; Caldwell, J. D.; Prange, A. J., Jr. Oxytocin potently enhances novelty-induced grooming behavior in the rat. Brain. Res. 368:287-295; 1986.
9. Everitt, B. J.; Stacey, P. Comparative effects of preoptic area infusions of opioid peptides, lesions and castration on sexual behaviour in male rats: Studies of instrumental behaviour, conditioned place preference and partner preference. J. Comp. Psychol. 102:407-419; 1987.
10. Ferris, C. F.; Albers, H. E.; Weslowski, S. M.; Goldman, B. D.; Leeman, S. E. Vasopressin injected into the hypothalamus triggers stereotypic behavior in golden hamsters. Science 224:521-523; 1984.
11. Ferris, C. F.; Potegal, M. Vasopressin receptor blockade in the anterior hypothalamus suppresses aggression in hamsters. Physiol. Behav. 44:235-239; 1988.
12. File, S. E.; Mabbutt, P. S.; Walker, J. H. Comparison of adaptive responses in familiar and novel environments: Modulatory factors. Ann. NY Acad. Sci. 525:69-79; 1988.
13. Hughes, A. M.; Everitt, B. J.; Lightman, S. L.; Todd, K. Oxytocin in the central nervous system and sexual behavior in male rats. Brain Res. 414:133-137; 1987.
14. Insel, T. R.; Winslow, J. T.; Witt, D. M. Homologous regulation of brain oxytocin receptors. Endocrinology 130:2602-2608; 1992.
15. Johnston, C.; Lopez, F.; Samson, W. K.; Negro-Vilar, A. Physiologically important role for central oxytocin in the preovulatory release of luteinizing hormone. Neurosci. Lett. 120:256-258; 1990.
16. King, M.; Brown, R.; Kusnecov, A. An increase in startle response in rats administered oxytocin. Peptides 6:567-568; 1985.
17. Koob, G.; Bloom, F. E. Corticotropin-releasing factor and behavior. FASEB J. 44:259-263; 1985.
18. Mahalati, K.; Okanoya, K.; Witt, D.; Carter, C. S. Oxytocin inhibits male sexual behavior in prairie voles. Pharmacol. Biochem. Behav. 39:219-221; 1991.
19. Meisenberg, G. Vasopressin-induced grooming and scratching behavior in mice. Ann. NY Acad. Sci. 525:257-269; 1988.
20. Melis, M. R.; Argiolas, A.; Gessa, G. L. Oxytocin-induced penile erection and yawning: Site of action in the brain. Brain Res. 398: 259-265; 1986.
21. Melis, M. R.; Argiolas, A.; Stancampiano, R.; Gessa, G. L. Oxytocin-induced motor disturbances: Relationship with penile erection and yawning. Pharmacol. Biochem. Behav. 34:673-675; 1989.
22. Meyerson, B. J.; Hoglund, U.; Spruijt, B. Influence of ACTH1-24 on grooming and sociosexual behavior in the rat. Ann. NY Acad. Sci. 525:169-179; 1988.
23. Murphy, M. R.; Seckl, J. R.; Burton, S.; Checkley, S. A.; Lightman, S. L. Changes in oxytocin and vasopressin secretion during sexual activity in men. J. Clin. Endocrinol. Metab. 65:738-741; 1987.
24. O'Bryne, K. T.; Lunn, S. F.; Coen, C. W. Central oxytocin stimulates luteinizing hormone release in the marmoset, a primate which fails to show lactationally-induced infertility. J. Neuroendocrinol. 2:419-421; 1990.

25. Pedersen, C.; Caldwell, J. D.; Drago, F.; Noonan, L. R.; Peterson, G.; Hood, L. E.; Prange, A. J., Jr. Grooming behavioral effects of oxytocin: Pharmacology, ontogeny, and comparisons with other nonapeptides. Ann. NY Acad. Sci. 525:245–256; 1988.
26. Stoneham, M. D.; Everitt, B. J.; Hansen, S.; Lightman, S. L.; Todd, K. Oxytocin and sexual behavior in the male rat and rabbit. J. Endocrinol. 107:97–106; 1985.
27. Winslow, J. T.; Insel, T. R. Social status in pairs of squirrel monkeys determines the behavioral response to central oxytocin administration. J. Neurosci. 11:2032–2038; 1991.
28. Witt, D. M.; Carter, C. S.; Walton, D. M. Central and peripheral effects of oxytocin administration in prairie voles (*Microtus ochrogaster*). Pharmacol. Biochem. Behav. 37:63–69; 1990.
29. Witt, D. M.; Insel, T. R. Interaction of gonadal steroids and oxytocin: Effects on sexual and social behavior in rats. Conference on Reproductive Behavior, Atlanta, GA, 1990, p. 120.