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High Doses of Oxytocin Cause Sedation and Low Doses Cause an Anxiolytic-Like Effect in Male Rats

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UVNÄS-MOBERG, K., S. AHLENIUS, V. HILLEGAART AND P. ALSTER. *High doses of oxytocin cause sedation and low doses cause an anxiolytic-like effect in male rats.* PHARMACOL BIOCHEM BEHAV **49**(1) 101–106, 1994.—The aim of the present investigation was to explore dose relationships for effects of oxytocin on spontaneous motor activity in the rat. Oxytocin in doses from 1–1000 μg/kg was given SC to male Sprague–Dawley rats, and spontaneous motor behavior was measured by means of photocell-operated open-field observations. In the rats treated with low doses of oxytocin (1–4 μg/kg), there was a decrease in peripheral locomotor activity. With increasing doses (250–1000 μg/kg), there were clear signs of sedative effects as indicated by a suppression of locomotor activity and rearing. The time course for the effect of oxytocin on peripheral activity (1 μg/kg) and rearing (1 mg/kg) was tested. A maximal effect was obtained within 1 h and, thereafter, the behavior gradually returned to normal within 24 h. This spectrum of effects caused by oxytocin was similar to that of midazolam but different from that induced by raclopride.

Oxytocin Sedation Anxiolytic-like effect Locomotor activity

OXYTOCIN is a hypothalamic peptide produced in the paraventricular nucleus from which neurons project to many brain areas (11). Oxytocin has been shown to have widespread central nervous system effects. It influences feeding behavior as well as maternal and sexual behaviors (2), and we have recently shown it to be pain relieving (13). Furthermore, based on observations of the pattern of rat motor activity in an open field, suggestive evidence was obtained for an anxiolytic effect of oxytocin. Spontaneous locomotor activity was reduced and the normally high proportion of locomotor activity along the perimeter of the open-field arena was shifted towards the center by the oxytocin treatment (14). Prompted by these latter observations, we have, in the present experiments, explored dose–effect relationships and the time course for effects of oxytocin on the patterns of spontaneous motor activity in the rat. For comparison, midazolam (10) and raclopride (6) were included as reference anxiolytic and antipsychotic compounds, respectively.

METHOD

Animals

Forty male Sprague–Dawley rats (270–320 g) were used (B&K Universal AB, Sollentuna, Sweden). The animals arrived at least 1 week before experiments and were maintained under controlled conditions of light : dark cycle (12 L : 12 D, lights on 0600 h), temperature 20 ± 2°C, and relative humidity (55–60%). Food (R36, Ewos, Södertälje, Sweden) and tap water were available ad lib in the home cage. The animals were housed five per cage (Makrolone IV).

Drugs

The following drugs were used: Oxytocin (Ferring, Malmö, Sweden), raclopride tartrate (Astra, Södertälje, Sweden) 0.08–1.25 ml/kg and midazolam (Roche, Basel, Switzerland). Midazolam was dissolved in a minimal amount of 1 M HCl and made up to volume in physiological saline. The other compounds were dissolved in physiological saline. All drugs were injected SC in a volume of 1 ml/kg.

Open-Field Studies

The animals were observed in a commercially available photocell-equipped open-field arena (Kungsbacka Mät & Reglerteknik, Kungsbacka, Sweden). The arena measured 680 × 680 × 450 mm and was equipped with two rows of eight photocells, sensitive to infrared light, placed 40 and 125 mm

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above the floor, respectively. The photocells were spaced 90 mm apart and the last photocell in a row was spaced 25 mm from the wall. Interruptions of photocell beams were collected by means of a microcomputer and allowed recording of the following variables: a) Locomotor activity (all horizontal activity as registered by the row of photocells 40 mm above the floor of the arena); b) rearing (vertical activity as registered by the second row of photocells, 125 mm above the floor of the arena); c) Peripheral activity (horizontal activity, provided that the photobeams spaced 25 mm from the wall also were activated); d) Forward locomotion (successive interruptions of photocells in the lower rows when the animal is moving in the same direction, i.e., initially, the location of the animal is defined by the photocell being interrupted, the next interruption indicates that the animal is moving, and successive interruptions are registered as locomotion, as long as the animal moves along the same vector) [for further details see (3)].

The observations started 10 min after the administration of drugs. The total time of observations in all cases was 15 min. The animals were naive to the open field and were used once only.

In studies on time course of action, observations were performed 0, 1, 4, and 24 h after administration of oxytocin.

Statistics

The results are presented as means ± SD. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's *t*-test for post hoc comparisons, or the Mann–Whitney *U*-test, as indicated in figure legends.

RESULTS

Effects on Spontaneous Motor Activity

Midazolam and raclopride. Midazolam: the administration of midazolam (0.2–3.3 mg/kg) produced a dose-dependent, moderate suppression of locomotor activity and a substantial suppression of rearing. In relation to the locomotor activity, the proportion forward locomotion was increased at the high-

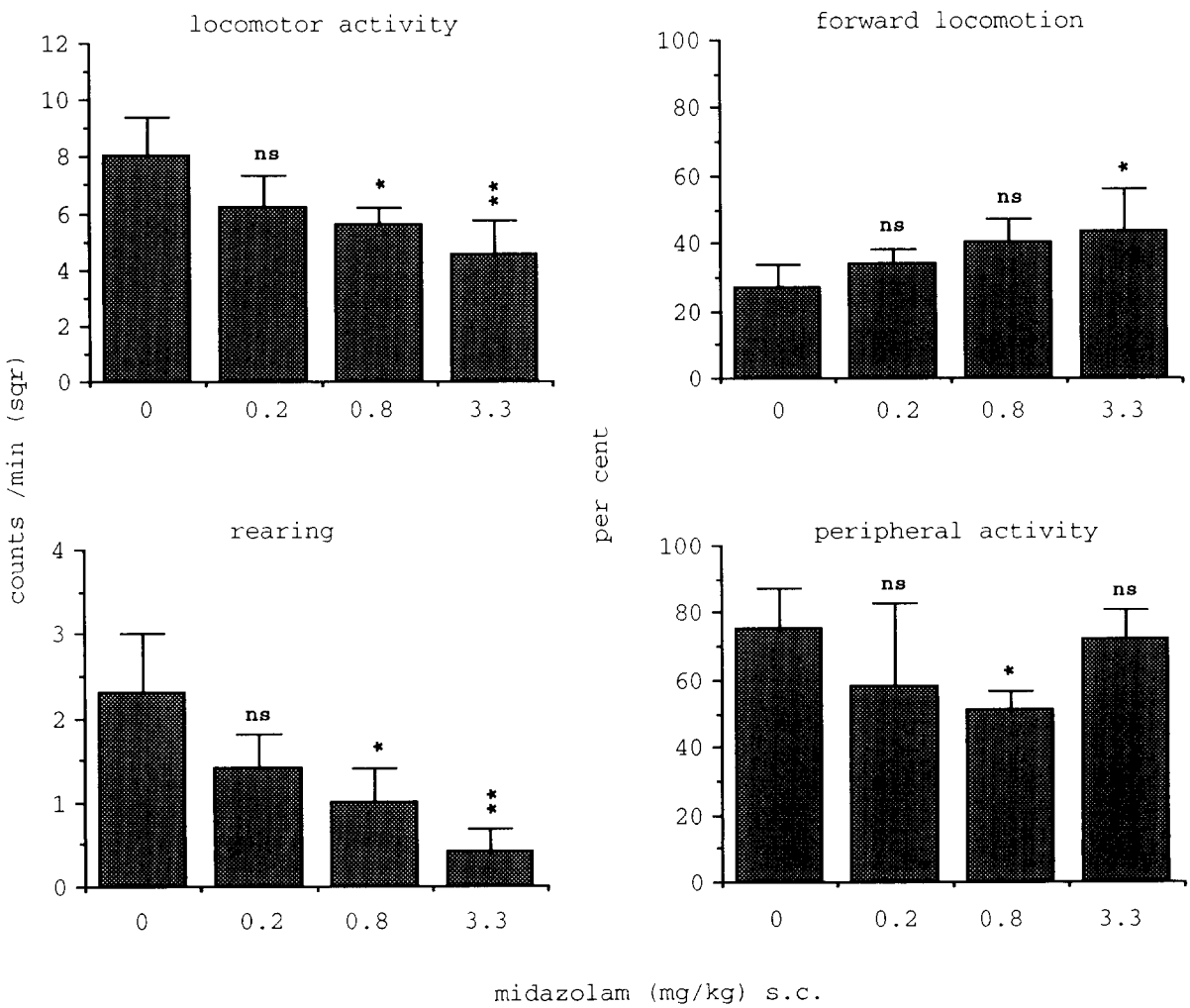

FIG. 1. Effects of midazolam on the patterns of rat spontaneous motor activity in an open field. Midazolam (0.2–3.3 mg/kg SC) was administered 10 min before a 15 min observation period in the open field. The figure shows means ± SD based on five to eight observations per group. Statistical analysis was performed by means of a one-way ANOVA followed by the Dunnett's *t*-test for posthoc comparisons with saline injected controls. $^{ns}p > 0.05$; $^{*}p < 0.05$; $^{**}p < 0.01$.

est dose and the peripheral activity was decreased at one of the intermediate doses (Fig. 1).

Raclopride: raclopride (0.08–1.25 mg/kg) produced a marked, dose-dependent suppression of locomotor activity and rearing and, further, there were no statistically significant changes in the proportion forward locomotion or peripheral activity in contrast to the weak but significant effects caused by midazolam on these parameters (Fig. 2).

Oxytocin. Dose effect: in the rats treated with low doses of oxytocin (4 μg/kg) the only statistically significant effect was a decrease in the proportion of peripheral activity (Fig. 3). With increasing doses (250–1000 μg/kg), there were clear signs of sedative effects, as indicated by a suppression of locomotor activity and rearing. The proportion forward locomotion or peripheral activity was not affected by these higher doses of oxytocin, indicating an unaltered pattern of activity within the open field (Fig. 3).

Time course of action: to study the duration of the most prominent effects of high doses of oxytocin (decreased amount of rearing and of low doses of oxytocin (decreased peripheral activity), complementary time-response curves (0, 1, 4, and 24 h) were performed.

Peripheral activity was like after administration of 4 μg/kg oxytocin significantly decreased immediately after 1 μg/kg of the drug. Thereafter, peripheral activity gradually returned to basal levels which were reached within 24 h (Fig. 4A).

Rearing was significantly reduced at 0 and 1 h after injection of the 1 mg/kg dose of oxytocin and after a gradual return, basal levels were reached 24 h later (Fig. 4B).

DISCUSSION

The major observations in the present study are that in male rats SC injections of 1–4 μg of oxytocin cause a specific shift of position in an open field from the periphery to the center, whereas injections of oxytocin in the dose range of 250–1000 μg/kg produced a general reduction of locomotor activity. In both cases, the effect is maximal within 1 h and, thereafter, gradually returns to normal within 24 h.

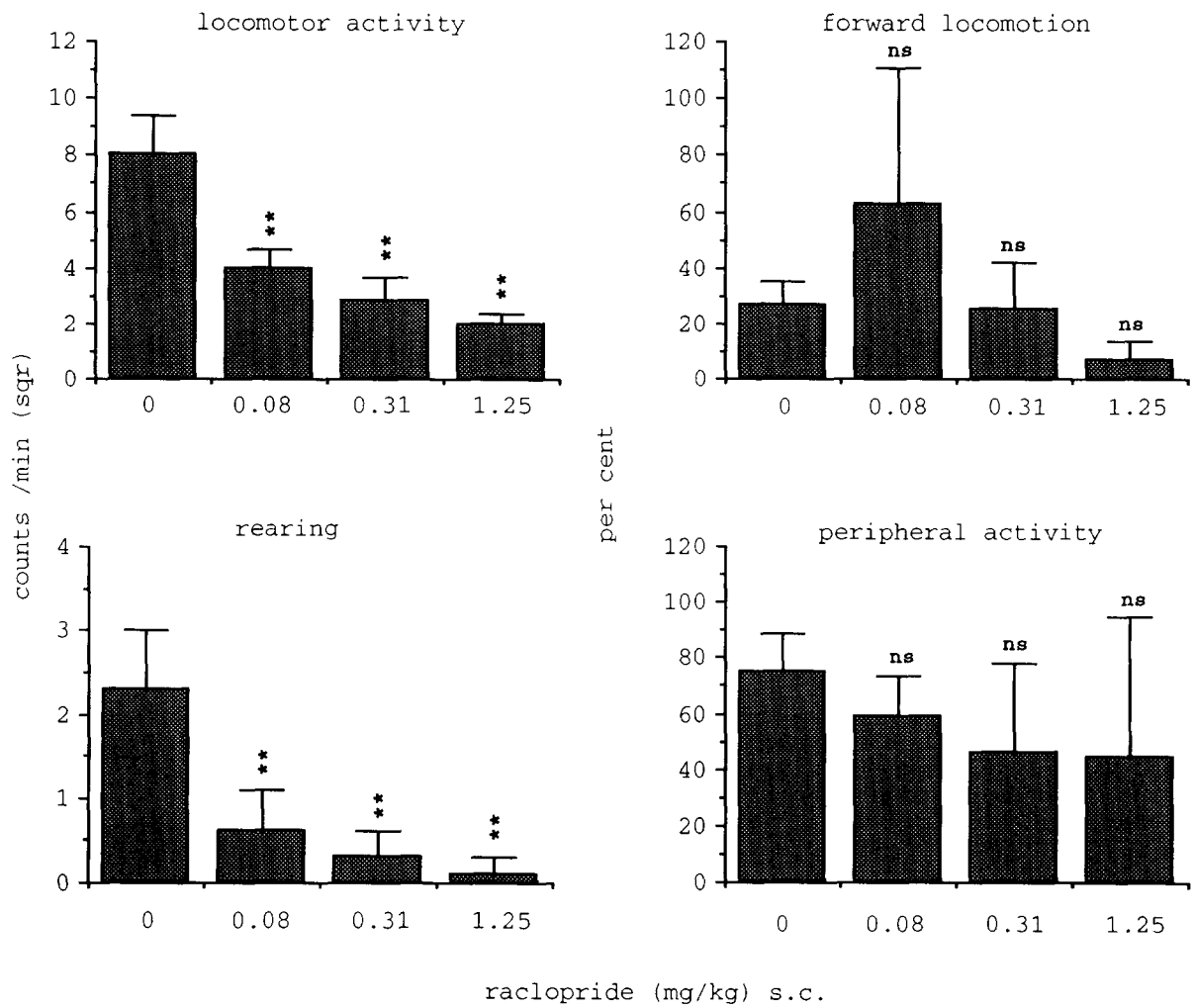

FIG. 2. Effects of raclopride on the patterns of rat spontaneous motor activity in an open field. For time of raclopride administration (0.08–1.2 mg/kg SC) in relation to motor activity measurements and other details, see legend to Fig. 1. $^{ns}p > 0.05$; $^{*}p < 0.05$; $^{**}p < 0.01$.

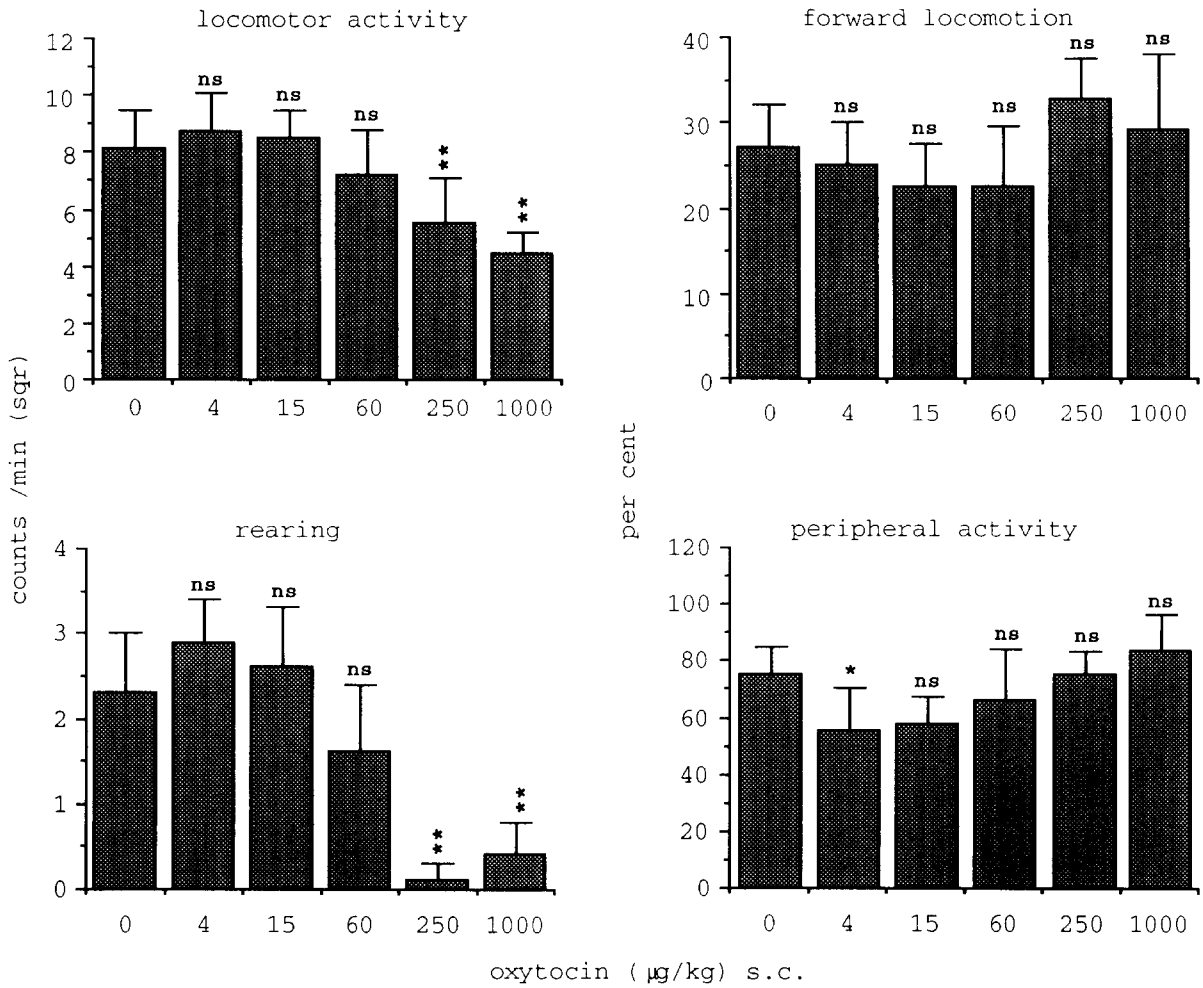

FIG. 3. Effects of oxytocin on the patterns of rat spontaneous motor activity in an open field. For time of oxytocin administration (4–1000 µg/kg SC) in relation to motor activity measurements and other details, see legend to Fig. 1. $^{ns}p > 0.05$; $*p < 0.05$; $**p < 0.01$.

A shift in activity from periphery to center in an openfield, as a result of experimental manipulations, has sometimes been taken as an index of anxiolytic-like effects in laboratory rats. Such measurements, however, are highly dependent on experimental variables such as physical aspects of the experimental situation (e.g., illumination, background noise, or size of the arena) or organismic variables (e.g., species, sex, strain, age, or habituation of the animals) (1). In keeping with its properties as an anxiolytic, midazolam, in the present study, produced an increase in the relative amount of activity spent in the center of the open field. In further support for this contention, there was a weak stimulatory effect by the midazolam treatment, as evidenced by an increase in the relative amount of forward locomotion (8). These two aspects of the openfield behavior were not affected by the raclopride treatment, indicating that the present test procedures allow a differentiation between a benzodiazepine anxiolytic and a dopmine D_2 receptor blocking antipsychotic agent like raclopride. Although both compounds produced a suppression of locomotor activity and of rearing, these effects were more pronounced for raclopride. Thus, in comparison with the effects produced by midazolam and raclopride, oxytocin, in the low dose range, had an anxiolytic-like profile, whereas higher doses produced a behavioral suppression more typical for the antipsychotic agent.

In a preliminary study, we found that 100 and 1000 µg/kg of oxytocin given intraperitoneally and that 2 and 20 ng of oxytocin given intracerebroventricularly (ICV) also caused a shift of locomotor activity from the periphery to the centre (14). The effects of oxytocin obtained in the present study were all obtained following SC injections of oxytocin. Thus, it can be assumed that the site of action resides within the central nervous system because, as mentioned above, similar effects were obtained following ICV administration of ng amounts of oxytocin. About 0.1% of oxytocin given systemically passes the blood-brain barrier, and sufficient amounts of oxytocin may, thus, reach the central nervous system (5).

Lactating rats in which oxytocin levels are repeatedly elevated by suckling of the young frequently display sedation and slow wave sleep (9). The present results indicate that oxytocin may lie behind the suckling-related sedation. In breast-feeding

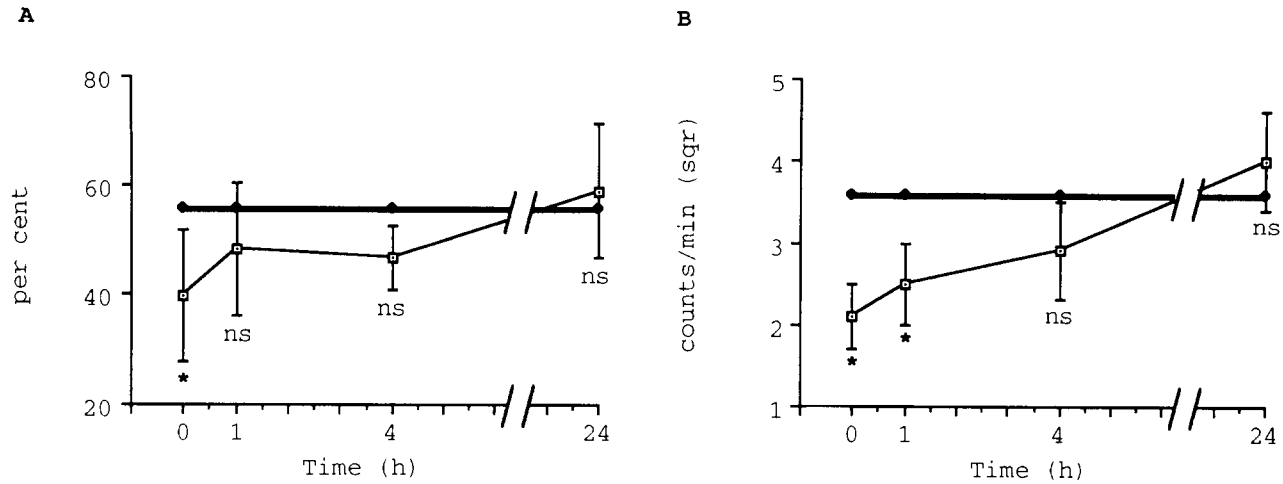

FIG. 4. (A,B) Time course of action for effects of oxytocin on peripheral activity (A) and on rearing activity (B). Oxytocin (1 μg kg^{-1} and 1 mg kg^{-1} SC for peripheral activity and rearing, respectively) was administered at time 0 (h) and the animals were observed in the open field for 15 min as the various time intervals shown in the figure. The results are presented as means ± SD based on observations of 6–11 animals per group. The behavior (mean ± SD) of pooled time-matched controls (n = 28 in both cases) is indicated by the hatched area. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's t-test for comparisons with saline-treated controls. $^{ns}p > 0.05$; $^{*}p < 0.05$.

women, women with high oxytocin levels express less anxiety and aggression and more preference for monotonous tasks than women with low levels, suggesting that oxytocin may have sedative effects also in women (12). Sexual behavior is also followed by oxytocin secretion in animals as well as in humans and also by a period of sedation [for a review, see (3)]. Therefore, oxytocin may exert sedative effects also in connection with sexual behavior.

We have recently shown that two atypical neuroleptic drugs, amperozide and clozapine, are potent oxytocin releasers and amperozide causes a similar effect spectrum as does oxytocin in our observational cage. In contrast, classical antipsychotic drugs, based on DA D_2 receptor antagonism, are without influence on oxytocin secretion (15). We postulated that amperozide-stimulated oxytocin secretion was caused by inhibition of 5-HT_2-receptors because ritanserin increased oxytocin secretion. However, 5-HT_{1A}-agonists are also potent releasers of oxytocin secretion (to be published) as are 5-HT_{1C} and D_1-receptor agonists (7). The present finding that oxytocin can cause sedation and anxiolytic-like effects suggests that some of the effects caused by the drugs mentioned above may be mediated by oxytocin and opens up the possibility for development of future drugs based on effects of oxytocin.

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REFERENCES

1. Archer, J. Tests for emotionality in rats and mice: A review. Anim. Behav. 21:205-235; 1973.
2. Argiolas, A.; Gessa, G. L. Central functions of oxytocin. Neurosci. Biobehav. Rev. 15:217-231; 1991.
3. Carter, S. Oxytocin and sexual behavior. Neurosci. Biobehav. Rev. 16:131-144; 1992.
4. Ericson, E.; Samuelsson. J.; Ahlenius, S. Photocell measurements of rat motor activity: A contribution to sensitivity and variation in behavioral measurements. J. Pharmacol. Methods 25:111-122; 1991.
5. Jones, P. M.; Robinson, I. C. Differential clearance of neurophysin and neurohypophysial peptides from the cerebrospinal fluid in conscious guinea pigs. Neuroendocrinology 34:297-302; 1982.
6. Köhler, C.; Hall, H.; Ögren, S. O.; Gawell, L. Specific binding of ^{3}H-raclopride, a potent substituted benzamide drug with high affinity for dopamine D_2 receptors in the rat brain. In vivo and in vitro studies. Biochem. Pharmacol. 34:2251-2259; 1985.
7. Levy, A. D.; Vandekaar, L. D. Endocrine and receptor pharmacology of serotonergic anxiolytics, antipsychotics, and antidepressants. Life Sci. 51:83-94; 1992.
8. Marriott, A. S.; Spencer, P. S. J. Effects of centrally acting drugs on exploratory behavior in rats. Br. J. Pharmacol. 25:432-441; 1965.
9. Numan, M. Maternal behavior. In: Knobil, E., et al., eds. The physiology of reproduction. New York: Raven Press; 1988:1569-1644.
10. Pieri, L.; Schaffner, R.; Scherschlicht, R.; Polc,P.; Sepinwall, J.; Davidson, A.; Möhler, H.; Cumin, R.; Da Prada, M.; Burkard, W. P.; Keller, H. H.; Müller, R. K. M.; Gerold, M.; Pieri, M.; Cook, L.; Haefely, W. Pharmacology of medazolam. Arzneimittelforschung 31:2180-2200; 1981.
11. Sofroniew, M. V. Vasopressin, oxytocin and their related neurophysins. In: Björklund, A.; Hökfelt, T., eds. Handbook of chemical neuroanatomy. Amsterdam: Elsevier Science Publishers; 1985:93-165.
12. Uvnäs-Moberg, K.; Widström, A. M.; Nissen, E.;Björvell, H. Personality traits in women 4 days postpartum and their correla-

tion with plasma levels of oxytocin and prolactin. J. Psychosom. Obstet. Gynaecol. 11:261–273; 1990.
13. Uvnäs-Moberg, K.; Bruzelius, G.; Alster, P.;Bileviciute. I.; Lundeberg, T. Oxytocin increases and a specific oxytocin antagonist decreases pain threshold in male rats. Acta Physiol. Scand. 144:487–488; 1992.
14. Uvnäs-Moberg, K.; Alster, P.; Hillegaart, V.; Ahlenius, S. Oxytocin reduces exploratory motor behaviour and shifts the activity towards the centre of the arena in male rats. Acta Physiol. Scand. 145:429–430; 1992.
15. Uvnäs-Moberg, K.; Alster, P.; Svensson, T. H. Amperozide and clozapine but not haloperidol or raclopride increase the secretion of oxytocin in rats. Psychopharmacology (Berlin) 109:473–476; 1992.