0013-7227/97/$03.00/0
Endocrinology

Vol. 138, No. 7
Printed in U.S.A.

Central Oxytocin Administration Reduces Stress-Induced Corticosterone Release and Anxiety Behavior in Rats*

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ABSTRACT

Endocrine responses to noise stress and anxiety-related behaviors were measured in groups of ovariectomized, estradiol-treated female rats given central infusions of oxytocin. Control animals receiving isotonic saline showed a large increase in plasma corticosterone concentrations in response to 10 min of white noise. This response to noise stress was significantly and dose dependently decreased by oxytocin administered intracerebroventricularly at 10 or 100 ng/h for 5 days. Oxytocin also significantly decreased rearing behavior during this stress. When a second noise stress was given 3 days after cessation of oxytocin infusion, corticosterone responses did not differ between the control and previously oxytocin-infused animals. Administration of vasopressin had no significant effect on either the corticosterone or behavioral responses to noise stress. Anxiety-related behaviors were measured on the elevated plus-maze. No significant differences were seen in maze exploration between saline- and oxytocin-treated animals when housed and tested in the same environment. However, when animals were mildly stressed by testing in an unfamiliar environment, oxytocin-treated animals showed a higher proportion of open arm entries and spent significantly more time in the open arms of the maze. Thus, oxytocin exerts a central anxiolytic-like effect on both endocrine and behavioral systems and could play a role in moderating behavioral and physiological responses to stress. (*Endocrinology* **138:** 2829–2834, 1997)

OXYTOCIN is released from the endocrine hypothalamo-neurohypophyseal system in response to a number of physical and psychological stresses (1–4). The significance of this increased peripheral concentration of oxytocin is still not clear, although the hormone may have some CRF-like activity (5). However, the peptide is also widely distributed throughout the central nervous system, and apart from its established roles in sleep/wake patterns, lactation, and sexual/maternal behavior (6), the peptide may have a central action in the regulation of responses to noxious or stressful stimuli. In this respect, oxytocin immunoreactive pathways are distributed in many brain regions associated with the stress response, including the bed nucleus of the stria terminalis (BNST) (7), the amygdala (8), and certain brain stem nuclei (9). Furthermore, oxytocin receptors are found in a number of limbic structures, including the BNST, central nucleus of the amygdala, septum, and hippocampus (10).

Recent observations have shown that peripheral administration of oxytocin in high doses can both elevate nociceptive thresholds (11, 12) and lessen the anxiety behavior of rats placed in a potentially stressful environment (13). Furthermore, in the rat, lactation is associated with an activation of central oxytocin pathways (6, 14) and with a down-regulation of the endocrine responses to stress (15–18). In humans, lactation has also been associated with decreased responses to stress (19) as well as decreased levels of anxiety (20) and the incidence of anxiety-related disorders (21). These effects may be a consequence of the increased central oxytocin release that is known to occur at this time (14, 22).

These observations suggest that oxytocin may function to attenuate stress responsiveness. To investigate this hypothesis, groups of rats were infused centrally with different doses of oxytocin, and their hypothalamo-pituitary-adrenal (HPA) responses to noise stress were assessed. These experiments were conducted in freely moving animals on an automated blood sampling apparatus to minimize all nonspecific forms of stress (23). To determine the specificity of the response to oxytocin, parallel groups of animals were infused with vasopressin. In addition, the anxiolytic effects of oxytocin were evaluated using an elevated plus-maze. This paradigm exploits the conflicting motivations experienced by the rat to either explore the maze or remain in the perceived security of the closed arms. Therefore, movement to the open arms of the maze is thought to reflect a lower level of anxiety (24). As the endocrine response to stress is known to vary over the estrous cycle (25) and as changing estradiol levels greatly affect the expression of oxytocin receptors in many areas of the central nervous system (26), all animals used in these studies were ovariectomized and estradiol treated. An abstract discussing some of these studies has been previously published (27).

Materials and Methods

Animals

All experiments used female Sprague-Dawley rats (225–250 g; Bantin and Kingman, Hull, UK) maintained under standard animal housing conditions, including a 14-h light (lights on at 0500 h), 10-h dark illu-

Received December 16, 1996.
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* This work was supported by the Wellcome Trust.

mination cycle. Because ovarian steroid variations occurring over the estrous cycle could influence the data, each rat underwent bilateral ovariectomy and simultaneous implantation of a SILASTIC brand capsule (Dow Corning, Midland, MI; id, 1.6 mm; 10 mm/100 g BW) containing 150 μg 17β-estradiol benzoate/ml vegetable oil. This is known to produce estradiol concentrations within the normal diestrous range (28). All surgical procedures were carried out under a combination of Hypnorm (0.32 mg/kg fentanyl citrate and 10 mg/kg fluanisone, im; Janssen Pharmaceuticals, Oxford, UK) and diazepam (2.6 mg/kg, ip; Phoenix Pharmaceuticals, Gloucester, UK) anesthesia. All procedures conformed to United Kingdom animal welfare legislation.

Central peptide administration and preparation of rats for blood sampling

Osmotic minipumps (model 1007D, Alzet Corp., Palo Alto, CA) were used to deliver oxytocin (Bachem, Essex, UK) or vasopressin (Bachem). The pumps, rated to deliver 0.52 μl/h over a 7-day period, were filled with the appropriate peptide, connected to an intracerebroventricular (icv) infusion cannula and then allowed to equilibrate overnight in isotonic saline. All pumps were assigned to animals using a coding unknown to those involved in subsequent procedures. On the day after ovariectomy, each animal was reanesthetized, an area of the parietal bone was exposed, and the icv cannula was stereotaxically positioned in the lateral ventricle. The minipump was positioned sc between the scapulae. To enable blood samples to be collected, animals used in studies 1 and 2 were also implanted with a SILASTIC-tipped right jugular venous cannula. This was passed sc, exteriorized on the top of the head, and passed through a protective spring held at an angle of 45°. The spring and/or the icv cannula were secured in position on the skull using self-curing dental acrylic and stainless steel anchoring screws. After recovery, all animals were housed individually. Where springs were fitted, these were attached to mechanical swivels, allowing the animals freedom of movement.

Study 1: effects of oxytocin and vasopressin on stress-induced release of corticosterone

To allow frequent small blood samples to be collected without disturbing the animals, an automated sampling apparatus was employed (23, 29); this was programmed to collect a 10- to 20-μl sample every 10 min. Sampling began at 0700 h on the fifth day after surgery and continued for 60 min. At this time a white noise generator was activated, and the animals were exposed to 114 decibels (dB) for 10 min. Sampling then continued for an additional 180 min. Throughout this period the behavior of animals from each group was recorded on videotape. Animals used in this study were infused centrally with isotonic saline or concentrations of oxytocin to produce infusion rates of 1, 10, or 100 ng/h oxytocin. To test for the specificity of the effect, additional groups of animals were infused with the closely related peptide arginine vasopressin at rates of 0, 10, or 100 ng/h. In addition, to examine the reversibility of the effect of oxytocin, groups of animals infused with oxytocin at 0 or 100 ng/h were subjected to the sampling and noise stress procedures twice, first on the fifth day after surgery when the pumps were active and then again on the eighth day, approximately 24 h after they had ceased to deliver the peptide.

Study 2: effect of oxytocin on anxiety behavior

Animals infused with isotonic saline or 100 ng/h oxytocin were housed in the behavioral testing facility from the time of implantation of the minipump. On the fifth day after surgery, each animal was placed in the center of an elevated plus-maze, and the experimenter immediately withdrew from the testing room. The maze was made of black wood. The four arms had equal lengths of 55 cm and were elevated 80 cm from the ground. The sides of the closed arms had a height of 12 cm. The behavior of each animal was recorded on videotape for a period of 15 min. Testing commenced at 1000 h and continued until 1600 h, with animals from both groups randomly tested over this time period. The maze was rigorously cleaned between animals.

To determine whether oxytocin could affect the exploration of the plus-maze in animals that were already mildly stressed, groups of animals infused with saline or 100 ng/h oxytocin were housed away from the behavioral testing facility and not placed in the testing room until 0800 h on the day of trial, a procedure known to have an anxiogenic effect in rats (Shanks, N., and R. Windle, unpublished data). Commencing at 1000 h, these rats were then tested on the plus-maze in exactly the same way as those that had been preconditioned to the testing facility.

Determination of plasma corticosterone concentrations

Total plasma corticosterone concentrations were measured directly in plasma by RIA using a citrate buffer at pH 3.0 to denature the binding globulin (1 μl plasma fraction diluted in 100 μl buffer), antiserum kindly supplied by Prof. G. Makara (Institute of Experimental Medicine, Budapest, Hungary), and [^{125}I]corticosterone (ICN Biomedicals, Irvine, CA; SA of 2–3 mCi/μg).

Behavioral analysis

The video recordings collected during the noise stress studies were divided into 10-min blocks using the start of the noise stress as the reference point. For each 10-min block, the amount of time that the animals spent active, engaged in activities such as locomotion, burrowing, or grooming (total activity), was recorded along with the number of rearings (defined as the raising of both forepaws and movement of body to a vertical plane). Behavioral determinations of animals on the plus-maze included the number of open or closed arm entries (defined as the movement of all four paws from one arm to another), and the time that the animals spent in each portion of the maze.

Statistical analysis

All values are expressed as the mean ± SE. ANOVA and *post-hoc* Tukey's tests were used to determine the effects of the various doses of oxytocin or vasopressin on plasma corticosterone and behavioral responses to the noise stress. Student's *t* tests were used to determine the effect of oxytocin infusion on behavioral activity on the plus-maze compared with that in the respective control group.

Results

Effects of oxytocin and vasopressin on corticosterone release during noise stress

Basal corticosterone concentrations were within the normal range seen for the intact female rat (23) and were not significantly altered by any of the doses of oxytocin studied (Fig. 1). On exposure to the noise stress, there was a rapid rise in plasma corticosterone concentrations in the saline-treated control animals (Fig. 1A), which reached a peak concentration of 547 ± 102 ng/ml 20 min after the onset of the noise and then declined rapidly to baseline. Although significant elevations in corticosterone concentrations were seen in animals treated with all doses of oxytocin (Fig. 1, B-D), the magnitude of the response was significantly decreased by the administration of oxytocin ($P < 0.05$; Fig. 1, B–D). This effect was statistically significant in animals given 10 and 100 ng/h oxytocin (Fig. 1, C and D). After the initial response to the noise, corticosterone concentrations remained low in all groups. The effect of oxytocin on the corticosterone response to noise stress was dose dependent (Fig. 1). The area under the response curve was calculated as 5.8 ± 1.2 μg in animals treated with saline and 3.6 ± 0.9, 1.7 ± 0.7, and 1.2 ± 0.6 μg in those animals treated with 1, 10, and 100 ng oxytocin/h, respectively (by ANOVA, $P < 0.02$).

In a separate series of experiments, reversal of the effect of oxytocin on stress-induced corticosterone release was studied. Similar to the data shown above (Fig. 1), infusion of 100 ng/h oxytocin significantly decreased the peak corticosterone response to noise to 43 ± 4% of that seen in the saline-

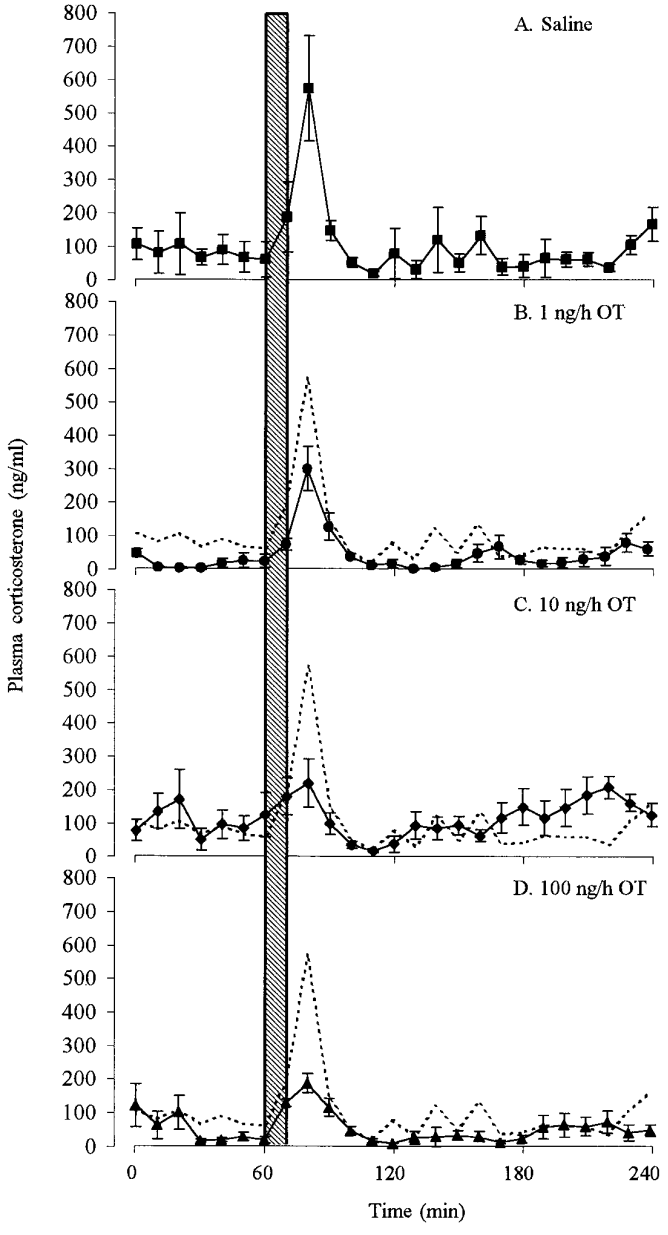

FIG. 1. The effects of white noise stress (114 dB for 10 min; *hatched bar*) on plasma corticosterone concentrations of ovariectomized, estradiol-treated female rats infused centrally with isotonic saline at a rate of 0.52 μl/h (A; n = 6) or supplemented with oxytocin at a rate of 0 1 ng/h (B; n = 5), 10 ng/h (C; n = 6), or 100 ng/h (D; n = 6). Each *point* represents mean ± SEM for the given group sizes. For comparison, the control values are shown in B–D by the *broken line*. ANOVA revealed a significantly smaller response to the stress in animals treated with either 10 or 100 ng/h oxytocin compared to that in the saline-infused controls ($P < 0.05$).

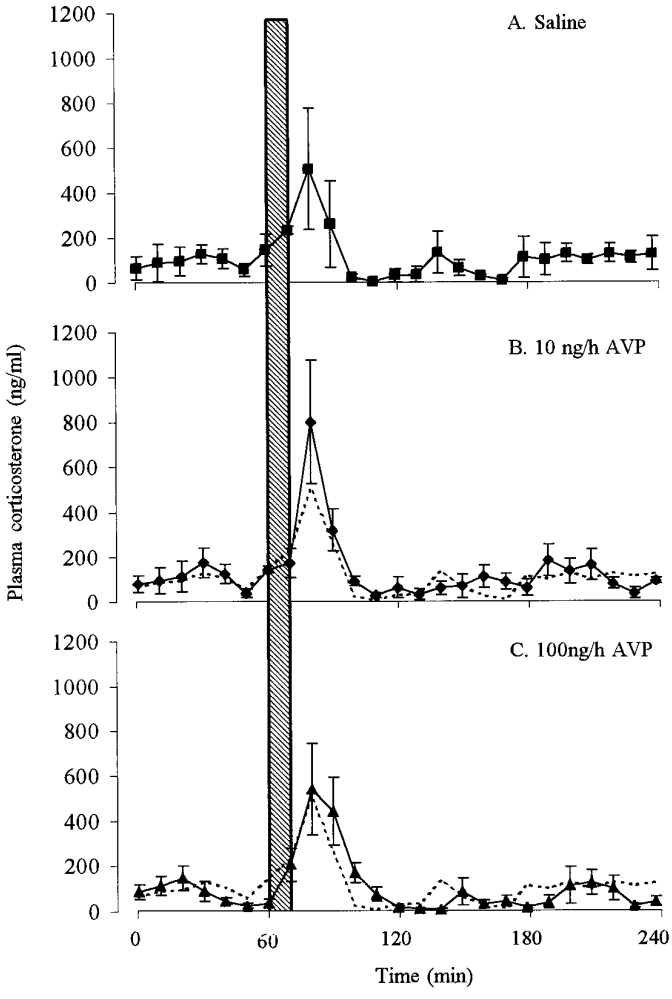

FIG. 2. The effects of white noise stress (114 dB for 10 min; *hatched bar*) on plasma corticosterone concentrations of ovariectomized, estradiol-treated female rats infused centrally with isotonic saline at a rate of 0.52 μl/h (A; n = 5) or supplemented with vasopressin at a rate of 10 ng/h (B; n = 5) or 100 ng/h (C; n = 5). Each *point* represents the mean ± SEM for the given group sizes. For comparison, the control values are shown in B and C by the *broken line*. ANOVA showed no significant effect of vasopressin on the corticosterone response to the stress at these doses.

treated animals ($P < 0.005$). However, once the pumps had ceased working, the response in the formerly oxytocin-infused animals was 109 ± 23% of that seen in animals formerly infused with saline.

No significant differences were seen in the basal corticosterone concentrations between control animals and those treated with either dose of vasopressin (Fig. 2). Unlike oxytocin treatment, neither dose of vasopressin tested had any significant effect on the corticosterone response to noise stress, which was of similar magnitude and duration in all groups (Fig. 2, A–C).

Effects of oxytocin and vasopressin on behavioral responses of animals to noise stress

Oxytocin had no significant effect on either the total activity (Fig. 3A) or the number of rearings (Fig. 3C) seen before application of the noise stress. In all groups, noise stress caused a significant increase in both the total activity ($P < 0.001$; Fig. 3A) and the number of rearings shown by the animals ($P < 0.001$; Fig. 3C). Although oxytocin had no significant effect on the increase in total activity during noise stress, the two higher doses of 10 and 100 ng/h significantly reduced the number of rearing events 0–10 min after introduction of the noise stress compared to that in the saline-treated controls ($P < 0.002$; Fig. 3C). Vasopressin infusion

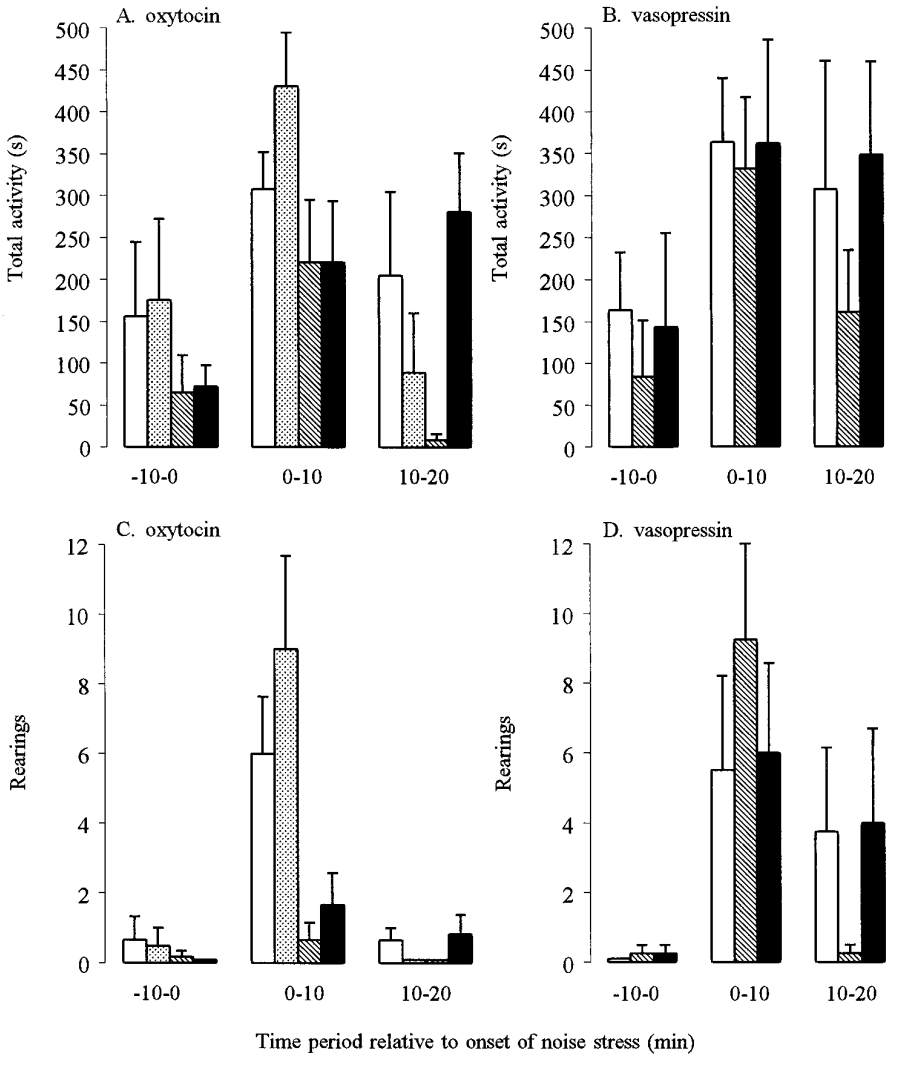

FIG. 3. The effect of noise stress on the total activity (A and B) and the number of rearings (C and D) of ovariectomized, estradiol-treated female rats infused centrally with oxytocin (A and C) or vasopressin (B and D). Values shown are the mean ± SE for 10-min periods before, during, and after application of a white noise stress (114 dB for 10 min). *Open bars* represent control infusion of isotonic saline (0.52 μl/h), *stippled bars* represent peptide infusion at 1 ng/h, *hatched bars* represent infusion at 10 ng/h, and *filled bars* represent infusion at 100 ng/h. *, $P < 0.05$ compared to control infusion values for the same period.

had no significant effect on the total activity (Fig. 3B) or the number of rearings (Fig. 3D) seen either before or after application of the noise stress.

Effect of oxytocin on the behavior on the elevated plus-maze

When animals were acclimatized to a familiar testing environment, no significant differences were seen in the amount of time that the animals spent in the open arm (Fig. 4A), the number of open arm entries (Fig. 4C), the total number of arm entries (Fig. 4E), or the percentage of arm entries that were into an open arm (Fig. 4G) between saline- and oxytocin-infused animals. However, when animals were moved into the testing suite on the day of the trials, the saline-treated animals spent significantly less time in the open arm of the maze than those that had not been moved ($P < 0.002$; Fig. 4, A and B). These animals also showed decreased numbers of total arm ($P < 0.002$; Fig. 4, E and F) and open arm ($P < 0.002$; Fig. 4, C and D) entries, and a significant decrease in the percentage of arm entries that were to an open arm ($P < 0.002$; Fig. 4, G and H). This suggests that the movement to the test environment could have been stressful and induced a mild anxiogenic state. Oxytocin infusion had marked anxiolytic effects in these animals, significantly increasing the amount of time spent in the open arm ($P < 0.02$; Fig. 1B). Oxytocin-treated animals were also more active in their exploration of the maze, as indicated by the significantly greater number of total arm entries ($P < 0.02$; Fig. 4F). These animals were more willing to enter the open arm, as indicated by the increased number of open arm entries ($P < 0.001$; Fig. 4D) and the significantly greater percentage of arm entries that were into the open arm ($P < 0.001$; Fig. 4H).

Discussion

These data demonstrate that oxytocin significantly decreased the corticosterone response to noise stress in a dose-dependent manner and, to our knowledge, is the first report of the effects of central oxytocin on HPA responses to stress. Behavioral measures indicate that oxytocin also had parallel anxiolytic-like actions. These data suggest that oxytocin may have a moderating effect on stress physiology.

There a several mechanisms by which oxytocin could act to decrease HPA responses to stress. The peptide may have leaked to the periphery during the chronic infusion and acted

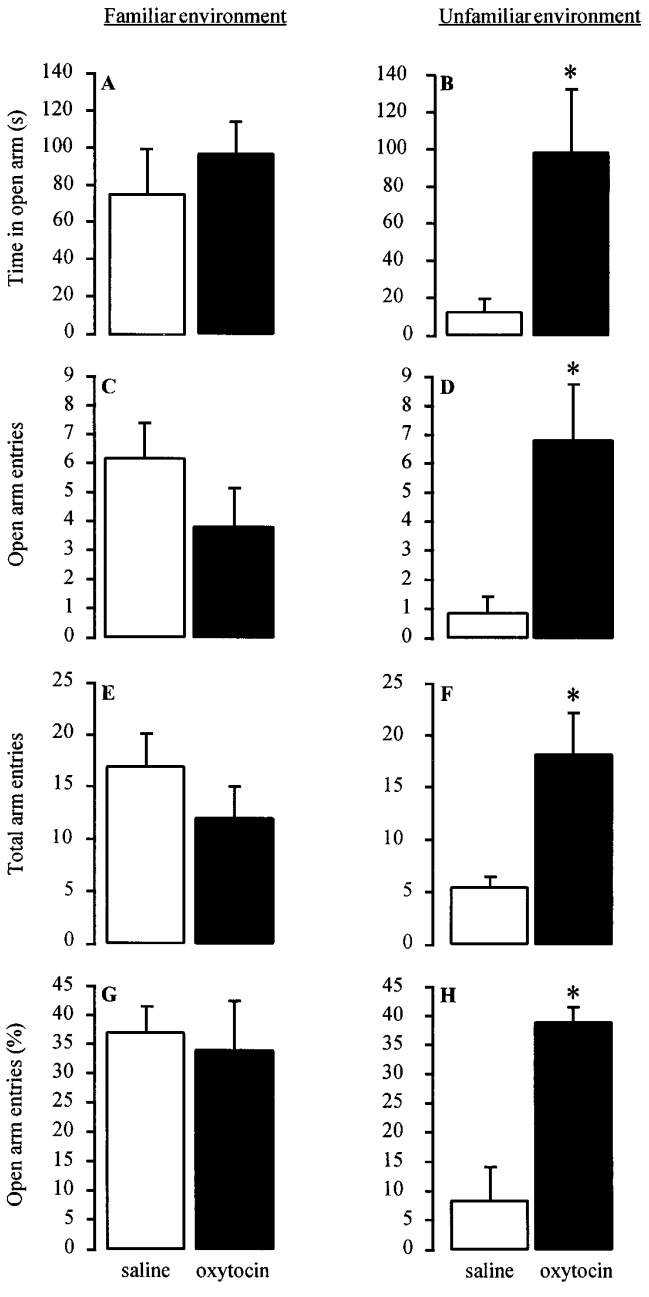

FIG. 4. The performance of ovariectomized, estradiol-treated rats during a 15-min period on the elevated plus-maze. *Open bars* represent animals infused centrally with isotonic saline alone (0.52 μl/h), and *closed bars* represent infusion of oxytocin at 100 ng/h. *Left panels* (A, C, E, and G) represent measurements from animals that were housed and tested in the same environment. *Right panels* (B, D, F, and H) represent measurements from animals that were tested in an unfamiliar environment. The parameters shown are time spent in the open arm (A and B), open arm entries (C and D), total arm entries (E and F), and open arm entries as a percentage of total arm entries (G and H). All values represent the mean ± SE for groups of six animals. *, $P < 0.05$, by Student's t test compared to saline-infused controls.

directly on the pituitary to release ACTH and consequently corticosterone (5), possibly leading to increased negative feedback. Furthermore, as a known PRL secretogogue (30) oxytocin could have stimulated the release of PRL, which is thought to increase the sensitivity of the HPA axis to negative feedback (31). However, a significant peripheral effect seems unlikely, as basal concentrations of corticosterone, which would have been increased by chronic stimulation of the adrenal or decreased by oversensitization to negative feedback, were unaffected by the oxytocin infusion. The lack of any effect of vasopressin on the HPA axis would also contradict the possibility of a peripheral site of action, as vasopressin is a well characterized ACTH secretogogue (32). It should also be noted that the effective dose was extremely low (10 ng/h), so any oxytocin that leaked to the periphery would have been very quickly degraded. It seems much more likely that oxytocin acts via a central site.

Oxytocin could have a direct effect on CRF production and secretion from parvocellular neurons of the paraventricular nucleus (PVN). As CRF itself is thought to stimulate oxytocin release from magnocellular neurons, such an effect might work as a negative feedback loop (33). Because oxytocin has mainly excitatory effects on neuronal activity (6–8, 34) an inhibitory effect on CRF-producing neurons would most likely need to involve activation of inhibitory interneurons. However, as many brain regions known to affect the HPA axis, such as the BNST (35) and the amygdala (36), also express oxytocin receptors (8, 10), it is possible that oxytocin acts on neurons in these areas to modulate pathways projecting to the PVN.

It is important to note that vasopressin had no central effect on the HPA responses to stress, suggesting that the response to oxytocin was specific and mediated by specific oxytocin receptors. It is interesting that although the V_1 receptor is known to be expressed centrally within the PVN and many of the limbic structures associated with the stress response (37), these central receptors appear to play no role in modulation of the HPA response to stress. An acute role for vasopressin cannot be excluded, as an inhibitory effect of acute central vasopressin infusion on corticosterone release in chronically stressed animals with lesions of the suprachiasmatic nuclei has been reported (38).

In the present studies oxytocin was also seen to have significant effects on behavior. During noise stress, the number of rearings, measured as a stereotypical response to a change in the environment signifying exploration and vigilance, was decreased by the same doses of oxytocin that caused down-regulation of the HPA axis. The total activity of the animals was not significantly reduced by oxytocin, thereby excluding a sedative effect of the peptide (13) and suggesting a specific anxiolytic action. This is supported by the observations from the elevated plus-maze, in which oxytocin had a clear anxiolytic effect in animals that were mildly stressed by the change in environment. As no such effects were seen in animals tested in a familiar environment, it would appear that oxytocin is acting specifically to counteract stress-related anxiety. Such an anxiolytic effect has previously been seen in an open field environment (13) when very high peripheral doses of oxytocin increased the amount of time spent away from the perceived security of the boundary wall. How oxytocin exerts its anxiolytic-like effect and whether this is related to its effect on the HPA axis are unclear. However, CRF itself is anxiogenic under many conditions and is associated with the production of rearing be-

havior and a shift of activity to the closed arms of the plus-maze (39). Oxytocin could, therefore, be acting to inhibit CRF release, causing both a down-regulation of the HPA responses to stress and inhibiting the anxiogenic effects of CRF. This would explain why oxytocin only showed its anxiolytic activity in stressed animals.

These data support the hypothesis that endogenous oxytocin can modulate physiologically important responses to stress. Lactation represents a physiological condition in which endogenous central oxytocin concentrations are elevated, and it is associated with a reduced neuroendocrine response to stress in the rat (15–18). Interestingly, the down-regulation of the corticosterone response to noise stress by exogenously applied oxytocin seen in these studies is very similar in magnitude and profile to that which we previously reported in the lactating rat (23). The down-regulation of the stress response and conservation of ACTH and corticosterone seem to be important adaptations in the lactating dam (40). Therefore, the changes in the central oxytocinergic systems that accompany the onset of lactation might serve not only to coordinate the milk ejection reflex (41) and the establishment of maternal behavior (6), but also to modify stress responses.

Acknowledgments

The authors express their thanks to Mrs. S. Wood, Mrs. P. Perks, and Miss Y. Herlihy for their technical assistance during these studies.

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