The present study was designed to determine the role of central oxytocin (OXY) in regulation of the cardiovascular responses to the alarming stress. Three groups of male, normotensive Sprague Dawley rats, received intracerebroventricular (i.c.v.) infusion of one of the following: 1) vehicle, 2) OXY or 3) OXY antagonist (OXANT). Mean arterial blood pressure (MABP) and heart rate (HR) were recorded at rest, during and after application of the alarming stressor (air jet). Under resting conditions the i.c.v. infusions of vehicle, OXY or OXYANT did not influence the cardiovascular parameters. The alarming stressor evoked significant increases in MABP and HR that were significantly greater in the rats receiving i.c.v. infusion of oxytocin antagonist than in those receiving vehicle or OXY. The study provides evidence that stimulation of the brain oxytocin receptors by endogenous oxytocin plays significant role in inhibition of cardiovascular responses to stress.

Key words: stress, oxytocin, oxytocin receptors, brain, neuropeptides

INTRODUCTION

Over the last two decades several studies provided evidence that oxytocin (OXY) may play an important regulatory role in the central nervous system. It has been reported that it participates in modulation of the cognitive processes, maternal behaviour, pain and stress-related release of neurohormones (1-6). There are also experimental data suggesting that oxytocin may be involved in the peripheral and central regulation of the cardiovascular functions (7-10). Namely, the studies of Braga et al (7) and Michelini et al (10) suggest that central oxytocin is involved in inhibition of tachycardia. However, the other studies provided evidence for central tachycardic and pressor actions of oxytocin (9, 11).
Because centrally released oxytocin is involved in the regulation of neurohormonal responses to stress it appeared interesting to find out whether it exerts also an essential influence on the cardiovascular adjustments to stressing. Thus far, the role of endogenous oxytocin in the control of the cardiovascular responses to stress has not been tested. The purpose of the present study was to determine the role of the brain endogenous oxytocinergic system in regulation of the cardiovascular responses to the alarming stress.

MATERIAL AND METHODS

Animals and surgical procedures

The experiments were performed on three groups of 15-17 weeks old male Sprague-Dawley (SD) rats (SPRD/Mol/Lod, Department of Animal Breeding of the Medical University of Warsaw). Before the experiments the rats were kept under standard conditions (12h /12h light/dark cycle; light on at 7.00 am), ambient temperature 22-25°C and had free access to tap water and a commercial rat diet. The rats were implanted with the guide tube leading to the lateral cerebral ventricle for the i.c.v. infusions and with the arterial catheter inserted into the femoral artery, which was used for recording the cardiovascular parameters by means of the BIOPAC system (MP100, Santa Barbara CA, USA). Both operations were performed under pentobarbital anaesthesia (40-50 mg/kg b wt, ip). The surgical and experimental procedures followed the international/EU guidelines on the use and care of laboratory animals and were approved by the Ethical Committee on the Animal Research.

Experimental protocol

During the experiment mean arterial blood pressure (MABP) and heart rate (HR) were recorded for 40 min under resting conditions, during application of the air jet (1 sec lasting blow of the compressed air on the top of the rat’s head), and during the next 10 min after the stressing. Group 1 (7 rats) received i.c.v. infusion of vehicle (0.9% NaCl; 0.83 µl/min), Group 2 (n = 6) i.c.v. infusion of oxytocin (1.66 pmol/min), and Group 3 (n = 7) i.c.v . infusion of oxytocin receptors antagonist (OXYANT; DesGly-NH₂-d(CH₂₉)[D-Tyr²-Thr⁴]OVT; 71.6 nmol/min). At the end of the experiments the rats were sacrificed by an overdose of 5% chloral hydrate and the brain was excised to determine the position of the i.c.v. cannula within the cerebroventricular system.

Statistical analysis

The results are presented as means ± standard errors. Significance of changes in MABP and HR from baseline was determined by one-way ANOVA and the post-hoc Tukey test. P<0.05 was considered significant.

RESULTS

Forty minutes lasting i.c.v. infusions of 0.9% NaCl, oxytocin and oxytocin antagonist did not have significant influence on mean arterial blood pressure or heart rate at rest. Immediately before application of the air jet MABP in these three groups of experiments was equal to 111 ± 3 mm Hg, 109 ± 4 mm Hg, and...
The corresponding values of heart rate amounted 375 ± 10 beats/min, 368 ± 7 beats/min, and 371 ± 10 beats/min. Air jet stress produced significant increases of the cardiovascular parameters (Fig. 1). Significant differences were found both in changes of MABP [F(2,17) = 13.055; P < 0.001] and HR [F(2,17) = 9.735; P < 0.01]. The maximum increases in MABP and HR were significantly higher in the rats receiving i.c.v. infusion of OXYANT than in those infused with 0.9% NaCl (MABP: P < 0.05, Tukey test; HR: P < 0.02, Tukey test) or oxytocin (MABP: P < 0.002, Tukey test; HR: P < 0.01, Tukey test) (Fig. 1). Both the pressor and the tachycardic responses to stress lasted 3-5 sec. No significant differences were found in duration of blood pressure and heart rate increases between the experimental groups.

DISCUSSION

The present study provides novel insight into the wide spectrum of central actions of the brain oxytocin system. Specifically, we have demonstrated that blockade of central brain oxytocin receptors elicits significant potentiation of the pressor and tachycardic responses to the alarming stress. The data suggest that oxytocin protects against excessive increases of blood pressure and heart rate under stressing conditions. Previous studies have shown that oxytocin manufactured by the brain oxytocinergic system plays an essential role in reducing anxiousness, aggression and pain, and in regulation of the maternal behaviour (1-6). Inhibitory influence of centrally acting oxytocin on release of the neurohormones engaged in the metabolic responses to stress has been also reported (4). Our results fit well to the general view on the role of oxytocin in the
central nervous system which is considered to be an endogenous stress-relieving compound (6). Infusion of OXY into the brain did not reduce the cardiovascular responses to stress. This finding may suggest that oxytocin receptors that are involved in regulation of the cardiovascular responses to stress are saturated by the endogenous oxytocin. However, we cannot exclude another possibility, namely that during i.c.v. infusion of OXY its concentration in the brain could reach a level at which it was able to stimulate V₁ vasopressin receptors in a non-specific manner. Because stimulation of vasopressin receptors leads to the enhancement of the cardiovascular responses to the alarming stressors (12-14) the unspecific action of oxytocin via V₁ receptors could mask its specific inhibitory effect.

The role of oxytocin in the central regulation of the cardiovascular system at rest was previously investigated by other authors but the results were inconclusive (7-11). In some studies intraventricular or intracisternal administration of oxytocin elicited the pressor or tachycardic effects (9, 11) whereas in others i.e.v. infusion of OXY for 5 days turned out to be hypotensive (15). It has been also found that oxytocin reduces acceleration of the heart rate during exercise (10). Our study shows that neither blockade of action of endogenous oxytocin nor administration of exogenous oxytocin cause significant destabilisation of the resting blood pressure or heart rate in conscious freely moving rats. However, we cannot exclude that oxytocin may be essential for regulation of blood pressure during some cardiovascular challenges (orthostatic adaptation, exercise) or under emergency conditions (haemorrhage, hypoxia).

In summary, our study demonstrates that after blockade of central oxytocin receptors the pressor and cardioacceleratory responses to the alarming stress are significantly augmented. Therefore we conclude that endogenous OXY released in the brain during stress may protect the cardiovascular system from the excessive work loading.

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