Oxytocin Causes a Long-Term Decrease of Blood Pressure in Female and Male Rats

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PETERSSON, M., P. ALSTER, T. LUNDEBERG AND K. UVNAS-MOBERG. Oxytocin causes a long-term decrease of blood pressure in female and male rats. PHYSIOL BEHAV 60(5) 1311–1315, 1996.—The aim of the present study was to investigate the long-term effects of oxytocin (OXY) on blood pressure (BP) and heart rate (HR) in conscious female and male rats. For this purpose, subcutaneous (SC) (0.01, 0.1, and 1 mg/kg) or intracerebroventricular (ICV) (1 μg/kg) injections of OXY were given during 5-day periods. BP and HR were measured daily. A significant decrease in BP, without affecting HR, compared to saline-treated controls was seen in response to 0.1 (males: p < 0.01, females: p < 0.001) and 1 mg/kg (p < 0.001) of OXY given SC. BP gradually returned to preexperimental levels within 10 days after the last injection in male rats but, in females, the significant lowering of BP remained unchanged during this period. Also OXY ICV (1 μg/kg) decreased BP (p < 0.05 after one day, p < 0.001 after 5 days of injections). This effect was still present 8 days after the last injection (p < 0.05). These results indicate that OXY may induce a long-term lowering of BP.

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OXYTOCIN (OXY) is a nonapeptide produced in neurons originating in the paraventricular nucleus (PVN) and projecting to many brain areas. Central actions of OXY induce multiple physiological and endocrine effects (2,17).

During suckling, behavioral, endocrinological, and physiological adaptations occur to make milk production possible. Lactating rats exhibit slow-wave sleep while nursing (19) and are less responsive to a variety of stressors during the entire lactation period (6). In women, cortisol levels (1) and blood pressure (BP) (10) fall in response to each nursing session.

Because OXY is released in response to nursing, this peptide might lie behind the adaptive effects observed during lactation. Central OXY neurons are, however, present also in nonlactating rats, and administration of OXY has been shown to cause sedation and to elevate pain thresholds in both male and nonlactating female rats (14,16).

In the present study, we explored how repeated administration of OXY influences BP and heart rate (HR) in such rats.

METHOD

Animals

Experiments were performed in 2 series. Female and male Sprague–Dawley rats (230–250 g) were used for SC injection and male Sprague–Dawley rats (335–375 g) for ICV injection (B&K Universal AB, Sollentuna, Sweden). The animals arrived at least 3 weeks before experiments and were housed 5 per cage, except animals provided with ICV cannulas that were housed individually, with free access to food and water. The light schedule was a 12/12 h light/dark cycle. The ambient temperature was 20 ± 2°C. In female rats, the stage of the estrous cycle was determined by microscopic examination of vaginal smears.

Surgery for ICV Injections

Following anesthesia with pentobarbitalnatrium (Apoteksbolaget, Sweden), 50 mg/kg injected intraperitoneally (IP), the skull was uncovered and a guide cannula (21 G) was stereotactically fixed to the skull by means of acrylic dental cement. The coordinates were 1.00 mm posterior and 1.30 mm lateral to the bregma. The guides reached, but did not penetrate, the dura mater. The injection needles (25 G) reached 3.80 mm below the dura mater, with the needle tip in the lateral ventricle. The animals were allowed 1 week of recovery after the operation. At the end of the experiment, the placement of the guide cannula was checked by injection of 2 μl of Toluidine Blue.

Experimental Design

NaCl, OXY 0.01, 0.1, and 1 mg/kg (Ferring, Malmö, Sweden) and NaCl again were given SC for consecutive 5-day pe-
Effects of OXY SC

In female rats, the BP of the control rats fell somewhat during the experiment and, compared to the male rats, the spontaneous fall in BP was significant ($p < 0.01$, as indicated by a significant interaction in the 2-way ANOVA) (Figs. 1A, 2A).

SC injections of OXY 0.01 mg/kg did not influence BP in female (Fig. 1A) or male rats (Fig. 2A). After 5 days of treatment with 0.1 mg/kg of OXY in female rats, the SBP was 109 ± 13.1 vs. 127 ± 9.0 mmHg in controls ($p < 0.05$) and, after an additional 5-day treatment period with 1 mg/kg of OXY SC, 93 ± 4.5 vs. 111 ± 12.3 mmHg ($p < 0.05$) (Fig. 3A). The corre-

RESULTS

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Oxytocin decreases blood pressure

Spending values in males were 114 ± 7.9 vs. 124 ± 4.4 mmHg (p < 0.05) and 106 ± 7.5 vs. 122 ± 1.8 (p < 0.01) (Fig. 3B).

DBP decreased in parallel with SBP in both sexes (data not shown).

In male rats, BP returned to basal levels 10 days after the end of the OXY treatment (Fig. 2A). In contrast, the lowering of BP persisted 10 days after the end of OXY treatment in the female rats (p < 0.05) (Fig. 1A). The lowering effect of OXY on BP was also more pronounced in the female rats compared to the male rats (p < 0.01, as indicated by a significant interaction in the 2-way ANOVA).

HR was not influenced by the OXY treatment. However, it tended to fall in both OXY- and saline-treated rats during the course of the experiment (Figs. 1B, 2B).

Effects of OXY ICV

In male rats, no significant effect on BP or HR could be established compared to controls or basal levels 10, 30, and 60 min after ICV injection of 1 μg/kg of OXY (data not shown). In contrast, a significant decrease in BP compared to controls was observed the following day (SBP: 115 ± 3.6 vs. 121 ± 2.7; p < 0.05).

After 5 days of treatment, SBP was 105 ± 4.6 vs. 122 ± 2.6 in OXY- and saline-treated rats, respectively (p < 0.001) (Fig. 4A). The corresponding values in DBP were 89 ± 11.6 vs. 108 ± 1.7 (p < 0.01).

A significant difference compared to controls persisted 8 days after the end of the treatment period, but had disappeared at 10 days.

HR was not influenced by the OXY treatment (Fig. 4B).

DISCUSSION

In the present study, BP was not affected when measured 1 h after the ICV injection. In contrast, BP decreased gradually during the course of the ICV and SC OXY treatment, amounting to a decrease of about 15 mmHg after a 5-day treatment period. A significant effect was, however, already observed after 1 day of OXY treatment ICV.

The effects of OXY observed here are obviously not related to direct effects of OXY, because the half-life is very short. Instead, they must have been induced by secondary, more long-lasting effects caused by the repeated OXY injections.
The mechanism behind these effects is not known and can only be speculated on. Because the decrease in BP was induced by both ICV injections (1 μg/kg) and SC injections (0.1 and 1 mg/kg), and the latter treatments are sufficient to allow biologically active amounts to cross the blood–brain barrier (8), it is presumed that the effect of OXY on BP must have been exerted centrally.

Oxytocinergic neurons originating in the paraventricular nucleus (PVN) project to many regions important for the cardiovascular control, such as the nucleus tractus solitarius (NTS), nucleus ambiguous, locus coeruleus (LC), the dorsal motor nucleus of the vagus nerve (DMX), and the intermediolateral cell column in the thoracolumbar segments of the spinal cord (3).

Previous results on OXY-induced effects on BP in these regions are based on short-term observations.

Electrical stimulation of the PVN decreases BP, an effect that has been suggested to be due to an inhibition of the sympathetic preganglionic neurons (20). In contrast, intrathecal administration of OXY has been shown to increase HR and sometimes also to cause a slight increase in BP, effects that have been suggested to be due to activation of oxytocinergic receptors on the preganglionic sympathetic neurons in the spinal cord (11). Furthermore, local application of OXY in the DMX is accompanied by excitation of cholinergic neurons and bradycardia (4). OXY also inhibits the serotonergic and noradrenergic (NA) activity in the NTS, thereby counteracting hypotensive effects of NA and 5-HT (18).

In lactating rats—a possible model of chronic OXY exposure—reduced corticotropin-releasing factor (CRF) synthesis, as determined by lower mRNA levels, have been demonstrated as well as a reduced responsivity to stress as measured by reduced stress-induced cortisol responses (1). An inhibition of CRF secretion could, therefore, in analogy to the effect in lactating animals, have been induced by our repeated injections of OXY and could explain the lowered BP because CRF has been shown to increase BP and HR via sympathetic activity (9). OXY may also have changed the activity in the serotonergic system, because oxytocinergic neurons reach the DRN, an area which is important in the pressor response (12). Or it could have changed activity in the noradrenergic pathways originating in the LC, because OXY recently has been shown to induce NA release in the ventromedial hypothalamus (5). Another possibility is a change in the electrolyte balance. OXY has natriuretic properties both by a central and a peripheral site of action (7).

Some differences were observed between the effects of OXY on female and male rats. The variations in BP and also between different days were larger in female rats than in males. This variation was related to the occurrence of the estrous cycle in females. The OXY injections were given during 5-day periods to ensure that female rats were treated on each day of the cycle. The lowering of BP in response to OXY was also more pronounced in females. This might be due to the fact that the release of OXY and, in particular, the binding of OXY to its receptors is strongly potentiated by estrogen and progesterone (13). There was a continuous fall in BP in the female control rats over the entire experimental period. This effect could possibly be a consequence of the handling of the animals because nonnoxious stimuli, including touch, have been shown to activate the release of central OXY, and even to cause an elevation of pain thresholds that are reversed by an oxytocin antagonist (15). Also, this effect, perhaps caused by a release of endogenous OXY, might have been potentiated by the female sex hormones.

Taken together, the present results show that OXY may induce a long-term lowering of BP by an as yet unidentified mechanism. This opens up the possible use of OXY or OXY-analogues as antihypertensive drugs in the future.

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