Oxytocin decreases blood pressure in male but not in female spontaneously hypertensive rats

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Received 14 March 1997; revised 22 April 1997; accepted 22 April 1997

Abstract

The aim of the present study was to investigate the effects of repeated injections of oxytocin on blood pressure and heart rate in spontaneously hypertensive rats (SHR). For this purpose subcutaneous (s.c.) injections of oxytocin 1 mg/kg or saline were given for 5 days to male and female SHR. Blood pressure and heart rate were measured daily before, during and after the oxytocin treatment period. In male rats, a significant decrease in blood pressure (systolic; \( p < 0.01 \), diastolic; \( p < 0.05 \) ), but no effect on heart rate, was seen the day after the first injection of oxytocin, when compared to saline-treated controls. Blood pressure decreased further in response to each injection and a maximal difference of 21 mmHg (systolic) \( ( p < 0.01 ) \), compared to controls, was reached after the last injection. The significant effect was gone 3 days after the last injection, although a tendency to a lower blood pressure in the oxytocin-treated rats persisted. On day 10, the oxytocin-treated SHR males again had a significantly lower systolic blood pressure \( ( p < 0.05 ) \). In female SHR, the same treatment with oxytocin affected neither blood pressure nor heart rate. These results show that oxytocin may cause a sustained decrease in blood pressure, without affecting heart rate, in male but not in female SHR.

Keywords: Blood pressure; Heart rate; Oxytocin; SHR; Long-term treatment

Oxytocinergic neurons which originate in the paraventricular nucleus (PVN) project not only to the posterior pituitary, but to many areas within the brain, where multiple physiological and endocrine effects are influenced [1,15].

Oxytocin has been shown to increase, as well as to decrease, blood pressure, depending on species, route or site of administration and time of observation, etc. We have recently shown that repeated injections of oxytocin given subcutaneously (s.c.) \( (1 \, \text{mg/kg}) \) or intracerebroventricularly (i.c.v.) \( (1 \, \mu\text{g/kg}) \) to Sprague-Dawley (SD) rats cause a sustained decrease in both systolic and diastolic blood pressure. During a 5-day treatment period with oxytocin, blood pressure fell gradually in both female and male SD rats and reached a maximal difference of about 15 mmHg, when compared to the saline-treated controls. In the male SD rats, blood pressure gradually returned to pretreatment levels within 10 days after the 5-day treatment period, whereas in females the reduced blood pressure remained unchanged 10 days after the last injection of oxytocin. No effect on heart rate was observed [12].

To our knowledge similar long lasting effects on blood pressure after treatment with an endogenous substance have not been reported previously. In an attempt to clarify how oxytocin mediates the decrease in blood pressure, we wanted to explore its effects in a model of hypertension, the SHR rat.

10 female and 10 male spontaneously hypertensive rats (SHR) with an initial weight between 180 and 210 g (Charles River Lab, Germany) were used. The animals arrived at least three weeks before experiments and were housed five per cage (Makrolon IV), with free access to food and water. The light schedule was a 12/12 h light/dark cycle. The temperature was 20 ± 2°C and relative humidity was 55–60%. Oxytocin (Ferring, Malmö, Sweden) \( 1 \, \text{mg/kg} \) s.c. or \( \text{NaCl s.c.} \) was given once a day during a 5-day treatment period to female and male SHR. Systolic and diastolic blood pressure and heart rate were measured on conscious animals on a daily basis by placing...
a cuff (Kent RTBP-002) on the base of the tail. The cuff was connected to a Grass 7P8 Sphygmomanometer and a Grass 7P8DC amplifier with a printer. The animals were habituated to the entire test procedure for two weeks before the experiments started.

The results are presented as means ± SD. Statistical analysis was performed by means of a two-way ANOVA followed by Dunnett’s t-test for post-hoc comparison with saline-injected controls.

In male SHR, pretreatment blood pressure was 185 ± 11.2 (systolic) and 168 ± 9.6 (diastolic) mmHg in the oxytocin-treated rats and 185 ± 8.9 (systolic) and 166 ± 7.8 (diastolic) mmHg in the saline-treated controls.

A significant decrease in both systolic and diastolic blood pressure was seen 24 h after the first injection of oxytocin (1 mg/kg s.c.) compared to the saline-treated controls (systolic blood pressure: 171 ± 7.2 versus 191 ± 9.0; \( p < 0.01 \)) (diastolic blood pressure: 152 ± 7.9 versus 174 ± 13.6; \( p < 0.05 \)).

Blood pressure continued to decrease and after 5 days of oxytocin treatment systolic blood pressure was 160 ± 7.0 versus 181 ± 6.0 mmHg (\( p < 0.01 \)) and diastolic blood pressure was 143 ± 9.6 versus 163 ± 7.8 mmHg in the controls (\( p < 0.01 \)) (Fig. 1).

The oxytocin-treated animals tended to have a lower blood pressure for more than two weeks after the end of the oxytocin treatment period but, except on day 10 after the treatment period (\( p < 0.05 \)), blood pressure was not significantly different when compared to the controls (Table 1).

Heart rate was not influenced by the oxytocin treatment (Fig. 1).

In contrast, no significant effect on blood pressure or heart rate could be established in the female SHR after s.c. injections of oxytocin 1 mg/kg for 5 days.

Pretreatment blood pressure was 178 ± 6.6 (systolic) and 158 ± 6.3 (diastolic) mmHg in the oxytocin-treated rats and 176 ± 4.2 (systolic) and 156 ± 2.8 (diastolic) mmHg in the saline-treated controls, whereas after 5 days of injections, blood pressure was 174 ± 2.1 (systolic) and 158 ± 4.6 (diastolic) mmHg and 173 ± 3.5 (systolic) and 160 ± 3.5 (diastolic) mmHg, in oxytocin-treated rats and controls, respectively (Fig. 2).

We have recently shown that oxytocin given s.c. or i.c.v. for 5 days to male and female Sprague-Dawley rats (SD) causes a sustained decrease of blood pressure without affecting heart rate. In male SD, blood pressure returned to basal levels within 10 days after the oxytocin treatment period, while in female SD the effect was stronger and the decrease in blood pressure remained unchanged after 10 days [12].

In the present study, we wanted to examine whether a similar treatment with oxytocin also lowers blood pressure in a rat model of hypertension, the spontaneously hypertensive rat (SHR). The present data show that in male SHR, blood pressure decreased gradually during the 5 day

![Fig. 1. The figures show the effect on systolic blood pressure (A), diastolic blood pressure (B) and heart rate (C) in male SHR in response to oxytocin 1 mg/kg given s.c. for 5 days, compared to controls given saline s.c. Each point shows the mean ± SD (\( n = 5 \)). (□) NaCl and (●) oxytocin. Statistical analysis was performed by means of a two-way ANOVA followed by Dunnett’s t-test for comparison with saline-injected controls. * \( p < 0.05 \), ** \( p < 0.01 \), *** \( p < 0.001 \).](image)

### Table 1

<table>
<thead>
<tr>
<th>Day</th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
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<tr>
<td></td>
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<td>Ox</td>
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<tr>
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</tr>
<tr>
<td>10</td>
<td>185±6.4</td>
<td>177±6.7 *</td>
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</table>

Blood pressure in male SHR. Oxytocin 1 mg/kg s.c. (\( n = 5 \)) or saline (\( n = 5 \)) was administered after the measurement of blood pressure, day 1–5.

Statistical analysis was performed by means of a two-way ANOVA followed by Dunnett’s t-test for comparison with saline-treated controls.

Systolic blood pressure: \( F_{1,32} = 21.1, p = 0.0013 \).

Diastolic blood pressure: \( F_{1,32} = 23.9, p = 0.0009 \).

* \( p < 0.05 \), ** \( p < 0.01 \), *** \( p < 0.001 \).
treatment period of oxytocin, to reach a maximal difference of about 20 mmHg when compared to the controls and to 25 mmHg when compared to the pretreatment values. In addition, the effect tended to persist during two weeks after the end of the treatment period. In contrast to the male SHR, oxytocin caused no effect on blood pressure in the female SHR.

As discussed in our previous paper [12], it is likely that the effect of oxytocin on blood pressure is exerted centrally since both 1 μg/kg i.c.v. and 1 mg/kg s.c of oxytocin, caused a decrease in blood pressure in SD rats. Because 0.2% of a systemically administered dose of oxytocin passes the blood–brain barrier [8], sufficient amounts of s.c. administered oxytocin should have reached the central nervous system in the previous and present studies.

The mechanism behind the lowering effect on blood pressure caused by centrally acting oxytocin is not known. Oxytocinergic neurons that originate in the paraventricular nucleus (PVN) project to many regions important for cardiovascular control, such as the nucleus tractus solitarius (NTS), nucleus ambiguus, locus coeruleus, the dorsal motor nucleus of the vagus nerve (DMX), the dorsal raphe nucleus and the intermediolateral cell column in the thoracolumbar segments of the spinal cord [3].

Furthermore, local application of oxytocin at various sites in the central nervous system has been shown to influence cardiovascular parameters. When injected into the DMX, oxytocin mediates excitation of cholinergic neurons and causes bradycardia [5], whereas oxytocin injected into the NTS does not influence heart rate or blood pressure. However, if oxytocin is injected simultaneously with noradrenaline (NA) into the NTS, the hypotensive effect of NA is abolished [16]. Oxytocin has also been shown to inhibit the firing of the preganglionic sympathetic neurons (SPN) [6], and electrical stimulation of the PVN decreases blood pressure, an effect which may be due to activation of oxytocinergic neurons and consequent inhibition of the SPN [6,18]. In contrast, Riphagen and Pittman have shown that intrathecal administration of oxytocin increases heart rate and also causes a slight increase in blood pressure. These effects have however been suggested to be due to an unspecific activation of vasopressinergic, and not oxytocinergic, receptors on the SPN, since oxytocin also binds to vasopressin receptors [13].

During lactation, a period when oxytocin is repeatedly released in response to the suckling stimuli, blood pressure is reduced in both rats [2] and women [11] and during the breastfeeding period, a possible model of chronic oxytocin exposure, the synthesis of corticotropin-releasing factor (CRF) is reduced [10]. Since CRF also increases the sympathetic nervous tone [9], an inhibition of CRF secretion could have been induced by our repeated injections of oxytocin thus explaining the lowered blood pressure.

Why no effect on blood pressure was observed in female SHR rats is not known. During lactation, blood pressure is reduced in SHR rats, as well as in SD rats [2].

In SD female rats, the decrease in blood pressure caused by oxytocin was more pronounced than in male SD rats [12], an effect which was attributed to the potentiating effect of female steroid hormones on oxytocin binding to its receptors [4]. Furthermore, in SD females, the variations in blood pressure were larger than in male SD rats. These variations were related to the estrous cycle and therefore to the variations in steroid hormone background. There was also a continuous fall in blood pressure in the female control SD rats during the experimental period. This effect could possibly be a consequence of the handling of the animals, because non-noxious stimuli, including touch, has been shown to release oxytocin [14]. In female SHR, variations in blood pressure during the experimental period were small and no continuous fall in blood pressure was seen during the experimental period. One possible mechanism for the lack of response to oxytocin in female SHR could be a decreased sensitivity in the oxytocin receptor.
The oxytocinergic system, determined by the content of mRNA in the supraoptic nucleus, PVN and the pituitary, is lower in activity in the SHR rats. In contrast, the activity in the vasopressinergic system, which increases blood pressure, is enhanced [17]. Blood pressure in SHR rats starts to increase around the 4th week after birth and that coincides with the decrease of the content of oxytocin [17]. Another explanation to the absence of effects of oxytocin in female SHR could be a lack of estrogen since treatment with estrogen decreases blood pressure in female SHR [7].

Since blood pressure in the female SHR is reduced during lactation, when oxytocin is released in extremely high amounts, it cannot be excluded that higher amounts of oxytocin would have reduced blood pressure also in the female SHR. However, the present study shows that oxytocin in a dose which lowers blood pressure in both female and male SD rats, as well as male SHR, does not reduce blood pressure in female SHR. Further studies in other types of hypertensive rats will be performed, but the present data suggest that it might be possible to try oxytocin as an antihypertensive drug in humans, at least in males.

Acknowledgements

This study was supported by grants from Axel och Margaret Ax:son Johnsons stiftelse and the Swedish Medical Research Council B96-04X-05207-19A. For generously supplying oxytocin, we thank Ferring AB, Malmö, Sweden.

References