Postnatal oxytocin treatment and postnatal stroking of rats reduce blood pressure in adulthood

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Abstract

The aim of the present study was to investigate the effects of postnatal oxytocin (OT) treatment and postnatal stroking on blood pressure and heart rate in adult rats. For this purpose, rats were treated subcutaneously with OT (1 mg/kg) once a day on days 1–14 after birth, or exposed to stroking on the ventral side of the abdomen for 5 min once a day on days 1–7 after birth. Blood pressure and heart rate were measured at the age of 7–8 months.

The OT-treated male rats had a significantly reduced diastolic blood pressure in adulthood (p<0.001), and in the female rats, both systolic (p<0.01) and diastolic blood pressures (p<0.001) were significantly lower compared to controls given saline postnatally. OT reduced blood pressure also in prenatally stressed female rats, which had a significantly higher blood pressure in adulthood compared to control rats that had not been exposed to prenatal stress. Also, the postnatal stroking reduced diastolic blood pressure in adulthood (p<0.05). No changes in heart rate were found.

In conclusion, both postnatal OT treatment and postnatal stroking reduced blood pressure in adulthood. In addition, in female rats, OT reduced the increase in blood pressure caused by prenatal stress.

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Keywords: Oxytocin; Massage; Stroking; Blood pressure; Stress; Rat; Prenatal; Postnatal

1. Introduction

Oxytocin (OT) is produced in neurones that originate in the hypothalamic paraventricular (PVN) and supraoptical (SON) nuclei. Parvocellular neurones within the PVN project to many areas in the brain. In addition to the well-known effects of OT during parturition and lactation, a number of studies have shown that OT has several other physiological and behavioural effects (see, for example, Argiolas and Gessa, 1991). Of particular importance for the present study is that repeated administration of exogenous OT to adult rats induces several long-lasting effects of antistress and growth promoting nature; blood pressure and plasma levels of corticosterone decrease, nociceptive thresholds increase, plasma levels of some gastrointestinal hormones are altered, as is the rat’s spontaneous motor activity (Petersson et al., 1996a,b, 1999a,b,c). Chronic infusion of OT also decreases the stress response to noise in rats (Windle et al., 1997).

If instead repeated OT injections are given to newborn rat pups, several of the antistress-like effects described above may be induced, but then not become apparent until adulthood. Postnatally administered OT increases nociceptive thresholds, plasma levels of cholecystokinin (CCK), growth rate, the adult body weight and the amount of retroperitoneal adipose tissue. In addition, in male rats, plasma levels of corticosterone and glucose decrease. Prenatal stress has been shown to increase blood pressure and to change the activity within the hypothalamic–pituitary–adrenal axis in adulthood (Barker, 1998). Indeed, the decrease in corticosterone in response to postnatal oxytocin treatment is particularly evident in rats that have been exposed to prenatal stress (Uvnäs-Moberg et al., 1998; Sohlström et al., 2000).

Sensory stimulation such as stroking and touch has been found to increase OT in plasma and cerebrospinal fluid in
adult rats (Stock and Uvnäs-Moberg, 1988; Uvnäs-Moberg et al., 1993). Repeated stroking of rats induces several effects similar to OT treatment; blood pressure decreases in both anaesthetised and conscious rats (Kurosawa et al., 1995; Lund et al., 1999), spontaneous motor activity changes (Uvnäs-Moberg et al., 1996b) and nociceptive thresholds increase. The increase in nociceptive thresholds in response to stroking of rats is abolished by an OT antagonist (Ågren et al., 1995), indicating that OT lies behind this effect.

Against this background, we examined if postnatal OT treatment and postnatal stroking could influence blood pressure or heart rate in adult rats. In addition, we also examined the effects of postnatal OT treatment on blood pressure and heart rate in rats exposed to prenatal stress.

2. Materials and methods

2.1. Animals

Sprague–Dawley (SD) rats (300 g) (B&K Universal, Sollentuna, Sweden), 25 females and 7 males, were used to produce offspring. The parent animals arrived 3 weeks before the experiments started. The animals were maintained under constant controlled conditions of light–dark cycle (12:12 h, lights on 06.00), temperature 20 ± 2 °C and relative humidity (55–60%). Food (R36: Ewos, Södertälje, Sweden) and tap water was freely available in the home cage. The animals were housed four per cage before pregnancy and one per cage during pregnancy (Macrolon IV). The offspring were housed three to four females per cage, or two to three males per cage.

2.2. Measurement of blood pressure and heart rate

Blood pressure and heart rate were measured on conscious animals by placing a cuff (Kent RTBP-002, Somedic Sales, Farsta, Sweden) on the base of the tail. The cuff was connected to a Grass 7P8 sphygmomanometer and a Grass 7P8DC amplifier with a printer. The rats were habituated to the entire test procedure for 2–3 weeks before the actual testing started.

2.3. Prenatal stress

Dams were stressed, both by light and by having their cages shaken by putting the cages on a rotation board. For practical reasons, the cages were put on top of one another on the rotation board and attached with tape. The light consists of a lamp directed towards the cage. The distance from the lamp to the cage differed between 10–35 cm and the power of the light varied from 30–710 lx depending on the position of the cage. The position of the cages was regularly changed and all cages had been in all positions for an equal number of sessions.

The stress treatment was performed three nights a week during the 3 weeks of pregnancy. The shaking and the light were randomly turned on/off by two separate preprogrammed timers. The two treatments were given in their own separate order. Sometimes, the treatments overlapped, but they were always applied with the same time duration. These treatment periods, 16 of shaking and 16 of light, were 15 min long.

2.4. Drugs

The postnatally OT-treated rats were injected s.c. with OT (1 mg/kg; PolyPeptide Laboratories, Denmark) or NaCl (0.9%). OT was dissolved in physiological saline and injected in a concentration of 1 mg/ml in pups with a weight over 10 g, and 10 mg/ml in pups with a weight under 10 g. Saline was injected in the same volume as OT.

2.5. Examination of vaginal smears

In female rats, vaginal smears from the days around the measurement of blood pressure were microscopically examined and registered.

2.6. Stroking

Rats were held with their backside down and stroked on their ventral ( ~ 2 cm²) side of the abdomen with a 1-in. thin camel hair brush. The pups were stroked for 5 min a day from days 1–7, with a speed of approximately 20 cm/s, with a frequency of 0.67 Hz, i.e. 40 strokes/min. This kind of stroking has been shown to be more efficient than stroking of the lateral side of the abdomen with the same frequency, or on the ventral side with other frequencies or other timespans (Kurosawa et al., 1995). Two pups were stroked at the same time to avoid isolation stress. The untreated pups were picked up at the same time as the stroked group but received no stroking.

2.7. Experimental design

2.7.1. Postnatal oxytocin treatment

(1) Twenty female SD rats were mated with five male SD rats. The females were matched according to weight and then randomly selected for either being exposed to stress during pregnancy or left undisturbed in the animal room during pregnancy.

(2) The offspring were left undisturbed on the day of birth, which was set as day 0. The injections and weighing started the day after birth, which was set as day 1. Half of the pups in each litter were randomly selected to be injected daily with either OT, 1 mg/kg, or with NaCl from days 1 to 14. The pups were sexed and weaned at day 21. In accordance with treatments, there were four different groups:

1. Unstressed rats injected with saline (U/NaCl): n = 9 males; n = 14 females.
2. Unstressed rats injected with OT (U/OT): \( n = 9 \) males; \( n = 14 \) females.

3. Prenatally stressed rats injected with saline (PS/NaCl): \( n = 12 \) males; \( n = 11 \) females.

4. Prenatally stressed rats injected with OT (PS/OT): \( n = 11 \) males; \( n = 12 \) females.

(3) Blood pressure and heart rate were measured at the age of 7 (females) or 8 months (males).

2.7.2. Postnatal stroking

Five female SD rats were mated with two male SD rats. The same procedure to produce offspring was used, but in this study, only the males were used. The offspring were left undisturbed on the day of birth, which was set as day 0. The stroking and weighing started the day after birth, which was set as day 1.

Two of the pups in each litter were randomly selected to be stroked for 5 min daily from days 1 to 7. The pups were sexed and weaned at day 21. In accordance with treatments, there were two different groups:

1. Postnatally untreated rats (U): \( n = 5 \) males.
2. Postnatally stroked rats (S): \( n = 9 \) males.

Blood pressure and heart rate were measured at the age of 8 months.

2.8. Statistical analysis

The results are presented as means ± S.D. Statistical analysis was performed by using a two-way analysis of variance (ANOVA) followed by an LSD test (Statistica®) or by a Student’s t-test only. \( p \)-values of 0.05 or less were regarded as statistically significant.

3. Results

3.1. Postnatal oxytocin treatment—blood pressure

3.1.1. Males

3.1.1.1. Systolic blood pressure. Prenatally stressed rats had a significantly higher systolic blood pressure than the unstressed rats (ANOVA; \( p = 0.011 \)).

There was no effect of postnatal OT treatment on systolic blood pressure (Table 1).

3.1.1.2. Diastolic blood pressure. There was no effect of prenatal stress on diastolic blood pressure. Postnatally OT-treated rats, prenatally stressed and unstressed rats studied together, had a significantly (ANOVA; \( p = 0.00057 \)) lower diastolic blood pressure compared to the NaCl-treated rats. When the effect of OT was studied separately in unstressed and stressed rats, OT treatment decreased diastolic blood pressure in both groups (unstressed \( p = 0.015 \); prenatally stressed \( p = 0.008 \)) (Table 2; Fig. 1).

Table 1

<table>
<thead>
<tr>
<th>Postnatal treatment/ prenatal treatment</th>
<th>U</th>
<th>PS</th>
<th>( p )-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>( 138.1 \pm 5.6 )</td>
<td>( 158.6 \pm 15.7 )</td>
<td>0.003</td>
</tr>
<tr>
<td>OT</td>
<td>( 151.3 \pm 19.7 )</td>
<td>( 155.2 \pm 13.0 )</td>
<td>0.56</td>
</tr>
<tr>
<td>( p )-values</td>
<td>0.06</td>
<td>0.58</td>
<td>a</td>
</tr>
</tbody>
</table>

Systolic blood pressure in male rats. NaCl = postnatal saline administration; OT = postnatal oxytocin administration; U = unstressed rats (\( n = 18 \)); PS = prenatal stress (\( n = 23 \)). a = significant effect of prenatal stress (\( F = 7.10 \); \( p = 0.011 \)).

Table 2

<table>
<thead>
<tr>
<th>Postnatal treatment/ prenatal treatment</th>
<th>U</th>
<th>PS</th>
<th>( p )-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>( 102.3 \pm 10.7 )</td>
<td>( 109.1 \pm 15.8 )</td>
<td>0.35</td>
</tr>
<tr>
<td>OT</td>
<td>( 82.8 \pm 9.4 )</td>
<td>( 90.0 \pm 23.4 )</td>
<td>0.33</td>
</tr>
<tr>
<td>( p )-values</td>
<td>0.015</td>
<td>0.008</td>
<td>b</td>
</tr>
</tbody>
</table>

Diastolic blood pressure in male rats. NaCl = postnatal saline administration; OT = postnatal oxytocin administration; U = unstressed rats (\( n = 18 \)); PS = prenatal stress (\( n = 23 \)). b = significant effect of oxytocin treatment (\( F = 14.21 \); \( p = 0.00057 \)).

Table 3

<table>
<thead>
<tr>
<th>Postnatal treatment/ prenatal treatment</th>
<th>U</th>
<th>PS</th>
<th>( p )-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>( 132.1 \pm 9.2 )</td>
<td>( 133.9 \pm 6.5 )</td>
<td>0.58</td>
</tr>
<tr>
<td>OT</td>
<td>( 126.8 \pm 9.1 )</td>
<td>( 126.9 \pm 5.1 )</td>
<td>0.97</td>
</tr>
<tr>
<td>( p )-values</td>
<td>0.08</td>
<td>0.038</td>
<td>b</td>
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</table>

Systolic blood pressure in female rats. NaCl = postnatal saline administration; OT = postnatal oxytocin administration; U = unstressed rats (\( n = 28 \)); PS = prenatal stress (\( n = 23 \)). b = significant effect of oxytocin treatment (\( F = 7.85 \); \( p = 0.0074 \)).
3.1.2. Females

3.1.2.1. Systolic blood pressure. There was no effect of prenatal stress on systolic blood pressure.

Postnatally OT-treated rats, prenatally stressed and unstressed rats studied together, had a significantly lower systolic blood pressure compared to the NaCl-treated rats (ANOVA; \( p = 0.0074 \)). When the prenatally stressed rats were studied separately, the OT-treated rats had a significantly lower systolic blood pressure than the NaCl-treated rats (\( p = 0.038 \)). Furthermore, the systolic blood pressure in the unstressed rats tended to be decreased in response to OT (\( p = 0.08 \)) (Table 3).

3.1.2.2. Diastolic blood pressure. Prenatally stressed rats had a significantly higher diastolic blood pressure compared to the unstressed rats (ANOVA; \( p = 0.047 \)).

Postnatally OT-treated rats, prenatally stressed and unstressed rats studied together, had a significantly lower diastolic blood pressure compared to the NaCl-treated rats (ANOVA; \( p = 0.00017 \)).

When unstressed rats and rats exposed to prenatal stress were studied separately, OT treatment decreased the diastolic blood pressure in both groups (unstressed \( p = 0.002 \); prenatally stressed \( p = 0.015 \)), respectively (Table 4; Fig. 2).

3.2. Postnatal oxytocin treatment—heart rate

No differences in heart rate related to prenatal stress or postnatal OT treatment were found (males: U/NaCl 421 ± 39.2, PS/NaCl 425 ± 33.4, U/OT 437 ± 26.0, PS/OT 410 ± 42.2; females: U/NaCl 457 ± 34.5, PS/NaCl 463 ± 41.4, U/OT 465 ± 34.1, PS/OT 443 ± 49.8).

3.3. Postnatal stroking—blood pressure

3.3.1. Systolic blood pressure

There was no effect of postnatal stroking on systolic blood pressure (Table 5).

3.3.2. Diastolic blood pressure

Postnatally stroked rats had a significantly \(( p < 0.05)\) lower diastolic blood pressure than the postnatally untreated rats (Table 5; Fig. 3).

3.4. Postnatal stroking—heart rate

No differences in heart rate were found (Table 5).

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### Table 4

<table>
<thead>
<tr>
<th>Postnatal treatment</th>
<th>U</th>
<th>PS</th>
<th>( p )-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>104.9 ± 14.8</td>
<td>111.6 ± 7.0</td>
<td>0.24</td>
</tr>
<tr>
<td>OT</td>
<td>87.3 ± 18.9</td>
<td>96.8 ± 11.4</td>
<td>0.095</td>
</tr>
</tbody>
</table>

**Diastolic blood pressure in female rats.** NaCl = Postnatal saline administration; OT = Postnatal oxytocin administration; U = Unstressed rats (\( n = 28 \)); PS = Prenatal stress (\( n = 23 \)). a = significant effect of prenatal stress (\( F = 4.18; \ p = 0.047 \)). b = significant effect of oxytocin treatment (\( F = 16.69; \ p = 0.00017 \)).

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### Table 5

<table>
<thead>
<tr>
<th>Blood pressure and heart rate in stroked rats</th>
<th>Postnatal treatment</th>
<th>U</th>
<th>S</th>
<th>( p )-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>143.6 ± 8.22</td>
<td>140.1 ± 4.58</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>92.4 ± 10.53</td>
<td>80.8 ± 6.51</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>444 ± 27.0</td>
<td>414 ± 53.9</td>
<td>N.S.</td>
<td></td>
</tr>
</tbody>
</table>

Blood pressure in male rats. U = Postnatal untreated rats (\( n = 5 \)); S = Postnatal stroking (\( n = 9 \)).

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**Fig. 2.** Diastolic blood pressure in female rats. NaCl = postnatal saline administration; OT = postnatal oxytocin administration; U = unstressed rats (\( n = 28 \)); PS = prenatal stress (\( n = 23 \)). a = significant effect of prenatal stress (\( F = 4.18; \ p = 0.047 \)). b = significant effect of oxytocin treatment (\( F = 16.69; \ p = 0.00017 \)). *\( p < 0.05 \) compared to PS-NaCl-treated control. **\( p < 0.01 \) compared to U-NaCl-treated control.

**Fig. 3.** Diastolic blood pressure in postnatally stroked male rats. Untreated = postnatally untreated rats (\( n = 5 \)); Stroked = rats postnatally stroked 5 min/day, days 1–7 in life (\( n = 9 \)). *\( p < 0.05 \) compared to the postnatally untreated rats. Statistical analysis was performed by a Student’s \( t \)-test.
4. Discussion

This study showed that administration of OT as well as stroking of rats early in life decreased blood pressure in adulthood. In addition, OT decreased blood pressure in female rats exposed to prenatal stress, which had a higher blood pressure compared to unstressed controls.

The ability of OT to reduce blood pressure in the present study extends the results of previous studies of OT treatment in adult rats, which show that one injection of OT per day for 5 days decreases blood pressure for 1–3 weeks after the last injection (Petersson et al., 1996b). A whole spectrum of antistress-like effects is induced by this OT treatment in adult rats; corticosterone levels are decreased, nociceptive thresholds are increased and an anxiolytic-like effect is induced. Furthermore, weight increase may be promoted and as the levels of some vagally controlled hormones change (Petersson et al., 1996a, 1999a,b,c; Uvnäs-Moberg et al., 1996a). Postnatal treatment with OT also enhances weight gain, increases nociceptive thresholds, increases plasma levels of CCK and reduces corticosterone levels in adult animals. Thus, several of the OT-induced effects observed in response to repeated treatment in adult animals may be lifelong if induced postnatally (Uvnäs-Moberg et al., 1998; Sohlström et al., 2000).

Systemic oxytocin treatment of adult rats induces changes in the amount and responsiveness of alpha 2-adrenoreceptors in the rat brain, which have been suggested to be involved in the reduction of blood pressure in response to OT (Petersson et al., 1998; Diaz-Cabiale et al., 2000). In adult rodents, about 0.2% of a dose of OT given s.c. passes the blood–brain barrier (Jones and Robinson, 1982), and in adult rats, the decrease in blood pressure in response to 1 mg/kg of OT given s.c. is mimicked by a thousand-fold lower dose of OT given intracerebroventricularly (i.c.v.) (Petersson et al., 1996b). Even a larger fraction of systemically administered OT may pass through the immature and more permeable blood–brain barrier of a rat pup. Thus, the effects of OT on blood pressure found in the present study are likely to have been induced within the central nervous system.

Stress during pregnancy has been shown to influence behaviour and physiology of the rat pups, both in the neonatal period and later on in adult life. For example, prenatal stress may cause hypertension in adulthood (Barker, 1998). In the present study, in which the pregnant rats were exposed to unpredictable light and movement, systolic blood pressure was increased in the adult male offspring and diastolic blood pressure was increased in the female offspring. The postnatal OT treatment of the prenatally stressed female rats reduced diastolic blood pressure in adulthood. However, whether this effect, at the mechanistic level, represents an antagonistic effect on the stress-induced elevation of blood pressure or merely reflects a reduction of blood pressure as also seen in nonstressed animals by OT remains to be established.

As mentioned in Introduction, OT has been shown to increase in plasma and in cerebrospinal fluid after treatment with various types of sensory stimulation. Touch and stroking as well as electro-acupuncture (2 Hz), thermal stimulation (40 °C) or vibration (100 Hz) all increase oxytocin levels (Stock and Uvnäs-Moberg, 1988; Uvnäs-Moberg et al., 1993). Repeated treatment of stroking of the abdomen in rats results in elevated basal levels of OT in plasma as well as in the periaqueductal grey (PAG) (Lund et al., to be published). Stroking of the abdomen of rats has also been shown to be followed by a decrease in blood pressure (Kurosawa et al., 1995; Lund et al., 1999), elevation of nociceptive thresholds (Lund et al., to be published) and changes in spontaneous motor activity (Uvnäs-Moberg et al., 1996b). These effects might have been induced by an increased OT release in response to stroking, since the increase in nociceptive thresholds is abolished by an OT antagonist (Ágren et al. 1995). In the present study, diastolic blood pressure decreased in response to postnatal stroking. Since the same effect was found by OT treatment postnatally, OT might be involved in the reduction of diastolic blood pressure in response to stroking. However, there are of course several other possible mechanisms behind this effect.

In conclusion, OT and stroking administered postnatally to rat pups induced a long-lasting, perhaps lifelong, decrease in blood pressure. In addition, OT reduced blood pressure also in female rats exposed to prenatal stress. These results indicate that postnatal treatment with OT or stroking may influence physiology in the newborn period, and perhaps, they also can reduce some of the detrimental effects of intrauterine stress.

Acknowledgements

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