Oxytocin reduces exercise-induced ACTH and cortisol rise in man

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Abstract. The effect of oxytocin on the ACTH, cortisol, GH and PRL response to physical exercise was investigated in 6 normal men. In addition, the possible involvement of endogenous opioids in the mediation of oxytocin action was evaluated. After fasting overnight, each subject was tested on four mornings at least 1 week apart. Exercise was performed on a bicycle ergometer. The workload was gradually increased at 3-min intervals until exhaustion and lasted about 20 min in all subjects. Tests were carried out under administration of oxytocin (2000 mIU as an iv bolus injection plus 32 mIU/min per 30 min) or naloxone (10 mg as an iv bolus injection) alone; furthermore, the effect of oxytocin together with naloxone (10 mg as an iv bolus injection) was evaluated. In the remaining test, normal saline was given instead of drugs. Plasma ACTH, cortisol, PRL and GH concentrations were significantly increased by physical exercise. Administration of oxytocin, naloxone or their combination was without effect on the PRL and GH rise elicited by exercise. In contrast, the exercise-induced ACTH and cortisol response was significantly raised by naloxone and reduced by oxytocin. These data show that oxytocin is capable of inhibiting the rise in ACTH and cortisol, but not in GH and PRL induced by physical exercise. Since naloxone abolished the inhibitory effect of oxytocin, oxytocin action on ACTH and cortisol secretion might be supposed to be mediated by an opioid pathway. However, we cannot exclude that oxytocin and naloxone act at different sites in the hypothalamic-pituitary system.

Administration of the neuropeptitary hormone oxytocin to normal men has been found to reduce the circulating concentrations of ACTH-cortisol (Legros et al. 1984, 1987) and the ACTH-cortisol response to various stimuli (Legros et al. 1982; Genazzani et al. 1985; Petraglia et al. 1986; Chiodera & Coiro 1987). These findings disagree with those of other authors who were unable to modify blood ACTH-cortisol levels by giving OT (Lewis & Sherman 1985). The possible reason for these different findings has been discussed elsewhere (Legros et al. 1987). In a previous paper, we found that naloxone abolishes the effect of OT on basal cortisol concentrations (Coiro et al. 1985) and suggested the possible involvement of opioid peptides in the mediation of the inhibitory action of OT. Plasma ACTH-cortisol concentrations are known to increase during physical exercise, together with a significant elevation in circulating GH and PRL levels (for review: Howlett 1987). In addition, exercise is accompanied by a rise in the circulating concentrations of endogenous opioids (Howlett 1987), which are thought to exert an inhibitory control on the exercise-induced ACTH increase (Brannert & Hökfelt 1987). These observations prompted us to investigate whether OT was capable of inhibiting the ACTH rise during physical exercise and whether endogenous opioids were involved in the mechanism of action of OT. In addition, we evaluated the effect of OT
on the rise in circulating GH and PRL levels induced by physical exercise. For these purposes a graded bicycle ergometer test was performed in normal men treated with OT in the presence or absence of the opioid-receptor antagonist naloxone.

**Subjects and Methods**

Six healthy non-obese men (mean weight ± SEM 70.0 ± 1.9 kg, mean height ± SEM 1.728 ± 0.2 m, mean body mass index 23.4), aged 21–29 years (mean age ± SEM 24.2 ± 1.1) volunteered for the study. All men took regularly physical exercise, but were not trained athletes. All had a negative history of endocrine or metabolic illness. None of them were taking any drugs since at least a month before the study; they were allowed to smoke until 12 h before the experiments. Each subject underwent four different tests which were performed in random order, in a single-blind design, and at least seven days apart. All tests were carried out after a 10-h overnight fast. Each subject arrived at the hospital at 7.30 h. Two venous catheters were inserted into antecubital veins; one in each forearm. One of them was kept patent with a slow saline infusion (NaCl 0.9%) and was used for blood sampling; the other was used for OT, naloxone or saline administration. Basal blood samples were collected at −30 and 0 min.

**OT test**

At time 0 blood sampling was followed by injection of 2000 mIU OT which lasted about 3 min and was followed by infusion of 32 mIU/min per 30 min. The solution was infused at a constant rate. Further blood specimens were taken 10, 20 and 30 min after the beginning of the infusion. The subjects exercised for a period on an electrically braked cycle ergometer. An initial load of 50 watt was increased by 50 watt every 3 min until subjective exhaustion. The maximal workload during this and all the following tests is reported in the results section. The subjects with a low maximal capacity (as established in a preliminary test carried out at least a week before the study) pedaled for 3–4 min against no workload at the beginning of the test, so that the total exercise lasted about the same time (20 min) in all individuals. The worktime in each individual test is reported in the results section. The 0 min sample was drawn just before the beginning of exercise, whereas those at 10 and 20 min were taken during exercise; the 30 min sample was taken after the end of exercise. The 0, 10 and 30 min blood samples were taken exactly on time. The 20 min blood sample was drawn just before the end of each exercise, and thus the mean sample time at 20 min varied slightly, according to the individual working time. During exercise subjects breathed through a low resistance one-way valve connected to a P. K. Morgan measurement system (Avinton Corp., Seattle, WA), which had been appropriately calibrated. The following parameters were measured: ventilation, frequency of breathing, tidal volume, oxygen consumption (V02), carbon dioxide production (VCO2), and respiratory exchange ratio (R). Determinations of heart rate and blood pressure were carried out by an experienced cardiologist. Heart rate was measured by auscultation over the precordium; blood pressure was evaluated with a sphygmomanometer.

**Naloxone test**

The above described exercise test was repeated in connection with an iv bolus injection of 10 mg of naloxone, but no OT, at time 0 min. Injection was followed by constant infusion for 30 min of normal saline (NaCl 0.9%).

**OT plus naloxone test**

This test was performed as the previous OT test, except for the administration of naloxone (10 mg injected as a bolus just before OT administration). In the previous OT test an equal amount of saline was given instead of naloxone.

**Control test**

This test was performed as previously described, except that an equal volume of saline was given instead of OT and naloxone.

Plasma samples from all experiments were stored at −20°C until used for ACTH, cortisol, GH and PRL assay. All samples from a single subject were analysed in duplicate and in the same assay. Measurements of ACTH, cortisol, GH and PRL were carried out by specific radioimmunoassay (Broughton 1975; Brock et al. 1978; Orth 1978; Schalch & Parker 1964; Sinha et al. 1973), with the reagents supplied by commercial kits. The intra-assay and inter-assay coefficient of variation was 5.3 and 9.8% for ACTH, 3.7 and 7.5% for cortisol, 3.8 and 8.0% for GH, and 3.1 and 10.5% for PRL, respectively. The sensitivity of the assays was 2.2 pmol/l for ACTH, 2.8 nmol/l for cortisol, 0.5 µg/l for GH, and 1.5 µg/l for PRL. Blood glucose concentrations were also measured in all samples utilizing an IL 918 auto-analyzer (Instrumentation Laboratory, Milan, Italy) and a glucose oxidase-peroxidase procedure.

Statistical analysis was performed with analysis of variance (Anova) and paired Student’s t-test, as appropriate. Results are reported as the mean ± SEM.

**Results**

Blood glucose levels remained constant in all men during all tests (control test, time −30 min: 4.58 ± 0.10 mmol/l; 0 min: 4.57 ± 0.11 mmol/l; 10 min: 4.59 ± 0.13 mmol/l; 20 min: 4.47 ± 0.08 mmol/l; 30 min: 4.55 ± 0.10 mmol/l; similar values were observed during the other tests).
Table 1.
Basal and peak values of physiological variables during physical exercise following the administration of saline, OT, naloxone, and OT plus naloxone.

<table>
<thead>
<tr>
<th></th>
<th>Saline Basal</th>
<th>Saline Peak</th>
<th>OT Basal</th>
<th>OT Peak</th>
<th>Naloxone Basal</th>
<th>Naloxone Peak</th>
<th>OT plus Naloxone Basal</th>
<th>OT plus Naloxone Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (Beats/min)</td>
<td>74 ± 9</td>
<td>140 ± 6</td>
<td>72 ± 10</td>
<td>144 ± 7</td>
<td>74 ± 7</td>
<td>147 ± 8</td>
<td>71 ± 10</td>
<td>138 ± 9</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>96 ± 4</td>
<td>110 ± 6</td>
<td>98 ± 5</td>
<td>111 ± 6</td>
<td>95 ± 5</td>
<td>108 ± 9</td>
<td>94 ± 6</td>
<td>112 ± 8</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>12.6 ± 1.0</td>
<td>30.4 ± 2.2</td>
<td>13.0 ± 0.9</td>
<td>29.6 ± 2.3</td>
<td>12.0 ± 1.3</td>
<td>28.9 ± 2.2</td>
<td>12.1 ± 1.1</td>
<td>30.0 ± 2.0</td>
</tr>
<tr>
<td>Ventilation (l/min)</td>
<td>10.4 ± 0.8</td>
<td>70.1 ± 3.0</td>
<td>10.8 ± 0.9</td>
<td>67.2 ± 2.8</td>
<td>10.7 ± 1.0</td>
<td>68.0 ± 2.7</td>
<td>11.2 ± 1.1</td>
<td>67.1 ± 3.0</td>
</tr>
<tr>
<td>Tidal volume (litres)</td>
<td>0.7 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>2.3 ± 0.4</td>
<td>0.9 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>332 ± 12</td>
<td>2256 ± 157</td>
<td>331 ± 11</td>
<td>2258 ± 149</td>
<td>335 ± 14</td>
<td>2273 ± 151</td>
<td>327 ± 11</td>
<td>2261 ± 160</td>
</tr>
<tr>
<td>VCO₂ (ml/min)</td>
<td>287 ± 18</td>
<td>2100 ± 140</td>
<td>291 ± 21</td>
<td>2116 ± 149</td>
<td>289 ± 17</td>
<td>2170 ± 153</td>
<td>288 ± 18</td>
<td>2158 ± 151</td>
</tr>
<tr>
<td>R</td>
<td>0.90</td>
<td>0.93</td>
<td>0.87</td>
<td>0.91</td>
<td>0.87</td>
<td>0.90</td>
<td>0.90</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Physical exercise resulted in highly significant increases (P < 0.001) in heart rate, blood pressure, respiratory rate, ventilation, and VO₂. None of the subjects experienced any adverse reactions after OT or naloxone administration.

Figure 1.
Plasma ACTH and cortisol levels during exercise (•••), exercise plus OT (2000 μg iv bolus at time 0) (○○○), or exercise plus OT plus naloxone (10 mg iv bolus injection just before OT administration at time 0) (●●●). The blood samples at 0, 10 and 30 min after the mean sample time was 20.3 min in the control tests, 20.1 min in the OT test, and 19.9 min in the OT plus naloxone test. Each point represents the mean ± SEM of six observations.
Plasma PRL and GH levels during exercise (●—●), exercise plus OT (2000 mIU as an iv bolus (time 0) plus 32 mIU per 30 min) (●—●), or exercise plus OT plus naloxone (10 mg as an iv bolus injection just before OT administration at time 0) (■—■). The blood samples at 0, 10 and 30 min were taken exactly on time. The 20 min blood samples were taken just before the end of each exercise; therefore, the mean sample time was 20.3 min in the control test, 20.1 min in the OT test, and 19.9 min in the OT plus naloxone test. Each point represents the mean ± SEM of six observations.

Fig. 2.

No differences were observed between the control and the experimental tests for any of the variables (Table 1). Maximal workload and worktime did not differ between the four tests (maximal workload: 3.73 ± 0.05 watt/kg (control test), 3.78 ± 0.04 watt/kg (OT test), 3.85 ± 0.08 watt/kg (naloxone test), 3.82 ± 0.07 watt/kg (OT plus naloxone test); worktime: 20.3 ± 0.3 min (control test), 20.1 ± 0.3 min (OT test), 19.8 ± 0.4 min (naloxone test), 19.9 ± 0.3 min (OT plus naloxone test). Physical exercise significantly enhanced plasma ACTH, cortisol, GH and PRL concentrations (Figs. 1,2,3,4,) (peak vs basal value $P < 0.001$). The administration of OT, naloxone or their combination did not alter the exercise-in-
Plasma ACTH and cortisol levels during exercise (●—●) and exercise plus naloxone (10 mg as an iv bolus injection at time 0) (●—○). The blood samples at 0, 10 and 30 min were taken exactly on time. The 20 min samples were taken just before the end of each exercise. The mean sample time was 20.3 min in the control test and 19.8 min in the naloxone test. Each point represents the mean ± SEM of six observations.

Produced GH and PRL rise (Figs. 2 and 4). Naloxone given alone significantly increased plasma ACTH ($F = 30.1$, $P < 0.01$) and cortisol ($F = 30.8$, $P < 0.01$) levels during physical exercise (Fig. 3). In contrast, OT given alone significantly reduced the ACTH (OT test vs control test: $F = 20.38$, $P < 0.01$) and cortisol rises (OT test vs control test: $F = 19.78$, $P < 0.01$) (Fig. 1). However, when OT was administered together with naloxone, the exercise-induced ACTH and cortisol rises were significantly higher than after OT alone (OT plus naloxone vs OT: $F = 29.03$, $P < 0.01$ for ACTH; $F = 27.88$, $P < 0.01$ for cortisol (Fig. 1) and were similar to those observed in the control test (OT plus naloxone vs control test: $F = 3.00$, NS for ACTH, $F = 2.89$, NS for cortisol) (Fig. 1).
Discussion

The ACTH, cortisol, GH and PRL increments during exercise did not correlate with variations in blood glucose concentrations. In fact, glycemia did not change significantly during control, OT, naloxone and OT plus naloxone tests.

This study extends the spectrum of observations indicating an inhibitory action of OT on plasma ACTH-cortisol levels in man. The administration of OT does not only reduce basal ACTH-cortisol concentrations (Legros et al. 1984, 1987) and the ACTH and/or cortisol rise induced by provocative stimuli such as metyrapone (Chiodera & Coiro 1987), arginine vasopressin, insulin-induced hypoglycemia (Legros et al. 1982; Petraglia et al. 1986) and labour (Genazzani et al. 1985), but
also significantly reduces the increase in blood ACTH-cortisol concentrations induced by physical exercise. At present, it is uncertain whether the same neuroendocrine mechanism mediates OT action in all these different experimental conditions; however, at least in basal conditions and during physical exercise an involvement of endogenous opioid peptides might be supposed. In a previous study, we found that naloxone abolishes OT action on the basal cortisol concentrations in the plasma (Coiro et al. 1985). Now we find that also the inhibiting effect of OT on the exercise-induced ACTH-cortisol rise disappears in the presence of naloxone. Since naloxone enhanced the exercise-induced ACTH-cortisol increase when given alone, an inhibitory action of endogenous opioids on ACTH during exercise may be hypothesized. In view of this observation, we suppose that the inhibitory action of OT on exercise-stimulated ACTH-cortisol rise could be mediated by the release of endogenous opioids. The effect of OT might be exerted at the pituitary level, where opioids are known to reduce ACTH secretion (del Pozo et al. 1980; Lamberts et al. 1983) or in the hypothalamus, where endogenous opioids are thought to inhibit corticotropin-releasing hormone release (Buckingham 1986; Nikolarakis et al. 1987). However, another explanation for our findings is that OT and naloxone acted by two entirely separate pathways, one blocked by oxytocin, the other by endogenous opioids and unmasked by the administration of naloxone. Our present experimental conditions cannot establish which of these possibilities is the correct one.

Concerning the GH and PRL responses to physical exercise, our present results failed to provide evidence of OT effects. The mechanism underlying the GH and PRL responses to physical exercise appears to be different from those of other stimuli. In fact, OT has been shown to reduce the GH response to arginine vasopressin (Chiodera et al. 1984) and to enhance the TRH-induced PRL release (Coiro et al. 1987).

Previous studies have demonstrated that in normal non-athletic subjects naloxone-sensitive opioid receptors are involved in an inhibitory mechanism controlling ACTH (Bramnert & Hökfelt 1987), but not GH and PRL responses to exercise (Mayer et al. 1980; Bramnert & Hökfelt 1987). Interestingly, our present data show an effect of OT and naloxone on plasma ACTH-cortisol, but not on GH and PRL levels. This finding supports the possibility that during exercise OT enhances the inhibitory action of endogenous opioids, thus influencing the exercise-induced plasma ACTH-cortisol, but not GH and PRL increase. Further studies are needed to substantiate this hypothesis.

References


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