

# Inhibitory Effect of Dexamethasone on Arginine-Vasopressin Release Induced by Physical Exercise in Man

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**Abstract:** To establish whether glucocorticoids inhibit the arginine-vasopressin (AVP) response to physical exercise, 10 healthy men underwent bicycle ergometer tests until exhaustion (exercise control test, exercise plus dexamethasone [2 or 4 mg in an intravenous bolus]). Physiological and biochemical variables were similar in all tests. Pretreatment with dexamethasone (2 or 4 mg) partially but significantly decreased the AVP response induced by physical exercise. Our results demonstrate a partial inhibition induced by glucocorticoids of AVP neurosecretion during cycle ergometer tests.

**Key Words:** dexamethasone, arginine-vasopressin, physical exercise

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Recently, a number of studies have shown that the administration of glucocorticoid affects the secretion of arginine-vasopressin (AVP).<sup>1</sup> In fact, studies performed in rats demonstrated that dexamethasone increases the AVP response induced by tail shock and intraperitoneal injection of polyethylene glycol decreases the AVP response to hypertonic saline, whereas it does not modify the AVP response to angiotensin II infusion.<sup>1</sup> On the other hand, experiments carried out in humans have shown that plasma AVP response to osmotic,<sup>2</sup> volumetric,<sup>1</sup> hypoglycemia, and cigarette smoking<sup>3</sup> are decreased by preadministration of glucocorticoids. Exercise represents a classic stimulus of AVP secretion.<sup>4,5</sup> Previous studies have demonstrated that pretreatment with dexamethasone favors the AVP responses to exercise in human subjects. This might derive from differential feedback sensitivity in man.<sup>6–8</sup> This question remains to be answered. For this reason, in the present study, dexamethasone's influence on AVP release induced by different physical exercise test (bicycle ergometer) was evaluated in a group of healthy men.

## PATIENTS AND METHODS

Ten male volunteers, 22 to 35 years old, participated in this study after giving informed consent. The study was in accordance with the Helsinki II declaration.

All men were in good health and were within 10% of their ideal body weight. None of them were taking drugs for at least 4 weeks before the experimental day. All men used to take regular physical exercise, but they were not trained athletes. All of them had a negative history of endocrine or metabolic illness.

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Each subject underwent 3 different tests that were performed in random order and at least 7 days apart. All tests were carried out after a 10-hour overnight fast.

## Experimental Protocol

### Control Exercise Test

At 8:30 AM of the experimental day, 2 intravenous cannulae were placed into 2 different antebraclial veins. One cannula was kept patent by a slow saline (0.9% NaCl) infusion and was used for blood sampling; the other served for the administration of dexamethasone. Basal blood samples were collected at time 0 minute. Further samples were taken 5, 10, 15, 20, 30, 40, and 50 minutes after the beginning of saline infusion.

Tests on an electrically braked cycle ergometer started at time 0 (time 8:30 AM). An initial load of 50 W was increased by 50 W every 3 minutes until subjective exhaustion. The cycling period ended when muscle fatigue and pain forced the subjects to stop exercise; in all subjects, exercise lasted the same time in all tests (15 minutes).

During exercise, the subjects breathed through a low-resistance 1-way valve connected to a PK Morgan Measurement System (Avinton Corp, Seattle, WA), which had been appropriately calibrated. The following nonendocrine physiological parameters (NEPPs) were measured: ventilation, frequency of breathing, tidal volume, maximal oxygen uptake ( $\dot{V}O_{2max}$ ), 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. The Borg Perceived Exertion Scale was used at the end of each exercise test to measure perceived effort and stress and intensity.<sup>9</sup> Measurements were performed just before the beginning of exercise (at rest) and at the end of exercise.

### Experimental Test

In all experimental tests, the exercise test was performed as described for the control exercise test.

### Exercise Plus Dexamethasone Test

The above-described exercise test was repeated in connection with an intravenous bolus injection of 2 mg of dexamethasone at time 0. In the control test, an equal volume of normal saline was injected instead of dexamethasone. On a different occasion, 4 mg of dexamethasone was given. The dose of 2 or 4 mg of dexamethasone was chosen because, in a previous study, these amounts did not change basal AVP concentrations.<sup>3</sup>

### Assays

Specimens from all experiments were used for the evaluation of plasma AVP concentrations, osmolality, serum sodium, and hematocrit level. Blood samples for AVP determinations were collected in chilled tubes containing Na<sub>2</sub>EDTA (336.2 mmol/mL) and aprotinin (100 kIU/mL). The tubes were placed in an ice bath

**TABLE 1.** Responses of NEPP and Biochemical Variables (Mean  $\pm$  SE) During Physical Exercise After the Administration of Normal Saline (Control Test), Dexamethasone in 10 Healthy Men

Test	Exercise	Exercise + Dexamethasone (2 mg)	Exercise + Dexamethasone (4 mg)
Variable	Peak	Peak	Peak
Heart rate (beats/min)	166.3 $\pm$ 6	170.7 $\pm$ 8	172.4 $\pm$ 9
Systolic BP (mm Hg)	157 $\pm$ 7	162 $\pm$ 9	165 $\pm$ 9
Diastolic BP (mm Hg)	53 $\pm$ 6	54 $\pm$ 6	56 $\pm$ 7
Respiratory rate (/min)	32 $\pm$ 3	32 $\pm$ 2	31.7 $\pm$ 3
Tidal volume (L)	2.5 $\pm$ 0.3	2.4 $\pm$ 0.3	2.6 $\pm$ 0.4
Ventilation (L/min)	74 $\pm$ 4	72 $\pm$ 3	70 $\pm$ 4
$\dot{V}O_{2\max}$ (mL/kg/min)	48.7 $\pm$ 3.8	49.07 $\pm$ 4.1	49.2 $\pm$ 4.3
R	1.06	1.09	1.08
Borg Scale Rating (RPE)	17.3 $\pm$ 0.4	17.4 $\pm$ 0.5	17.0 $\pm$ 0.4
Serum sodium (mEq/L)	140.7 $\pm$ 0.9	141.6 $\pm$ 0.8	142.3 $\pm$ 1.0
Plasma osmolality (mOsmol/kg)	287.2 $\pm$ 0.9	289.4 $\pm$ 0.8	290.1 $\pm$ 1.1
Hematocrit	0.49 $\pm$ 0.008	0.493 $\pm$ 0.010	0.495 $\pm$ 0.013

and centrifuged in the cold; plasma was separated and stored at  $-20^{\circ}\text{C}$  until assayed. Arginine-vasopressin was measured by radioimmunoassay using commercial kits (Bühlmann Laboratories AG, Basel, Switzerland). All samples were run in the same assay and in duplicate. The intra-assay and the interassay coefficients of variation were 6% and 12.8%, respectively; the sensitivity of the radioimmunoassay was 1.2 pg/mL.

Osmolality was measured with an advanced osmometer (Osmette S; Sedas, S.r.l., Milan, Italy), hematocrit level was measured by Drummond microhematocrit (Drummond Scientific, Broomall, CA), and blood sodium and glucose concentrations were measured by routine methods. Pulse and blood pressure were monitored throughout the study at each sampling time by the same experienced cardiologist.

Data were statistically analyzed by a 2-way analysis of variance for repeated measures and Student *t* test for paired data, as appropriate. Results are reported as mean values  $\pm$  SE.

## RESULTS

There were no adverse effects after dexamethasone administration. No significant differences in maximum workload and work time were observed between tests (data not shown).

### Exercise Control Test

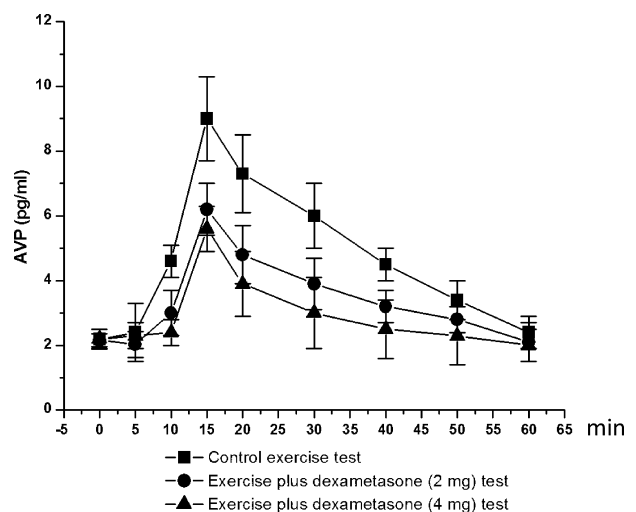
Blood glucose levels did not change at any time during tests (exercise test: time 0,  $4.57 \pm 0.82$  mmol/L; 5 minutes,  $4.59 \pm 0.84$ ; 10 minutes,  $4.59 \pm 0.90$ ; 15 minutes,  $4.60 \pm 0.83$ ; 20 minutes,  $4.57 \pm 0.85$ ; 30 minutes,  $4.56 \pm 0.82$ ; 40 minutes,  $4.56 \pm 0.80$ ; 50 minutes,  $4.55 \pm 0.86$ ). Similar values were observed during the other tests. Table 1 presents the peak responses of NEPP and biochemical variables to physical exercise.

The exercise-induced changes in NEPP were unaltered by administration of dexamethasone. Physical exercise produced a significant increase in plasma AVP levels ( $P < 0.001$  versus basal values) with a mean maximum peak at 15 minutes (end of exercise), which was 4 times higher than baseline (Fig. 1). When the AVP response to exercise was studied in the presence of 2 mg of dexamethasone, the AVP rise was partial, with a mean peak response 2.9 times higher than baseline ( $P < 0.02$  versus basal value;  $F = 7.49$ ,  $P < 0.05$  dexamethasone + exercise test versus exercise control test). Similar results were obtained when 4 mg of dexamethasone was administered, with a mean peak response 2.5 times higher than baseline ( $P < 0.02$  versus basal

values;  $F = 7.80$ ,  $P < 0.05$  exercise plus dexamethasone versus exercise control test).

## DISCUSSION

The results of the present study show that the AVP rise elicited by physical exercise is inhibited by glucocorticoids. Similar results in humans have been reported when AVP release was elicited by osmotic, volumetric stimuli, hypoglycemia, or nicotine inhaled by cigarette smoking.<sup>1-3</sup> The different AVP response between the control exercise test and the exercise plus dexamethasone tests cannot be attributed to differences in blood glucose, osmolality, hematocrit level, serum sodium concentration, and blood pressure, whose patterns were similar during all tests. The inhibitory effect of dexamethasone was partial, even when the dose was increased to 4 mg, suggesting that the dexamethasone-insensitive pathway participates in the control



**FIGURE 1.** Plasma AVP levels (mean  $\pm$  SE) during physical exercise and physical exercise plus 2 mg ( $P < 0.02$  versus basal value;  $F = 7.49$ ,  $P < 0.05$  dexamethasone + exercise test versus exercise control test) or 4 mg of dexamethasone ( $P < 0.02$  versus basal values;  $F = 7.80$ ,  $P < 0.05$  exercise plus dexamethasone versus exercise control test) in 10 healthy men.

of AVP response to physical exercise. Therefore, it is likely that the responses observed with either 2 or 4 mg of dexamethasone represent a maximal effect of glucocorticoid inhibition of AVP secretion. These results agree with previous data that report attenuation but not complete inhibition by glucocorticoids of the AVP response to various stimuli.<sup>1,3</sup> In agreement with this hypothesis, dexamethasone-sensitive glucocorticoid receptors have been found in the hypothalamus.<sup>10</sup> Furthermore, dexamethasone implants placed in the close surroundings of the paraventricular nucleus have been found to decrease AVP immunostaining in the parvocellular neurons.<sup>11,12</sup> However, we must point out that dexamethasone-sensitive receptors have been demonstrated in various brain areas, which are known to influence the control of AVP secretion.<sup>13,14</sup> The results of the present study disagree with those reported by other authors<sup>6–8</sup> who describe an augmentation of the AVP response to high-intensity exercise by previous glucocorticoid administration. However, those investigations used an oral dosage of dexamethasone 4 and 8 hours before a treadmill exercise challenge. Therefore, the different type of exercise (cycling versus running) plus route of dexamethasone administration (intravenous versus oral) might explain the discrepancy between the disparate responses of AVP to previous glucocorticoid administration. Furthermore, there are known differences between treadmill and cycle ergometer tests, which might affect the level of physical stress induced. In conclusion, our study shows a partial inhibitory effect of dexamethasone on the AVP secretion induced by physical exercise (bicycle ergometer during a submaximal test). Further studies are needed to clarify the complex interaction between glucocorticoids and AVP secretion in healthy nonathletic males.

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