Dexamethasone in resting and exercising men. I. Effects on bioenergetics, minerals, and related hormones

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Marquet, P., G. Lac, A. P. Chassain, G. Habrioux, and F. X. Galen. Dexamethasone in resting and exercising men. I. Effects on bioenergetics, minerals, and related hormones. J. Appl. Physiol. 87(1): 175–182, 1999.—A placebo and a low and a high dose of dexamethasone (Dex) were administered for 4.5 days, at 3-wk intervals, to 24 healthy men, following a double-blind, random-order, crossover procedure. After the last dose the subjects performed a maximal cycling exercise, during which respiratory exchanges, electrocardiogram, and blood pressures were monitored. Blood was sampled just before and after each exercise bout. Dex showed no significant effect on fitness, sleep, exhaustion during exercise, maximal O2 consumption, ventilatory threshold, maximal blood lactate, or rest and exercise blood pressures. On the contrary, both doses of Dex significantly decreased heart rate at rest and during maximal exercise. Blood glucose at rest was higher after both doses of Dex than after placebo; the opposite was found during exercise. Blood levels of ACTH, β-endorphin, cortisol, and cortisol-binding globulin were lowered by Dex at rest and after exercise. Dex stimulated the increase in atrial natriuretic factor during exercise and lowered rest and postexercise aldosterone. Finally, no difference between “fit or trained” and “less fit or untrained” subjects could be found with respect to Dex effects.

dexamethasone suppression test; performance; aldosterone; atrial natriuretic factor; β-endorphins

CORTICOSTEROIDS, the use of which is restricted by the International Olympic Committee to local applications and sprays (6), are probably also used per os or intravenously as doping agents because of their supposed stimulating, analgesic, and anxiolytic effects. On the other hand, if therapeutic and side effects of corticosteroids are well known in humans at rest, to our knowledge no study has been conducted on their effects on or during muscular exercise.

Exercise is one of the strongest physiological stimuli, for which nervous, cardiovascular, respiratory, and several hormonal systems are solicited to fulfill the energetic demand and the necessary elimination of metabolites. Steroids inhibit the hypothalamic-pituitary-adrenal system, which is highly solicited during exercise and partly regulates the renin-angiotensinaldosterone system (RAAS) and atrial natriuretic factor (ANF) secretions via pro-opiomelanocortin, the common precursor of ACTH and endorphins (18). Aldosterone secretion, which is principally under the control of adrenergic stimulation (13), is probably also stimulated by ACTH (4), whereas ANF secretion, principally induced by auricular stretching (19), is also enhanced by endorphins and catecholamines (17). Moreover, ANF and the RAAS are involved in the acute cardiovascular response to exercise (1).

The purpose of this study is to show the effects of a short-term administration of dexamethasone (Dex) in young healthy men with various fitness and training statuses 1) on the hypothalamic-pituitary-adrenal axis by measuring ACTH, cortisol, and cortisol-binding globulin (CBG) plasma levels at rest and during a short and maximal physical exercise bout; 2) on bioenergetics and acute cardiovascular response during physical exercise, by measuring maximal O2 uptake (V̇O₂max), ventilatory threshold (VT), blood levels of glucose and lactate, heart rate, and blood pressures; 3) on water and mineral regulation, by determining plasma aldosterone, ANF, potassium, and total protein content, as well as diuresis and urinary creatinine and sodium excretion; and 4) on quality of sleep and physical fitness during the treatment period, as well as on perceived difficulty of the test, by means of a questionnaire.

MATERIALS AND METHODS

Subjects

Twenty-four healthy male volunteers, athletes and nonathletes [24 ± 3.7 (SD) yr], with no adverse medical history were recruited from a local university, from sports clubs, and among the patients of a sports medicine center (Table 1). Informed consent was obtained from each subject after clear explanation of the protocol. Hypertensive subjects and those undergoing any other pharmacological treatment during or just before the study protocol were excluded. Before definitive inclusion, each candidate underwent a submaximal exercise test on a Siemens 930 cycle ergometer to assess his V̇O₂max (2) and check his blood pressure and cardiac rhythm (Siemens Cardiostat 701 electrocardiograph) during the testing. None had arrhythmia or showed an excessive blood pressure response.

Secondarily and to take into account its eventual influence in this study, subjects’ fitness and/or training was evaluated by means of an index, constructed by summing measured V̇O₂max (in ml·min⁻¹·kg⁻¹), mean weekly training time over the year (in h), mean weekly training time during the study, and an arbitrarily defined sports participation criterion (Table 1). The values obtained from this index, consistent with V̇O₂max and competitive level, allowed the separation of our population into a subgroup of 12 “less fit or untrained” subjects (index between 32.5 and 86) and a subgroup of 12 “fit

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Clinical Trial

Each subject received three treatments, successively and in double-blind random order, at 3-wk intervals. The experimental scheme was conceived as a Latin square repetition, where the subjects were randomly assigned to one of four groups of six subjects each on arrival. Each treatment consisted of nine 0.5-ml, 375 ± 10 mg capsules, apparently identical, administered one every 12 h for 4.5 days. This duration was chosen to minimize both the functional inhibition of adrenal glands induced by continuous corticosteroid administration but, nevertheless, to allow time for the expected effects to take place. Because the doses used by sportsmen are unknown (and probably variable), two Dex doses were compared with a placebo to study an eventual dose-effect relationship: a low dose consisting of 4.5 mg of Dex (0.5 mg/capsule), usually prescribed in nonvital chronic diseases, such as lupus erythematosus and sarcoidosis. This schedule was recommended by the Ethics Committee.

On the morning of the 5th day of each treatment period, after having ingested the last capsule, each subject reported at a designated time (8 or 10 AM) to the laboratory to minimize nycthemeral variations (particularly for cortisol). He underwent a medical examination and replied to a questionnaire that was particularly concerned with eventual side effects of Dex or contraindications to maximal exercise. Then a silicone-coated Vasolon 2 catheter was introduced into a vein of the forearm, and the subject was allowed to rest lying down for 1 h to minimize the stressing influence of the puncture on the analytic results. Just before the beginning of the cycling trial and within 2 min after the end of the trial, 100 ml of blood were drawn through the catheter with a dry sterile syringe. Urine was collected on the same morning and over the next 24 h. The maximal incremental cycling exercise was designed to be 12–18 min long by adapting the load of the 3-min increments, (30, 40, or 50 W) for each subject’s previously estimated \( V_{\text{O}_2\text{max}} \). To ensure that \( V_{\text{O}_2\text{max}} \) was always near or above the respiratory quotient \( (R = \frac{V_{\text{CO}_2}}{V_{\text{O}_2}}) \) was near or above 1.1. Thus, for a given subject, the three tests were identical and performed under the same dietary and time conditions.

Physiological Measurements

Respiratory exchanges were continuously monitored using an Oxycon 4 Mijnhardt spirometer and analyzer, and arterial pressure was measured every 3 min by means of a mercury sphygmomanometer. Every 30 s, heart rate was computed from the electrocardiogram, and \( V_{\text{O}_2}, V_{\text{CO}_2} \), and \( R \) were computed from gas exchanges. \( VT \), defined as the theoretical load leading to \( R = 1 \) after 3 min, was computed by interpola-
tion between the highest workload giving $R \leq 1$ after 3 min and the following workload and its corresponding $R$ value.

Biological Analyses

The hematocrit was measured on fresh blood. The blood was centrifuged immediately after collection, and the plasma was divided into aliquots, which were kept frozen at $-20^\circ$C until the assays. Blood levels of glucose, potassium, and protein, as well as urinary creatinine and sodium, were analyzed by automated techniques; blood lactate was analyzed by an enzymatic method using spectrophotometry; and CBG was analyzed by the technique described by Ferlund and Laurell (9). The following plasma hormone determinations were performed by validated RIAs with use of calibrating standards and controls for each set of assays: ACTH and aldosterone (EISA-ACTH, 125I and SB-ALDO-H-M-H-M kits, respectively, CIS-Biointer). β-endorphin (NCSTAR 125I kit, Sorin Biomedica), ANF (3), and cortisol (14).

Questionnaire

During the preexercise rest, subjects were asked about their fitness and quality of sleep, digestive or neuropsychic disorders, or any other sign or symptom, especially evocative of corticosteroid adverse effects, over the treatment period; after exercise, during the second and third treatment periods, they were asked to evaluate the difficulty of the trial compared with the preceding trial(s) in order to rank them.

Statistical Analysis

Four repetitions of a $6 \times 3$ Latin square (6 subjects submitted to 3 treatments) were regarded as a good compromise between the need for a powerful statistical tool and the material and financial cost of the study. The ANOVA of this procedure took into account the eventual differences between subjects, between time periods, between groups of subjects (Latin squares), and between treatments. This analysis was applied to resting and end-of-exercise values and, whenever possible, to their difference to check for an eventual influence of Dex on the intensity of physiological response to exercise. The level of statistical significance was set at 5%. In the case of a significant “treatment” or “time period” effect (i.e., a variance over the 3 groups considered significantly higher than the residual variance), a $2 \times 2$ comparison of groups, by computation of their contrasts, was performed to show the origin and the direction of the difference (e.g., plasma cortisol at rest significantly lower with high-dose Dex than with placebo, with no statistical difference between high- and low-dose Dex).

Exercise effects on each variable within each treatment group were evaluated by paired t-tests between resting and end-of-exercise values.

The influence of the “fitness and training” status on the effects of treatments and, more largely, on the physiological and biological variables monitored was evaluated using two-way ANOVAs, with “fitness” and “treatment” taken into account but without consideration of time period and “Latin square” effects, which were included in the residual variance, therefore leading to a lower significance of the treatment effect than in the previous Latin square ANOVA. Nevertheless, when fitness and treatment effects were significant, treatment effect was tested in each subgroup of fitness and training status.

Questionnaire data were analyzed by $\chi^2$ tests, with a 5% level of significance.

For this part of the study the computation of $\sim 720$ mean values, 120 ANOVAs, and 240 other statistical tests was needed. Therefore, only the significant or otherwise interesting results are presented and discussed.

RESULTS

Inasmuch as there was no missing value for the parameters recorded, all could be studied in the entire population.

Influence of Fitness and Training Status

The influence of the fitness and training status was not significant on most of these parameters, except those concerned with metabolic and acute cardiovascular response to exercise: highly significant differences were found for $V_{O_2max}$ (53.4 and 42.5 ml·min$^{-1}$·kg$^{-1}$ for the fit or trained and the less fit or untrained groups, respectively, $P < 0.001$), VT (178 and 123 W, respectively, $P < 0.01$), and end-of-exercise heart rates, which were lower in the fit or trained than in the less fit or untrained subjects (182.28 ± 1.41 and 188.67 ± 1.36 beats/min, $P < 0.05$), whereas there was no difference for heart rate at rest. Because of the lack of a significant influence of fitness and training on Dex effects, the 24 subjects were considered a single group for the rest of the study.

Confusing Variables

The intersubject variability was almost always significant, as is usual for biological variables. The variability between inclusion groups was more rarely, and randomly as it seemed, significant. The time period significantly influenced VT, which was higher during the first exercise bout than during the other two bouts ($P < 0.05$), this difference originating essentially from the fit and trained subgroup (VT = 193.2 ± 17.4 W during the 1st exercise bout, 164.3 ± 16.2 W during the 2nd bout, and 177.5 ± 15.6 W during the last bout). On the contrary, ANF and CBG plasma levels were significantly lower at the end of the first exercise bout: mean blood ANF was 30.0, 38.8, and 37.0 pg/ml after the first, second, and third exercise bouts, respectively ($P < 0.05$ between the 1st and 2nd trials); mean blood CBG was 38.9, 39.6, and 41.6 mg/l, respectively ($P < 0.05$ between the 1st and 3rd trials). However, for the rest of the study the comparisons between treatments were adjusted for the effects of these confusing variables by means of the multiparametric ANOVAs used.

Treatment Effects

Effects on the pituitary-adrenocortical function. ACTH levels fell at rest as well as after exercise ($P < 0.001$ for both) when the corticosteroid was administered (Fig. 1). Graphically, this effect seemed to be dose dependent [not significant (NS)]. Whatever the treatment, ACTH levels were greatly increased by the exercise bouts, but in a highly significant dose-dependent way (+550% with placebo, +324% with low-dose Dex, and +151% with high-dose Dex, $P < 0.001$). Blood cortisol was decreased by Dex at rest as well as after exercise ($P < 0.001$) and was strictly unaffected by cycling, whatever the treatment. CBG blood level was also
decreased by Dex at rest (−4.4% with low-dose Dex (P = NS) and −7.3% with high-dose Dex (P < 0.05)) and after exercise (−7.5% with low-dose Dex (P < 0.01) and −10.8% with high-dose Dex (P < 0.01)); moreover, after exercise it was increased by −20% from the level at rest (P < 0.001), whatever the treatment. β-Endorphin evolution was very similar to that of ACTH, with a significant decrease at rest and during exercise with Dex (P < 0.001 for all), whereas the exercise-induced rise recorded with placebo was significantly reduced but not totally suppressed by Dex (+98% with low-dose Dex and +132% with high-dose Dex vs. +230% with placebo, P < 0.001; Table 2).

Metabolic and cardiovascular effects. At rest, blood glucose was higher with Dex than with placebo (P < 0.05), apparently in a dose-dependent way (P = NS). During physical exertion, blood glucose increased by 35% with placebo (P < 0.001) but did not increase above the level at rest with either Dex dose (Fig. 2, Table 2). As a consequence, postexercise blood glucose was significantly higher with placebo than with either Dex dose (P < 0.01), with no dose effect (5.79, 5.18, and 5.20 mmol/l with placebo, low-dose Dex, and high-dose Dex, respectively).

\[ V_O^{2\text{max}} \]

VT, and blood lactate at rest and end of exercise were not modified by the treatments; the high mean blood lactate (10 mmol/l) at the end of exercise is a good indicator of the high intensity of the cycling trials (Fig. 2). Heart rates at rest and at maximum workload were lower with Dex than with placebo (P < 0.01 and P < 0.05, respectively). Treatment effect was even significant on the increase in heart rate between rest and exercise with low-dose Dex (P < 0.05) but not with high-dose Dex (Table 2).

Treatments had no effects on diastolic, systolic, and pulse blood pressures at rest or at the end of the exercise bout. Exercise induced a diastolic pressure decrease and a systolic pressure increase (P < 0.05 and P < 0.001, respectively) independently of the treatment (Table 2).

Effects on water and mineral regulation. At rest the ANF level (Fig. 3) tended to be increased by Dex, whereas it was significantly increased after exercise (P < 0.01). Physical exertion significantly increased ANF levels, regardless of treatment (P < 0.001).

Dex induced a decrease of aldosterone blood levels (Fig. 3) at rest (P < 0.01) and after cycling (P < 0.001). Inasmuch as postexercise levels were increased by
DISCUSSION

Although both Dex doses administered in this study significantly decreased ACTH and cortisol (as well as β-endorphin) blood levels at rest and especially after a short, maximal exercise bout, they did not induce any improvement in perceived fitness or exertion or on

-100% compared with respective levels at rest (P < 0.001). Dex showed a significant treatment effect on the absolute but not relative postexercise aldosterone increase (P < 0.05 between placebo and low-dose Dex and between placebo and high-dose Dex; Table 2).

Blood potassium was not significantly affected by exercise (Fig. 3) but seemed to be lowered by Dex, particularly by high-dose Dex, after cycling (~4.6% between low- and high-dose Dex, P < 0.05).

The cycling exercise bouts increased hematocrit and total plasma proteins by 12% (P < 0.001) and 16% (P < 0.01), respectively, above values at rest, whereas Dex had no effect at rest or after exercise.

Diuresis, as well as 24-h creatinine excretion, was unaffected by Dex, perhaps because of the overriding effects of exercise on these parameters.

Subjective effects. The analysis of the questionnaire revealed that very few digestive, neuropsychic, or other symptoms evocative of Dex side effects were reported by the subjects and that their frequency did not significantly vary according to the treatments. Treatments induced no significant effect on fitness or fatigue or on quality of sleep. There was no difference between the first time period, which was potentially more stressing, and the following time periods. The perceived difficulty of the different exercise bouts was not statistically different between treatments.
objective performance parameters (VO2max, rest and maximal blood lactate, VT) during exercise. Unexpect-
edly, the VT was affected by the time period essentially in the fit or trained subgroup: it decreased between the first and the third exercise tests, possibly because of a progressive “detraining” of trained subjects, inasmuch as the first test was performed at the end of the sports season (between September and November) and the third test was performed between November and January.

The only noticeable cardiovascular effect of Dex is a slight decrease in rest and maximal heart rates (from -4 to -8 and from -3 to -5 beats/min, respectively), but with no dose-response relationship. Whether this effect resulted from a decrease in peripheral vascular resistance, which would mean an improvement in response to muscular exercise, or from a modification in the nervous command of the heart, which could mean a simple decrease in total blood flow, was beyond the scope of this study.

Compared with placebo, Dex increased blood glucose at rest by stimulating hepatic gluconeogenesis. However, during exercise, this exogenous stimulation was probably unable to compensate for the endogenous stimulation due to cortisol, the secretion of which is physiologically increased by exercise but here was drastically inhibited by Dex. The result was that postexercise blood glucose with Dex was significantly lower than with placebo. Hence, the glucocorticoid effects of both Dex doses were probably higher than the effect of the cortisol level at rest but lower than the effects of the physiologically exercise-induced cortisol levels. However, future studies will require tests of longer duration, together with the determination of catecholamines, insulin, and glucagon, to reveal the eventual modification induced by corticosteroids on the exercise metabolic regimen and on the metabolism of carbohydrates.

The significant lowering of plasma aldosterone by Dex at rest and after exercise was probably due to a secondary regulation of its synthesis by ACTH, which was also decreased (4). On the other hand, whatever the treatment, physical exercise induced a twofold increase in blood aldosterone, which reflects RAAS adrenergic stimulation (13). Blood potassium was decreased by high-dose Dex after exercise, despite the lowering of aldosterone, revealing the slight mineralocorticoid effect of Dex. Exercise by itself did not modify blood potassium, with Dex or placebo, contrary to previous reports for exercise of longer duration (3), where blood potassium was increased by a probable extrusion of potassium from exercising muscle fiber, owing to the β-agonist effects of epinephrine and norepinephrine (15). The postexercise increase in ANF plasma level with Dex (with a dose-effect relationship) was probably due to an overexpression of the gene coding for pro-ANF in cardiac myocytes, as previously reported (7, 10). So the previously evoked hypothesis of a partial dependence of ANF secretion with respect to β-endor-

![Graph](image_url)
levels at rest were almost unaffected by Dex, one can hypothesize that Dex increased the synthesis of pro-ANF and/or ANF in cardiac myocytes but not the excretion of ANF, whereas exercise would more likely act by stimulating pro-ANF maturation and ANF excretion. The postexercise increase in blood ANF with Dex seemed to have no effect on sodium and potassium 24-h urinary excretion, which, rather, reflected unaffected ANF levels at rest, or on blood pressures, which are regulated by ANF in the intermediate term only.

The increase in hematocrit and blood protein level at the end of exercise, which is a common finding (21), was not affected by Dex. It reflected partly dehydration through sweating and hyperventilation and mainly redistribution of body fluid from the intravascular compartment to the interstitial compartment, inasmuch as dehydration is unlikely to reach 12–16% of total body water as a result of such a short exercise bout (5, 11). No correction for dehydration was applied to the various plasma concentrations measured in this study, inasmuch as most of the compounds studied (except proteins and the bound, inactive fraction of hormones) can freely diffuse in extracellular water.

The decrease in blood CBG induced by Dex, at rest and after muscular exertion, could be due to a downregulation of its synthesis as a result of the much larger decrease in cortisol blood levels (even at rest): it has been reported that a hormone can regulate the plasma level of its own binding protein (22). The 20% CBG increase with exercise was probably mostly due to hemoconcentration being constant regardless of the treatment and, therefore, could not modify the influence of Dex on total or free cortisol plasma concentrations.

Because of the experimental procedure, which notably reduced residual variances, therefore enhancing deterministic effects such as those of treatments, the relatively small number of subjects in this study was sufficient to point out numerous significant effects of Dex. Unfortunately, this experimental scheme could not be applied to the study of the effects of fitness and training, and this may be the reason why they were more rarely significant. Nevertheless, the apparent absence of influence of the fitness and training status on hormone variations observed with exercise or with Dex is consistent with a previous study, which reported that adrenergic response and ACTH and cortisol secretions were identical in trained and untrained subjects for equal relative workloads (8). Further studies should confirm and develop the main results found here; other studies should include women, where hormone effects might be different.

If doping effects of Dex are still to be proven, except for its well-known analgesic and anti-inflammatory properties, this study has pointed out numerous hormone and metabolic effects, which, for some of the effects, could impair short-term and for others long-term adaptation to intense physical loads. The treatment duration of this study was short to minimize Dex adverse effects in the subjects. Indeed, none reported signs evocative of any corticoid side effect. In the case of real doping, chronic or iterative administrations could favor bone demineralization, proteolysis, weight increase, carbohydrate disorders, and above all myopathy, as reported in rats (16).

We thank Rose Chaisemartin and François Dalmay for excellent technical assistance.

This research was supported by a grant from the French Youth and Sports Ministry.

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Received 4 June 1998; accepted in final form 25 February 1999.

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