Glucocorticoids: A Doping Agent?

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KEYWORDS

• Glucocorticoids • Exercise • Performance • Doping
• Adrenal insufficiency • Adverse effects

Certain international sports federations are requesting that glucocorticoids (GCs) be removed from the World Antidoping Agency's (WADA) list of banned products. This pharmacologic class is banned by WADA after systemic administration, but only in competition. Their arguments are based on the fact that GC are in widespread use in sports medicine and have no demonstrated ergogenic activity (ie, are not performance enhancers). To be included on the list of banned products a substance should meet any two of the following three criteria: (1) evidence that the substance improves athletic performance, (2) evidence that the substance represents a health risk for the athlete, and (3) the use of the substance violates the spirit of sports.

This article shows that, using appropriate testing based on physiologic effects, GCs have real and demonstrated ergogenic activity and that the use of GCs poses a real danger to athletes' health.

PHYSIOLOGIC EFFECTS OF GCS AND EXPECTED EFFECTS OF GC ABUSE

Cortisol is a steroid hormone secreted from the adrenocortical glands under hypothalamic and pituitary control defining the hypothalamic-pituitary-adrenal (HPA) axis. The activation of the HPA axis represents a physiologic response to the energetic, metabolic, vascular, neurophysiologic, or psychologic needs of exercise.[1–3] GCs, the end product of the HPA axis, exert many beneficial actions in exercising humans. GCs increase the availability of metabolic substrates for the need of energy of muscles (increased lipolysis and plasma free fatty acids [FFA], increased glycogen synthesis) and maintain normal vascular integrity and responsiveness during exercise. In

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addition, GCs prevent an overreaction of the immune system as a result of exercise-induced muscle damage (immunosuppressive and anti-inflammatory effects).[3] Cortisol also prepares the organism for the next bout of exercise, explaining why when an acute bout of endurance-exercise is stopped, cortisol levels may return to pre-exercise values with a delay ($\leq$2 hours postexercise).[3,4] At the central level (central nervous system), GCs may exert positive hedonic effects by an increase of dopamine release in the nucleus accumbens.[5] The interplay between central noradrenergic systems and GC is also involved in the physiology and physiopathology of GC-induced mood changes (euphoria, depression, and withdrawal syndrome).[6]

These physiologic properties of GCs suggest that GCs could enhance performance, and this explains why GCs are in such widespread use in the sporting world. Indeed, the expected effects of the use and abuse of GCs are numerous: neurostimulatory effects at cerebral GC receptors could attenuate central impressions of fatigue, and anti-inflammatory and analgesic effects could inhibit sensations of muscle pain on effort and raise the fatigue threshold. The metabolic effects of these compounds consolidate glycogen reserves in muscle tissue and accelerate lipolysis and glycolysis mechanisms induced by catecholamines and growth hormone, thereby leading to more efficient use of energy sources by the muscles in the course of exercise.[1,2]

GCs have pleiotropic effects, however, causing several adverse effects, especially at higher doses and for long periods, such as osteoporosis, insulin resistance, and cardiovascular effects (hypertension and atherosclerosis).[7] In addition to their presumed ergogenic effects, the salient question is whether these adverse effects may be counteracted by intensive and regular exercise or limited by intermittent intake.

ERGOGENIC ACTIVITY OF GCS: SCIENTIFIC EVIDENCE

Human Data

Few studies have been performed on GC administration and exercise performance. The main characteristics and results of these studies are summarized in humans (**Table 1**) and animals (**Table 2**).

Review of the scientific literature clearly shows two types of results: studies supporting the hypothesis that there is no relationship between performance and corticosteroid use in humans (negative studies)[8–13]; and studies supporting the hypothesis that there are relationships between performance and corticosteroid use in humans (positive studies).[14–16] A third, intermediate tendency, however, can also be found in studies with data showing relationships between performance and GC use in humans but interpreting these data as negative taking into account the initial hypothesis of the authors.[17]

It should be noted that inconsistencies found regarding the ergogenic effect of GC administrations in humans may be attributed to (1) the GC administration dosage, route, and mode (acute or short term); (2) the type, duration, and intensity (submaximal, maximal) of exercise tested; (3) the participants (highly trained or professional vs recreational trained); (4) the differences in diet, such as whether or not experiments are food-controlled and whether or not subjects fasted; and (5) GC intake coupled or not with intensive training.

Negative studies

Marquet and colleagues[8] and Petrides and colleagues[9] have evaluated the effects of GCs (dexamethasone, 4.5 or 13.5 mg; hydrocortisone, 100 mg) on performance in terms of GC effects either on maximal oxygen consumption (V_{O_2}max) (maximum exercise duration 10–12 minutes)[8] or on a short series of submaximal exertions (10 bouts of 30 seconds of exercise at 90% V_{O_2}max)[9] (see **Table 1**) and found no difference

between the placebo and the treatment groups. Taking into account the physiologic effects of GCs, these results were foreseeable because it is difficult to hypothesize that GCs may increase $V_{O_2}max$[8] or maximal heart rate[9] during brief exercises. Respiratory exchange ratio was also considered in the study of Petrides and colleagues[9] but values of respiratory exchange ratio should be interpreted with caution because no respiratory steady-state can be reached in 30 seconds (duration of the measure in this study). Moreover, the metabolic state of their subjects (fasted, postprandial) and the time of exercise (GCs were taken 4 hours before exercise without notification of the exercise's timing) are unknown.

Considering the effects of GCs, studies conducted during a prolonged endurance test to exhaustion or using a series of brief high-effort exercises to exhaustion in which GCs might attenuate impressions of fatigue and pain are more appropriate to demonstrate an ergogenic effect of GCs. Using trials to exhaustion (cycling) at intensity varying from 70% to 75% $V_{O_2}max$[12] to 80% to 85% $V_{O_2}max$[13] or during a maximal exercise (steady-state exercise followed by a ramped test)[17] or a fatiguing sprint session followed by a time trial (time to complete 20 km),[10] however, no study has demonstrated any ergogenic effect of acute systemic adrenocorticotropic hormone (ACTH)[10] or GC administration.[12,13,17]

The main limitation of these studies is the dosage of GC used, which remained within the physiologic ranges of plasma cortisol levels (but at high-stress level). For example, Kuipers and colleagues[11] have tested the ergogenic effects of therapeutic GC inhalation (800 μg/day). Such local low-dose administration failed to improve performance probably because of the lack of significant systemic bioavailability of inhaled GC. The study of Baume and colleagues[10] is another good illustration of this limitation. The design of their study comprised injection of 0.25 mg ACTH (Synacthen), resulting in a doubling cortisol levels.[10] Although significantly increased compared with placebo, the ACTH-induced value of cortisol (900 vs 500 nmol/L in the placebo study) remained within physiologic high range (stress levels) of cortisol concentrations. The 0.25-mg dose of ACTH is the dose normally administered during studies of pituitary function. With this dose plasma cortisol generally peaked 30 to 60 minutes after injection, remaining at maximal values for 100 to 120 minutes and thereafter cortisol rapidly returned to control values. In the study by Baume and coworkers,[10] ACTH injection elevated cortisol (two times compared with placebo study) for 2 hours and the 20-km time trial was performed at the peak cortisol concentration with no difference in time to complete the 20-km trial compared with the placebo group. Moreover, as anticipated, on day 2 of the trials, there was no difference in ACTH and cortisol profiles between the placebo and ACTH groups indicating that the single intramuscular injection received 24 hours previously had no further influence on the HPA axis. The intense effort exhibited during the 20-km time trial on day 2 normally stimulated the production of cortisol in both groups without any significant difference between the groups.

Administration of Synacthen at a higher dose or for a longer time period inducing a permanent high cortisol concentration in the body is more near the real state of ACTH intake by athletes. As suggested by the authors, ''in appropriate forums on Internet, it appeared that athletes from different levels take up to 2.5 mg of Synacthen.'' The authors also assumed that this substance is administered on a short time period to boost the cortisol production right before an event. The potential positive effects of cortisol ''would allow a higher energetic state and better feelings for athletes during exercise.'' Real athletes would also use Synacthen during recovery of competition, for its anti-inflammatory and metabolic effects (favoring glycogen resynthesis and storage) to prepare for the next event in a situation of repeated intense challenges,

Table 1
GC administration and exercise performance: results of the studies in humans

Study	Methods	Participants	Interventions	Outcomes	Results
8	Double-blind Randomized Crossover	12 untrained ♂ 12 trained ♂	3 treatments for each subject: - Pla - Dex for 4.5 d (per os) ➢ Low dose: 0.5 mg/12 h (total: 4.5 mg) ➢ High dose: 1.5 mg/12 h (total: 13.5 mg) Last capsule ingested 1 h before EX 3 experimental sessions per subject 2-wk intervals between each session	Maximal incremental cycling exercise (12–18 min long)	No effect of GC on performance measured on: - Vo_2max - ventilatory threshold - perceived difficulty of the exercise bouts Other effects of GC: - ↑ blood G at rest vs pla - but lower G in post-EX vs pla
9	Double-blind Randomized Crossover	19 moderately trained ♂	3 treatments for each subject: - Dex 4 mg - Hydrocortisone 100 mg - Pla 4 h before EX 3 experimental sessions per subject 1-wk intervals between each session	Submaximal high-intensity exercise test (25 min) (treadmill): - 5 min warm-up: 50% Vo_2max - 10 min high-intensity intermittent run: 10 bouts of 30 s of exercise at 90% Vo_2max alter nated with 30 s of rest at 10% grade - 10 min cool down of walking (3.3 mph)	No effect of GC on performance measured on: - Heart rate - RER - absolute Vo_2 - relative Vo_2 (%) - blood lactate (parameters averaged over the last 4 intermittent bouts of high intensity EX) Other effects of GC: - ↑ pre-EX and peak EX-induced G responses (Dex-hydrocortisone vs pla)

10	Double-blind Randomized Crossover	8 highly trained ♂ cyclists	2 treatments for each subject: ACTH (0.25 mg) or pla (saline) IM 2 consecutive days: D1 and D2 S1: D1 pla or ACTH D2: no injection 2 experimental sessions (S1 and S2) per subject separated by 7–10 d Diet controlled	- D1: 90 min fatiguing sprint period: (50% power max interspersed with multisprint sessions: 3 × 1 min sprints at 90% power max and 2 × 4 min sprints at 70% power max) followed by a maximal effort: 20 km time trial - D2: 20 km time trial	No effect of GC on performance measured on: time to complete the 20 km time trial No ≠ in resting perceived exertion on either day of the trials (vs pla)
11	Double-blind Placebo-controlled study No crossover (parallel groups)	28 well-trained ♂ endurance athletes (involved in cycling and rowing)	1 treatment for each subject: - Pla or budenoside Daily inhalation of 800 μg for 28 d 1 experimental session per subject	3 incremental cycle ergometer tests until exhaustion Before and after 2 and 4 wk of pla or budenoside	No effect of inhaled GC on performance measured on: maximal power output (at 4 wk of treatment) (pla: 374 ± 26 vs budesonide: 378 ± 37 W) No ≠ in POMS score every week
12	Double-blind Randomized Crossover	14 recreationally trained ♂	2 treatments for each subject: - 20 mg pred per os (0.25 mg/kg BW) - Pla 3 h before EX 2 experimental sessions per subject 3 weeks (of normal training) between the 2 sessions	Trial to exhaustion during submaximal exercise (cycling) at 70%–75% Vo_2max	No effect of GC on performance measured on: cycling time: 48.8 ± 2.9 (pla) vs 55.9 ± 5.2 min (pred) Other effects of GC: blood hormonal and metabolic parameters - ↑G under pred during rest, EX, and recovery - No ≠ in insulin - ↑basal levels of inter leukin-6 during EX but this increase is significantly blunted at exhaustion and during recovery under GC vs pla

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Table 1
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Study	Methods	Participants	Interventions	Outcomes	Results
13	Double-blind Randomized Crossover	7 recreationally trained ♂	3 treatments for each subject: - Pla - 20 mg pred per os (2 h before EX) - Pred-salb (4 mg) (3 h before EX for salb) 3 experimental sessions per subject 72-h intervals between the 3 sessions 1 h after ingesting a small meal (500 kcal) identical for each trial	Cycling until exhaustion at 80%–85% Vo_2max	No effect of GC on performance measured on: cycling time during intense submaximal EX: 21.5 ± 2.9 (pla), 22 ± 2.5 (pred), 24.2 ± 2.8 min (pred-salb) Other effects of GC: ↑G at rest and during recovery but not during EX, no ≠ in insulin (pred, pred-salb vs pla)
17	Double-blind Crossover	16 ♂ professional cyclists	2 treatments for each subject: - Injection of ACTH (Synacthen: 1 mg) IM - Pla 45 min before the start of each session 4 experimental sessions (S): S1 (day 1) and S2 (day 2) were conducted on consecutive days during the 1st week S3 (day 3) and S4 (day 4) were conducted on consecutive days during the second week. ACTH or pla at S1 (day 1) or S3 (day 3) and day 2 and 4 were included to examine the influence of ACTH on recuperation	Steady-state cycling followed by a ramped test: 1 h cycling at submax level (60% maximal performance) and after 1 h, load was increased by 10 W/min until exhaustion	No effect of GC on performance measured on: submaximal performance (in watts) Other effects of GC: - performance beneficial: sequential effect from the first to the second day of 2 consecutive days and the increase was larger for ACTH than for pla: day 1 vs day 2 Pla: 311 vs 322 W = +3.5% ACTH: 300 vs 325 W = +8.3% (day effect: $P<.01$; drug effect: $P>.05$) - ↓feeling of fatigue: fatigue score ACTH <pla ($P<.001$) on both days - POMS: ↑ total vigor score: ACTH > pla on S2 or S4 - ↑blood G and free fatty acids levels (ACTH > pla)

14	Double-blind Randomized Crossover	10 recreationally trained ♂	2 treatments for each subject: - Pred: 60 mg per os at 7–8 AM for 7 d - 3-wk drug free - Pla for 7 d 2 experimental sessions per subject 4-wk intervals between each session 1 h after ingesting a small meal (500 kcal) identical for each trial	Trial to exhaustion during submax cycling at 70%–75% Vo_2max - at the end of each treatment (2 h after a final capsule ingestion: (pla-pred) - after the drug washout period	Effect of GC on performance measured on: time of cycling to exhaustion: ↑ +54% (pla: 46.1 ± 3.3 vs pred: 74.5 ± 9.5 min; *P*<.01) Other effects of GC: - ↑G at rest and during exercise and recovery - ↑ insulin at rest and during the first 30 min of exercise
15	Double-blind Randomized Crossover	8 recreationally trained ♂	2 treatments for each subject: - Pred: 60 mg per os at 7–8 AM for 7 d - 3-wk drug free - Pla for 7 d + 1 wk of strenuous training 2 h/d 2 experimental sessions per subject 3-wk intervals between each session	Trial to exhaustion during submax cycling at 70%–75% Vo_2max - before (pla1-pred1) - at the end of each ttt (3 h after a final capsule ingestion (pla2-pred2)	Effect of GC on performance measured on: time of cycling to exhaustion: ↑ +80%(pla1/pla2/pred1: 50.4 ± 6.2/64 ± 9.1/56.1 ± 9.1 min vs pred2: 107 ± 20.7 min; *P*<.05) Other effects of GC: - ↑ G basal and during EX (insulin no ≠)

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Table 1
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Study	Methods	Participants	Interventions	Outcomes	Results
16	Double-blind Randomized Crossover	9 recreationally trained ♂	2 treatments for each subject: - 4 mg dex per d - 4 mg pla for 5 d 2 experimental sessions per subject 4-wk intervals between each session	One-legged knee extensor exercise with 3 EX periods separated by more than 45 min of rest 1. Low intensity EX (LI): 10 min 2. Moderate intensity EX (MI) 5 min MI + 2 min rest + MI EX until exhaustion (MI2) 3. High-intensity EX (HI) 1 min, 40 s HI + 2 min rest + HI EX until exhaustion (HI2)	Effect of GC on performance measured on: MI2: time to exhaustion tended to be prolonged in dex vs pla 393 ± 50 vs 294 ± 41 s (P = .07) No effect of GC on performance during HI2: dex = pla time to exhaustion: 106 ± 10 vs 108 ± 9 s
26	Double-blind Randomized Crossover	9 recreationally trained ♂	2 treatments for each subject: - 20 mg pred per os (0.25 mg/kg BW) - Pla 2 h before EX 2 experimental sessions per subject 72-h intervals between each session Overnight fasted	Steady-state exercise (cycling) at 60% Vo_2max for 1 h	Effect of GC during exercise: → Higher fat oxidation and lower G oxidation during submax EX - ↑ Total EX energy expenditure (+2.3%) - ↓ Total G oxidation (−23.2%) - ↑ Fat oxidation: +42.9% No effect of G at rest: no change in energy metabolism in fasting humans

Abbreviations: ACTH, adrenocorticotropic hormone; BW, body weight; dex, dexamethasone; EX, exercise; G, glucose; GC, glucocorticoids; IM, intramuscular; pla, placebo; POMS, positive influence of ACTH-induced increased cortisol on mood; pred, prednisolone; RER, respiratory exchange ratio (Vco_2/Vo_2); salb, salbutamol.

such as during international cycling competitions (eg, the 3 weeks of consecutive competitions of the Tour de France or the 3700 km covered in 22 stages over the 3-week period of Vuelta a España). No study has as yet examined whether it is actually possible to maintain a higher work intensity during several weeks of competition, however, when GC is ingested daily to favor recovery. Regarding article 25 of the UNESCO International Convention on the Fight against Doping,[18] which reads ''When promoting anti-doping research…States parties shall ensure that such research will…b) Avoid the administration to athletes of prohibited substances and methods; c) Be undertaken only with adequate precautions in place to prevent the results of anti-doping research being misused and applied for doping,'' there is no authorization to administer GCs (and even less at high doses) to elite athletes during real competitive conditions. This attractive hypothesis will never be able to be tested.

Finally, Arlettaz and colleagues[12] reported that acute GC intake (20 mg prednisolone) does not improve performance during endurance exercise. This dose of GC is considered as a ''relatively modest therapeutic dose.'' Actually, this dose of prednisolone is comparable with 80 mg hydrocortisone (a pharmaceutical reference for cortisol), but in conditions of maximal stress-induced endogenous cortisol production (such as seen in sepsis), approximately 150 to 300 mg hydrocortisone equivalents daily should be given to the subjects corresponding to 6 mg dexamethasone or 30 to 70 mg prednisolone.[19] This is much less than the acute dose used by Arlettaz and colleagues.[12] This hypothesis of too weak a dose to increase performance is corroborated by the fact that increased prednisolone dose (60 mg) for a longer duration significantly increased performance.[14]

The whole of these data suggest that to search for an ergogenic effect of GCs, high doses of GCs or longer periods should be used. This has been tested in the studies described next.

Positive studies

Contrary to acute intake, after short-term prednisolone administration (60 mg for 7 days) Arlettaz and colleagues[14] found a significant improvement of performance (+54% compared with placebo) measured by time to exhaustion at 70% to 75% V_{O_2}max in healthy, recreationally trained men. To determine if the effects of GC treatment could be extrapolated to elite athletes, Collomp and colleagues[15] investigated in a further study the influence of short-term prednisolone administration (60 mg for 7 days) combined with a standardized training (2 hours per day) on performance measured by time to exhaustion at 70% to 75% V_{O_2}max. Compared with the placebo condition, strenuous training associated with the GC treatment resulted in a marked improvement in endurance performance (average increase of about 80% compared with an average increase of 54% in their previous study without training).[14] Interestingly, the greatest increase in time to exhaustion with GCs was obtained in the subject performing the best trial with placebo, suggesting that elite male athletes may be more sensitive to the ergogenic effect of GCs during endurance exercise. Even if it seems necessary to verify whether elite athletes are more sensitive to the ergogenic effects of GCs than recreationally trained subjects, these results bring scientific evidence of an increased performance effect of GCs.

Using another exercise protocol (one-legged knee extension) in recreationally trained men, Nordsborg and colleagues[16] showed that time to exhaustion tended to be prolonged after dexamethasone treatment (393 $\pm$ 50 vs 294 $\pm$ 41 seconds; $P = .07$; dexamethasone vs placebo, respectively) during one-legged knee extension at moderate intensity exercise lasting 3 to 8 minutes. These differences were explained through the increased capacity of muscle to regulate (maintain) K+

Table 2
GC administration and exercise performance: results of the studies in animals

Study	Participants	Interventions	Outcomes	Results
22	Female Sprague-Dawley rats	Single sc injection of CA (100 mg/kg body weight) 21 h before treadmill running or NaCl (sal) Rats acquired treadmill familiarity (3 wk)	Treadmill running (30.8 m/min) (7% incline) until exhaustion To determine the effects of increasing substrate availability (glycogen, plasma free fatty acids) by GC on energy metabolism during EX to exhaustion	Effects of GC on performance ↑ EX time to exhaustion: 114 ± 5 vs 95 ± 6 min (approximately +20 min) (CA vs sal, $P<.05$) Other effects of GC - At the start of EX: ↑ glycogen in liver (+40%), ↑ glycogen in muscles: slow-twitch soleus: +61%, fast twitch white vastus: +38%, fast twitch red vastus: +85% and heart: +32% ↑ plasma free fatty acids: +40% with no ≠ during EX - At the time of exhaustion: no ≠ in glycogen concentration in liver and muscles - V_{O_2} and RER: no ≠ in RER but ↓in running economy (↑V_{O_2} for a given work rate)

23	Female Sprague-Dawley rats	14 consecutive daily sc injections of CA 100 mg/kg or sal Dosage selected because it is effective in producing skeletal wasting	- Vo_2max and maximal EX test run times - prolonged treadmill running test (28.7 m/s up a 5.5% incline) until exhaustion	Effects of GC on performance CA enhanced performance despite muscle atrophy (predominantly in white muscle: no ≠ in ventricular or soleus muscle weights but plantaris muscle weights were 27% less in the CA-treated group) 1. Maximal EX test: - ↑Vo_2 peak (CA: 95.6 ± 3.2 vs 79.5 ± 1.8 mL/kg/min) - ↑ total run times: 962 ± 61 vs 825 ± 33 s (CA vs sal, *P*<.05) 2. Prolonged endurance test: ↑ total run times: 158 ± 12 vs 116 ± 11 min (CA vs sal, *P*<.05) Unchanged oxygen uptake by homogenates of all fiber types

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Table 2
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Study	Participants	Interventions	Outcomes	Results
25	Male Wistar rats	Daily intraperitoneal injection of dex (1 mg/kg) or sal for 12 d	Investigation of the effects of contraction (electric stimulation) on G uptake, insulin signaling, and glycogen synthesis in isolated skeletal muscles from dex-treated rats	- Insulin resistance but no impairment of G uptake during contraction in soleus or epitrochlearis muscle - ↑ glycogen content (P<.02) in rested muscles either incubated with or without insulin for epitrochlaeris (150 vs 200 mmol/kg dry weigh) and soleus (100 vs 150 mmol/kg dry weigh) (dex vs saline) - After contraction, insulin-stimulated glycogen synthesis was improved in soleus from dex-treated rats (20 vs 24 mmol/kg dry weigh/h)

20	Male Lewis rats	Experiment 1: ad libitum fed rats 5 groups: Sham-ADX (Sham) or ADX implanted with sc pellet containing 0 (ADX-0), 12.5 (ADX-12.5), 50 (ADX-50), or 100 mg (ADX-100) corticosterone (CORT) that continuously deliver a constant dosage of CORT for 10 d Experiment 2: food-restricted rats (access to food 1.5 h/d): effects of chronic increase in corticosterone levels on wheel running activity Same 5 groups than experiment 1 Experiment 3: effects of acute increase in corticosterone levels in ad libitum and food-restricted rats (access to food 1.5 h/d) on wheel running activity Injection of corticosterone or vehicle sc once daily at 11 h on D2–D4	Permanent access to a running wheel: determination of wheel activity (number of kilometers run per day) Experiments 1 and 2: effects of chronic administration of increasing doses of CORT (implanted capsules) on wheel running activity Experiment 3: effects of acute administration of CORT (injection of CORT) on wheel running activity	Effects of GC on performance (wheel activity) Experiment 1: no effect of ≠ in CORT levels in ad libitum fed rats Experiments 2 and 3: in food restricted rats - Experiment 2: ↑ wheel running activity in a dose dependent-fashion ADX100>ADX50> ADX12.5>ADX0 - Experiment 3: acute ↑ wheel running activity after acute CORT injection ADX100>ADX50> ADX12.5>ADX0 - Experiment 3: acute ↑ wheel running activity after acute CORT injection

Abbreviations: ADX, adrenalectomized; CA, cortisol acetate; dex, dexamethasone; EX, exercise; GC, glucocorticoids; RER, respiratory exchange ratio (V_{CO_2}/V_{O_2}); sal, saline; sc, subcutaneous.

homeostasis and muscle fatigue development because short-term dexamethasone increased the Na+, K+ pump $\alpha 1$, $\alpha 2$, $\beta 1$, and $\beta 2$ subunits protein expression in human skeletal muscle (with lower thigh K+ release during low and moderate one-legged knee extension). By contrast, dexamethasone did not affect performance of repeated high-intensity exercises lasting 1 to 3 minutes.

The results of the study of Soetens and colleagues[17] should also be considered. Although the authors concluded that their results demonstrate that there is no influence of an ACTH injection on maximal performance as measured with a standardized bicycle ergometer design, however, other data obtained from their experiment demonstrate positive effects of ACTH during submaximal exercise. Soetens and colleagues[17] injected a high dose of ACTH depot (1 mg). The use of a depot preparation gave them the opportunity to study recuperation on the second day because plasma cortisol concentration doubled for 2 consecutive days (day 1 and day 2 of the protocol) (see **Table 1**).

They reported four points: (1) Decreased feelings of fatigue with ACTH during submaximal performance (1 hour cycling at 60% maximal performance). The decrease is systematic over the whole interval of submaximal performance. As stated by the authors: ''With ACTH, subjects seem to postpone the increase in feelings of fatigue as long as the load is low to moderate. It means that ACTH, for that matter, could help competitors in long races to bridge over the long and boring first hours of a competition more pleasantly or less wearily.'' That delay of fatigue in submaximal conditions is not translated, however, into increase of maximal performance during the ramped test that followed the steady-state exercise. (2) Positive influence of ACTH-induced increased cortisol on mood; on the second day of the protocol subjects indicate significantly more vigor after the test with ACTH than after placebo. (3) Metabolic effects; there was a significant supplementary increase of glucose after exercise, and the mobilization of extra FFAs was also notable after the test with ACTH (increased compared with placebo). (4) Recuperation on the second day of the protocol. After the test with ACTH, feelings of fatigue are suppressed during the submaximal exercise test realized on day 2 but, compared with the placebo group, there is no increase of maximal performance during the ramped test that followed the steady state exercise (day 2). The authors concluded that ''despite all these impressive physiologic changes'' under influence of ACTH (1 mg Synacthen depot), there was no performance enhancement during at least a ramped test.

These results also leave open the more important question as to what is the ergogenic significance of these reduced feelings of fatigue and increased vigor during submaximal performance in real conditions of competition, during the complex of events necessary to elicit a victory during a race. The absence of increased performance from a statistical point of view does not exclude the fact that this nonstatistical gain in performance (in terms of distance ran) may translate into a gain during a final sprint, and could make the difference between the winner and second place. The other question arising from these results is to what extent laboratory tests can be assimilated to real competition and what could be the effect of reduced feelings of fatigue and more vigor during long races lasting more than 3 to 4 hours (instead of the 1 hour protocol of Soetens and colleagues[17]) on the final sprint.

Data obtained in animal experiments clarify the mechanisms of the ergogenic effects of GCs adding insights into the central and peripheral (metabolic) effects of GCs.

Animal Data

Experiments conducted in rats also support the ergogenic effect of GCs with demonstrated positive effects of GCs on performance. In food-restricted rats with ad libitum

access to a running wheel, wheel activity (number of kilometers run in 24 hours) was significantly increased (times two) when they had been given a subcutaneous injection of corticosterone (the rat natural GC hormone).[20] In addition to this stimulatory effect of acute corticosterone, the administration of increasing doses of corticosterone (by implanted capsules that continuously deliver a constant dosage of corticosterone for 10 days) to adrenalectomized rats increased wheel running activity in a dose-dependent fashion. The range of corticosterone achieved in the different experiments represented reference values from low to high (stress-induced) HPA axis activity. These observations show that GC can enhance physical activity in rats after both acute (injected corticosterone) and chronic (subcutaneous implants continuously delivering corticosterone) administration.[20] These effects are probably caused by central effects of GCs with the stimulation of dopamine production in the nucleus accumbens and, possibly, the activation of other parts of the brain involved in motor activity (M. Duclos, unpublished results, 2008).[21]

With regard to the peripheral (metabolic) effects of GC, Gorostiaga and colleagues[22] have reported in rats that a single injection of cortisol acetate 21 hours before treadmill running induced an increase in glycogen content in liver and muscles (slow-twitch, fast-twitch, white and red fibers) and increased plasma FFA. In these conditions where both carbohydrate (glycogen) and fatty acid availability were increased, endurance improved significantly with increased time during exercise (treadmill running) to exhaustion (+20 minutes compared with the placebo group).

After 14 consecutive daily injections of cortisol acetate[23] in rats at a dose selected to produce skeletal wasting, and despite muscle atrophy, cortisol acetate–treated groups showed enhanced performance with increased total run times during maximal exercise ($V_{O_2}max$) (962 $\pm$ 61 vs 825 $\pm$ 33 seconds, cortisol acetate vs placebo) and increased running time during endurance test (158 $\pm$ 12 vs 116 $\pm$ 11 minutes, cortisol acetate vs placebo).

With regard to the known metabolic effects of GCs, some of these results can seem intriguing. Indeed, GCs in excess induce insulin resistance. Skeletal muscles dispose of the major part of glucose during insulin stimulation and GCs impair metabolic regulation, at least in part, by reducing insulin-stimulated glucose uptake in skeletal muscles. Muscle contraction, however, like insulin, stimulates glucose uptake but by different mechanisms than insulin and contraction stimulates glucose uptake by an insulin-independent mechanism.[24] This has been well demonstrated by Ruzzin and Jensen[25] who investigated in muscles from dexamethasone-treated rats whether contraction (1) normally stimulates glucose uptake, (2) activates glycogen synthase, and (3) enhances insulin action, and whether insulin's ability to stimulate glycogen synthesis is improved after contraction. They demonstrated that glucose uptake is stimulated normally during contraction in insulin-resistant muscles from dexamethasone-treated rats. Moreover, following contraction, glycogen synthase activity increased to a similar extent in muscles from control and dexamethasone-treated rats. Finally, dexamethasone stimulated the resynthesis of muscle glycogen after exercise (dexamethasone more than placebo), whereas less glycogen was stored at rest than in placebo animals as a result of dexamethasone-induced insulin resistance.[25] This enhanced glycogen production following exercise promotes metabolic recuperation and is a crucial factor for optimal, high-intensity endurance performance explaining the previous results of Gorostiaga and colleagues[22] and Capaccio and colleagues.[23] It should be noted that similar metabolic effects (increased plasma glucose and FFA levels) have been reported in most of the previously cited studies in humans dealing with GC administration after both acute and short-term intake (see **Table 1**).[8,9,12–15,17,26]

Altogether, these studies clarify the effects of GC based on scientific evidence. They clearly demonstrate both in animals and humans that GCs have ergogenic effects (performance-enhancing effects). Many more questions have been raised, however, which demand answers:

Can GCs indirectly affect performance by helping athletes to recover from exhaustive competitions?
It is actually possible to maintain higher work intensity during several weeks of training when GC is ingested during the training sessions?
Are the results obtained in male athletes gender dependent?
Are the results obtained in recreationally trained athletes applicable to elite athletes?
Are highly trained athletes more sensitive to the ergogenic effects of GCs during endurance exercise than recreationally trained subjects?

GC DOPING AND THE DEMONSTRATED RISKS TO HEALTH

Long-term GC use has been shown incontrovertibly to lead to complications, notably on bone tissue (osteoporosis); metabolism (insulin resistance); and the cardiovascular system (hypertension and atherosclerosis).[7] Cases of GC dependence have been reported.[6] In addition to these well-characterized effects, other complications are beginning to emerge.

Short and colleagues[27] showed that, after a 6-day course of prednisone (0.5 mg/kg/d) in healthy, young adults, blood flow in the leg had dropped by 25%. This is consistent with the results of recent experiments in pigs that showed that a single pharmacologic dose of prednisone significantly reduced blood flow in the muscles, the skin, and hip bone tissue. This effect was of rapid onset, being detectable within 1 hour of administration and persisting for at least 24 hours, which suggests that it involves a nongenomic mechanism; it is probably mediated at endothelial cells by GC-induced inhibition of nitric oxide (NO)–dependent endothelial relaxation because in vitro experiments have shown that umbilical cord epithelial cells produce less NO when exposed to dexamethasone because of increased levels of free radicals. Reduced NO production inhibits endothelial vessel relaxation and leads to diminished blood flow. Iuchi and colleagues[28] defined the role of free radicals in this phenomenon and established the link with GC. When blood flow in the arm of a healthy subject was artificially inhibited using a tourniquet (a cuff inflated to 250 mm Hg for 5 minutes), increased blood flow was observed in the forearm 60 and 90 seconds after removal of the tourniquet as a result of NO-dependent vasodilatation of the vascular endothelium. When the same measurement was performed in subjects who had been prescribed GCs to treat autoimmune disease before and after the beginning of the course of treatment, a reduction of 43% was induced by the drug (on average, 28 days after the beginning of the course of treatment [range, 12–50 days]). This effect is dependent on dosage and the duration of exposure to the GCs. In parallel, the same researchers showed that GCs induced a dose-dependent increase in free radical production in cultured endothelial cells. Free radicals cut down the availability of NO by inducing the production of superoxide, which interacts with NO to generate peroxynitrites, which leads to an increase in NO consumption. Reduced NO availability can impair endothelial function leading to hypertension and atherosclerosis, both of which are major cardiovascular complications associated with excessive GC use.

GCs induce free radicals by interfering with mitochondrial electron transfer systems, pointing to impaired mitochondrial function. In previous experiments in rats, however,

Duclos and colleagues[29] have shown that excessive endogenous corticosterone (the equivalent of cortisol in rats) production induced by repetitive stress led to a reduction in mitochondrial density in muscle tissue. The mitochondrion is the main seat of energy production in cells and worries about potential adverse effects on mitochondrial metabolism in muscle tissue are justified if supraphysiologic doses of synthetic GC are being taken by athletes to enhance their performance.

Another series of experiments warrants attention. A number of studies have shown that increasing blood cortisol (by the infusion of cortisol or ACTH) to stress-related levels (880 and 1100 nmol/L) inhibited hyperglycemic hormone responses (adrenaline, noradrenalin, glucagon) and lowered glucose production in the liver in response to subsequent pharmacologically induced hypoglycemia.[30,31] In the course of prolonged exercise (lasting hours), blood glucose levels significantly fall, but not usually below 0.6 to 0.7 g/L (3.3–3.9 nmol/L) in healthy subjects, although a few cases of full-blown hypoglycemia have been reported in marathon and long-distance runners. In sports involving prolonged exertion or repetition over several days in a row (bicycle races, desert marathons, long-distance races), problems of blood glucose counterregulation could explain certain phenomena in subjects who had taken a pharmacologic dose of a GC the day before, such as sudden exhaustion forcing the athlete to withdraw from the event or to considerably drop in the race positioning.

Above and beyond chronic effects, a major (possibly life-threatening) complication can arise on the withdrawal of GCs: acute adrenal insufficiency. This risk is real and is not anecdotal. When top-level cyclists from the French Cycling Federation were surveyed, a nonnegligible number of cases of crude adrenal insufficiency (undetectable cortisol coupled with a negative ACTH test result) were identified.[32] Of 659 elite cyclists monitored during the 2001 and 2002 sporting seasons, 34 (5.2%) had low blood cortisol levels (at least two standard deviations below the mean of the test kit used). More seriously, of these 34 cyclists, 8 of the 15 who agreed to undergo an ACTH test had crude adrenal insufficiency (low cortisol levels and a negative ACTH test result).

The effects of long-term corticosteroid use on endogenous cortisol production are well characterized in the literature; this inhibition has been documented even at low doses. Henzen and colleagues[33] detected adrenal insufficiency in 45% of subjects who had been given a short (<1 month) course of a systemic GC at a dosage of greater than 25 mg of prednisone in 24 hours. Broide and colleagues[34] and Kannisto and colleagues[35] found respective incidences of impaired adrenal function of 25% and 35% in children with asthma being treated with inhaled GCs. The duration of HPA inhibition ranges from 2 to 4 weeks at doses of greater than 25 mg of prednisone per 24 hours (low doses), but can be sustained for a matter of months.

Limited data are available on the effect of biologic adrenal insufficiency on athletic performance. The most current signs of adrenal insufficiency in subjects taking inhaled corticosteroids are lethargy and nausea.[36] Other subjects (mainly children but cases in adults have been reported) presented with acute hypoglycemia and decreased levels of consciousness, coma, or coma and convulsions.[36,37] It is plausible that atypical forms of adrenal crisis (hypoglycemia, feeling of faintness) could explain some apparently unexplained decreased performances observed in some athletes. Whereas most adults presented with insidious onset of symptoms, the potential severity of the decompensation of subclinical adrenal insufficiency induced by corticosteroids is reported in sedentary subjects[36–38] and requires evaluation in a population exposed to other stresses than sedentary subjects. Indeed, competitive or intensive exercising may require intense and prolonged physical effort, sometimes in extreme conditions that can change suddenly (heat, cold, hypoxia). Moreover some athletes (eg, cyclists,

rugby players, soccer players) are at risk of severe injuries that may require surgery and have a high risk of infections, affecting the upper respiratory tract in particular. Although biologic insufficiency did not seem to be always associated with clinical symptoms, in view of the severity of cases of adrenal crisis described in subjects taking corticosteroids,[36,37] in the event of some form of superimposed stress (eg, infection, physical injury entailing surgery), there is a real risk of life-threatening acute adrenal insufficiency in athletes abusing GCs.

SUMMARY

There is scientific evidence that GCs mediate ergogenic effects in animals and humans. It is difficult to understand why GCs are the type of product most commonly detected in doping tests if they had no beneficial effect on performance (or recuperation). Moreover, the health risks of using GCs are well characterized. GCs are doping agents and should remain on WADA's list of banned products. Moreover, it is necessary to prohibit systemic use of this class of drugs at all times (in- and out-of-competition) and not just with in-competition controls as in the current WADA legislation.

REFERENCES

1. Duclos M. Hypothalamo-pituitary-adrenal axis adaptation to repeated and prolonged exercise-induced cortisol secretion in endurance training: physiology is the first target. In: Selkirk TB, editor. Focus on exercise and health research. New York: NovaScience Publishers; 2005. p. 131–61.
2. Duclos M, Guinot M, Le BY. Cortisol and GH: odd and controversial ideas. Appl Physiol Nutr Metab 2007;32(5):895–903.
3. Sapolsky RM, Romero M, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev 2000;21:55–89.
4. Duclos M, Gouarne C, Bonnemaison D. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. J Appl Physiol 2003;94:869–75.
5. Piazza PV, Rouge-Pont F, Deroche V, et al. Glucocorticoids have state-dependent stimulant effects on the mesencephalic dopaminergic transmission. Proc Natl Acad Sci U S A 1996;93(16):8716–20.
6. Hochberg Z, Pacak K, Chrousos GP. Endocrine withdrawal syndromes. Endocr Rev 2003;24(4):523–38.
7. Buttgereit F, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an old spear. Lancet 2005;365(9461):801–3.
8. Marquet P, Lac G, Chassain AP, et al. Dexamethasone in resting and exercising men. I. Effects on bioenergetics, minerals, and related hormones. J Appl Physiol 1999;87(1):175–82.
9. Petrides J, Gold PW, Mueller GP, et al. Marked differences in functioning of the hypothalamic-pituitary-adrenal axis between groups of men. J Appl Physiol 1997;82(6):1979–88.
10. Baume N, Steel G, Edwards T, et al. No variation of physical performance and perceived exertion after adrenal gland stimulation by synthetic ACTH (Synacthen) in cyclists. Eur J Appl Physiol 2008;104(4):589–600.
11. Kuipers H, Van't Hullenaar GA, Pluim BM, et al. Four weeks' corticosteroid inhalation does not augment maximal power output in endurance athletes. Br J Sports Med 2008;42(11):568–71.
12. Arlettaz A, Collomp K, Portier H, et al. Effects of acute prednisolone administration on exercise endurance and metabolism. Br J Sports Med 2008;42(4):250–4.

13. Arlettaz A, Collomp K, Portier H, et al. Effects of acute prednisolone intake during intense submaximal exercise. Int J Sports Med 2006;27(9):673–9.
14. Arlettaz A, Portier H, Lecoq AM, et al. Effects of short-term prednisolone intake during submaximal exercise. Med Sci Sports Exerc 2007;39(9):1672–8.
15. Collomp K, Arlettaz A, Portier H, et al. Short-term glucocorticoid intake combined with intense training on performance and hormonal responses. Br J Sports Med 2008;42(12):983–8.
16. Nordsborg N, Ovesen J, Thomassen M, et al. Effect of dexamethasone on skeletal muscle Na+, K+ pump subunit specific expression and K+ homeostasis during exercise in humans. J Physiol 2008;586(5):1447–59.
17. Soetens E, De MK, Hueting JE. No influence of ACTH on maximal performance. Psychopharmacology 1995;118(3):260–6.
18. UNESCO. United Nations Educational, Scientific and Cultural Organization; International convention on the fight against doping, 2005. Available at: http://portal.unesco.org/en/ev.phpURL_ID=31037&URL_DO=DO_TOPIC&URL_SECTION=201.html. Accessed October 19, 2005.
19. Brotman DJ, Girod JP, Garcia MJ, et al. Effects of short-term glucocorticoids on cardiovascular biomarkers. J Clin Endocrinol Metab 2005;90(6):3202–8.
20. Duclos M, Gatti C, Bessiere B, et al. Tonic and phasic effects of corticosterone on food restriction-induced hyperactivity in rats. Psychoneuroendocrinology 2008;34(3):436–45.
21. Roug-Pont F, Deroche V, Le Moal M, et al. Individual differences in stress-induced dopamine release in the nucleus accumbens are influenced by corticosterone. Eur J Neurosci 1998;10:3903–7.
22. Gorostiaga EM, Czerwinski SM, Hickson RC. Acute glucocorticoid effects on glycogen utilization, O2 uptake, and endurance. J Appl Physiol 1988;64(3):1098–106.
23. Capaccio JA, Galassi TM, Hickson RC. Unaltered aerobic power and endurance following glucocorticoid-induced muscle atrophy. Med Sci Sports Exerc 1985;17(3):380–4.
24. Lund S, Holman GD, Schmitz O, et al. Contraction stimulates translocation of glucose transporter GLUT4 in skeletal muscle through a mechanism distinct from that of insulin. Proc Natl Acad Sci U S A 1995;92(13):5817–21.
25. Ruzzin J, Jensen J. Contraction activates glucose uptake and glycogen synthase normally in muscles from dexamethasone-treated rats. Am J Physiol Endocrinol Metab 2005;289(2):E241–50.
26. Arlettaz A, Portier H, Lecoq AM, et al. Effects of acute prednisolone intake on substrate utilization during submaximal exercise. Int J Sports Med 2008;29(1):21–6.
27. Short KR, Nygren J, Bigelow ML, et al. Effect of short-term prednisone use on blood flow, muscle protein metabolism, and function. J Clin Endocrinol Metab 2004;89(12):6198–207.
28. Iuchi T, Akaike M, Mitsui T, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circ Res 2003;92(1):81–7.
29. Duclos M, Gouarne C, Martin C, et al. Effects of corticosterone on muscle mitochondria identifying different sensitivity to glucocorticoids in Lewis and Fischer rats. Am J Physiol 2004;286:E159–67.
30. Davis SN, Shavers C, Costa F, et al. Role of cortisol in the pathogenesis of deficient counterregulation after antecedent hypoglycemia in normal humans. J Clin Invest 1996;98(3):680–91.

31. McGregor VP, Banarer S, Cryer PE. Elevated endogenous cortisol reduces autonomic neuroendocrine and symptom responses to subsequent hypoglycemia. Am J Physiol Endocrinol Metab 2002;282(4):E770–7.
32. Guinot M, Duclos M, Idres N, et al. Value of basal serum cortisol to detect corticosteroid-induced adrenal insufficiency in elite cyclists. Eur J Appl Physiol 2007; 99(3):205–16.
33. Henzen C, Suter A, Lerch E, et al. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. Lancet 2000;355(9203): 542–5.
34. Broide J, Soferman R, Kivity S, et al. Low-dose adrenocorticotropin test reveals impaired adrenal function in patients taking inhaled corticosteroids. J Clin Endocrinol Metab 1995;80(4):1243–6.
35. Kannisto S, Korpi M, Arikoski P, et al. Biochemical marker of bone metabolism in relation to adrenocortical and growth suppression during the initiation phase of inhaled steroid therapy. Pediatr Res 2002;52:258–62.
36. Todd GR, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis Child 2002;87(6): 457–61.
37. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003;348(8):727–34.
38. Oelkers W. Adrenal insufficiency. N Engl J Med 1996;335(16):1206–12.