Effects of short-term dexamethasone administration on corticospinal excitability

Effects of Short-Term Dexamethasone Administration on Corticospinal Excitability

Baudry, Stéphane; Lanfranco, Fabio; Merletti, Roberto; Duchateau, Jacques; Minetto, Marco A

ABSTRACT

Purpose: The short-term administration of glucocorticoids increases maximal voluntary force in healthy humans, but the underlying mechanisms remain poorly understood. The present study investigated the glucocorticoid effects on spinal and corticospinal pathways and on electromechanical properties of the tibialis anterior muscle in response to nerve stimulation.

Methods: Twelve healthy men participated in a single-blind randomized study to receive either dexamethasone (8 $mg \cdot d^{-1}$, n = 8 subjects) or placebo (n = 4 subjects) for 7 d. Group Ia afferent and corticospinal pathways were assessed, respectively, by recording the amplitude of the Hoffmann (H) reflex and motor-evoked potential (MEP) by transcranial magnetic stimulation. The ankle dorsiflexor torque and EMG activity during a maximal voluntary contraction (MVC) and muscle twitch evoked by electrical stimulation were also assessed before and after the intervention.

Results: The MVC torque (+14%) and the associated tibialis anterior EMG (+16%) increased after glucocorticoid treatment ($P < 0.05$), whereas muscle twitch parameters did not change ($P > 0.05$). The H-reflex amplitude did not change ($P = 0.58$), but the MEP threshold was significantly ($P = 0.008$) reduced after treatment. Moreover, the slope of the MEP input–output relation and the silent period/MEP ratio increased ($P = 0.049$) and decreased ($P = 0.029$), respectively, after treatment. The amount of change in MEP amplitude and MVC torque were positively associated ($r^2 = 0.59$) for the dexamethasone group.

Conclusion: This is the first study indicating that short-term glucocorticoid administration in healthy subjects increased corticospinal excitability that contributed to enhance MVC torque.

Glucocorticoids are widely used for replacement therapy in patients with Addison's disease, for treatment of immune, neurological, oncological diseases, and misused by athletes to improve the physical performance (4). In most of these uses, individuals receive more glucocorticoids than the normal endogenous production, raising concerns about potential adverse effects. Until now, the glucocorticoid actions and side effects on neural circuits and synaptic mechanisms involved in motor control have been mainly studied in animal models. In these studies, glucocorticoids have been shown to increase the excitability of the spinal motor neurons (8,21). Moreover, glucocorticoid treatment enhanced the serotonergic neuromodulatory inputs to spinal motor neurons (6,7) and improved the monosynaptic transmission between Ia excitatory muscle afferents and spinal motor neurons (9–11).

In humans, maximal voluntary force has been documented to increase after short-term glucocorticoid administration (16,26), despite a glucocorticoid-induced decrease in muscle protein turnover (16). In this context, the increase in torque during maximal voluntary contraction (MVC) should mainly rely on changes in some neural aspects of the force production involving spinal and/or supraspinal mechanisms. In agreement, a recent study using transcranial magnetic stimulation (TMS) has revealed that motor cortical excitability could be increased immediately after cortisol injection (15). Nonetheless, the effect of single cortisol injection can differ from chronic intake of glucocorticoids, and the influence of such change has not been investigated in relation to functional aspects. Moreover, glucocorticoid-related increases in motor neuron excitability and monosynaptic transmission between muscle spindle afferents and motor neurons have not been investigated so far in humans and could also contribute to influence the maximal force output. For example, a change in the synaptic input from Ia afferents could alter the firing rate of motor neurons voluntarily activated, which should influence maximal voluntary torque (13).

Therefore, the purpose of this study was to investigate the effects of a short-term glucocorticoid administration on the excitability of spinal and corticospinal pathways and on the electromechanical properties of the tibialis anterior (TA) muscle in healthy young subjects. The respective changes in group Ia afferent and corticospinal pathways in response to short-term glucocorticoid administration was

investigated by the Hoffmann (H) reflex induced by electrical nerve stimulation and motor-evoked potential (MEP) in response to TMS (2,12,19,22,25). We hypothesized that glucocorticoid administration would increase maximal voluntary torque of the ankle dorsiflexors due to glucocorticoid actions on corticospinal and/or spinal pathways.

MATERIALS AND METHODS

Subjects and Study Design

Twelve healthy men from age 20 to 38 yr participated to a single-blind (pretest/posttest comparison design) randomized study. Before participating in the study, the subjects received a detailed explanation of the protocol and gave written informed consent. The study conformed to the guidelines of the Declaration of Helsinki and was approved by the local ethics committee. Subjects were randomized to receive dexamethasone (8 mg once daily per os, n = 8 subjects) or placebo (n = 4 subjects) for 1 wk. Electrophysiological tests and torque measurements were performed before and after the intervention (within 24 h before starting the administration and within 24 h after stopping the administration) in both groups of subjects. For each subject, the two experimental sessions (pre- and postintervention) were performed at the same time of the day. Saliva sampling was performed before and after treatment only for the subjects assigned to dexamethasone to assess the compliance to the treatment.

Laboratory Assays

Fasting 0800-h saliva samples were obtained the day of each experiment (before and after the intervention) in the treated subjects. Salivary cortisol levels were measured by an electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Basel, Switzerland). The analytical sensitivity of the method was 0.5 $nmol \cdot L^{-1}$ and mean inter- and intra-assay coefficients of variation were less than 10% and 6%, respectively.

Torque Recordings

During the experimental sessions, the subject sat on a chair in a slightly reclined position with the foot of the nondominant leg tightly attached to a footplate that was connected to a force transducer (model TC 2000-500; Kulite, Basingstoke, UK). The position of the subject was adjusted to obtain ankle and knee angles of 90° and 50°–60° (full extension = 0°), respectively. The signal from the strain gauges was amplified by a custom-made amplifier and low-pass filtered at 300 Hz.

EMG Recordings

The EMG signals were recorded from TA and soleus (SOL) muscles of the nondominant leg with surface electrodes filled with gel (silver–silver chloride electrodes, 8-mm diameter, 20-mm interelectrode distance) placed at one-third of the distance between the fibular head and the lateral malleolus, 1 cm lateral to the tibia for TA, and 3 cm below the muscle–tendon junction of the medial gastrocnemius and in line with the Achilles tendon for SOL. The reference electrodes were placed on the skin over the tibia. Before electrode placement, the skin was shaved and cleaned with a solution of alcohol, ether, and acetone to reduce the impedance of the skin–electrode interface. The EMG signals were amplified (1000×), band-pass filtered (10–1000 Hz), sampled at 2kHz, A/D converted (Power 1401, 16-bit resolution; Cambridge Electronic Design, UK), and stored on a computer.

Electrical Stimulation

The fibular nerve of the nondominant leg was stimulated by a constant current stimulator (DS7A; Digitimer Ltd., Welwyn Garden City, UK). Monophasic rectangular pulses of 1-ms duration were delivered through two electrodes (silver disks, 8-mm diameter), with the cathode and anode placed over the nerve close to the fibular head and on the opposite side of the leg, respectively.

TMS

MEPs in TA were elicited by TMS applied over the contralateral motor cortex via a double-cone coil (Magstim 200 stimulator; Magstim, Dyfed, UK). The optimal site and orientation of the coil were determined as those eliciting a response in the TA with the largest amplitude at the lowest intensity. The coil was held in position by using a custom-made fixing system and the position of the coil was checked throughout the experiment.

Experimental Protocol

MVC

After adjusting the subject position and placing electrodes, subjects performed 5-s duration isometric MVC of the dorsiflexor muscles, with subjects resting for 90–120 s between trials to minimize fatigue. If the peak forces were within 5% of each other, the greatest value was taken as the maximum and used as a reference for subsequent submaximal contractions. Otherwise, additional trials were performed until the 5% criterion was achieved. Thereafter, two MVC of the plantarflexor muscles (5-s duration) were performed, and the highest EMG value was taken as reference to normalize the EMG activity of the SOL.

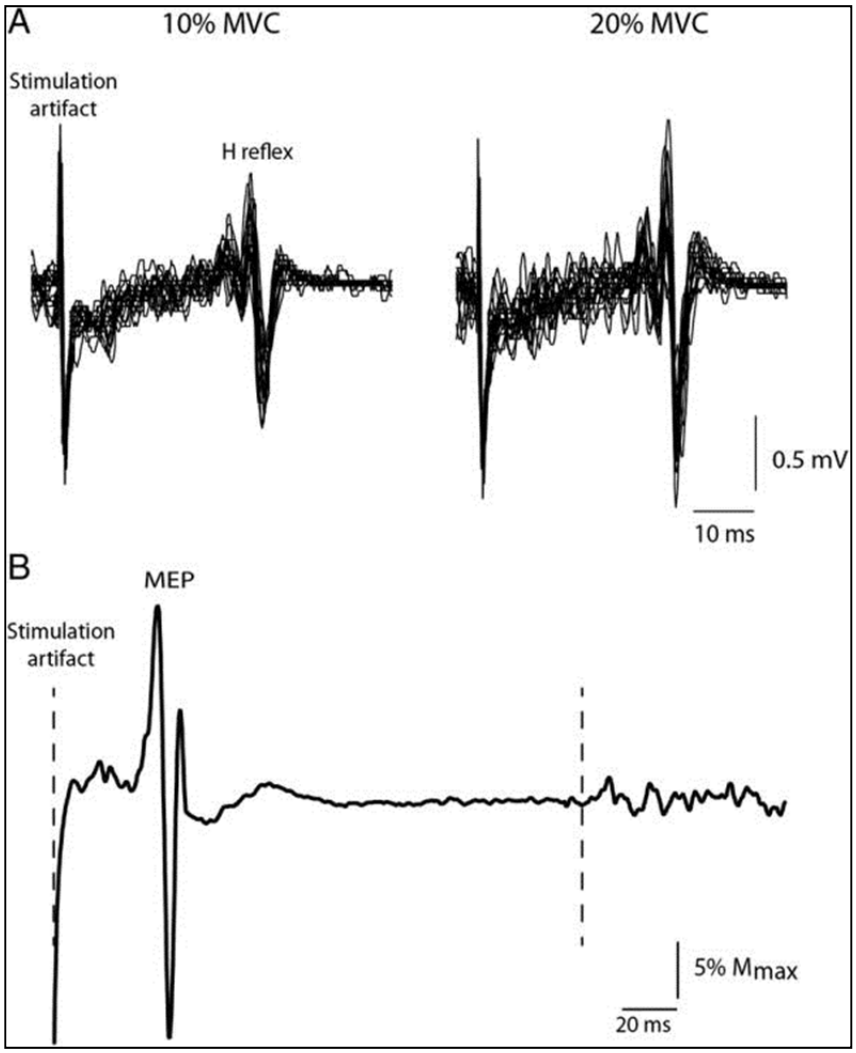
Muscle contractile properties

After 10 min of rest to avoid any effect due to previous muscle activity (1), three 3-pulse trains (pulse of 1-ms duration, 10 ms apart) were delivered at rest with a supramaximal intensity (20% above the intensity required to obtain a maximal M wave [compound muscle action potential; M_{max}]; see next section), with a 3-s interval between trains.

H reflexes and M_{max}

The maximal amplitudes of the H reflex (H_{max}) and M wave (M_{max}) were obtained, during voluntary contractions of the dorsiflexor muscles at 10% MVC, by increasing the intensity of the stimulation applied over the fibular nerve until the amplitude of the M wave reached a plateau (25). For the rest of the experiment, thecurrent intensity evoking H reflexes was set to obtain H-reflex amplitude of 80% of the H_{max} during 10% MVC contractions. Then, the subject performed isometric contractions of the dorsiflexor muscles at 10% and 20% MVC torque during which 20 H reflexes and 1 M_{max} were evoked for both contraction intensities (Fig. 1A).

Figure 1



A, Representative traces of Hoffmann (H) reflex during isometric voluntary dorsiflexions performed at 10% (left panel) and 20% MVC torque (right panel) for one subject. Each panel represents an overlapping of 20 sweeps (20 stimulations). B, Motor-evoked potential (MEP) by transcranial magnetic stimulation (TMS; averaged over five sweeps) for one subject at 100% of the maximal stimulator output. The vertical dashed lines identified the SP.

MEP threshold and input–output relation

The MEP threshold was defined as the intensity at which three out of four evoked responses were discerned above background EMG levels (24) and was determined during 10% MVC contractions. TMS intensity was increased in steps of 2% of the maximal output of the stimulator, starting below the MEP threshold. Thereafter, the MEP input–output relation was completed with steps of 10% of the stimulator output (five pulses for each intensity) during 10% MVC contractions, starting at 20% of maximal stimulator output, until 100% of stimulator output or when MEP amplitude reached a plateau (MEP_{max}) (Fig. 1B).

Data Analysis

Torque and EMG

The peak torque of MVC performed with ankle dorsiflexors, and the average value of the rectified EMG (aEMG) of TA and SOL were measured over a 1-s epoch around the MVC peak torque. In addition, the TA aEMG associated with dorsiflexors MVC was normalized to the M_{max} to improve the comparison between the two experimental sessions. During 10% and 20% MVC contractions, the aEMG of TA and SOL were

measured for 5-s epochs and normalized to the respective MVC values. The coactivation ratio was calculated as follows: aEMG for SOL/aEMG for TA × 100.

H reflex, M_{max}, and MEP

Peak-to-peak amplitude of the H reflexes (averaged over 20 H reflexes) and M_{max} was computed offline from the unrectified EMG signal. The H-reflex and MEP amplitudes were normalized to M_{max}. The H-reflex gain was calculated as the ratio between the H-reflex amplitude recorded during 20% and 10% MVC contractions and expressed as percentage of increase.

The input–output relation was generated from the MEP peak-to-peak amplitude. A sigmoidal Boltzmann function was used to fit the data points:

where MEP_{max} is the maximal MEP defined by the function, S is the stimulus intensity, and S_{50} is the stimulus intensity at which the MEP size is 50% of the maximal MEP. The MEP_{slope} parameter was calculated by differentiating the input–output equation.

The duration of the period of EMG silence that followed MEP, known as silent period (SP) (18), was measured for the SP associated with the MEP_{max} from the stimulation artifact to the return of continuous EMG (Fig. 1B). The end of the SP was determined when TA EMG returned to the mean value (extended by two SD) of the background aEMG level measured during 1 s before TMS stimulation (2). The SP/MEP_{max} ratio was calculated to reduce intersubject variability in SP duration (18).

Muscle contractile properties

Peak torque, time to peak torque, and one-half relaxation time were measured from the mechanical responses to three-pulse trains. In addition, the maximal rate of torque development and the maximal rate of torque relaxation were obtained from the first derivative of the torque signal.

Statistical analysis

The normality of the data was assessed using the Kolmogorov–Smirnov test. The pre- to postintervention changes in the following variables were analyzed with either paired Student t-tests (for Gaussian distributions) or Wilcoxon tests (for non-Gaussian distributions): MVC torque and associated aEMG, aEMG during submaximal contractions, coactivation ratio, amplitude of the evoked responses (H reflexes and MEP_{max}), H-reflex gain, MEP threshold, MEP_{slope}, SP duration associated with MEP_{max}, and SP/MEP_{max} ratio. The coefficient of determination (r^2) extracted from the Pearson product–moment correlation was calculated for the relations between the following changes: 1) MVC torque and MEP_{max}, 2) MVC torque and MEP threshold, and 3) MVC torque and SP/MEP_{max} ratio. The level of statistical significance was set at $P < 0.05$ for all comparisons. Values are expressed as the mean ± SD in the text and Table 1 and mean ± SEM in the figures.

Table 1.

	Pre	Post
MVC torque (N·m)	60.3 ± 14.0	62.1 ± 19.2
MVC TA aEMG (mV)	0.15 ± 0.05	0.15 ± 0.04
TA aEMG 10% MVC torque (% MVC)	17.4 ± 4.9	17.5 ± 5.7
TA aEMG 20% MVC torque (% MVC)	27.4 ± 5.8	26.5 ± 6.0
Coactivation—10% MVC torque (% MVC)	47.9 ± 34.9	51.4 ± 36.1
Coactivation—20% MVC torque (% MVC)	37.4 ± 24.2	37.5 ± 26.0
H_{max}/M_{max} ratio (%)	11.4 ± 8.9	12.5 ± 6.0
Reflex gain (%)	35.6 ± 22.6	33.7 ± 24.1
M_{max} (mV)	13.5 ± 5.3	14.0 ± 5.9
MEP_{max} (% M_{max})	60.5 ± 29.4	56.8 ± 30.8
MEP_{slope} (% M_{max}/% maximal stimulator output)	7.3 ± 4.2	7.1 ± 4.3
SP/MEP_{max} (ms/% M_{max})	4.0 ± 0.9	4.0 ± 1.0
Three-pulse train—torque (N·m)	14.9 ± 5.6	15.4 ± 6.2
Three-pulse train—time to peak (ms)	109.4 ± 14.4	115.4 ± 16.3
Three-pulse train—1/2 relaxation time (ms)	75.4 ± 14.1	78.2 ± 16.1
Three-pulse train—rate of torque development ($N \cdot m \cdot s^{-1}$)	189.4 ± 43.4	175.4 ± 36.3
Three-pulse train—rate of torque relaxation ($N \cdot m \cdot s^{-1}$)	119.4 ± 11.7	114.1 ± 16.3

Data are presented as mean ± SD.

Maximal voluntary contraction (MVC) torque and associated EMG activity, and the TA aEMG and coactivation ratio during 10% and 20% MVC contractions, Hmax/Mmax ratio, maximal amplitude of M wave (Mmax) and motor-evoked potential (MEPmax), slope of the input-output recruitment curve for MEP (MEPslope), SP/MEPmax ratio (SP/MEPmax), 3-pulse train torque, time to peak, one half (1/2) relaxation time, rate of torque development, and relaxation before (Pre) and after (Post) placebo administration (n = 4 subjects).

Results

Electrophysiological and mechanical variables remained stable between the two experimental sessions in the group of four subjects assigned to placebo (Table 1). Data reported in the following sections are relative to the eight subjects assigned to dexamethasone.

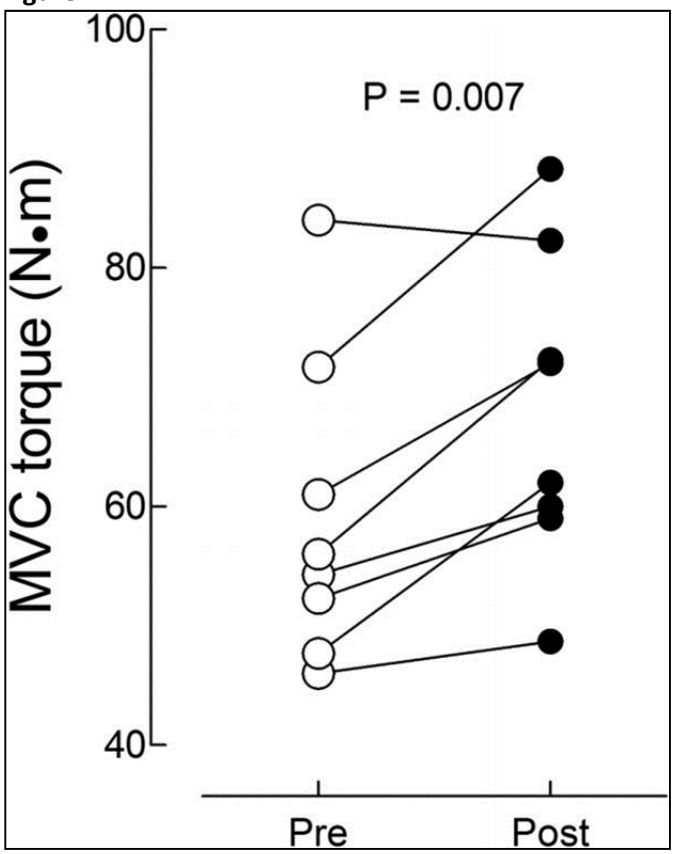
Salivary cortisol

All subjects completed the experiments, and compliance to administration was confirmed in all dexamethasone-treated subjects on the basis of the significant reduction in the postintervention levels of salivary cortisol (before: 14.4 ± 6.0 nmol·L^{-1}; after: 2.3 ± 2.0 nmol·L^{-1}; $P < 0.001$).

Maximal voluntary contractions

The dorsiflexion MVC torque increased (+14.1% ± 9.8%) after dexamethasone administration (before: 59.1 ± 12.9 N·m; after: 68.1 ± 13.1 N·m; P = 0.007) (Fig. 2). The corresponding aEMG of TA increased (+15.7% ± 14.7%) also after treatment (before: 0.14 ± 0.03 mV; after: 0.16 ± 0.05 mV; P = 0.031), andsimilar results were obtained after normalization of aEMG to M_{max} (before: 0.030 ± 0.006; after: 0.037 ± 0.007; P = 0.042).

Figure 2.



Peak torque recorded during maximal voluntary contraction (MVC) of the ankle dorsiflexor muscles for each subject before (Pre) and after (Post) dexamethasone administration. The P value indicates statistical difference after versus before treatment.

Submaximal voluntary contractions

The TA aEMG during 10% MVC and 20% MVC contractions (normalized to the aEMG obtained during MVC) was 16.3% ± 4.0% and 24.0% ± 4.8%, respectively, before glucocorticoid administration and did not change after treatment (10%: 17.3% ± 6.3%, P = 0.60; 20%: 23.6% ± 6.7%, P = 0.95). Similarly, the SOL aEMG did not change after the intervention during 10% (before: 7.1% ± 3.4%; after: 6.2% ± 3.5%; P = 0.86) and 20% MVC

contractions (before: 7.7% ± 3.4%; after: 7.0% ± 3.9%; P = 0.84). Accordingly, the coactivation ratio was not influenced by the treatment during 10% MVC (before: 46.3% ± 32.3%; after: 48.9% ± 31.8%; P= 0.87) and 20% MVC contractions (before: 35.1% ± 22.5%; after: 39.8% ± 25.3%; P = 0.75).

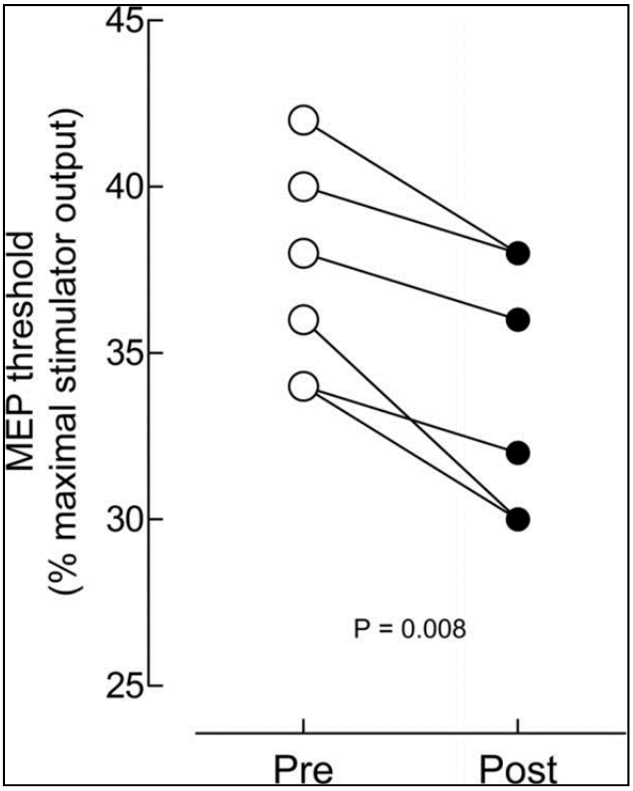
M_{max} and H reflex

The M_{max} evoked in the TA did not change after treatment (before: 14.2 ± 6.3 mV; after: 12.0 ± 5.1 mV; P = 0.20). The H_{max}/M_{max} ratio (before: 16.5% ± 6.5%; after: 16.1% ± 7.5%; P = 0.58) and H-reflex gain did not change (before: 39.5% ± 24.2%; after, 45.5% ± 23.2%; P= 0.56) after glucocorticoid administration.

MEP threshold and input–output relation

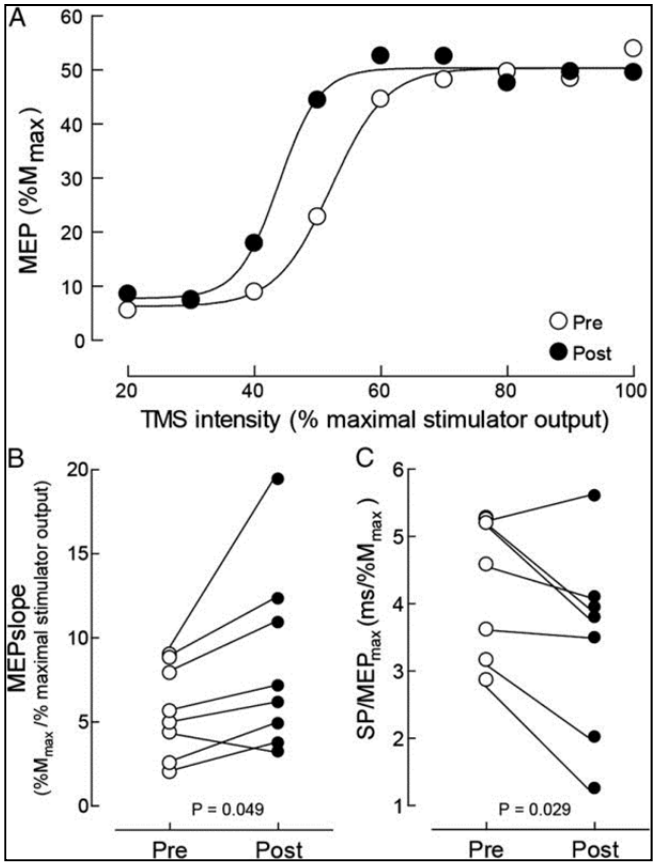
The MEP threshold was significantly reduced (P = 0.008) after treatment (-8.6% ± 4.2%) when assessed during contractions performed at 10% MVC (Fig. 3). Figure 4A illustrates the MEP input–output relation for one subject showing an increase in the MEP_{slope} after glucocorticoid administration. For the whole treated group, the MEP_{slope} increased (P = 0.049) after the intervention (Fig. 4B), whereas the MEP_{max}/M_{max} ratio did not change significantly (before: 48.5% ± 14.1%; after: 57.1% ± 20.3%; P = 0.14). Nonetheless, the amount of change in MEP_{max} was significantly (P = 0.043) and positively (r^2 = 0.59) associated with the amount of change in MVC torque. The SP associated with the MEP_{max} did not differ significantly for the whole group before (201.6 ± 68.5 ms) and after glucocorticoid administration (182.4 ± 78.7 ms; P = 0.07), but the SP/MEP_{max} ratio decreased significantly from 4.3 ± 1.0 to 3.5 ± 1.5 ms/% M_{max} (P = 0.029) after administration (Fig. 4C).

Figure 3.



Threshold of the motor-evoked potential (MEP) for each subject when assessed during isometric voluntary contraction performed at 10% of the peak torque recorded during a maximal voluntary contraction. Data from two subjects are overlapped. The P value indicates statistical difference after versus before treatment.

Figure 4.



Input-output relation of motor-evoked potentials (MEP) in one dexamethasone-treated subject before (Pre: open circles) and after (Post: filled circles) the intervention. B. The MEPslope for each subject before (open circles) and after (filled circles) glucocorticoid administration. C. Silent period (SP)/MEPmax ratio for each subject before (open circles) and after (filled circles) glucocorticoid administration. The P values indicate statistical difference after versus before treatment.

Muscle contractile properties

The twitch peak torque did not change after treatment (before: 15.2 ± 6.4 N·m; after: 13.9 ± 3.7 N·m; P = 0.44). Similarly, the time to peak torque (before: 105.0 ± 11.5 ms; after: 106.4 ± 12.3 ms; P = 0.73) and one-half relaxation time (before: 79.6 ± 12.6 ms; after: 81.1 ± 14.0 ms; P = 0.18) did not vary with treatment. Accordingly, neither maximal rate of torque development (before: 180.7 ± 42.1 $N \cdot m \cdot s^{-1}$; after: 174.9 ± 40.6 $N \cdot m \cdot s^{-1}$; P = 0.43) nor relaxation (before: 114.6 ± 11.9 $N \cdot m \cdot s^{-1}$; after: 108.9 ± 24.9 $N \cdot m \cdot s^{-1}$; P = 0.56) changed after treatment.

DISCUSSION

The new findings of this study were as follows: an increase in MEP_{slope} and a decrease in SP/MEP_{max} ratio and MEP threshold in response to 7 d of dexamethasone administration in eight healthy subjects. In addition, the increase in MVC torque after treatment was positively associated with the change in the amplitude of MEP_{max}. In contrast, the H_{max} and reflex gain and the electromechanical properties of TA did not change. These results suggest that the increase in maximal voluntary torque after glucocorticoid administration results from an enhanced drive due to changes at a supraspinal level.

The increase in MVC torque after glucocorticoid administration confirms previous work targeting elbow flexors (16,26) and knee extensors (16) despite a reduction in muscle protein turnover has been observed for these muscles in response to the treatment (16). Furthermore, the subjects assigned to the placebo group did not exhibited changes in the variables recorded, as previously reported (16). Such contrasting results (increase of muscle force and impairment of muscle composition and function) after glucocorticoid

administration could be explained by: (i) an increase in the excitation–contraction coupling and the force generating capacity of the muscle, (ii) an increase in the excitability of the spinal motor neurons, and (iii) an increase in the excitatory drive or neuromodulatory inputs received by the motor neuron pool.

Muscle contractile properties

Analysis of electrically evoked contraction of a muscle provides relevant informationon its contractile properties that depend on theintegrity of the excitation–contraction coupling (1,14). Sevendays of glucocorticoid administration did not change the torque, time to peak, and one-half relaxation time of the mechanical response evoked by a three-pulse train. Moreover, the M_{max} amplitude did not vary, as previously reported (16). These results suggest that dexamethasone administration did not alter the electromechanical properties of the ankle dorsiflexor muscles.

Spinal mechanisms

The H_{max} amplitude did not change after treatment, but this lack of change could reflect dual changes involving an increase in the excitability of spinal motor neurons (8,21) counteracted by an increase in presynaptic inhibition acting on Ia afferents originating from the muscle spindles (17), reducing the synaptic efficacy between Ia afferents and spinal motor neurons (23), as observed in cats (11). Nonetheless, such possibility is rather unlikely. Given the different effects of glucocorticoids on H-reflex and MEP parameters (see next section), a change in spinal motor neuron excitability or in serotonergic facilitation of spinal motor neurons, as observed in cats (6,7), is rather unlikely. Indeed, such adaptations should influence the motor neurons responses from both spinal and corticospinal pathways. Furthermore, a decreased synaptic input from Ia afferents reduces the firing rate of motor neurons voluntarily activated, which should decrease maximal voluntary torque (13). This is in contrast with the increase in muscle force observed in this study and reported previously (16,26). In addition, the reflex gain did not change after the intervention, suggesting that the modulation of muscle afferent feedback was not influenced by the glucocorticoid administration. Overall, these observations suggest that the short-term dexamethasone administration did not influence spinal mechanisms involved in voluntary contractions.

Corticospinal excitability

Combined with the lack of change in M_{max} and H_{max} (see previous section), the decrease in MEP threshold and the increase in MEP_{slope} observed after glucocorticoid treatment indicate an enhanced corticospinal excitability. In addition, the decrease in SP/MEP_{max} ratio suggests a decrease in cortical inhibitory pathways (18). In agreement, it has been shown that intracortical inhibition, assessed by TMS, was decreased immediately after cortisol injection in healthy subjects (15). This suggests that glucocorticoids can increase the excitability of corticocortical axons and/or their excitatory synaptic contacts with the corticospinal neurons (27), presumably by changes in GABAergic pathways (5,28). Nonetheless, in Milani et al. (15), the decrease in intracortical inhibition was observed at the time intervals for which cortisol concentrations reached is maximal value (~15 min). In the current study, corticospinal excitability was assessed several hours after glucocorticoid intake, suggesting that several oral doses (short-term administration) of glucocorticoids can induce chronic changes in cortical excitability. Furthermore, as mentioned previously, the increased corticospinal excitability was accompanied by an increase in TA EMG during MVC. This suggests that the effects of short-term (7 d) dexamethasone treatment on corticospinal excitability contribute to enhance the descending drive during maximal effort that should increase maximal voluntary force. In agreement, the change in MEP_{max} was associated with that of MVC torque.

Clinical implications

Glucocorticoids have been widely abused to enhance athletic performance (4). Given their well-known side effects, in the interest of the athlete's health, the World Anti-Doping Agency prohibits all orally, rectally, intravenously, and intramuscularly administered glucocorticoids. Nonetheless, a debate exists on whether they should remain in the World Anti-Doping Agency list (3,20). In fact, some international sports

federations request a removal of glucocorticoids from the list of prohibited products since conflicting evidence has been reported on their ergogenic activity (3). We found that the short-term administration of glucocorticoids, in doses well within the range used clinically, had positive ergogenic effects because it increased corticospinal excitability and maximal torque during voluntary contractions. On the basis of these findings, it should be recommended not only that glucocorticoids remain in the World Anti-Doping Agency list of banned substances but also that their use is prohibited at all times (in and out of competition) and not just in competition as in the current legislation.

In conclusion, this is the first study showing that dexamethasone administration for 7 days to healthy subjects influences the corticospinal tract (likely at supraspinal level) and contributes to increase maximal descending drive and torque during voluntary contractions. These findings provide experimental evidence that glucocorticoids mediate ergogenic effects in humans and should thus be viewed as doping agents.

The authors are grateful to Dr. A. Botter (LISiN, Politecnico di Torino, Italy) for carefully reviewing the final version of the manuscript and Dr. G. Mengozzi and Dr. G. Motta (University of Turin, Turin, Italy) for performing laboratory assays.

This study was supported by the foundations “Compagnia di San Paolo” of Torino, Italy (project “Glucocorticoid Actions on Motor Control in the Elderly”) and “Fondazione CARIPLO” of Milano, Italy (project “Steroid Myopathy: Molecular, Histopathological, and Electrophysiological Characterization”). Dr. Baudry was supported by a grant of the “Fonds National de la Recherche Scientifique (FRS-FNRS)” of Belgium.

The authors declare no conflict of interest.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Baudry S, Duchateau J. Postactivation potentiation in human muscle is not related to the type of maximal conditioning contraction. Muscle Nerve. 2004; 30: 328–36.

2. Duclay J, Pasquet B, Martin A, Duchateau J. Specific modulation of corticospinal and spinal excitabilities during maximal voluntary isometric, shortening and lengthening contractions in synergist muscles. J Physiol. 2011; 589: 2901–16.

3. Duclos M. Evidence on ergogenic action of glucocorticoids as a doping agent risk. Phys Sportsmed. 2010; 38: 121–7.

4. Dvorak J, Feddermann N, Grimm K. Glucocorticosteroids in football: use and misuse. Br J Sports Med. 2006; 40 (1 Suppl): i48–i54.

5. Florian J, Muller-Dahlhaus M, Liu Y, Ziemann U. Inhibitory circuits and the nature of their interactions in the human motor cortex a pharmacological TMS study. J Physiol. 2008; 586: 495–514.

6. Hall ED, Baker T, Riker WF Jr. Glucocorticoid effects on spinal cord function. J Pharmacol Exp Ther. 1978; 2060: 361–70.

7. Hall ED. Glucocorticoid effects on serotonergic and noradrenergic facilitation of spinal monosynaptic transmission. Psychiatry Res. 1980; 2: 241–50.

8. Hall ED. Glucocorticoid enhancement of serotonergic facilitation of cat spinal monosynaptic motor neuron excitation. Exp Neurol. 1980; 68: 589–94.

9. Hall ED. Glucocorticoid effects on the electrical properties of spinal motor neurons. Brain Res. 1982; 240: 109–16.

10. Hall ED, Baker T. Acute effects of methylprednisolone sodium succinate on spinal reflexes. Exp Neurol. 1979; 63: 476–84.

11. Hall ED, Baker T. Further studies of glucocorticoid effects on spinal cord function: single and repetitive monosynaptic transmission and apparent Ia afferent transmitter turnover. J Pharmacol Exp Ther. 1979;

210: 112–5.

12. Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007; 55: 187–99.

13. Macefield VG, Gandevia SC, Bigland-Ritchie B, Gorman RB, Burke D. The firing rates of human motoneurones voluntarily activated in the absence of muscle afferent feedback. J Physiol. 1993; 471: 429–43.

14. MacIntosh BR, Gardiner PF, McComas AJ. Skeletal Muscle. 2nd ed. Human Kinetics; 2006. pp. 160–6.

15. Milani P, Piu P, Popa T, et al. Cortisol-induced effects on human cortical excitability. Brain Stimul. 2010; 3: 131–9.

16. Minetto MA, Botter A, Lanfranco F, Baldi M, Ghigo E, Arvat E. Muscle fiber conduction slowing and decreased levels of circulating muscle proteins after short-term dexamethasone administration in healthy subjects. J Clin Endocrinol Metab. 2010; 95: 1663–71.

17. Morita H, Petersen N, Christensen LO, Sinkjaer T, Nielsen J. Sensitivity of H-reflexes and stretch reflexes to presynaptic inhibition in humans. J Neurophysiol. 1998; 80: 610–20.

18. Orth M, Rothwell JC. The cortical silent period: intrinsic variability and relation to the waveform of the transcranial magnetic stimulation pulse. Clin Neurophysiol. 2004; 115: 1076–82.

19. Pierrot-Deseilligny E, Mazevet D. The monosynaptic reflex: a tool to investigate motor control in humans. Interest and limits. Neurophysiol Clin. 2000; 30: 67–80.

20. Pigozzi F, Di Gianfrancesco A, Zorzoli M, et al. Why glucocorticosteroids should remain in the list of prohibited substances: a sports medicine viewpoint. Int J Immunopathol Pharmacol. 2012; 25: 19–24.

21. Riker WF Jr, Baker T, Okamoto M. Glucocorticoids and mammalian motor nerve excitability. Arch Neurol. 1975; 32: 688–94.

22. Rothwell JC. Physiological studies of electric and magnetic stimulation of the human brain. Electroencephalogr Clin Neurophysiol. 1991; 43 (Suppl): 29–35.

23. Rudomin P, Schmidt RF. Presynaptic inhibition in the vertebrate spinal cord revisited. Exp Brain Res. 1999; 129: 1–37.

24. Sacco P, Thickbroom GW, Thompson ML, Mastaglia FL. Changes in corticomotor excitation and inhibition during prolonged submaximal muscle contractions. Muscle Nerve. 1997; 20: 1158–66.

25. Schieppati M. The Hoffmann reflex: a means of assessing spinal reflex excitability and its descending control in man. Prog Neurobiol. 1987; 28: 345–76.

26. van der Hoeven JH. Decline of muscle fiber conduction velocity during short-term high-dose methylprednisolone therapy. Muscle Nerve. 1996; 19: 100–2.

27. Wassermann EM. Variation in the response to transcranial magnetic brain stimulation in the general population. Clin Neurophysiol. 2002; 113: 1165–71.

28. Ziemann U. TMS and drugs. Clin Neurophysiol. 2004; 115: 1717–29.