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Differential effects of hydrocortisone on sympathetic and hemodynamic responses to sympathoexcitatory manoeuvres in men

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ABSTRACT

Aim of the present study was to investigate the influence of hydrocortisone on muscle sympathetic nerve activity (MSNA) and hemodynamic parameters during different sympathoexcitatory manoeuvres in humans. The study focuses on the interaction of the hypothalamo-pituitary-adrenal system and the sympathetic nervous system. Hydrocortisone 100 mg or placebo was administered intravenously to eight young healthy subjects in a double-blind crossover design. After 6 h, blood pressure, heart rate and MSNA from the peroneal nerve were recorded at rest, during an arithmetic stress task, an apnea and a cold pressor test. Hydrocortisone treatment increased serum cortisol levels to the upper physiological range and suppressed basal levels of adrenocorticotropin. During mental stress, MSNA, heart rate and blood pressure levels were elevated independently of hydrocortisone pre-treatment. However, hydrocortisone induced a sustained increase in basal heart rate throughout the whole experiment. A stronger increase in diastolic blood pressure was observed during apnea and cold pressor test in the hydrocortisone experiments. MSNA or plasma catecholamines at rest or during the manoeuvres were not affected by hydrocortisone. The observed hydrocortisone effects may be due to an increased responsiveness of adrenergic receptors towards catecholamines or a central modulation of the baroreflex involving parasympathetic mechanisms. Further studies are needed to confirm that the increase in MSNA during mental stress does not depend on a concomitant activation of the hypothalamo-pituitary-adrenal system.

1. Introduction

In order to maintain homeostasis under stressful conditions, the hypothalamic–pituitary–adrenal (HPA) system and the sympathetic nervous system (SNS) interact. Both ACTH and CRH are known to increase sympathetic activity, most likely mediated via central nervous system autonomic centers [1,2]. Sympathoexcitatory effects of the HPA system could occur during stressful situations and might contribute to the increase in sympathetic outflow to the muscle vascular bed during mental stress [3–5]. Such activating hormonal influence could be of clinical interest, because the sympathetic neural response to mental stress in subjects with borderline hypertension and even in normotensive offspring of hypertensive parents is enhanced compared with that of control subjects [6,7]. The same group of patients has also been reported to show signs of an increase in HPA activity during mental stress [8].

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On the other hand, glucocorticoids have been reported to blunt sympathoexcitatory responses to different metabolic stimuli in humans in several publications [2,9,10]. A previous study performed in our own laboratory also suggested a sympathoinhibitory effect of acutely administered pharmacological doses of hydrocortisone [11]. This led to the hypothesis that sympathoexcitation during various manoeuvres like hypoglycemia, hyperinsulinemia or alcohol exposure could in part be due to sympathostimulatory effects of central nervous parts of the hormonal stress system like CRH or proopiomelanocorticotropin derivates which are suppressed by glucocorticoids.

The present study investigates the effects of hydrocortisone on muscle sympathetic nerve activity (MSNA) and hemodynamic parameters at rest and during the sympathoexcitatory manoeuvres mental stress, end-inspiratory apnea and cold pressor test. The specific focus of the study was the question whether the sympathoexcitation during a physiological mental stressor depends on the activation of the HPA stress system. Parameters were assessed 6 h after i.v. injection of 100 mg hydrocortisone in a double-blind, placebo-controlled design. The short interval of 6 h allows to investigate short-term effects of glucocorticoids without interference of long-term peripheral effects such as increase of total body water and sodium content. Activation of the muscle branch of the SNS was specifically determined by microneurographic recordings of MSNA in the superficial peroneal nerve. MSNA has been shown to correlate with cardiac sympathetic outflow [12] and is widely used to monitor rapid changes of sympathetic activity in humans [13].

2. Methods

2.1. Subjects

We included four male and four female subjects aged 18–35 years with normal body mass index. All subjects were healthy, non-smokers and were not taking any medications. They were asked to abstain from alcohol the day before the experiment and to abstain from caffeine for $\geq$6 h before the start of the experiment. Subjects were examined in the post-absorptive state, more than 2 h after their last meal. The female subjects, who did not use oral contraceptives, were investigated during the follicular phase of the menstrual cycle. The present study was conducted in accordance with the guidelines in The Declaration of Helsinki and formally approved by the local ethics committee. All subjects gave their written informed consent.

2.2. Measurements of MSNA and hemodynamic parameters

Sympathetic activity was measured using microneurographic recordings of efferent muscle sympathetic nerve activity in the peroneal nerve as described previously [11,14]. ECG was recorded with standard chest leads. Blood pressure was measured oscillometrically (Welch Allyn Tycos, Skaneateles Falls, NY, USA) 10 min after the subjects had resumed the supine position at the beginning of the experiment. Relative blood pressure changes were monitored with blood pressure measurements from a finger with the hand resting at the level of the heart, with the volume-clamp technique (Finapres®, Ohmeda Monitoring Systems, Englewood, CO, USA). Respiratory movements were monitored with a strain gauge strapped around the chest with a rubber band to control for inadvertent apneas and irregular breathing, which are known to affect MSNA.

Analogue signals of all parameters (mean voltage neurogram, ECG, blood pressure and respiration) were digitised on-line with a sampling rate of 200 Hz (CED 1401, Cambridge Electronic Design, Cambridge, England) and stored on a computer disk. Signals were also printed out with a Nihon Kohden 4421 Neurofax.

2.3. Experimental protocol

Each subject was examined twice in a placebo-controlled, double-blind, crossover design with an interval of 4 weeks (women) or at least 1 week (men) in between the experimental sessions. On the experimental day at 08:00 h, a single bolus injection of 100 mg hydrocortisone or placebo (10 ml isotonic saline) was given intravenously in a randomised order. At 12:00 h, an intravenous cannula was inserted into an antecubital vein for blood sampling. Then, monitoring of ECG, finger blood pressure and respiratory movements started. Thereafter, subjects resumed a comfortable supine position and the microelectrodes for nerve recording were inserted. After a satisfactory nerve signal had been obtained, data sampling started with a 15-min baseline resting period. Subjects were then asked to perform an end-inspiratory apnea of maximal length. After another resting period of 10 min, subjects had to perform an arithmetic stress task over a period of 10 min. The task consisted in serial subtractions of a two-digit number from a four-digit number as described before [3]. The two-digit number (13 or 17) was indicated by the investigator in a randomised order between the two experimental sessions to avoid training effects. Mental stress was increased by pressing the subjects to calculate as fast as possible in a foreign language (English) and by correcting any mistake immediately. The investigators took care that the subjects did not move and breathed regularly during the arithmetic task. Mental stress was followed by a 10-min recovery period. After an additional resting period of 10 min, a cold pressor test (CPT) was performed by immersing the subject's left hand into ice water (4 °C) for 90 s.

Blood samples for the determination of cortisol, ACTH, catecholamines, renin, serum electrolytes and serum osmolality were taken during the baseline period. Additionally, cortisol and catecholamines were determined at the beginning and the end of the mental stress (minutes 1 and 10) and at the end of the recovery period (minute 10). ACTH was determined in 1-min intervals during mental stress (minutes 1–10) and the recovery period (minutes 1–10).

2.4. Biochemistry

Blood samples for the analysis of hormones were centrifuged immediately and stored at −30 °C (cortisol, ACTH, renin) or at −80 °C (catecholamines). Serum cortisol levels were determined with enzyme-linked immunosorbent assay (Enzymun-