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ORIGINAL PAPER

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Is there an inhibitory role of cortisol in the mechanism of male sexual arousal and penile erection?

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Abstract Background. It has been speculated for more than 2 decades whether there is a significance of adrenal corticosteroids, such as cortisol, in the process of normal male sexual function, especially in the control of sexual arousal and the penile erectile tissue. However, only few in vivo studies have been carried out up until now on the effects of cortisol on human male sexual performance and penile erection. In order to evaluate further the role of cortisol in male sexual activity, the present study was conducted to detect serum levels of cortisol in the systemic and cavernous blood taken during different penile conditions from healthy males. Material and Methods. The effects of cortisol derivative prednisolone, catecholamine norepinephrine (NE) and the peptide endothelin-1 (ET-1) on isolated human corpus cavernosum (HCC) were investigated using the organ bath technique. Fifty-four healthy adult male subjects were exposed to erotic stimuli in order to elicit penile tumescence and rigidity. Whole blood was simultaneously aspirated from the corpus cavernosum and the cubital vein during different penile conditions. Serum levels of cortisol (μg/dl) were determined by means of a radioimmunoassay (ELISA). Results. In the healthy volunteers, cortisol serum levels significantly decreased in the systemic circulation and the cavernous blood with increasing sexual arousal, when the flaccid penis became rigid. During detumescence, the mean cortisol level remained unaltered in the systemic circulation, whereas in the cavernous compartment, it was found to decrease further. Under all penile conditions, no significant differences were registered between cortisol levels in the systemic circulation and in the cavernous blood. Cumulative addition of NE and ET-1 (0.001–10 μM) induced contraction of isolated HCC strips, whereas the contractile response to prednisolone was negligible. Conclusion. Our results strongly suggest an inhibitory role for cortisol in the mechanism of male sexual response and behaviour. These properties are mediated rather via an effect on central structures than on the penile erectile tissue. Future studies to include patients suffering from erectile dysfunction may reveal whether or not there are differences in the cortisol serum profiles of healthy subjects and patients under different stages of sexual arousal.

Keywords Corticosteroids · Cortisol · Human male sexual response · Cavernous blood · Systemic blood

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Introduction

The regulation of normal male sexual and reproductive function including penile erection is a complex physiological mechanism brought about by the interaction of various physiological mediators produced by neuronal, endothelial and endocrine structures [1, 14, 15]. It is without doubt that the release of neurotransmitters, such as adrenaline, noradrenaline, acetylcholine, dopamine, nitric oxide (NO) and serotonin, mainly contribute to the control of sexual arousal and the tone of penile erectile tissue. It is well established that hormones, in particular androgens such as testosterone, are necessary although not pivotal to maintain sexual desire, sexual arousability and erectile function. As to the adrenal control of normal male sexual function, it still remains uncertain as to whether the glucocorticoid cortisol (=hydrocortisone), a major product of the adrenal gland, rather elicits facilitatory or inhibitory effects on male sexual interest and activity. Contradictory findings have emerged from studies on the influence

of cortisol on mammalian male libido and erectile capability. Some studies using animal models presented evidence that the endocrine secretion or administration of cortisol significantly contributes to mating activities (mounting, penis extension, intromission, ejaculation) in bulls and boars and exerted pro-erectile effects in adrenalectomized male rats [4, 17]. These results are supported by the finding that the administration of adrenocorticotropic hormone (ACTH 1–17) notably increased the sexual performance of male patients affected by psychogenic erectile dysfunction (ED) [11]. ACTH is secreted by the hypothalamic pituitary gland and is known to stimulate the adrenal production of cortisol by binding to specific receptor sites located in the zona fasciculata of the adrenal gland cortex [16, 20]. On the other hand, symptoms of insomnia, depression and decreased libido have been reported in male and female patients suffering from the so-called Cushing syndrome, which is characterized by a permanent condition of hypercortisolism [21]. Studies conducted in humans revealed that the levels of circulating cortisol remained either unaltered or decreased only slightly in sexually aroused healthy male subjects [5, 18]. Although it has been demonstrated that endocrinological alterations with age are also related to others but sex hormones such as cortisol, melatonin and thyroxine, no differences were registered in the age-dependent secretion of cortisol and ACTH in healthy men and patients with ED [7, 9]. Thus, to date no incidence of impotence in men has been reported in association with alterations in the adrenal synthesis of corticosteroids.

Since the role of cortisol in the control of human male copulatory ability is not fully understood, the present study was conducted to evaluate the effects of corticosteroids on isolated human erectile tissue and to detect the profile of cortisol in the systemic and cavernous blood of healthy males during different penile conditions.

Material and methods

Organ bath studies

Human erectile tissue was obtained from five patients (mean age 38 years) who had undergone male to female transsexual surgery. Cavernous smooth muscle strips were mounted in an organ bath system (MAYFLOWER Organ bath, Hugo Sachs Elektronik GmbH, March, Germany) under standard conditions [3]. A pretension of 0.5 g was applied and the tissue was allowed to equilibrate for at least 60 min. Contractile responses of the tissue to the cortisol derivative prednisolone (11β,17,21-trihydroxy-1,4-pregnadien-3,20.ion) (0.001–1.0 μM) were investigated using strips at basal tension. The potent vasoconstrictors norepinephrine (NE) and endothelin-1 were used as reference compounds in the study. Isometric responses of the tissue were registered using a MacLab data acquisition system (Analog Digital Instruments, Castle Hill, Australia). Each drug concentration was tested six times.

Blood withdrawal

Fifty-four healthy adult males (mean age 26 years) with normal erectile function were enrolled in the study. Participants were placed in a supine position with the upper part of the body upright (approximately 30°). A 20-gauge (G) intravenous cannula (Vasofix Braunüle, B. Braun AG, Melsungen, Germany) was inserted into the left cubital vein and a 19-G butterfly needle (Abbott Laboratories, Sligo, Ireland) was placed in the left corpus cavernosum. Blood samples, starting with the flaccid state, were simultaneously taken from the corpus cavernosum and the cubital vein during the penile conditions flaccidity (F), tumescence (T), rigidity (R) and detumescence (D). Penile tumescence and rigidity were induced by presenting the volunteers sexually explicit movie sequences and allowing them self-stimulation of their glans penis. The blood was drawn into syringes (5.5 ml S-Monovetten, Sarstedt, Nümbrecht, Germany), immediately stored on ice and then centrifuged by +4°C at 3000 rpm for 10 min. The serum was separated and stored at −80°C.

Determination of cortisol

A radioimmunoassay (DSL 2100 ACTIVE Cortisol RIA, Diagnostic Systems Laboratories, Webster TX, USA; supplied by IBL GmbH, Hamburg, Germany) was used to determine cortisol serum levels. In the case of a discrepancy greater than 10% between duplicate values, these results were disregarded. All data are given in µg/dl serum as mean ± standard deviation of the mean.

Statistical analysis

Evaluation of the data was carried out with SPSS 7.5 for Windows (SPSS Inc., Chicago, IL, USA). The *t* test for paired samples was applied for comparison of the systemic and cavernous 5-HT levels. A probability (p) value <0.05 was considered statistically significant. Only those cortisol serum levels registered in blood samples simultaneously drawn from the cubital vein and the cavernous body were statistically evaluated.

Chemicals

Prednisolone (Solu-Decortin) was kindly provided by Merck KG (Darmstadt, Germany), norepinephrine-HCl (Arterenol) by Hoechst AG (Frankfurt, Germany). Endothelin-1 was obtained from BACHEM Biochemica (Heidelberg, Germany).

Results

Organ bath studies

Cumulative addition of NE and ET-1 (1 nM–1 μM) induced contraction of isolated HCC strips. Median generation of tension ranged from 2.5 mg and 500 mg in the presence of 1 nM NE and ET-1, respectively, to 1,800 mg and 3,800 mg at the maximum concentration. In contrast, the force generation in response to the addition of prednisolone (10 nM–1 μM) amounted to a mean of 60 mg only. The results of the organ bath studies are summarized in Fig. 1.

Course of cortisol serum levels in healthy males

Simultaneous blood withdrawal from the cubital vein and the corpus cavernosum was commenced in 29, 54,

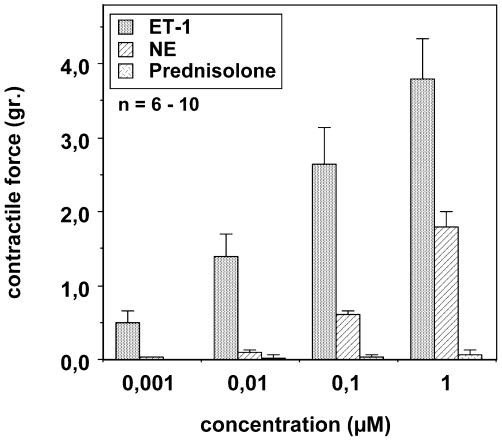

Fig. 1 Contractile effects of increasing concentrations (0.001–1.0 μM) of prednisolone, endothelin 1 (ET-1), and norepinephrine (NE) on isolated human corpus cavernosum at basal tension. n = number of cavernous strip preparations evaluated for each drug concentration

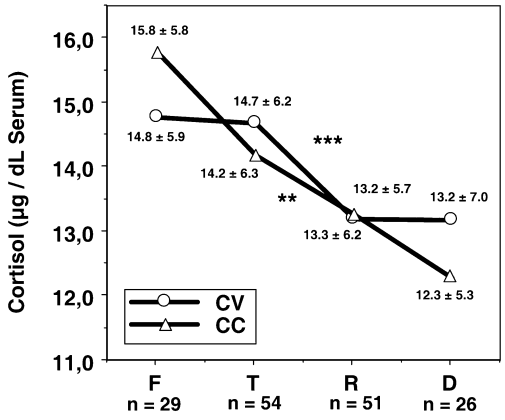

Fig. 2 Course of cortisol (µg/dl serum) in the systemic and cavernous blood of healthy male volunteers through different penile conditions (*F* flaccidity, *T* tumescence, *R* rigidity, *D* detumescence). *Asterisks* close to the line traces indicate significant differences in cavernous or systemic cortisol levels, respectively, under different penile conditions. *n* denotes number of volunteers where simultaneous blood withdrawal was performed from the corpus cavernosum (*CC*, *solid line*, *triangles*) and the cubital vein (*CV*, *dashed line*, *circles*). $^{**}p = 0.005$, $^{***}p < 0.001$

51 and 26 subjects at penile flaccidity, tumescence, rigidity, and detumescence, respectively. Mean cortisol serum level in the nonaroused subjects in the phase of penile flaccidity was 14.8 ± 5.9 in the blood taken from the cubital vein (CV) vs 15.8 ± 5.8 in the blood taken from the corpus cavernosum (CC). With the beginning of sexual stimulation and penile erection, cortisol significantly decreased in the systemic circulation and the cavernous blood from tumescence to rigidity (CV: to 13.2 ± 5.7; CC: to 13.3 ± 6.2). From penile rigidity to detumescence, mean cortisol level remained unaltered in the systemic circulation (13.2 ± 7.0), whereas it dropped further in the cavernous compartment (12.3 ± 5.3). Nevertheless, this decline was not of statistical significance. Under all penile conditions, no significant differences were registered in cortisol serum levels of the systemic and cavernous blood (Fig. 2).

Discussion

A variety of actions of adrenal steroidal glucocorticoids on the mammalian body have been described, including the regulation of ion homoeostasis in brain, kidney and intestine, the stimulation of gluconeogenesis, cell proliferation and differentiation, as well as the involvement in certain diseases in animals and man [6, 10, 12, 19, 22]. It has also been speculated as to the role of adrenal corticosteroids in the control of normal male sexual and reproductive function including the mechanism of sexual arousal and penile erection. Results from animal studies indicated that cortisol might be essential to the successful performance of sexual behavioural events. It has been demonstrated that cortisol rose during sexual mating activities in male bulls and boars, and it was suggested from a study using adrenalectomized rats that the steroids of the adrenal gland mainly contribute to the maintenance of penile erection via a preservation of the expression of penile neuronal nitric oxide synthase protein [4, 17]. From studies in human males, contradictory findings emerged with regard to the excitatory or inhibitory properties of adrenal steroids in the control of normal male sexual activity: While some authors speculated a pivotal role of the pituitary–adrenal axis in the maintenance of sexual behaviour, others concluded that the secretion of cortisol is mainly attributed to the depression of erectile function [11, 18]. In contrast, others assumed that there is at least no significance of cortisol with regard to the inhibition or facilitation of sexual arousal and penile erection [5].

The aim of our study was to evaluate further the effects of cortisol derivative prednisolone on isolated human erectile tissue and examine the course of systemic and cavernous cortisol serum levels in healthy males under different conditions of the penile erectile tissue, indicating different stages of sexual arousal.

With the initiation of penile erection, mean cortisol serum levels significantly declined in the systemic circulation as well as in the cavernous compartment. Although this decline persisted in the cavernous blood when the rigid penis became detumescent, it was not of statistical significance. During all stages of sexual arousal, no notable differences were registered with regard to the mean cortisol levels in the systemic circulation and the cavernous blood. Therefore, it seems unlikely that the course of cavernous cortisol, which we registered in our study, indicates a local mechanism of corticosteroid degradation. Moreover, from the cavernous profile, a release or binding of cortisol from or to specific receptor sites in the corpus cavernosum can be ruled out [2]. Hence, due to the changes in penile

hemodynamics with the initiation of penile erection, the cavernous cortisol profile solely reflects the alterations in the corticosteroid level that occurred in the systemic blood with sexual arousal. Due to the dramatic increase in arterial flow into the cavernous compartment and the simultaneous reduction in outflow that occurs during tumescence and rigid erection, a diluent effect on the local cortisol concentration should also be taken into consideration. The apparent drop in systemic cortisol levels is in support of the hypothesis of inhibitory properties of the steroid on male sexual activity and might be explained by the inhibition of adrenal cortisol secretion into the circulation. Thus, this decline might be a prerequisite to enable an adequate physiological and genital response to sexual stimulation. This view is well in accordance with the hypothesis that increased circulating cortisol may inhibit the response to the intracavernous injection of vasoactive agent prostaglandin E1 in men with erectile dysfunction [8]. The findings from our study raised the question as to the mechanism of action of corticosteroids on male sexual and reproductive function. According to the results from our organ bath studies using isolated human erectile tissue, it is questionable that there are marked local effects of cortisol on the smooth musculature of the corpus cavernosum and penile arteries. To the best of our knowledge, a relaxing effect of cortisol on isolated mammalian corpus cavernosum has never been reported in the literature. The view of a systemic action of corticosteroids is—to a certain degree—supported by a study from Isidori et al. Even though they reported beneficial effects of the administration of hypothalamic pituitary hormone ACTH, known to stimulate the adrenal secretion of cortisol, on the sexual performance of male patients affected by psychogenic impotence, they speculated that these effects might be due to a direct action on the central nervous system rather than the penile erectile tissue [11]. This action may include inhibitory effects on central as well peripheral nerves that supply the male reproductive organs. Interestingly, peripheral mechanisms of action in terms of maintenance of the central nerve supply, necessary for an unimpaired penile response to sexual stimulation, have also been suggested with regard to the pro-erectile activity of androgen testosterone and the hypothalamic hormone somatotropin (=human growth hormone) [13, 23].

In conclusion, our results strongly suggest an inhibitory role for cortisol in the mechanism of male sexual response and behaviour, including the control of penile erection. These properties are presumably mediated rather via an effect on central nervous structures than on peripheral reproductive organs.

Future studies to include patients suffering from erectile dysfunction of both organogenic and psychogenic cause may reveal whether or not there are differences in the cortisol serum profiles of healthy subjects and patients under different stages of sexual arousal, and whether or not such differences might be of significance in the pathophysiology of male erectile dysfunction.

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