Original Article

Is cortisol an endogenous mediator of erectile dysfunction in the adult male?

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Background: It has been speculated for decades whether there is a significance of the adrenal corticosteroid cortisol in the process of male sexual function, including the control of sexual arousal and penile erection. In order to investigate further the role of the adrenocorticotropic axis in the physiological process of penile erection, we aimed to determine the course of cortisol in the cavernous and systemic blood through different stages of sexual arousal in patients suffering from erectile dysfunction (ED) in comparison to a cohort of healthy males.

Methods: Fifty-four healthy adult males and 45 patients with ED were presented sexually explicit visual material in order to elicit tumescence and (in the healthy males) rigid erection. Blood was collected from the cavernous space (corpus cavernosum penis, CC) and a cubital vein (CV) at different stages of the sexual arousal cycle as indicated by the penile stages flaccidity, tumescence, rigidity (attained only by the healthy males) and detumescence. Cortisol (µg/dL serum) was measured using a radioimmunometric assay (RIA).

Results: In healthy males, cortisol decreased in both the cavernous and systemic blood with the beginning of sexual stimulation (CV: 15 to 13, CC: 16 to 13). At detumescence, in the systemic circulation, no alterations in cortisol levels were registered, whereas it decreased further in the CC (to 12). In the ED patients, no significant changes in cortisol were noticed in the systemic and cavernous blood.

Conclusions: The findings indicate that cortisol might act as an antagonist of the normal sexual response cycle of the adult male. A dysregulation of the secretion and/or degradation of the hormone might well play a role in the manifestation of ED.

Keywords: Cortisol; erectile dysfunction; systemic blood; cavernous blood

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Introduction

In adult males, the normal physiological response to sexual stimulation is a complex process involving different mediators and neurotransmitters of the sympathetic, parasympathetic, dopaminergic and non-adrenergic/cholinergic system (adrenaline/noradrenaline, acetylcholine, dopamine, serotonin, nitric oxide). These interactive mechanisms require intact endothelial, neuronal and endocrine structures (1-3). Following secretion of adrenocorticotropic hormone (ACTH 1-17) from the hypothalamic region, cortisol (hydrocortisone) is produced

in the zona fasciculata of the adrenal gland (4,5). Although a wide range of actions of adrenal glucocorticoids have been identified, up until to date, it is still uncertain as to whether cortisol plays a role in terms of facilitating or inhibiting the male sexual response including penile erection (6,7). A permanent condition of hypercortisolism, manifested as Cushing syndrome, has been associated with decreased libido, and some studies reported that increased levels of cortisol were negatively correlated with sexual function in men (8,9). In contrast, in animal models, the administration or stimulation of the endocrine secretion of cortisol has been shown to promote mating activities (penis extension, mounting, intromission) in boars, bulls, jackass and male rats (10,11). In patients with a psychogenic cause of erectile dysfunction (ED), the administration of ACTH 1-17 can lead to enhanced sexual performance, whereas no differences were seen in healthy males and patients with ED with regard to the secretion of cortisol and ACTH (12,13). While some authors demonstrated a perpetual course of cortisol in the systemic circulation during sexual arousal, others reported that the level of circulating cortisol decreased in sexually aroused male subjects (14,15). However, it has also been supposed that there is no significance of cortisol with regard to the inhibition or facilitation of sexual arousal and penile erection (16). Although it has been demonstrated that others but sex hormones, such as cortisol, melatonin and thyroxine, are affected by age-related endocrinological alterations, no differences were registered in the secretion of cortisol and/or ACTH in healthy men and patients with ED (12). Up until to date, no incidence of impotence in men has been reported in association with alterations in the adrenal synthesis of corticosteroids such as cortisol. These contradictory findings serve as a rationale to explore further the potential association between cortisol and erectile function in the adult male. As of today, no convincing evidence has been presented linking impotence in men to alterations in the production and turn-over of adrenal corticosteroids. Our study aimed to investigate through the different stages of the sexual arousal cycle, exemplified by different functional states of the penis, in healthy men and patients with ED the levels of cortisol in the cavernous blood and systemic circulation.

This article is presented in accordance with the MDAR reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-566/rc).

Highlight box

Key findings

- The results are in support of the hypothesis that cortisol may have inhibitory effects on the male sexual response.

What is known and what is new?

- It is still uncertain whether cortisol plays a role in facilitating or inhibiting the male sexual response including penile erection.
- The findings indicate that cortisol might act as an antagonist of the sexual response cycle of the adult male.

What is the implication, and what should change now?

- Given the premise that a decline in circulating cortisol is a prerequisite to facilitate an erectile response to sexual stimulation, a dysregulation of the secretion/degradation of the hormone might play a role in the pathophysiology of erectile dysfunction.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of the Hannover Medical School (Be 2045/1-2), informed consent was obtained from all participants. Fifty-four healthy males (mean age: 26 years) with normal erectile function (according to a questionnaire based on questions 1, 3, 4 and 5 of the IIEF) and no signs of physical or psychological diseases were enrolled into this cohort. In addition, 45 patients with ED (mean: 52 years) of both organogenic and/or psychogenic causes (as ED is assumed to be likely multifactorial, with a psychogenic component playing a role in many men) were screened by the outpatient clinic of the Department of Urology and Urological Oncology of the Hannover Medical School and empanelled into the study. Concomitant diseases to the ED were cardiac insufficiency (n=10), high blood pressure (n=17), diabetes (n=9), atherosclerosis (n=8), neurological dysfunctions (n=12), respiratory dysfunctions (n=6), hypogonadism (n=4) and psychological disturbances (n=14, as characterized by abnormal findings in the psychosexual evaluation but without signs of neurological diseases and no pathological duplex sonography after the injection of 5 µg prostaglandin E1). A cannula (20 gauge) was placed into a cubital vein (CV), a 19-gauge needle was inserted into the corpus cavernosum (CC) penis. Blood was taken from a cubital vein and the corpus cavernosum at penile flaccidity, tumescence, rigid erection (attained only by the healthy males) and detumescence. Tumescence and rigid erection were brought about by presenting the subjects sexual explicit visual scenes (15,17). The different phases of erection were visually defined by the investigator who was

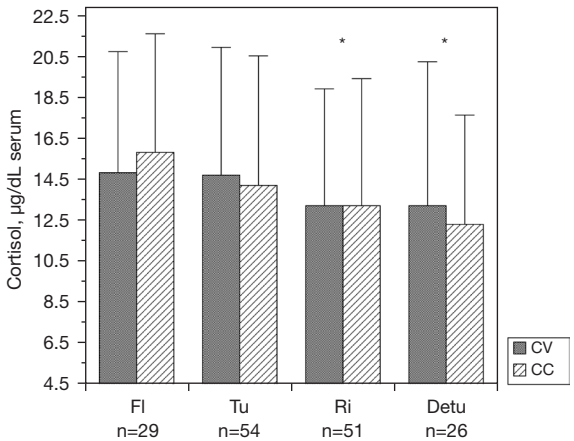

Figure 1 Course of cortisol (given in µg/dL serum) in the systemic and penile blood of healthy males through the sexual response cycle, as exemplified by the penile stages Fl, Tu, Ri and Detu. n = number of subjects in whom simultaneous blood collection was performed from the CV and CC. Cortisol levels significantly different from those measured in the non-aroused state (at penile flaccidity) are marked by an asterisk (*P<0.05). CV, cubital vein; CC, corpus cavernosum penis; Fl, flaccidity; Tu, tumescence; Ri, rigidity; Detu, detumescence.

Table 1 Serum levels of cortisol (hydrocortisone) (given in µg/dL serum) in peripheral and cavernosal blood samples taken from healthy male volunteers during different conditions of sexual arousal, exemplified by the penile conditions flaccidity, tumescence, rigidity and detumescence

Penile condition	Blood source	Blood withdrawals commenced	Cortisol (µg/dL serum)
Flaccidity	CV	29	14.8±5.9
	CC	29	15.8±5.8
Tumescence	CV	54	14.7±6.2
	CC	54	14.2±6.3
Rigidity	CV	51	13.2±5.7*
	CC	51	13.3±6.2*
Detumescence	CV	26	13.2±7.0*
	CC	26	12.5±5.3*

All data are given as mean ± standard deviation (SD). Asterisk (*) indicates that the concentration of cortisol is significantly different from those measured in the phase of penile flaccidity (P<0.05). CC, corpus cavernosum. CV, cubital vein.

present in the room during the entire session. Blood (up to 5 mL) was collected into syringes (Sarstedt, Nümbrecht, Germany) and immediately stored on ice. Then, serum was separated and kept frozen (at –80 ℃) until measurement. A radioimmunometric assay (ACTIVE 2100, Diagnostic Systems Labs, Webster, TX, USA) was used to measure serum levels of cortisol (µg/dL).

Statistical analysis

All data are given as mean ± standard deviation. Results were disregarded if the discrepancy between duplicate values was ≥15%. Statistical analysis to compare cortisol levels in the cavernous and systemic blood was carried out with the Igor Pro integrated program (Mac version) (WaveMetrics Inc., Lake Oswego, OR, USA) using the *t*-test. A probability (P) value <0.05 was considered significant. Only plasma levels of cortisol assayed in blood samples that were drawn from both the cubital vein and the cavernous compartment of the volunteers were statistically evaluated.

Results

In the healthy men, withdrawal of blood from a CV and the CC was conducted in 29, 54, 51 and 26 individuals at flaccidity, tumescence, rigid erection, and detumescence, respectively. At penile flaccidity, mean cortisol level was 15.8±5.8 in the blood from the CC *vs.* 14.8±5.9 in the blood aspirated from the CV. After the on-set of sexual arousal, when the penis became rigid, the level of cortisol significantly dropped in the systemic blood (13.2±5.7) and the cavernous compartment (13.3±6) (P<0.05). After the termination of rigid erection, at detumescence, serum cortisol remained unchanged in the systemic circulation (13±7), while it declined further in the penile blood (to 12±5.3) (P<0.05). At all penile stages, no marked differences were registered in serum cortisol in the blood aspirated from the CV and CC. Results are shown in *Figure 1* and *Table 1*. In the cohort of ED patients, none achieved the stage of rigid erection. Whole blood was collected from 29, 33 and 22 individuals at penile flaccidity, tumescence, and detumescence, respectively. In contrast to the course seen in healthy males, in the systemic and penile blood, no drop in cortisol levels was registered at penile tumescence, with the

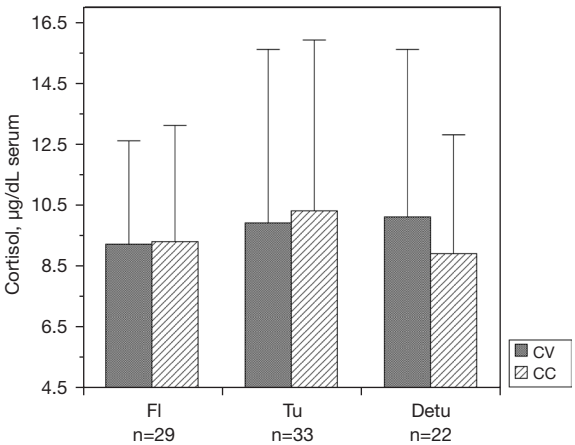

Figure 2 Course of cortisol (µg/dL serum) during visual sexual stimulation in the systemic and cavernous blood of patients with ED. The aroused state is exemplified by the penile condition of Tu. n = number of subjects in whom simultaneous blood collection was performed from and the CV and the CC. ED, erectile dysfunction; CV, cubital vein; CC, corpus cavernosum penis; Fl, flaccidity; Tu, tumescence; Detu, detumescence.

Table 2 Serum levels of cortisol (hydrocortisone) (given in µg/dL) in peripheral and cavernosal blood samples taken from patients with erectile dysfunction (ED) during different conditions of sexual arousal, exemplified by the penile conditions flaccidity, tumescence and detumescence

Penile condition	Blood source	Blood withdrawals commenced	Cortisol (µg/dL serum)
Flaccidity	CV	29	9.2±3.4
	CC	29	9.3±3.8
Tumescence	CV	33	9.9±5.7
	CC	33	10.3±5.6
Detumescence	CV	22	10.1±5.5
	CC	22	8.9±3.9

All data are given as mean ± standard deviation (SD). CC, corpus cavernosum; CV, cubital vein.

beginning of sexual arousal (CV: 9.2±3.4 to 9.9±5.7, CC: 9.3±3.8 to 10.3±5.6). Following the termination of sexual stimulation, serum cortisol in the CV continued to rise very slightly (to 10.1±5.5), whereas it declined in the cavernous compartment (to 8.9±3.9). The findings were regardless of the underlying cause (organogenic/psychological) of the ED. As in the healthy males, no marked differences in cortisol levels in the cavernous blood and systemic circulation were seen in the ED patients throughout the interval of the sexual response cycle. Results are displayed in *Figure 2* and *Table 2*. Overall, cortisol serum levels were higher in the healthy men than in the subjects with ED.

Discussion

Cortisol, a hormone produced in the adrenal gland, is known to be involved in the regulation of homoeostasis in brain, kidney and intestine, can raise blood pressure and glucose levels, cause sterility, dysfunction of the immune system and has also been associated with the sexual response cycle in males, including the erection process. The level of circulating cortisol is elevated in conjunction with increased activity of the sympathetic nervous system (for example, in response to stress) and may have a detrimental effect on sexual function in the adult male, whereas the aging process itself does not necessarily affect the adrenal production of cortisol (18,19). Although physiological concentrations (10 nM – 1 µM) of corticosteroids, such as the cortisol derivative prednisolone, did not exert contraction of isolated human penile erectile tissue (corpus cavernosum), ED has been frequently linked to stress and increased cortisol levels (16,20). Moreover, ED can be caused by conditions such as diabetes mellitus (DM), obesity, depression or alcoholism, all of which may chronically activate the hypothalamic-hypophyseal-adrenal axis, thus potentially leading to a permanent state of hypercortisolism (3). In humans, serum and saliva cortisol levels showed negative correlations with erectile function (according to the IIEF score), sexual desire and intercourse satisfaction (9). It has been demonstrated that hypercortisolemic subjects with DM and late onset hypogonadism are characterized by higher body mass index, lower testosterone and inferior parameters of sexual function when compared to normo-cortisolemic individuals (21). The findings from our study are in accordance with the aforementioned observations. In healthy male subjects, serum cortisol declined in the cavernous and systemic blood with the initiation of sexual arousal and the development of penile rigidity. This could possibly be explained by the inhibition of the adrenal secretion of cortisol into the systemic circulation. It does not seem likely that the course seen in the cavernous blood is due to local events, such as the degradation or binding of cortisol to receptors within the penile erectile tissue. In the patients with ED, no decline but a slight increase in serum cortisol in the systemic

circulation and the cavernous blood was noted when the individuals got sexually aroused and developed penile tumescence. One can speculate as to whether the immanent absence of a decline in the course of cortisol in the systemic circulation might impair an adequate physiological response to sexual stimulation. This point of view is in accordance with the hypothesis that increased circulating cortisol may inhibit the response to the intracavernous injection of prostaglandin E1 (PGE1) in men with ED (20). A study conducted by Kalaitzidou *et al.* (2014) reported a significant reduction in perceived stress score and a lower daily exposure to cortisol in men with ED subjected for 8 weeks to treatment with the phosphodiesterase 5 (PDE5) inhibitor tadalafil plus stress management in comparison to men treated with tadalafil only. Interestingly, the level of cortisol in the ED patients was overall lower than in the healthy males (22). In light of the findings from earlier investigations, this could possibly be interpreted in terms of an imbalance of the adrenocortical system (not necessarily linked to an immanent state of hypercortisolemia) that may also affect adrenal synthesis, central and peripheral sympathetic transmission and, hence, the ability to become sexually aroused (23,24). This point of view is supported by the fact that age is one of the risk factors for ED. In the group of patients, individuals were of older age (mean: 52 *vs.* 25 years in the group of healthy males) and exhibited some age-related comorbidities, such as hypertension, atherosclerosis, obesity, diabetes. With aging, the activity of the neurohypophyseal and adrenocorticotropic axis may alter (25).

Conclusions

The results are in accordance with the hypothesis that cortisol may have inhibitory effects on the male sexual response. Given the premise that a decline in circulating cortisol is one physiological prerequisite (among other prerequisites) to facilitate an erectile response to sexual stimulation, a dysregulation of the secretion and/or degradation of the hormone might well play a role in the pathophysiology of ED.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-566/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-566/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of the Hannover Medical School (Be 2045/1-2), informed consent was obtained from all participants.

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