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Systemic and cavernous plasma levels of vasopressin in healthy males during different functional conditions of the penis

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Abstract The role of the sympathetic adrenergic system in mediating the constant tone of penile flaccidity and returning the erect penis to its flaccid state is fairly well established. However, it is not yet known whether additional nonadrenergic-noncholinergic transmitters are involved in this process. Arginine-vasopressin (AVP, ADH), a pituitary peptide hormone with potent vasoconstrictor activity, may be one of the factors contributing to such control. The present study was undertaken to determine whether or not plasma levels of AVP change during penile flaccidity, tumescence, rigidity, and detumescence. We determined the plasma levels of AVP in the systemic as well as the cavernous blood of 25 healthy adult male volunteers who were exposed to visual and tactile erotic stimuli in order to elicit penile tumescence and erection. Whole blood was aspirated from the corpus cavernosum and the cubital vein, and AVP was quantified in plasma aliquots obtained from the whole blood samples. A marked decline in mean AVP plasma levels from 5.4 ± 2.7 ng/l during flaccidity to 2.9 ± 2.5 ng/l during rigidity was registered in the systemic blood of the subjects. No further decline was observed when the rigid penis became detumescent. In contrast, no alterations in AVP plasma levels were detected in the cavernous blood under the different penile conditions. The results from our study are contrary to the hypothesis of a local release and uptake of AVP in the cavernous compartment in the control of penile flaccidity and detumescence. Moreover, our findings are not in favour of AVP as an important mediator involved in adrenergic neurotransmission in the corpus cavernosum penis. Nevertheless, our data indicate that the decrease in systemic AVP levels in response to sexual arousal might be a prerequisite to facilitate penile tumescence and rigidity in healthy males.

Keywords Vasopressin · Cavernous and systemic blood · Penile erection · Sexual arousal

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Introduction

The regulation of penile cavernous and vascular smooth muscle tone is a complex physiological mechanism which involves the interaction of various centrally and locally acting transmitters and effector compounds which are produced by neuronal, endothelial and glandular structures [3, 12, 17]. There is no doubt that the release of neurotransmitters from the sympathetic and parasympathetic nervous system, as well as other mediator substances, e.g. nitric oxide (NO), contribute to the regulation of penile smooth muscle tone. However, it still remains to be clarified as to how other nonadrenergic-noncholinergic (NANC) factors mediate the tone of cavernous smooth muscle necessary for penile tumescence, rigidity and detumescence. It is already well established that the release of peptides is one of the most important mechanisms by which the normal function of mammalian tissues is maintained. Based on the results of numerous basic studies, some peptides, such as neuropeptide Y, vasoactive intestinal polypeptide and calcitonin gene-related peptide, are assumed to play a prominent role in the control of the penile erectile tissue [2].

The vasoconstrictory peptide arginine-vasopressin (AVP) has also been supposed to be one of the factors contributing to such control. AVP is synthesized in the hypothalamic area of the brain (nucleus supraopticus) and is stored in the pituitary gland. Upon neuronal stimulus, the peptide is released into the systemic circulation. AVP is mainly involved in the inhibition of diuresis by increasing the resistance of the vascular bed

of the kidneys, but it is also widely distributed in sympathetic nerve fibers innervating peripheral tissues of mammals, such as the penis [10]. AVP was found to potently contract isolated human cavernous smooth muscle, corpus spongiosum, and penile blood vessels; effects which can be inhibited by AVP antagonists [11]. Moreover, it induces penile erection when injected into the paraventricular nucleus of the hippocampus of male rats, although it is several-fold less potent than oxytocin [15]. On the other hand, there is no convincing evidence to date that AVP is involved in synaptic neurotransmission in the corpus cavernosum [18]. As the presence of AVP has been demonstrated in human cavernous tissue by means of radioimmunoassay, the hypothesis was developed that the peptide is either stored and/or synthesized locally [15]. Nevertheless, the role of AVP in the mechanisms controlling corpus cavernosum smooth muscle tone remains unclear. Therefore, the present study was undertaken to determine whether or not systemic and cavernous plasma levels of AVP change during penile flaccidity, tumescence, rigidity, and detumescence.

Materials and methods

Blood withdrawal

A total of 25 healthy adult males (mean age 26 years) with normal erectile function were empaneled into the study. The 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, Melsungen, Germany) was inserted into the left cubital vein and a 19 G butterfly needle (Abbott Laboratories, Sligo, Ireland) was placed into the left corpus cavernosum. Blood samples, starting with the flaccid state, were simultaneously taken from the corpus cavernosum and the cubital vein during penile flaccidity, tumescence, rigidity and detumescence. Penile tumescence and rigidity were induced by presenting the volunteers sexually explicit movie sequences and allowing them to stimulate their glans penis. The blood was drawn into syringes (9 ml S-Monovetten, Sarstedt, Nümbrecht, Germany) which were supplemented with 500 kallikrein inhibitor units/ml blood of protease inhibitor aprotinin (Trasylol, Bayer, Leverkusen, Germany) in order to avoid rapid degradation of peptides. The whole blood samples were immediately stored on ice and centrifuged at +4°C and 3,000 rpm for 10 min. The plasma was then separated and stored at −80°C.

Determination of AVP

AVP was extracted from plasma aliquots using ice-cold ethanol (100%). Samples were gently vortexed for 2 min, centrifuged (2,000 *g*, 15 min) and the ethanol phase was then aspirated and lyophilized. Following resuspension, a radioimmunoassay (Peninsula Laboratories, Belmont, Calif., USA) was used to determine AVP. In the case of a discrepancy greater than 15% between duplicate values, the results were disregarded. All data are given in ng/l plasma as mean ± SD.

Statistical analysis

Evaluation of the data was assisted by the Department of Biomathematics of the Hannover Medical School and carried out with SPSS 7.5 for Windows (SPSS, Chicago, Ill., USA). For a comparison of the systemic and cavernous AVP levels, the Student's *t*-test for paired samples was applied. $P < 0.05$ was considered statistically significant. Only AVP plasma levels registered in blood samples which were simultaneously drawn from the cubital vein and the cavernous body were statistically evaluated.

Results

AVP plasma levels in the systemic and cavernous blood

Simultaneous blood withdrawal from the cubital vein and the corpus cavernosum was facilitated in 14, 25, 24, and 17 subjects during penile flaccidity, tumescence, rigidity and detumescence, respectively. One subject failed to achieve an erection. Mean systemic AVP plasma level in the volunteers during penile flaccidity was 5.4 ng/l. Plasma AVP then dropped to 3.8 ng/l with the beginning of sexual arousal, when the flaccid penis became tumescent, and declined further to 2.9 ng/l and 3.0 ng/l during rigidity and detumescence, respectively. In the cavernous blood, no significant alterations in AVP plasma levels were detected for the respective penile conditions: mean plasma AVP in the cavernous blood was 3.3 ng/l during flaccidity, 3.4 ng/l during tumescence, 2.9 ng/l in the phase of rigidity, and 2.8 ng/l when the erect penis returned to flaccidity. The mean plasma AVP during the phase of penile flaccidity was higher in the systemic circulation than in the blood taken from the corpus cavernosum but systemic AVP concentrations adjusted to the cavernous levels in the phases of tumescence, rigidity and detumescence. The results are summarized in Fig. 1.

Discussion

Penile erection results from a complex interaction between the central nervous system and the local release and degradation of either mediating or inhibitory compounds. Apart from the classical transmitters of the sympathetic, parasympathetic and NANC nervous systems (adrenaline, noradrenaline, acetylcholine and NO), various peptides are assumed to play a role as inhibitory or excitatory transmitters or modulators involved in the regulation of penile flaccidity, erection, and detumescence [6, 7]. Recent as well as earlier work has shown that hypothalamic peptides, including human growth hormone and AVP, are commonly associated with the control of important behavioural actions including the components of male sexual function: arousal, erection, intromission and seminal emission [4, 8]. The potent contractile effects of AVP on human erectile tissue and cavernous arteries have been demonstrated and it was thought that this peptide might play a role in antagonizing the NO- and cGMP-mediated relaxation of human erectile tissue and, thus, in maintaining penile flaccidity and facilitating detu-

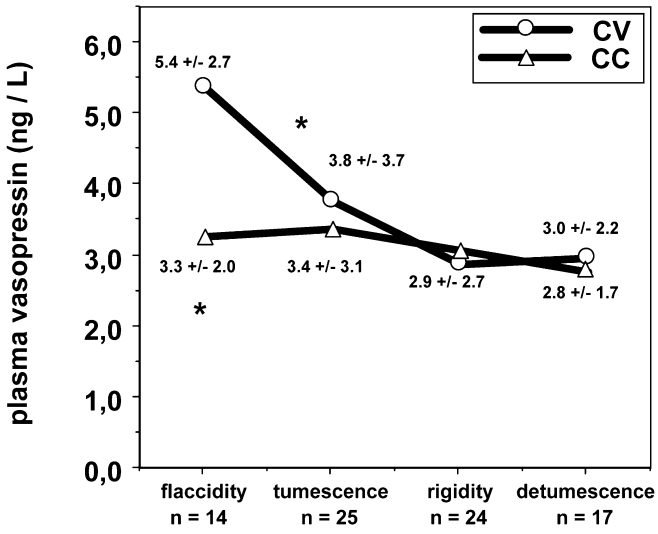

Fig. 1 Vasopressin (AVP) plasma levels (ng/l) in blood samples taken from the corpus cavernosum (*CC*, *triangles*) and the cubital vein (*CV*, *circles*) of healthy volunteers under different penile conditions. An *asterisk* close to the line indicates significant difference ($P < 0.05$) in systemic AVP levels under different penile conditions. An *asterisk* below a data point indicates a significant difference ($P < 0.05$) between systemic and cavernous AVP at the respective stage. *n* denotes number of volunteers from whom simultaneous blood withdrawal was performed from the corpus cavernosum and the cubital vein

mescence. Nevertheless, knowledge on the involvement of AVP in the regulation of human corpus cavernosum smooth muscle is still sparse. The detection of relevant amounts of AVP in human erectile tissue has led to the hypothesis that the peptide might be locally synthesized, stored and released [11]. Although the significance of AVP in synaptic transmission in the corpus cavernosum is still controversial, Segarra et al. presented some evidence that there might be a role for the peptide in the adrenergic control of human penile blood vessels [18].

Our finding that the cavernous plasma levels of AVP did not significantly alter from penile flaccidity to rigid erection and back to flaccidity strongly contradicts the hypothesis of a local synaptic or paracrine release of AVP. It has recently been demonstrated that cavernous plasma levels of norpepinephrine (NE) dropped significantly when a penile erection developed and increased again in the detumescence phase [5]. Thus, in the case of AVP being considered a co-transmitter of the sympathetic system, one would expect a course similar to that of NE in the cavernous blood. The apparent difference in systemic and cavernous AVP plasma levels during penile flaccidity also does not support the theory of a local release of AVP in the corpus cavernosum, although the cavernous compartment has been demonstrated to possess paracrine properties [13]. Nevertheless, one must take into account mechanisms of peptide degradation or AVP binding to V_1-receptors. While no V_1-receptors have yet been identified in the human corpus cavernosum, the activity of peptidase enzymes was shown in the human blood.

In contrast to the situation in the cavernous compartment, alterations were registered in systemic AVP levels with sexual arousal, penile erection and detumescence. The apparent drop in systemic AVP when the flaccid penis became tumescent can be due to the inhibition of pituitary AVP secretion into the circulation. It is well known that an increase in blood pressure correlates with a reduction in pituitary AVP release (Gauer-Henry reflex) [9, 14]. An increase in systemic blood pressure is the normal cardiovascular response to excitement and sexual arousal [1]. Hence, the dramatic increase in the inflow of systemic blood into the cavernous compartment in the phases of penile tumescence and rigidity did not result in an elevation in cavernous AVP levels, which, in turn, would probably hinder penile tumescence and erection. The decline in systemic AVP levels might be a prerequisite to facilitate the relaxation of penile arteries and cavernous smooth muscle and, thus, penile tumescence and rigidity in healthy males.

In an earlier study, Murphy et al. measured AVP plasma levels only in the systemic circulation of 13 healthy males during sexual arousal and ejaculation. In contrast to our data, they reported a fourfold increase in mean plasma AVP during arousal [16]. The measurement of AVP necessarily requires the extraction of the peptide from the plasma in order to avoid the interference of substances, such as albumin and reduced thiols, with the assay protocol. Thus, these conflicting results might be explained by the lack of accurate extraction procedures in their study.

In conclusion, our study indicates that AVP does not appear to be an important local mediator involved in sympathetic or NANC control of penile flaccidity and detumescence. Nevertheless, future studies to include patients suffering from erectile dysfunction of both organogenic and psychogenic causes may reveal whether or not there are differences in the systemic and cavernous courses of AVP in healthy males 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. Such studies might indicate potential dysregulations in the release or degradation of AVP, which may contribute to the impairment of erectile function.

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