Urol Res (2003) 31: 55–60
DOI 10.1007/s00240-002-0292-z

ORIGINAL PAPER

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Is serotonin significant for the control of penile flaccidity and detumescence in the human male?

Received: 18 July 2002 / Accepted: 14 November 2002 / Published online: 5 March 2003
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Abstract For more then 15 years, there has been speculation on the significance of serotonergic pathways in the control of male sexual function, especially in the maintenance of penile flaccidity and the initiation of detumescence. However, only a few in vivo studies on peripheral serotonergic transmission have been carried out. The aim of the present study was to evaluate further the effects of serotonin (5-HT) on isolated human erectile tissue and to detect serum levels of 5-HT in the systemic and cavernous blood taken during different penile conditions from healthy males. The effects of 5-HT on isolated human corpus cavernosum (HCC) were investigated using the organ bath technique. A total of 41 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 5-HT (ng/ml) were determined by means of an enzyme-linked immunosorbent assay. The cumulative addition of 5-HT (0.001–10 μM) induced contraction in the isolated HCC strips. The contractile response was abolished in the presence of 5-$HT_{1\alpha}$-receptor antagonist NAN-190. No attenuating effect of 5-HT was observed on electrically induced relaxation of the tissue. Moreover, amplitudes of relaxation remained unaltered in the presence of NAN-190. In the healthy volunteers, a significant increase in 5-HT levels was detected in the cavernous serum from flaccidity (113 ± 62) to tumescence and rigidity (140 ± 69 and 141 ± 54, respectively), followed by a decrease in the detumescence phase (123 ± 79). Changes in 5-HT levels in the systemic serum were less pronounced. Under all penile conditions, systemic 5-HT levels were higher than those registered in the cavernous serum. Although 5-HT does not appear to be involved in postsynaptic transmission in the HCC, our results may provide evidence for a physiological significance of 5-HT in the control of penile flaccidity and detumescence. Thus, our findings may give a rationale for the use of 5-HT antagonists in the pharmacotherapy of erectile dysfunction.

Keywords Human penile tissue · Serotonin · Penile erection · Cavernous blood · Systemic blood

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Introduction

The regulation of penile corpus cavernosum and vascular smooth muscle tone is a complex physiological mechanism involving the interaction of various centrally and locally acting transmitters produced by neuronal structures [14, 24]. There is no doubt that the release of neurotransmitters from the sympathetic, parasympathetic, dopaminergic and serotonergic nervous systems, e.g. adrenaline, noradrenaline, acetylcholine, dopamine and serotonin, mainly contribute to the regulation of penile smooth muscle tone. While parasympathetic and dopaminergic activity induces dilatation of the penile blood vessels and the corpus cavernosum smooth musculature, thus promoting penile tumescence and rigidity, the activation of the sympathetic outflow is related to the inhibition of erectile response in men [7]. As to serotonergic pathways, it still remains to be clarified whether this system elicits facilitatory or inhibitory effects on male sexual function. Our current knowledge

of the serotonergic influence on erectile capability has been gained mainly from in vivo experiments using the male rat model [17, 26, 30]. From these studies, contradictory findings emerged with regard to the pro-erectile or anti-erectile properties of serotonin (5-hydroxytryptamine, 5-HT) and the stimulation of serotonergic receptors located on lumbosacral spinal cord neurons sending axons into pelvic nerves which supply the penis. Immunohistochemical studies have revealed the presence of 5-HT positive nerve fibers and 5-HT receptors in the hypothalamic areas, brain stem, and sacral parasympathetic nucleus of the spinal cord of the male rat, all of which are anatomical regions involved in the control of copulatory function [25]. Some authors have presented morphological and pharmacological evidence for the involvement of 5-HT in mediating the inhibition of spinal sexual reflexes including the rat's ability to achieve penile intromission [19]. Others have demonstrated that a decrease in 5-HT brain levels by the inhibition of 5-HT synthesis enhances sexual activity in the male rat [2, 20, 29].

With regard to mammalian erectile tissue, in vitro experiments revealed that 5-HT causes contraction of the retractor penis muscle of the bull and, more recently, 5-HT_1-receptors were identified in human penile tissue by means of autoradiography [9, 15]. Although there is yet no evidence that relevant amounts of 5-HT are produced in the human corpus cavernosum, it is well documented that almost all 5-HT is located in the periphery of the human body, whereas less than 1% of the total 5-HT can be detected in serotonergic centers of the central nervous system [13]. It has been reported that 5-HT receptor agonists, such as 8-OH-DPAT, and several other drugs that facilitate or activate the 5-HT system, produce sexual stimulation in rats [1,2]. In men, an increased incidence of impotence has been reported in association with the administration of some selective serotonin reuptake inhibitors (SRIs) in male patients with depression and anxiety disorders [16, 18]. Although the details of the pathophysiological mechanism underlying this finding are as yet unknown, the inhibition of central 5-HT_2-receptors as well as the activation of peripheral 5HT_1-receptors have been taken into account [21].

Since the role of serotonergic pathways in the control of human male copulatory ability is not fully understood, the present study was conducted to further evaluate the effects of 5-HT on isolated human erectile tissue and to detect serum levels of 5-HT in the systemic and cavernous blood taken during different penile conditions from healthy male subjects.

Material and methods

Organ bath studies

Human erectile tissue was obtained from five patients (aged 21–57 years, mean age 38 years) who underwent male to female transsexual surgery. All experiments were performed within 12 h after tissue excision. Human corpus cavernosum (HCC) strips were mounted in a horizontal organ bath system (Mayflower organ bath, Hugo Sachs Elektronik, March, Germany) under standard conditions. Bath chambers (10 ml) were filled with a modified Ringer-Krebs solution (pH 7.4) of the following composition: NaCl 120 mM, $NaHCO_3$ 25.6 mM, KCl 4.7 mM, $CaCl_2$ 2.5 mM, NaH_2PO_4 1.2 mM, $MgCl_2$ 1.2 mM, glucose 22 mM, $2Na^+(Ca^{2+})$ EDTA 0.1 mM. A pre-tension of 0.5 g was applied and the tissue was allowed to equilibrate for at least 60 min. Contractile responses of the tissue to 5-HT (0.001–10 μM) in the absence and presence of 5-HT_{1A}-receptor antagonists NAN-190 and spiroxatrine (10 μM) were investigated using strips at basal tension.

In another setup, HCC tissue was exposed to 1 μM norepinephrine (NE). Once a stable adrenergic tension had been reached, electrical field stimulation (EFS, frequency 10 Hz, supramaximal current, single pulses of 0.8 ms, train duration 5 s, train interval 120 s) was commenced in order to produce tissue relaxation. After reproducible amplitudes of relaxation had been reached, either 5-HT or NAN-190 was added. Isometric responses of the tissue were registered using a MacLab data acquisition system (Analog Digital Instruments, Castle Hill, Australia). Each drug concentration was tested sixfold.

Blood sampling

A total of 41 healthy, adult males (mean age 26 years) with normal erectile function were empanelled into the study. Participants were placed in a supine position with the upper part of the body angled at 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 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 centrifuged by +4°C at 3,000 rpm for 10 min. The serum was separated and stored at −80°C.

Determination of 5-HT

An ELISA (supplied by IBL, Hamburg, Germany) was used to determine 5-HT serum levels. In the case of a discrepancy greater than 10% between duplicate values, these results were disregarded. All data are given in ng/ml serum as mean ± SD.

Statistical analysis

Evaluation of the data was carried out with SPSS 7.5 for Windows (SPSS, Chicago, Ill., USA). The Student's *t*-test for paired samples was applied to compare the systemic and cavernous 5-HT levels. A probability (P) value < 0.05 was considered statistically significant. Only 5-HT serum levels measured in blood samples simultaneously drawn from the cubital vein and the cavernous body were statistically evaluated.

Chemicals

Serotonin was obtained from ACROS Organics (Geel, Belgium), NAN-190 and spiroxatrine were from Tocris Cookson, (Bristol, UK), norepinephrine-HCl (Arterenol) was kindly provided by Hoechst (Frankfurt, Germany). All other laboratory chemicals were either purchased from Sigma Chemicals (St. Louis, Mo., USA), Merck (Darmstadt, Germany) or Tocris Cookson.

Results

Organ bath studies

The cumulative addition of 5-HT (0.001–10 μM) induced the contraction of isolated HCC strips. The median generation of tension was 11 mg, 116 mg, 446 mg, and 850 mg in the presence of 0.01, 0.1, 1 μM, and 10 μM of 5-HT, respectively. The contractile response was nearly abolished in the presence of 5-HT_{1A}-receptor antagonist NAN-190 (10 μM) but not spiroxatrine (Fig. 1). Relaxation of NE-stimulated HCC induced by means of EFS was abolished by tetrodotoxin, guanylyl cyclase inhibitor ODQ, and nitric oxide synthase inhibitor L-NNA (Nω-nitro-L-arginine) (data not shown). Amplitudes of relaxation were neither attenuated by the addition of 5-HT up to 10 μM nor enhanced in the presence of NAN-190 (10 μM) (Fig. 2, 3).

Course of 5-HT serum levels in healthy males

All data are given in ng/ml as mean ± SD.

The mean cavernous 5-HT level during flaccidity was 113 ± 62. This increased markedly from flaccidity to tumescence (140 ± 69) but did not rise further during penile rigidity (141 ± 54). During detumescence, the mean cavernous 5-HT serum level dropped to 123 ± 79. In contrast, alterations in 5-HT levels in the systemic circulation were less distinct (F: 151 ± 6, T: 162 ± 75, R: 156 ± 69, D: 154 ± 69). Under all penile conditions, 5-HT serum levels in the systemic blood were higher than those registered in the blood samples taken from the cavernous compartment (Fig. 4).

Discussion

There has been speculation for more then a decade as to whether serotonergic pathways are significant for the control of male sexual function, especially in the maintenance of penile flaccidity and the initiation of detumescence. 5-HT positive nerve terminals were shown to be present in autonomic centers controlling mammalian male copulatory activity and 5-HT_1-receptors were identified by means of autoradiography in human erectile tissue [9, 25]. Although it has been demonstrated that the central and local physiology may show significant interspecies differences [5, 6], almost all studies on serotonergic influence on male sexual behaviour were performed using the rat model [8, 17, 26, 27, 30]. From these studies, contradictory findings emerged with regard to the excitatory or inhibitory properties of 5-HT. These conflicting reports can, in part, be explained by the fact that selective 5-HT agonists and antagonists act on different receptors interacting with different effector systems to control male copulatory behaviour. For example, the depression of erectile function has been mainly attributed to the activation of 5-HT_{1A}, 5-HT_{1B}- and 5-HT_{2A}-receptors, whereas the activation of 5-HT_{1C}- and 5-HT_{2C}-receptors is supposed to facilitate erections [7].

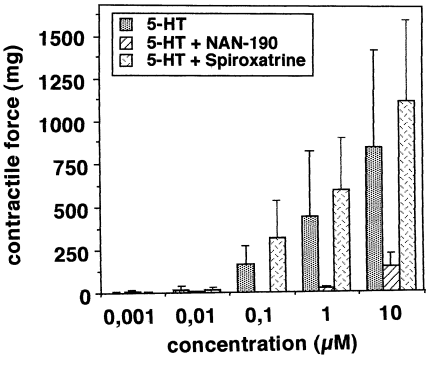

Fig. 1 Contractile effects of increasing concentrations of serotonin (5-HT) in the absence and presence of 10 μM of 5-HT_{1A}-receptor antagonists NAN-190 and spiroxatrine on isolated human erectile tissue. Each experimental setup was performed using $n = 9$–14 cavernous strip preparations

The aim of our study was to evaluate further the effects of 5-HT on isolated human erectile tissue and examine the course of systemic and cavernous 5-HT serum levels in healthy males under different functional conditions of the penile erectile tissue, indicating the different stages of sexual arousal.

The mean 5-HT serum level in the cavernous blood during penile flaccidity was found to be significantly lower than that registered in the blood samples taken from the systemic circulation. This might be due to the binding of 5-HT to respective recognition sites on the surface of cavernous smooth muscle cells and small arteries. Cavernous levels of 5-HT increased from penile flaccidity to tumescence. The immense arterial inflow into the cavernous body during the developing and rigid erection might contribute to the change in mean cavernous 5-HT serum level. Nevertheless, this increase may be explained not only by the flushing of the cavernous spaces with systemic blood but also by the potential release of 5-HT from cavernous receptor sites and, thus, by a change in the local 5-HT equilibrium. This hypothesis of a decreased but not totally abolished local receptor binding is strongly supported by the fact that the rise in cavernous 5-HT levels, which is partly due to the inflow of systemic blood, does not hinder penile rigidity. In the phase of detumescence, the mean cavernous 5-HT level dropped to 123 ± 79 ng/ml, whereas a concentration of 154 ± 69 ng/ml was registered in the systemic serum. This decrease is not solely due to the changes in penile hemodynamics which occurred during the termination of rigidity. During detumescence, arterial blood flow into the cavernous compartment is still several-fold higher than in the phase of flaccidity [28]. Thus, the significant drop in 5-HT might also be triggered by an increase in the binding of 5-HT to the receptor sites in the corpus cavernosum. A similar mechanism involving the recognition and release of mediator compounds at and from specific receptors has

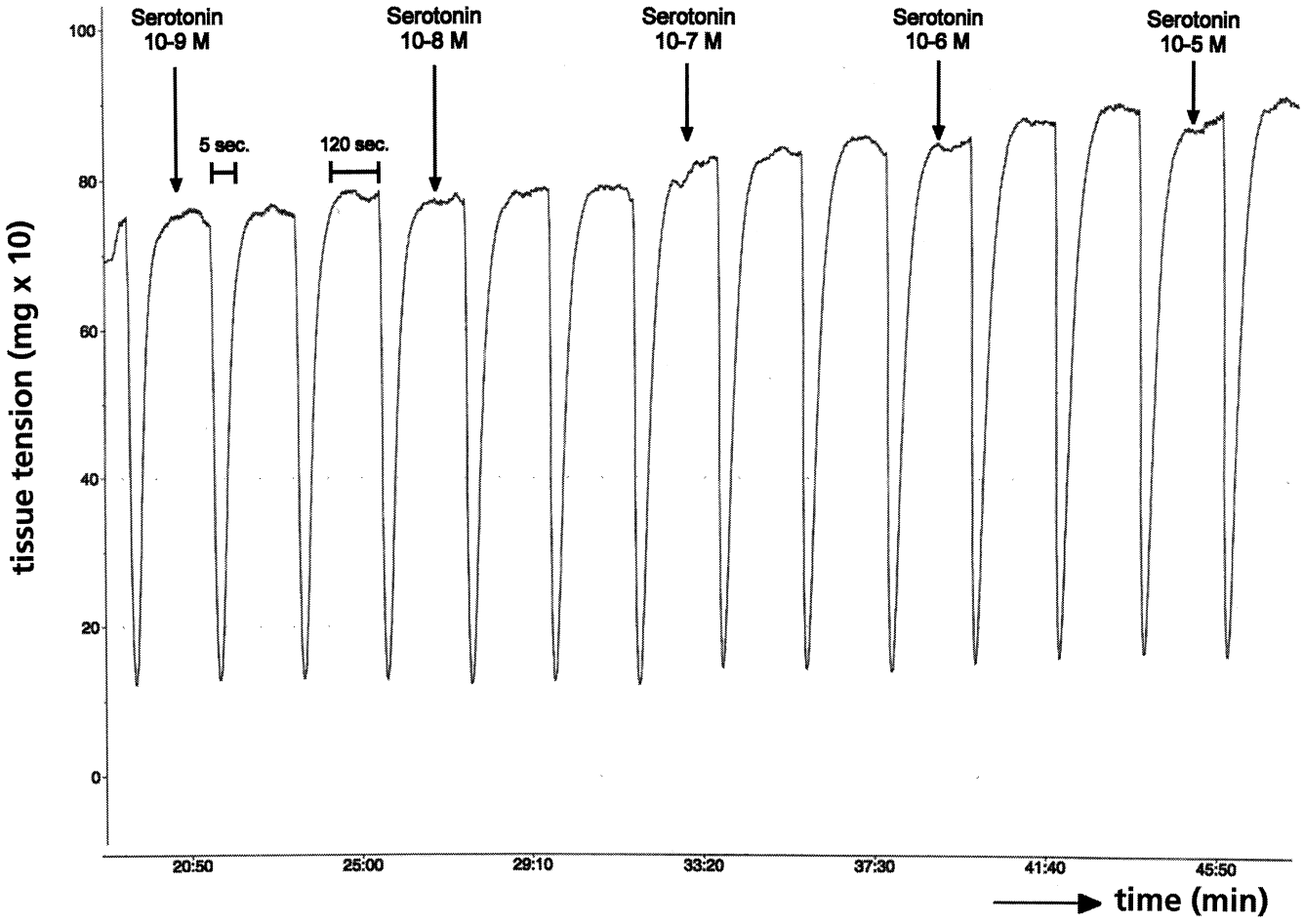

Fig. 2 Representative trace of an organ bath experiment presenting the lack of effect of the cumulative addition of 5-HT (0.001–10 μM) on EFS-induced relaxation of a NE-contracted human corpus cavernosum strip

been indicated recently by Becker et al. and Ness et al. with regard to the concentrations of the steroid hormone testosterone and the peptide vasopressin, respectively, in the systemic and cavernous blood of healthy males during different penile stages [10, 23]. Selected literature suggests that some side effects of SRIs may result from the actions of increased 5-HT levels at the periphery rather than in the central nervous system, e.g. on the genital tract smooth musculature [22]. According to our results, it is questionable that there are marked local effects of SRIs, since we demonstrated that – due to presumed alterations in the binding of 5-HT to receptors sites in the erectile tissue – a rise in cavernous 5-HT levels does not impair penile erection. Nevertheless, we believe that our results provide a physiological basis to explain the beneficial effects of the administration of 5-HT antagonists ketanserin and mianserin in the treatment of erectile dysfunction [4, 12]. These compounds may eject 5-HT from the recognition sites in the HCC, thus facilitating the induction of penile erection.

It is unlikely that the course of cavernous 5-HT registered in our study, reflects any changes in the activity of local serotonergic innervation. If this were the case, one would expect an inverted course of 5-HT in the cavernous blood: a peak level during flaccidity, a decrease with developing erection and rigidity, and again a rise with the initiation of detumescence. This conclusion is supported by the results from our organ bath studies. We demonstrated that the EFS-induced relaxation of isolated HCC was not attenuated by the cumulative addition of 5-HT. Moreover, 10 μM of 5-HT_{1A}-receptor antagonist NAN-190 did not affect HCC relaxation in terms of an enhancement of amplitudes. These findings are not in favour of the hypothesis of the existence of pre- and postsynaptic mechanisms involving 5-HT in the human corpus cavernosum. Therefore, one can conclude that serotonin is more likely to be transported from the systemic circulation into the cavernous compartment than being locally produced and released by nerve terminals. Our finding that the contractile responses of isolated HCC was nearly abolished in the presence of 10 μM of 5-HT_{1A}-receptor antagonist NAN-190 but not spiroxatrine might be explained by the fact that spiroxatrine has been described to act in vitro as a potent $alpha_2$-adrenergic receptor ligand rather than to interact with 5-HT_{1A}-receptors [11, 31].

In conclusion, our results suggest a role for 5-HT in keeping the penis flaccid and in facilitating detumescence although it is unlikely that 5-HT is produced in the

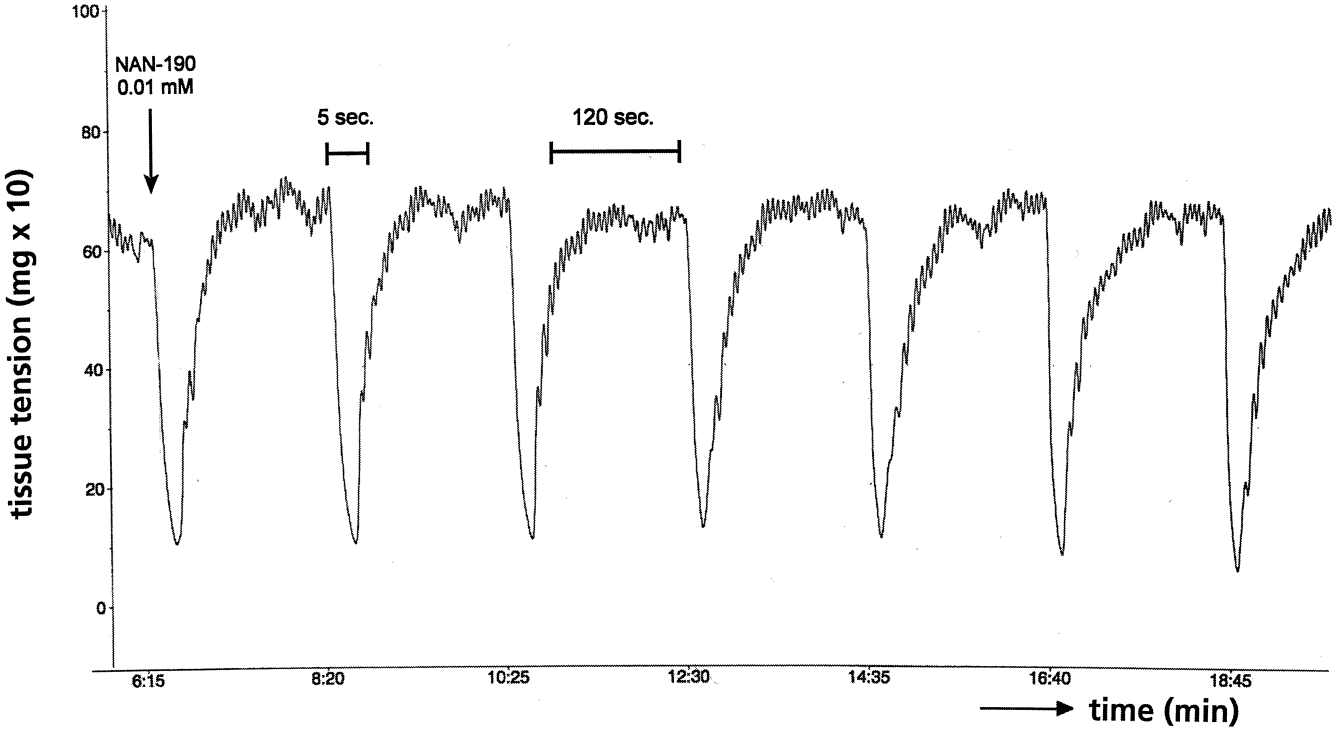

Fig. 3 Representative trace of an organ bath experiment presenting the lack of effect of a single dose of 5-HT_{1A}-receptor antagonist NAN-190 (10 μM) on EFS-induced relaxation of a NE-contracted human corpus cavernosum strip

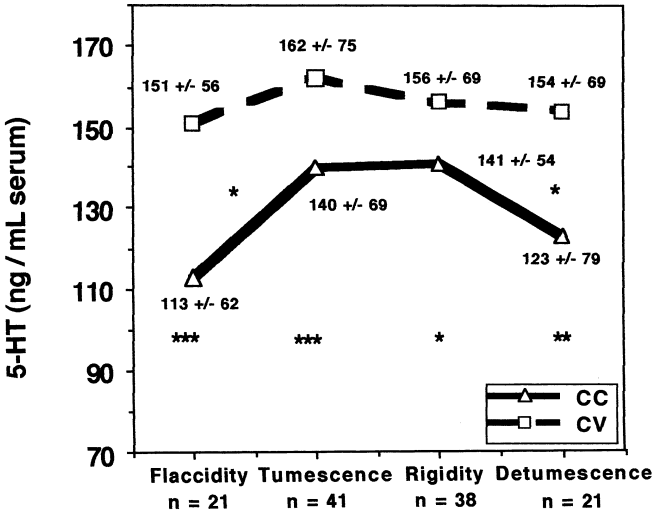

Fig. 4 Course of 5-HT serum levels (ng/ml) in blood samples taken from the corpus cavernosum (*CC*, *solid line*, *triangles*) and the cubital vein (*CV*, *dashed line*, *squares*) of healthy volunteers under different penile conditions. *Asterisks* close to the line traces indicate significant differences in cavernous or systemic 5-HT levels, respectively, under different penile conditions. *Asterisks* below the data points indicate significant differences between systemic and cavernous 5-HT in a respective stage. *n* denotes number of volunteers from whom blood was sampled simultaneously from the corpus cavernosum and the cubital vein. $*P < 0.05$, $**P = 0.005$, $***P < 0.001$

HCC. Moreover, 5-HT does not seem to be involved in the synaptic transmission in the HCC. It appears more likely that the effects of 5-HT on the HCC are rather mediated by alterations in the ratio of recognition and release to and from 5-HT receptor sites on the surface of the cavernous smooth muscle cells than by an active release of the compound from nerve endings.

Future studies including patients suffering from erectile dysfunction of both organogenic and psychogenic causes may reveal whether or not there are differences in the 5-HT 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. Such studies might indicate potential dysregulations in central serotonergic transmission and/or alterations in local receptor recognition mechanisms, all of which may contribute to the impairment of erectile function.

Acknowledgement We gratefully acknowledge support by a grant from the Deutsche Forschungsgemeinschaft DFG (Be 2045/1-1/1-2).

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