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# Doxazosin and Serotonin (5-HT) Receptor (1A, 2A, and 4) Antagonists Inhibit 5-HT-Mediated Human Cavernosal Contraction

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## Abstract



Penile erection results from the balance between relaxation and contractile mechanisms of the corpus cavernosum. Only a few studies suggest a role for endogenous contractile agents such as 5-hydroxytryptamine (5-HT). Our aim was to confirm the possible role of 5-HT in human erection. The effect of 5-HT on human cavernosal tissues, as well as those of doxazosin (shown previously to have 5-HT inhibitory action), ketanserin (5-HT (2A) receptor antagonist), NAN-190 (5-HT (1A) receptor antagonist), and SB 203186 (5-HT (4) receptor antagonist) on 5-HT-mediated effects, were assessed using the organ bath technique, including electrical field stimulation study (EFS). Results are presented as median (mg/mg = mg contraction/mg of tissue). Consistent 5-HT-mediated ($10^{-3}$ M) contractions were demonstrated (n = 18; 63 mg/mg). These contractions were inhibited with ketanserin by 90% (n = 8), NAN-190 by 68% (n = 12), and SB 203186 by 55% (n = 12). Doxazosin showed a similar 5-HT inhibitory action in a concentration-dependent manner ($10^{-4}$ M; 94% reduction; n = 8, $10^{-6}$ M; 68.3% reduction; n = 8). Our EFS studies indicated the presence of neuronally derived 5-HT and that a majority of the nonnoradrenogenic contraction (54%) was mediated via 5-HT(2A) receptors. These findings suggest that 5-HT may play a role in the human detumescence process via 5-HT(1A), 5-HT(2A), and 5-HT(4) receptors. Neuronally released 5-HT is probably an

important contractile neurotransmitter in the erectile process. Doxazosin, ketanserin, and 5-HT(1A) and 5-HT(4) receptor antagonists may be useful as part of combination therapy used to treat erectile dysfunction.

Key words: 5-hydroxytryptamine, erectile dysfunction, corpus cavernosum, cavernosal tone

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Erectile dysfunction (ED) is broadly defined as the inability to achieve or maintain an erection sufficiently rigid for satisfactory sexual intercourse (NIH Consensus Development Panel on Impotence, 1993). ED affects as many as 50% of men over the age of 40 years to some degree and has substantial impact on quality of family life (Carson, 2004).

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine transmitter found with its receptors both in the central and peripheral nervous system (CNS/PNS), as well as in a number of nonneuronal cells in the gut, cardiovascular system, and blood. 5-HT is one of the oldest neurotransmitters in evolution. It has been implicated in the etiology of numerous disease states, including depression, anxiety, hypertension, and irritable bowel syndrome. 5-HT receptors are divided into 7 distinct classes (5-HT (1) to 5-HT(7)) based on their structural and functional characteristics. These receptors are part of the G-protein-coupled receptor (GPCR) superfamily, with the exception of the 5-HT(3) receptor, which is a ligand-gated ion channel (Martin et al, 1994).

5-HT neuron participation in the control of sexual behaviour, both in humans and in animals, is well established (Hull et al, 2004). Specifically, Bancila et al (2002) demonstrated a possible role of the paraventricular nucleus (brain) in penile erection through the control of descending serotonergic raphe-spinal neurons. In general, central (brain) activation of the 5-HT(1A) receptor inhibits (Ahlenius et al, 1989; Rehman et al, 1999), and activation of 5-H(2A) and 5-HT(2C) receptor facilitates, erection (Steers et al, 1990; Bancila et al, 1999; Brotto et al, 2000). Central acting drugs that influence the 5-HT pathway can affect erectile function. For example, serotonin-specific reuptake inhibitors such as paroxetine can increase the incidence of ED due to inhibition of nitric oxide synthase (NOS) activity (Angulo et al, 2001). Also, trazodone, an antidepressant, which exerts its effect via its major metabolite, metachlorophenylpiperazine (m-cpp, a neuronal 5-HT releaser) can cause priapism (Myrick et al, 1998; Rothman et al, 2002).

Peripherally, evidence has emerged of the involvement of the serotonergic pathway in the erectile process. Previous studies on penile vessels demonstrated an in vivo 5-HT-mediated inhibitory action on penile erection in rats due to vasoconstriction of the cavernosal arteries (Finberg et al, 1990). The in vitro 5-HT-mediated contractile response in human penile veins was augmented in patients with veno-occlusive disease (Esen et al, 1997). Animal studies indicated the involvement of 5-HT(1A) (Hayes et al, 2002; Furukawa et al, 2003), 5-HT(1B) (Hayes et al, 2002), and 5-HT(2A) receptors (Furukawa et al, 2003) in contracting cavernosal smooth muscle. In addition, Uckert et al (2003) had shown 5-HT(1A)—mediated contractile response (in vitro) in human corpus cavernosal strips. A human study by Hayes et al (1999) also suggested the presence of 5-HT(4) receptors in cavernosal muscle.

Doxazosin (an alpha-1—blocker shown to have 5-HT inhibitory action (Khan et al, 2000; Jagroop et al, 2001) and ketanserin (5-HT(2A) receptor antagonist) have been shown to have a beneficial action on ED. Doxazosin also acts on ED in combination with either sildenafil (de Rose et al, 2002) or intracavernosal prostaglandin E(1) therapy (Kaplan et al, 1998) when either sildenafil or the cavernosal therapy alone has failed. The combined intracavernosal injection therapy of ketanserin and prostaglandin E(1) was effective in producing an erection sufficient for sexual intercourse in 76% of patients with ED when the prostaglandin E(1) therapy alone had failed (n = 45; Mirone et al,

1996). Petersen et al (1985) noted concomitant penile tumescence in their study, which showed improved maximum urinary flow rates in patients with benign prostatic hyperplasia who were treated with ketanserin.

Since most functional (organ bath) studies were performed on animals, we aimed to further evaluate the involvement of 5-HT in the human erectile process via 5-HT(1A), 5-HT(2A), and 5-HT(4) receptors. We also evaluated whether doxazosin exhibits a protumescence effect.

## Materials and Methods


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### Tissues

Human penile organs were obtained from patients undergoing gender reassignment surgery at Charing Cross Hospital, London, United Kingdom (15 patients, age range 23–57, mean age 30). Approval was obtained from the Riverside Ethics Committee, and all the patients gave their informed consent prior to surgery. Their penile organs were excised and immediately placed in Krebs solution and kept in an ice-containing box. The Krebs solution was made up of NaCl 120 mM, $NaHCO_3$ 25.6 mM, KCl 4.7 mM, $CaCl_2$ 2.5 mM, $NaH_2PO_4$ 1.2 mM, and glucose 22 mM with a pH of 7.4.

All patients underwent gender reassignment surgery and had no significant previous illness (including diabetes) and were not on any medication apart from estrogen for 2 years. However, the estrogen therapy was discontinued 2 months prior to surgery.

### Materials

The following drugs and other materials were supplied by Sigma Chemical Co. (Poole, Dorset, United Kingdom): atropine hydrochloride, guanethidine, indomethacin, and phenylephrine. Tetrodotoxin was provided by Bachem Fine Chemicals (Switzerland). Tocris Cookson Ltd, Bristol (United Kingdom), provided the following chemicals: corynanthine, yohimbine, NAN-190, SB 203186 and ketanserin. Doxazosin and 5-hydroxytryptamine were gifts from Pfizer (United Kingdom).

### Organ Bath Studies

*Tissue Preparation*— The tunica albuginea was opened to expose the cavernosal tissues. Once they were isolated, the cavernosal tissue was cut into 5 x 5 x 6-mm strips. The tissues were dissected following the penile trabecular structure. The strips were strung up in vertical organ bath systems. Each bath chamber was filled with 10 ml of Krebs solution maintained at 37 °C and continuously gassed with a mixture of 95% $O_2$ and 5% $CO_2$. An initial tension of 2 *g* was applied, and the strips were allowed to equilibrate for 1 hour without any further mechanical manipulation (Thompson et al, 2001).

*Establishment of 5-HT-Mediated Response*— Adding 5-HT $10^{-3}$ M to the bath chamber assessed the response of cavernosal tissue strips to 5-HT. Accumulated dose-incremental 5-HT-mediated responses were not performed, as we had previously demonstrated tachyphylaxis of 5-HT with accumulative doses in human cavernosal strips. Specifically, we showed 43.8% reduction of maximal/overall 5-HT contraction with accumulative doses (5 x $10^{-7}$ M, 3 x $10^{-6}$ M, $10^{-5}$ M, 3 x $10^{-5}$ M, $10^{-4}$ M, and $10^{-3}$ M) of 5-HT 30 minutes following initial same accumulative doses of 5-HT followed by washout x 3 (initial: median 11.88 mg/mg, minimum 5.83 mg/mg, maximum 25.65 mg/mg; at 30 minutes: median 6.68 mg/mg, minimum 3.65 mg/mg, maximum 21.29 mg/mg; $P < .02$ Wilcoxon test, n = 7 each group). Others had

also shown similar 5-HT tachyphylaxis responses (Sicuteri, 1983; Javid et al, 1999; Whalen et al, 2000; Lopez-Tudanca et al, 2003). However, a single-dosage exposure of human cavernosal strips to 5-HT $10^{-3}$ M and subsequent same 5-HT reexposure 30 minutes after vehicle (distilled water) addition both gave similar 5-HT–mediated contractile responses, with no significant difference (Table 1). Thus, this single-dosage 5-HT addition was adopted in our study. The dose of $10^{-3}$ M was chosen because it was shown to give optimal results when assessing the responses of 5-HT with and without preexposure to its antagonists in our previous study (Khan et al, 2000).

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Table 1. *5-HT-mediated contraction of human cavernosal tissues before (control) and after the addition of a chemical agent (antagonist or distilled water [vehicle]). Results are presented as median (range) in mg tension/mg of tissue. N denotes number of patients studied. Wilcoxon test is used for statistical analysis. Significance is described as P < .05*

*Characterization of 5-HT Receptor Subtype*— The effect of distilled water, NAN-190 ($10^{-5}$ M; 5-HT (1A) receptor antagonist), ketanserin ($10^{-5}$ M; 5-HT (2A) receptor antagonist), SB 203186 ($10^{-5}$ M; 5-HT (4) receptor antagonist), corynanthine ($10^{-5}$ M; alpha(1) receptor blocker), yohimbine ($10^{-5}$ M; alpha(2) receptor blocker) and doxazosin ($10^{-4}$ and $10^{-6}$ M; alpha(1) receptor blocker) on 5-HT-mediated responses were also assessed. This was carried out by adding the substance concerned including distilled water ($DH_2O$) (as controls) to the bath after initial exposure to 5-HT $10^{-3}$ M. The bath was then left for 30 min prior re-exposure to 5-HT $10^{-3}$ M.

*Electrical Field Stimulation (EFS) Studies to Assess Possible Neuronally Released 5-HT*— EFS studies were also carried out to assess the effect of ketanserin on the possible neuronally released 5-HT in cavernosal tissues. Each tissue strip was positioned between 2 metal rings connected to an electrical circuit and was also subjected to an applied tension of 2 g for 1 hour. Tissues were then exposed to atropine $10^{-5}$ M, guanethidine 5 x $10^{-6}$ M, L-NAME 3 x $10^{-4}$ M, and indomethacin $10^{-6}$ M (by adding the substances to the organ baths) to inhibit the parasympathetic, sympathetic, NO, and prostaglandin pathways, respectively. This treatment would enable the EFS studies to unmask any nonadrenergic-mediated contraction, which could include 5-HT–induced contraction. The tissues were left for 30 minutes following the addition of these substances. Electrical currents of increasing intensity (0.5, 1, 2, 5, 8, 16, and 32 Hz) were applied across the tissue strips. Each stimulus was applied for 5 seconds, with a rest interval of 2 minutes between each stimulus. Tissue strips with contractile responses were then exposed to ketanserin $10^{-5}$ M. After 30 minutes of exposure to ketanserin, the EFS (described above) were repeated in the tissues concerned to assess the possible neuronal 5-HT–mediated contractions. Tetrodotoxin $10^{-6}$ M, a neurotoxin, was used to determine the magnitude of contractions related to direct muscle stimulation as opposed to neuronal-mediated contraction. Tetrodotoxin was added to organ baths, and the tissue strips were exposed for 20 minutes before EFS was started. This was the last stage of each EFS study. We had previously shown that repeated EFS x 3 did not cause desensitization of the tissue (Calvert et al, 2001; Banks et al, 2006).

*Establishing Tissue Viability at the Beginning and the End of the Experiments*— All cavernosal tissues used in this study showed a similar potassium chloride (120 mM)-induced contraction at the beginning and the end of the experiments (variability < 10%). Those with variability in responses > 10% were excluded from the study.

*Measurement of Tissue Response*— Isometric responses of the tissue were amplified and recorded

using a Chart 4 Windows program. The tissue used in the organ bath was weighed and this value recorded. The contractile/relaxant response of the tissue to a contractile, relaxant, or drug agent was reported in mg/mg (contraction/mg of tissue) by dividing the amount of contraction/relaxation occurring on exposure to an agent by the weight of the tissue concerned.

### *Statistical Analysis*

A statistical analysis software (PRISM, Graph Pad Inc., San Diego, Calif) was used for the statistical analysis of the human functional studies. Comparisons were made using the 2-tailed nonparametric paired (Wilcoxon) test.

## Results


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Consistent 5-HT–mediated ($10^{-3}$ M) contractions from baseline recordings were demonstrated in human cavernosal tissues (n = 25, median 63 mg/mg, range 10.2–178.5 mg/mg).

Experiments with the vehicle (ie, distilled water) used to dissolve the substances evaluated in this study revealed a similar magnitude of 5-HT–mediated contraction before (median 98.8 mg/mg) and after (median 92.0 mg/mg, n = 14) adding $DH_2O$ ($P > .1$, Table 1). These contractions were inhibited by ketanserin by 91% (n = 11, Table 1), NAN-190 by 68% (n = 12, Table 1), and SB 203186 by 55% (n = 12, Table 1).

Doxazosin showed a similar 5-HT inhibitory action in a concentration-dependent manner ($10^{-4}$ M; 94% reduction; n = 8, $10^{-6}$ M; 84% reduction; n = 10, Table 2). The doxazosin response was not attributable to alpha blockade, since alpha-1 and 2 antagonists (corynanthine and yohimbine) had no significant effect on 5-HT–induced contractions (Table 2).

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Table 2. *5-HT–mediated contraction of human cavernosal tissues before (control) and after the addition of a chemical agent (antagonist or distilled water [vehicle]). Results are presented as median (range) in mg tension/mg of tissue. N denotes number of patients studied. Wilcoxon test is used for statistical analysis. Significance is described as P < .05*

Optimal human cavernosal contractions of 6.3 mg/mg were observed at 32 Hz in the EFS studies where tissues were preexposed to indomethacin, guanethidine, atropine, and L-NAME (Figures 1 and 2). The subsequent addition of ketanserin led to abolition of 54% of the EFS-induced cavernosal contractions (Figure 1). Adding tetrodotoxin inhibited a further 34% of these reduced EFS-induced contractions (Figure 1).

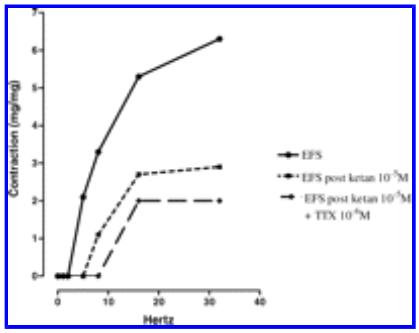


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Figure 1. The effects of increasing frequencies of electrical field stimulation (median 6.3, range 3.0–89.7, control) on human corpus cavernosum (n = 8) pretreated with atropine $10^{-5}$ M, guanethidine 5 x $10^{-6}$ M, L-NAME 3 x $10^{-4}$ M, and indomethacin $10^{-6}$ M and the changes seen in EFS following the exposure to ketanserin (ketan) $10^{-5}$ M (median 2.9, range 1.3–5.4, *P* = .001 versus control) and then plus tetrodotoxin (TTX) $10^{-6}$ M (median 1.9, range 0.9–4.6, *P* = .001 versus control). Contractions are expressed as median and range values (mg tension/mg of tissue).

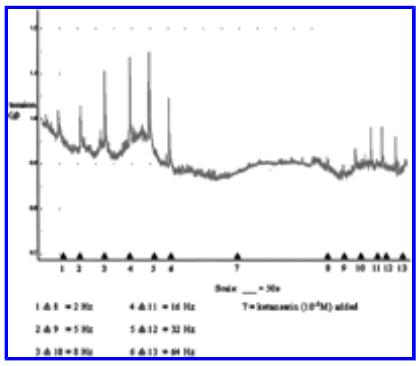

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Figure 2. A representative tracing showing the contractile response following electrical field stimulation (EFS: 2, 5, 8, 16, 32, 64 Hz) of human cavernosal strips (preexposed to atropine $10^{-5}$ M, guanethidine 5 x $10^{-6}$ M, L-NAME 3 x $10^{-4}$ M, and indomethacin $10^{-6}$ M). Addition of ketanserin ($10^{-5}$ M), a 5-$HT_2$ antagonist, reduced the EFS-induced contractions. The response was measured in grams (g).

## Discussion



Our findings show for the first time that there is possibly preterminal neuronal storage of 5-HT in the human corpus cavernosum, which is released by EFS and acts on 5-HT(2A) receptors. This is shown following blockade of the effects of prostaglandin, neuronal- and endothelial-derived NO, sympathetic and parasympathetic pathways with indomethacin, L-NAME, guanethidine, and atropine, respectively, prior to EFS with and without ketanserin addition. The EFS-contractile responses in our study are nonnoradrenergic, as guanethidine leads to effective inhibition of noradrenaline release from sympathetic nerves. The neuronally released 5-HT acting on 5-HT(2A) receptors comprises 54% of the nonnoradrenergic (neuronal)-mediated human cavernosal contraction. Thus, neuronally released 5-HT is probably a contractile neurotransmitter in the erectile process in addition to noradrenaline (NA). This is in contrast to the findings of Uckert et al (2003). They concluded in their study that 5-HT did not contribute to neuronal derived function of the human corpus cavernosum (HCC). They added a 5-HT(1A) antagonist following EFS of precontracted cavernosal strips with phenylepherine. They showed a brief relaxation response (attributed to neuronal nitric oxide release) with each EFS, which was not altered following subsequent addition of the 5-HT antagonist. If neuronally derived 5-HT acts on 5-HT(1A) receptors, this method did not guarantee effective blockage of the 5-HT(1A) receptors, as activation of the receptors by neuronally derived 5-HT would have occurred prior to the addition of the antagonist. It may also be that 5-HT(2A)

(shown in our study) and not 5-HT(1A) receptors contribute to neuronal-derived 5-HT action on HCC.

Uckert et al (2003) also reported a significant increase in 5-HT levels in cavernous serum (mean ng/ml) from flaccidity (113) to tumescence and rigidity (140 and 141, respectively) and also the detumescence phase (123) in normal human subjects. There were less pronounced changes in 5-HT levels in the systemic circulation at all stages. This variation in local 5-HT levels in different stages of erection may be important in ensuring detumescence. It is possible that neuronally released 5-HT contributes to this variation. Therefore, 5-HT may have a physiological role in the control of penile flaccidity.

We show in our studies that 5-HT $10^{-3}$ M does not act on alpha-1 or alpha-2 receptors, as corynanthine and yohimbine, respectively, have no significant effect on the 5-HT-mediated contraction. Therefore, the antagonistic effects of ketanserin and doxazosin on 5-HT-mediated contraction are via 5-HT and not alpha-receptors.

We provide a new finding of the effect of a 5-HT(2A) receptor antagonist on HCC, suggesting possible antierectile role of the 5-HT(2A) receptor subtype. Furthermore, we support previous evidence (Mirone et al, 1996; De Rose et al, 2002) that doxazosin and ketanserin may be beneficial in the treatment of ED (findings presented at the 2nd International Consultation on Erectile and Sexual Dysfunction in Paris, 28th June–1 July 2003) as well as that the 5-HT(1A) receptor subtype might play a role in human detumescence (Uckert et al, 2003). Our previous and present studies have demonstrated that doxazosin had 5-HT inhibitory action not just in the human corpus cavernosum but also in rabbit bladder detrusor muscle (Khan et al, 2000) and human platelets (Jagroop et al, 2001). These suggest that doxazosin also acts on 5-HT receptors. Our studies set the precedent for future studies to evaluate the mechanisms of 5-HT-inhibitory actions by doxazosin.

The possible serotonergic-related action noted with doxazosin raises the question whether other alpha-blockers (e.g. alfuzosin or tamsulosin) exert a 5-HT-mediated effect. It is possible that similar bioprofile of serotonergic-induced action to that of doxazosin might account for the improvement in erection in men with lower urinary tract symptoms and concomitant sexual dysfunction treated with alfuzosin (van Moorselaar et al, 2005). Apart from erection, this possible blocking of 5-HT–mediated effect by alpha-blockers may also simultaneously improve bladder symptoms related to bladder outlet obstruction (Khan et al, 2005). Therefore, the beneficial effect of alpha-blockers on the bladder may not be exclusively mediated via alpha-receptor.

Our study suggests a contractile effect on HCC via 5-HT(4) receptors, which is in contrast to what was observed in rabbits (Furukawa et al, 2003), where a 5-HT(4) receptor antagonist potentiated 5-HT-mediated contraction. Therefore, 5-HT(4) receptor activation may contribute to cavernosal relaxation in rabbits. These findings indicate interspecies variability in 5-HT–mediated action via different receptor subtypes.

The potency of 5-HT receptor–mediated responses according to different receptor subtypes are in the order (% inhibition of 5-HT-mediated contraction by its respective antagonist): 5-HT(2A) 90% > 5-HT (1A) 68% > 5-HT(4) 55%. This order indicates the relative importance of each of the 3 receptors in affecting the 5-HT-mediated contraction, with the dominant receptor being 5-HT(2A). Therefore, 5-HT (2A) may play a greater part in the antitumescence process compared with 5-HT(1A) or 5-HT(4) receptor subtypes.

Erection depends on the balance of local contractile and relaxant forces in the corpus cavernosum (Cellek, 2000; Kim et al, 2000). Tumescence/erection is favored if the overall relaxant force

dominates to lower cavernosal tone to a critical level and vice versa. Therefore, it is not inconceivable that by targeting the contractile pathway such as 5-HT as well as promoting a relaxant pathway (eg, with a phosphodiesterase-5 (PDE-5) inhibitor), the critical level will be achieved more readily in patients with ED. Our findings indicate that doxazosin and 5-HT(1A), 5-HT(2A) (such as ketanserin), and 5-HT(4) receptor antagonists may be useful as part of a multitherapy regime, especially when a single therapy with a PDE-5 inhibitor fails.

Normal HCC is limited in its availability. In previous studies, HCC tissues were obtained from patients with Peyronie disease or diabetes or undergoing penile prosthesis implants for ED (Mirone et al, 2000). These samples are clearly pathological. Mirone et al (2000) and Rees et al (2001) proposed the use of HCC tissue obtained from patients undergoing gender reassignment surgery. These patients are normally on estrogen for 2 years prior to withdrawal 2 months before their surgery, as with the majority of patients involved in our study. We cannot exclude the effect of estrogen on the cavernosal tissue, as Adaikan et al (2003) showed that estrogen causes pathophysiological changes in erectile function in rats. However, in our study, 1 patient who refused estrogen therapy prior to surgery had similar 5-HT responses (with or without pre-exposure to its antagonists) to those on estrogen. Furthermore, those gender-reassigned patients previously on estrogen seem to have "normal" erections (indicated by the presence of early morning erections), based on clinical interviews post–estrogen withdrawal prior to surgery.

Future work should involve immunohistochemical studies using cavernosal tissue to further identify/confirm the 5-HT receptor subtype and distribution as well as their anatomical location (eg, nerve terminals and/or endothelium).

In conclusion, neuronally-released 5-HT may play a role in the human detumescence process. Doxazosin and 5-HT(1A), 5-HT(2A) (such as ketanserin) and 5-HT(4) receptor antagonists possess proerectile effects that may prove useful in the treatment of ED, possibly in combination with other therapy.

## Footnotes

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