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ORIGINAL ARTICLE

Investigation of serotonin receptors in the isolated penile bulb of rats

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The aim of this study was to investigate serotonin (5-HT) receptors in the penile bulb, which have been suggested to play a role in penile erection. Serotonin (10^{-7}–3×10^{-4} M) contracted penile bulbs in a concentration-dependent manner. Ketanserin (5-HT_{2A} antagonist, 10^{-9}–10^{-7} M) and prazosin (α_1-adrenergic receptor blocker, 10^{-9}–10^{-7} M) suppressed the lower and upper parts of concentration–response curves to 5-HT, respectively. Guanethidine (adrenergic neuron blocker, 5×10^{-5} M) reduced the responses to 5-HT at only 10^{-4} and 3×10^{-4} M concentrations. NAN-190 (5-HT_{1A} antagonist, 10^{-8}, 10^{-7} M) shifted the concentration–response curve to the right with a reduction in the maximum response to 5-HT. While ondansetron (5-HT_3 antagonist, 10^{-6}–10^{-5} M) and GR55562 (5-$HT_{1B/1D}$ antagonist, 10^{-6}–10^{-5} M) had no effect on the concentration–response curve to 5-HT. The 5-HT_{1A} agonist 8-OH-DPAT (10^{-7}–3×10^{-4} M) contracted penile bulbs in a concentration-dependent manner with a lower pD_2 value than that of 5-HT. Sumatriptan (5-$HT_{1B/1D}$ agonist, 10^{-8}–10^{-4} M) did not produce any contractile response in the penile bulbs. Prucalopride, a selective 5-HT_4 agonist (R093877, 10^{-7}–3×10^{-4} M) produced concentration-dependent relaxation in penile bulbs contracted by phenylephrine (10^{-5} M). 5-HT_4 agonists cisapride (10^{-7}–10^{-4} M) and metoclopramide (10^{-7}–3×10^{-4} M) also relaxed the tissue, concentration-dependently. Selective 5-HT_4 antagonists GR125487 (10^{-6}–10^{-5} M) and GR113808 (10^{-6}–10^{-5} M) slightly, but not significantly, decreased prucalopride- and cisapride-induced relaxation. Propranolol (β-adrenergic receptor blocker, 10^{-6}–10^{-5} M) and L-NOARG (nitric oxide synthase inhibitor, 10^{-4} M) had no effect on prucalopride-induced relaxation. These results suggest the existence of α_1-adrenergic, 5-HT_{1A} and 5-HT_{2A} serotonergic receptors in the penile bulb of rats, which are responsible for 5-HT-induced contraction. Additionally, a serotonergic receptor resembling a 5-HT_4-type plays a role in the relaxation. The latter receptor is activated by 5-HT_4 agonists, but is not antagonized by 5-HT_4 antagonists.
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Keywords: penile bulb; serotonin receptors; ketanserin; prazosin; prucalopride

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) receptors are classified into seven different subtypes, namely 5-$HT_{1,2,3,4,5,6,7}$, and 5-HT_1 and 5-HT_2 receptors are subdivided into five subtypes (5-$HT_{1A,\ 1B,\ 1D,\ 1E,\ 1F}$) and into three subtypes (5-$HT_{2A,\ 2B,\ 2C}$), respectively[1,2] (Table 1). Fenfluramin (5-HT-releasing agent) induced penile erection in rats through the central nervous system.[3] On the other hand, the stimulation of 5-HT_{1A} or 5-HT_2 receptors by administration of 5-HT agonists inhibits penile erection in rats.[4] It is unknown whether peripheral administration of 5-HT agonists *in vivo* produces penile erection via central and/or peripheral mechanisms. Serotonin has been reported to induce contraction in the isolated corpus cavernosum penis (CCP) of rabbits.[5] Therefore, it has been suggested that 5-HT agonists may peripherally inhibit penile erection and contractile response to 5-HT *in vitro,* and may play an opposite role in the penile erectile response to 5-HT via central 5-HT receptors *in vivo*.[5] 5-HT_4 agonists cause relaxation, which is not suppressed by selective 5-HT_4 antagonists in human CCPs.[6] The existence of dual contractile and relaxing responses to 5-HT via 5-HT_1, 5-HT_2, and 5-HT_4 receptors, respectively, in the CCP of rabbits has also been reported.[7]

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Table 1 Serotonin receptor subtypes[2]

Receptor type	*Principle transduction*	*Selective agonists*	*Selective antagonists*
5-HT_{1A}[a]	$G_{i/0}$	8-OH-DPAT	NAN-190
5-$HT_{1B/D}$[a]	$G_{i/0}$	Sumatriptan	GR55562
5-HT_{1E}	$G_{i/0}$	—	—
5-HT_{1F}	$G_{i/0}$	LY334370	—
5-HT_{2A}[a]	$G_{q/11}$	α-Me-5-HT	Ketanserin
5-HT_{2B}	$G_{q/11}$	α-Me-5-HT	RS127445
5-$HT_{2C/1C}$	$G_{q/11}$	α-Me-5-HT	SB242084
5-HT_3[a]	Ionotropic (Na^+ channel)	2-Methyl-5-HT	Ondansetron
5-HT_4[a]	G_s	Prucalopride	GR113808
		Cisapride (nonselective)	GR125487
		Metoclopramide (nonselective)	
5-ht_{5A}	G_i/G_0	—	—
5-ht_{5B}	None identified	—	—
5-HT_6	G_s	—	SB271046
5-HT_7	G_s	—	SB656104

[a]Subtypes which were investigated in this study.

Penile erection is caused by the relaxation of the CCP. The penile bulb, which is the proximal part of the corpus spongiosum, contains two layers of smooth muscle, the parenchyma layer consisting of spongy cells, and the outer layer.[8] These structures of the penile bulb have been suggested to play a role in erection. An important role for the penile bulb in initiating the erection of the glans penis has been proposed because the onset of the hemodynamic changes was found to be more rapid in the penile bulb than in the corpus cavernosum.[9]

It has not been shown whether or not 5-HT and its agonists participate in contractile and/or relaxant responses in the penile bulb. The aim of this study was to determine the effects of 5-HT and which subtypes of the 5-HT receptor participate in 5-HT- and its agonists-induced responses in the penile bulb of rats. In this study, we used the selective 5-HT receptor subtype antagonists NAN-190 (5-HT_{1A}), GR55562 (5-$HT_{1B/D}$), ketanserin (5-HT_{2A}), ondansetron (5-HT_3), and GR125487 (5-HT_4) in addition to the adrenergic antagonists prazosin (α_1) and propranolol (β) to determine their antagonistic effects on 5-HT responses. Furthermore, we tested the serotonergic agonists sumatriptan (5-$HT_{1B/1D}$) and 8-OH-DPAT (5-HT_{1A}) for further clarification of contractile receptor subtypes and prucalopride- (R093877, 5-HT_4) induced relaxation response in the penile bulb of rats.

Additionally, cisapride, a 5-HT_4 agonist, and metoclopramide, with both 5-HT_3 antagonistic and 5-HT_4 agonistic effects, were used to further test the existence of 5-HT_4 receptors.

Materials and methods

Tissue preparation

The procedures described were approved by the Animal Experimentation Ethics Committee of Hacettepe University.

Rats (male, 250–300 g) were killed by exsanguination under general anesthesia with urethane (1.25 g/kg, i.p.). Penile bulbs were isolated and mounted under a resting tension of 1 g in a 30 ml organ bath filled with Krebs-Henseleit solution at 37°C and aerated with a 95% O_2 and 5% CO_2 gas mixture. The composition of the Krebs-Henseleit solution was (in mM): NaCl, 118; KCl, 4.7; $MgSO_4$, 1.2; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11.1. Isometric changes in tension were recorded with an isometric force displacement transducer (FT03C) connected to a polygraph (Grass Model 7B).

Experimental protocol

The contractile responses to 5-HT, sumatriptan, and 8-OH-DPAT, and the relaxation response to the 5-HT_4 agonist prucalopride, in precontracted tissues (10^{-5} M phenylephrine; 60–80% of maximum contraction) were evaluated. The concentration–response curve to each agonist was made at the end of the equilibration period of 1 h. All antagonists were present in the organ bath 20 min. before the agonist was administered.

Data analysis and statistics

Contractions and relaxations were expressed as percentages of the 5-HT-induced maximum response and phenylephrine (10^{-5} M)-induced submaximal contraction, respectively. The maximum response elicited by the agonist (E_{max}) and the concentration required to achieve half-maximum contraction and relaxation (EC_{50}) were obtained from individual concentration–response curves. EC_{50} values were given as pD_2 values, which are defined as the negative logarithm of EC_{50} ($pD_2 = -\log EC_{50}$).

All values were expressed as the mean ± standard error of the mean (s.e.m.). Statistical significance

was determined by paired Student's *t*-test for analysis of variance (ANOVA) with repeated measurements followed by Bonferroni's test. *P*-values <0.05 were considered to be significant.

Drugs used

The study protocol included the following drugs: 8-OH-DPAT (Sigma, St Louis, MO, USA), Cisapride monohydrate (Mustafa Nevzat İlac Sanayi AS, İstanbul, Turkey), GR 113808 maleate (Glaxo Wellcome, Stevenage, Herts, UK), GR 125487 sulphamate (Glaxo Wellcome), GR55562 di-*p*-toluenesulphonate (Glaxo Wellcome), guanethidine monosulphate (Ciba-Geigy, Basel, Switzerland), ketanserin (Janssen Pharmaceutica, Beerse, Belgium), metoclopramide hydrochloride (Sigma), NAN-190 (Sigma), N^G-nitro-L-arginine (L-NOARG, Sigma), ondansetron (GR 38032, Glaxo Wellcome), phenylephrine hydrochloride (Sigma), prazosin hydrochloride (Sigma), propranolol hydrochloride (Sigma), prucalopride (R093877, Janssen Pharmaceutica), serotonin creatinine sulphate (Sigma), and sumatriptan succinate (GR 43175, Glaxo Wellcome).

Results

Serotonin (10^{-7}–3×10^{-4} M) contracted penile bulbs in a concentration-dependent manner (Figure 1). Maximum response was obtained by 3×10^{-4} M of 5-HT. The actual force of maximum response developed by 5-HT was 53.75 ± 4.12 mg per mg wet tissue. There were no significant differences among four concentration–response curves of 5-HT and the maximum responses of 5-HT obtained by four repetitions.

Ketanserin (5-HT_{2A} antagonist; 10^{-9}–10^{-7} M) shifted the concentration–response curves to 5-HT to the right (Figure 1). In the presence of different concentrations of antagonist, the lower parts of the curves were parallel to each other, however the upper parts were not. Similar maximum responses were obtained by the same concentration of 5-HT (3×10^{-4} M) in the presence of the three concentrations of the antagonist (Figure 1). pD_2 values for 5-HT before and after the three concentrations of ketanserin administration changed significantly (5.50 ± 0.20 and 4.97 ± 0.12, 4.69 ± 0.04, 4.40 ± 0.06, respectively).

Prazosin (α_1-adrenergic receptor blocker; 10^{-9}–10^{-7} M) significantly suppressed 5-HT-induced contraction (Figure 2). In the presence of prazosin, the suppression of the responses to lower doses of 5-HT was less when compared to those of higher doses. However, we could not perform the experiment with 5-HT concentrations over 3×10^{-4} M because of its solubility, to which contractile response was not maximal after prazosin administration. Nevertheless, the two concentration–response curves to 5-HT in the presence of 10^{-9} and 10^{-8} M prazosin were parallel to each other. Prazosin at the concentration of 10^{-7} M suppressed 5-HT responses noncompetitively, since the maximum response to 5-HT was significantly decreased (Figure 2). Guanethidine (adrenergic neuron blocker, 5×10^{-5} M) attenuated the responses to 5-HT only at the two highest concentrations applied (Figure 3). In the presence of guanethidine and prazosin (10^{-8} M) together, there was no additional inhibition in comparison to the effect of prazosin (10^{-8} M) alone (Figure 3). NAN-190 (selective 5-HT_{1A} antagonist, 10^{-8}, 10^{-7} M) inhibited the responses to 5-HT noncompetitively (Figure 4). Ondansetron (5-HT_3 receptor antagonist, 10^{-6}, 10^{-5} M) did not affect 5-HT-induced contractions (Figure 5).

8-OH-DPAT (selective 5-HT_{1A} receptor agonist, 3×10^{-6}–3×10^{-4} M) contracted the penile bulbs in a concentration-dependent manner (Figure 6). The pD_2 value for 8-OH-DPAT was lower than that of 5-HT (pD_2 values for 5-HT and 8-OH-DPAT were

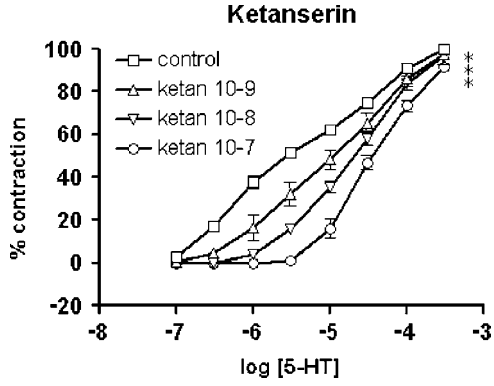

Figure 1 Effect of ketanserin (5-HT_{2A} antagonist, 10^{-9}–10^{-7} M) on the concentration–response curves of 5-HT in the penile bulb of rats ($n=6$). *$P<0.05$ vs control.

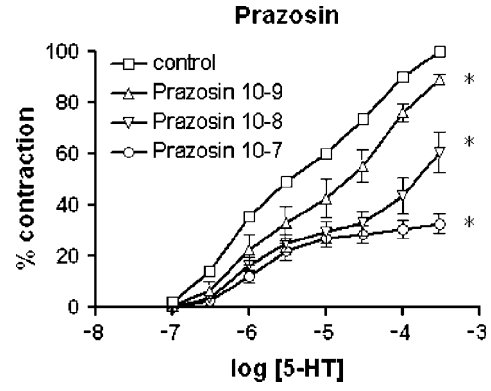

Figure 2 Effect of prazosin (α_1-adrenergic receptor blocker, 10^{-9}–10^{-7} M) on the concentration–response curves of serotonin (5-HT) in the penile bulb of rats ($n=6$). *$P<0.05$ vs control.

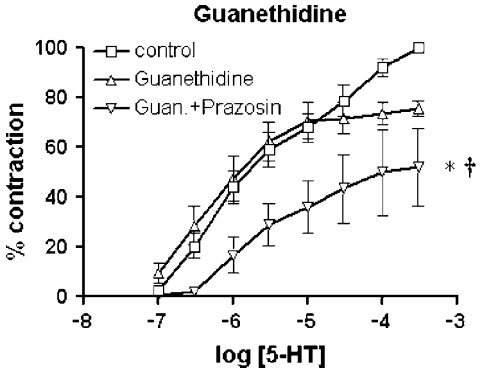

Figure 3 Effect of guanethidine (adrenergic neuron blocker, 5×10^{-5} M) and prazosin (α_1-adrenergic receptor blocker, 10^{-8} M) + guanethidine (5×10^{-5} M) on the concentration–response curves of serotonin (5-HT) in the penile bulb of rats ($n = 5$). *$P < 0.05$ vs control. †$P < 0.05$ vs guanethidine.

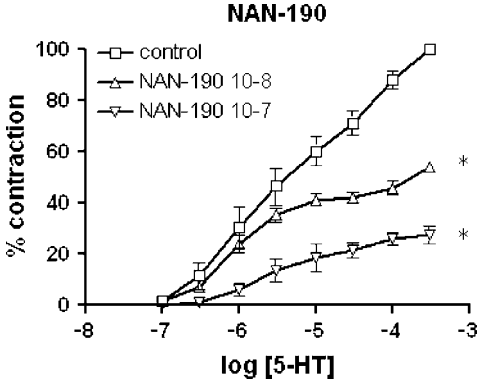

Figure 4 Effect of NAN-190 (5-HT_{1A} antagonist, 10^{-7}, 10^{-6} M) on the concentration–response curves of serotonin (5-HT) in the penile bulb of rats ($n = 6$). *$P < 0.05$ vs control.

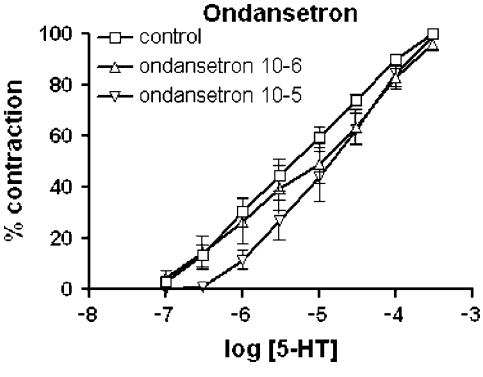

Figure 5 Effect of ondansetron (5-HT_3 antagonist, 10^{-6}, 10^{-5} M) on the concentration–response curves of serotonin (5-HT) in the penile bulb of rats ($n = 5$).

5.50 ± 0.20 and 4.29 ± 0.10, respectively). Sumatriptan (selective 5-$HT_{1B/1D}$ agonist, 10^{-8}–10^{-4} M) did not cause any contraction in penile bulb tissues (not shown). GR55562 (5-$HT_{1B/1D}$ antagonist,

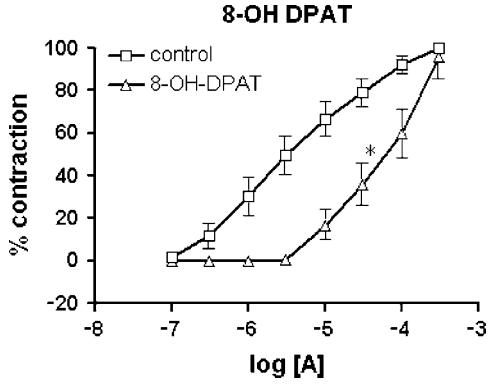

Figure 6 Concentration–response curve of 8-OH-DPAT (5-HT_{1A} agonist) and 5-HT in the penile bulb of rats ($n = 6$). *$P < 0.05$ vs control EC_{50} value.

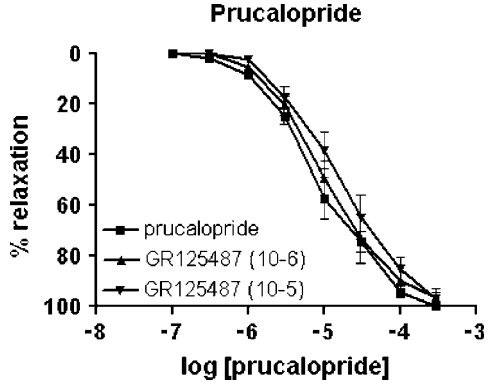

Figure 7 Effect of GR125487 (5-HT_4 antagonist, 10^{-6}, 10^{-5} M) on the concentration–response curves of prucalopride (5-HT_4 agonist), in the penile bulbs contracted by phenylephrine (10^{-5} M), in rats ($n = 6$).

10^{-6}, 10^{-5} M) had no effect on 5-HT-induced contractions (not shown).

Prucalopride, a selective 5-HT_4 agonist (R093877, 10^{-7}–3×10^{-4} M), caused concentration-dependent relaxations in penile bulbs that were contracted by 10^{-5} M phenylephrine (Figure 7). The contraction produced by phenylephrine was 43.86 ± 4.12 mg per mg wet tissue. Relaxation obtained with 3×10^{-4} M prucalopride was 100% of the phenylephrine submaximal contraction. The pD_2 value for prucalopride was 5.07 ± 0.05. GR125487 (selective 5-HT_4 antagonist, 10^{-6}, 10^{-5} M) slightly, but not significantly, decreased the 5-HT_4 agonist-induced relaxation (Figure 7). The pD_2 values after these two concentrations of antagonist were 5.00 ± 0.20 and 4.80 ± 0.04, respectively. L-NOARG (nitric oxide synthase inhibitor, 10^{-4} M) did not change prucalopride-induced relaxation (not shown). Neither GR113808, another selective 5-HT_4 antagonist (10^{-6}–10^{-5} M), nor propranolol (β-adrenergic receptor blocker, 10^{-6}, 10^{-5} M) significantly affected the responses to prucalopride (not shown). Cisapride,

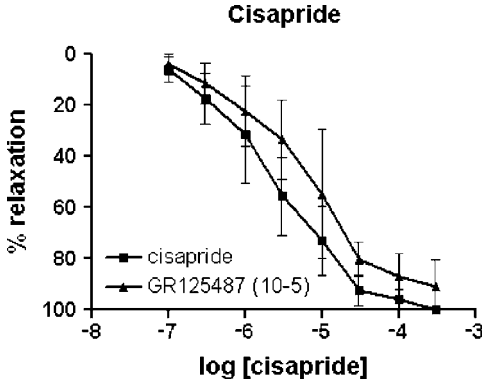

Figure 8 Effect of GR125487 (5-HT_4 antagonist, 10^{-5} M) on the concentration–response curve of cisapride (5-HT_4 agonist) in the penile bulbs contracted by phenylephrine (10^{-5} M), in rats ($n=5$).

a 5-HT_4 agonist (10^{-7}–3×10^{-4} M), also caused a concentration-dependent relaxation in penile bulbs (Figure 8). The pD_2 value for cisapride was 5.55 ± 0.07. Additionally, cisapride-induced relaxation could not be significantly suppressed by GR125487 (10^{-6}, 10^{-5} M) (Figure 8).

Metoclopramide (5-HT_4 agonist) caused concentration-dependent relaxations (not shown). The relaxation induced by metoclopramide was not significantly decreased by GR113808 (not shown).

Discussion

It has been shown that 5-HT has an inhibitory effect on sexual function in the central nervous system.[10] Selective 5-HT reuptake inhibitors (SSRIs) which cause 5-HT to accumulate in nerve endings and potentiate the effect of 5-HT, cause sexual dysfunctions such as decreased sexual desire (libido) and erectile dysfunctions.[11] SSRIs have been reported to peripherally have the possibility of causing erectile dysfunction.[7] Serotonin, by a peripheral mechanism, exerts an inhibitory action on penile erection through the activation of 5-HT_{1D} type of receptor.[12] On the other hand, *p*-chloroamphetamine (5-HT releasing agent) causes penile erection and ejaculation in anesthetized rats, which is limited to the lower spinal cord and/or peripheral sites.[13] Therefore, there is a difference in the peripheral action of 5-HT when comparing *in vivo* and *in vitro* experiments.

Since an important role for the penile bulb in initiating erection of the glans penis has been proposed, it would be of great importance to investigate the effect of 5-HT and 5-HT agonists in this structure. To the best of our knowledge, there is no literature reporting the effect of 5-HT and 5-HT receptor subtypes in the penile bulb tissue of rats. In our current study, we observed that 5-HT and selective agonist for the 5-HT_{1A} receptor caused concentration-dependent contractions and that selective and nonselective 5-HT_4 agonists induced concentration-dependent relaxations in the isolated resting and previously contracted penile bulbs in rats, respectively.

Ketanserin, which is a highly selective 5-HT_{2A} antagonist, strongly suppressed 5-HT-induced contraction. The pD_2 values for 5-HT were changed significantly by the administration of ketanserin. Therefore, the 5-HT_{2A} receptor partially participates in the 5-HT-induced contraction in rat penile bulbs. The pA_2 value (used to compare antagonists potencies for a certain receptor) for ketanserin could not be calculated, because the relationship between 5-HT and ketanserin was not competitive. On the other hand, the selective α_1-adrenergic receptor antagonist prazosin significantly inhibited 5-HT-induced contractions, however, differently from that obtained with ketanserin. Ketanserin is known to block α_1-adrenergic receptors, as well.[14] Additionally, it has been reported that 5-HT may activate α_1-adrenergic receptors as well as its own receptors in some tissues.[15,16] Therefore, the contribution of α_1-adrenoceptors to 5-HT-induced contractions could not be excluded. Here, another possibility could be the indirect action of 5-HT through the release of noradrenaline, which has been reported in some tissues.[17] However, guanethidine did not change the responses to 5-HT except at two concentrations, and prazosin at the same concentration exhibited the same degree of antagonism when applied either alone or in combination with guanethidine. Thus, the response to higher concentrations of 5-HT may have been partly due to noradrenaline displacement from nerve endings. The patterns of blockade by the two antagonists, namely prazosin and ketanserin, were not similar. For this reason, the inhibitions induced by them could have resulted from the blockade of their own receptors. Thus, it could be suggested that both 5-HT_{2A} and α_1-adrenergic receptors participate in the responses to 5-HT in the penile bulb of rats.

Sumatriptan, which is a selective 5-$HT_{1B/1D}$ agonist, did not cause contractions, and the selective 5-$HT_{1B/1D}$ receptor antagonist GR55562 did not affect the concentration–response curve to 5-HT, in contrary to the findings related to the rat corporal tissue.[12] In contrast to sumatriptan, the selective 5-HT_{1A} receptor agonist 8-OH-DPAT caused concentration-dependent contractions. Furthermore, 5-HT-induced contractions were inhibited by NAN-190, a selective 5-HT_{1A} receptor antagonist. Consistently, in the human isolated corpus cavernosum, 5-HT-induced contractions were abolished by NAN-190.[18] Therefore, it can be proposed that a third contractile receptor, namely 5-HT_{1A}, participates in the contraction of the penile bulb of rats. It has been shown that selective 5-HT_{1A} and 5-HT_{1B} agonists have different effects in different models of erection.[19] The 5-HT_1 receptor family and α_1-adrenergic recep-

tors couple mainly to G_i/G_0-type of G-protein and the stimulation of 5-HT_1 receptors and α_1-adrenergic receptors inhibits adenylyl cyclase.[1,20] Therefore, the stimulation of 5-HT_{1A} and α_1-adrenergic receptors result in smooth muscle contraction. 5-HT_2 receptors couple mainly to G_q/G_{11}-type of G-protein and the stimulation of 5-HT_2 receptors activates phospholipase-C.[1] These signal transduction mechanisms cause the contraction of the smooth muscle. From the above results it can be suggested that three types of receptors, namely 5-HT_{1A}, 5-HT_{2A}, and α_1-adrenoceptors may participate in the 5-HT-induced contraction in the isolated penile bulb of rats. Our results are in agreement with the finding that the stimulation of 5-HT_{1A} or 5-HT_2 receptors inhibits penile erection by administration of 5-HT agonists in rats.[4] Furthermore, it has been reported that detumescense results predominantly from the activity of α_1-adrenoceptors of corporal smooth muscle.[21]

Lack of effect of ondansetron (a potent 5-HT_3 receptor antagonist) on the concentration–response curve to 5-HT suggests that 5-HT_3 receptors do not participate in the 5-HT-induced contraction in the penile bulb of rats.

On the other hand, prucalopride (a selective 5-HT_4 agonist)[22] caused relaxation in contracted penile bulbs, indicating the existence of a 5-HT_4 receptor in this tissue. The results of this study may indicate the participation of 5-HT_4 receptors in the relaxation of the penile bulb of rats. Our results are consistent with the results obtained in the CCP of rabbits.[7] However, the pD_2 value of prucalopride for 5-HT_4 receptors in rat penile bulbs was found to be 5.07, which was significantly different from those obtained in isolated guinea-pig proximal colon (7.48 ± 0.06) and rat oesophagus (7.81 ± 0.17).[23] *In vitro* studies on isolated strips have shown that prucalopride has no effect on 5-HT_{2A}, 5-HT_{2B}, and 5-HT_3 receptors and muscarinic cholinoceptors, and does not inhibit cholinesterases.[23] Additionally, in this study, we showed the ineffectiveness of prucalopride on β-adrenoceptors and on nitric oxide release, since propranolol and L-NOARG did not change the responses to prucalopride. Although prucalopride has been shown to be a potent, highly specific, and selective 5-HT_4 receptor agonist, our results related with the pD_2 value of prucalopride indicated that another 5-HT receptor or receptor subtype, which caused relaxation, should be present in the penile bulb of rats. This finding was further supported by the lack of effect of GR125487 and GR113808 (potent 5-HT_4 receptor antagonists) on the contraction–response curves to prucalopride in our study. The enterokinetic effects of prucalopride have been reported to be antagonized by GR125487[24,25] and by GR113808.[26] Moreover, our results are in accordance with the finding showing that in human CCP, selective 5-HT_4 antagonist fails to suppress the relaxation caused by 5-HT_4 agonist.[6]

Our results also showed that cisapride and metoclopramide, which are 5-HT_4 agonists,[27] caused concentration-dependent relaxations in penile bulbs. Prins *et al*.[28] have reported that pD_2 value of cisapride for 5-HT_4 receptors in canine isolated rectum circular smooth muscle is 6.8 ± 0.25.[28] Whereas in our study, we found pD_2 values for cisapride and metoclopramide to be 5.55 and 5.40, respectively. The value for cisapride in the penile bulb was significantly different from that of rectum. Furthermore, the relaxations induced by cisapride and metoclopramide could not be antagonized by the 5-HT_4 antagonists GR125487 and GR113808. In the light of these findings, we suggest that the 5-HT receptor in the penile bulb, which is responsible for relaxation, is different than the known 5-HT_4 receptor, or is a 5-HT_4 receptor subtype, which has not yet been reported.

Finally, we conclude that α_1-adrenergic, 5-HT_{1A} and 5-HT_{2A} receptors participated in the contraction induced by 5-HT in the penile bulb of rats. As far as relaxation is concerned, we suggest that an as yet undefined receptor type or a 5-HT_4 receptor subtype is responsible for the relaxation of the penile bulbs, although no 5-HT_4 receptor subtype has been reported as of this writing.

Conclusion

α_1-adrenergic, 5-HT_{1A} and 5-HT_{2A} receptor subtypes participate in the contractile response to 5-HT, and a receptor or a receptor subtype resembling 5-HT_4 receptor participates in relaxation, which was masked by 5-HT-induced contraction in the penile bulb of rats. The drug development of selective 5-HT_{1A} and 5-HT_{2A} receptor antagonists and/or yet undefined, but 5-HT_4-resembling receptor agonists in penile bulbs may have therapeutic advantages for erectile dysfunction owing to peripheral disorders of the 5-HT system.

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