Psychopharmacology (1990) 101:57–61

Psychopharmacology

Involvement of 5-HT_{1C}-receptors in drug-induced penile erections in rats

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Received June 7, 1989 / Final version November 17, 1989

Abstract. Drug-induced penile erections (PE) were initially suggested to be 5-HT_{1B} receptor mediated. However, since the discovery of the 5-HT_{1C} receptor a number of compounds, considered to be 5-HT_{1B} selective, appear to bind more strongly to the 5-HT_{1C} receptor and this prompted a re-evaluation of the receptor subtype involved in PE induction. PE could be induced by the 5-HT agonists mCPP (0.22–2.2 mg/kg), TFMPP (0.46–1.0 mg/kg) and MK 212 (0.1–1.0 mg/kg). The 5-HT agonist DOI (0.022–0.22 mg/kg) did not induce PE in placebo-pretreated rats but in rats pretreated with various 5-HT_2 antagonists it did. These compounds have in common a strong affinity for the 5-HT_{1C} receptor. mCPP (0.46 mg/kg)-induced PE could be antagonized by the 5-HT antagonists metergoline, cyproheptadine, mesulergine, mianserin, ritanserin and ketanserin. Their ED_{50}s were 0.04, 0.4, 0.03, 0.06, 0.4 and 2 mg/kg, respectively. The potency of both the agonists to induce, and the antagonists to inhibit, PE was found to be dependent on their selectivity for the 5-HT_{1C} receptor versus the 5-HT_2 receptor. Spiperone (0.1–1.0 mg/kg) and GR 38032F (1–10 mg/kg) did not antagonise mCPP-induced PE. 8-OH-DPAT and 5MeODMT counteracted mCPP (0.46 mg/kg)-induced PE. Their ED_{50}s were 0.03 and 0.4 mg/kg, respectively. DOI counteracted mCPP induced PE only at doses above 1 mg/kg, whereas CGS 12066B (1.0–10 mg/kg) was inactive. The results suggest that PE are induced by activation of the 5-HT_{1C} receptor and are functionally inhibited by activation of 5-HT_{1A} or 5-HT_2 receptors.

Key words: Penile erections – 5-HT_{1C} receptors – Functional antagonism – 5HT_{1C}-receptor selectivity ratio – Rat

Penile erections (PE) can be induced in rats by the serotonin (5-HT)-releasing compound fenfluramine, 5-HT reuptake inhibitors, the 5-HT agonist mCPP, the 5-HT agonist quipazine in 5-HT_2 antagonist-pretreated rats and by 5-hydroxytryptophan (5HTP) in rats pretreated with a monoamine oxydase inhibitor and a peripheral decarboxylase inhibitor (Baraldi et al. 1977; Berendsen and Broekkamp 1987). Fenfluramine and mCPP also induce PE in non-human primates (Szele et al. 1988). Previously we have investigated the pharmacology of induction of penile erections and suggested that it is probably mediated by the 5-HT_{1B} receptor (Berendsen and Broekkamp 1987). However, recently Pazos et al. (1985) and later Heuring and Peroutka (1987) showed that, in the 5-HT_{1B} binding test, 5-HT_{1C} and perhaps 5-HT_{1D} sites were also labelled. The affinity of various compounds for the 5-HT_{1C} receptor has now been described (Engel et al. 1986; Hoyer 1988a) and a number of reference compounds including both mCPP and quipazine appear to bind more strongly to the 5-HT_{1C} receptor than to one of the other 5-HT receptor subtypes. These developments necessitate a re-evaluation of the interpretation of PE induction. In this paper the effect of a number of 5-HT agonists TFMPP, MK 212, DOI and of the 5-HT antagonists metergoline, cyproheptadine, mesulergine, mianserin and ritanserin, which all share potent 5-HT_{1C} activity, on PE are described. The results strongly suggest that the 5-HT_{1C} rather than the 5-HT_{1B} receptors are involved in the induction of PE by 5-HT compounds.

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Materials and methods

Animals. Naive male Wistar rats (Cpb:WU, Harlan Sprague Dawley, Zeist, The Netherlands), weighing 200–400 g were used. The animals were housed in white PVC cages (40 × 40 × 18 cm) with a wire mesh lid, five animals per cage, under controlled 12 h light-dark cycle, with lights on at 06:00 a.m. The rats were allowed free access to standard food pellets and tap water. The rats were used up to three tims with at least 1 week rest between two successive tests.

Procedure. The test procedure was the same as described before (Berendsen and Broekkamp 1987). All experiments were performed

between 08:30 and 13:30 hours. Groups of five rats, one control and four drug-treated ones, were observed simultaneously. Immediately after agonist injection the rats were placed individually in perspex cages (7.5 × 18 × 30 cm). A mirror was placed behind the observation cages of facilitate observation of the animals. Antagonists were injected 30 min prior to the agonist. During 30 min following the agonist injection, the number of penile erections were counted.

A penile erection is defined as previously described (Berendsen and Gower 1986): repeated pelvic thrusts immediately followed by an upright position presenting an emerging, engorged penis which the rat proceeds to lick, eating the ejaculate.

In the experiments with DOI, the number of wet dog shakes were counted as well during the same period. Other symptoms induced by the various treatments are discussed in the Results section.

Drugs and solutions. The following drugs were used: cyproheptadine HCl and 2-chloro-6-(1-piperazinyl)pyrazine monohydrochloride (MK 212) (Merck, Sharpe and Dome); 1-(meta-chlorophenyl)-piperazine 2HCl (mCPP) (EGA-chemie); (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl (DOI) (Research Biochemicals Inc.; RBI); (±)-8-hydroxy-dipropylamino tetralin HBr (8-OH-DPAT) (RBI); mesulergine (Sandoz); metergoline (Pharmitalia); 5-methoxy-N,N-dimethyltryptamine hydrogenoxalate (5MeODMT) (RBI); mianserin HCl (Organon Int.); ketanserin, pirenperone, ritanserin and spiperone (Janssen Pharmaceutica); *m*-trifluoromethylphenylpiperazine HCl (TFMPP) (Duphar); 7-trifluoromethyl-4(4-methyl-1-piperazinyl)-pyrrolo[1,2-a]quinoxaline dimaleate (CGS 12066 B) (RBI); 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazal-1-yl)methyl]-4H-carbazol-4-one HCl $2H_2O$ (GR 38032 F) (Glaxo). Pirenperone, spiperone, metergoline and cyproheptadine were suspended in an aqueous solution of 5% mulgofen (EL 719®, GAF-corp., New York) and 0.9% NaCl. All the other drugs were dissolved in sterile saline solution. All drug solutions or suspensions were freshly prepared and were injected subcutaneously into the loose skin at the back of the neck. A dose volume of 5 ml per kg body weight was used. Control animals were injected with an equivalent volume of vehicle. When drug solutions were made up from the salt of the compound the doses refer to the weight of the salt.

Statistics. The results are expressed as the mean number of penile erections per group ± SEM. The statistical significance of the drug effect was determined by comparing the results of each group with the results of the relevant control group using the non-parametric Rank Sum test on Scores (Lehman 1974).

Results

Induction of penile erections (PE)

TFMPP and MK 212 induced penile erections (Fig. 1) comparable to those previously described (Berendsen and Broekkamp 1987). MK 212 was more potent than TFMPP, the highest number of PE after TFMPP being 1.8 ± 0.5 at 1.0 mg/kg, whereas for MK 212 the maximal score was 4.7 ± 0.8 at 1.0 mg/kg. The dose response curves for both compounds were bell-shaped. At higher doses the number of PE decreased. TFMPP also induced some yawning but did so at higher dose levels. Optimal dose for PE induction was 1.0 mg/kg, whereas at 4.6 mg/kg a significant increase in yawning was seen: at 4.6 mg/kg the mean number of yawns ± SEM was 4.0 ± 0.8, ($P < 0.05$) and 0.3 ± 0.2 for placebo-treated animals (data not shown).

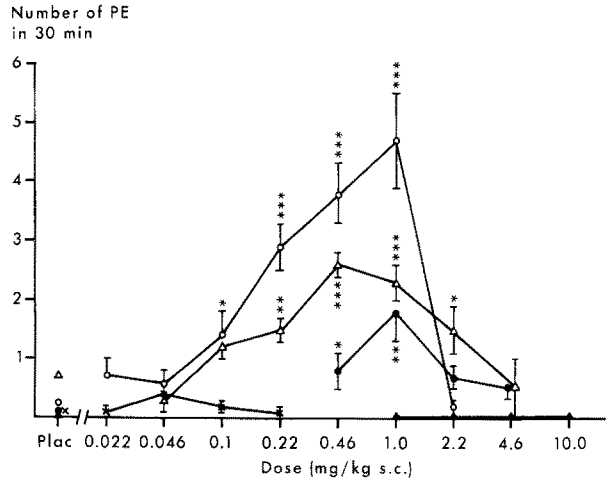

Fig. 1. Induction of penile erections (PE) by 5-HT-agonists. Each point represents the mean number of PE from at least ten animals ± SEM. In the experiment with CGS 12066B, five animals per group were used. o– – –o MK212; △– – –△ mCPP; ●– – –● TFMPP; × – – – × DOI; ▲– – –▲ CGS 12066B. * $P<0.05$; ** $P<0.01$; *** $P<0.001$ if compared to the appropriate control group. mCPP values are from Berendsen and Broekkamp (1987)

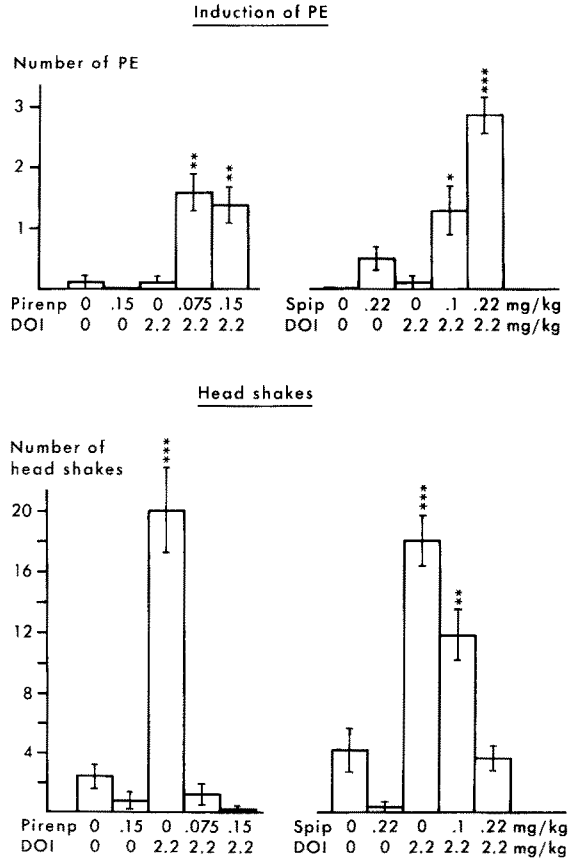

Fig. 2. Effect of pirenperone (*Pirenp*) and spiperon (*Spip*) on DOI (2.2 mg/kg SC)-induced penile erections (*PE*) and head shakes. Bars represent mean number of PE and mean number of head shakes ± SEM measured during 30 min after treatment with DOI. Pirenp and Spip were injected 30 min before DOI. * $P<0.05$; ** $P<0.01$; *** $P<0.001$ if compared to control groups

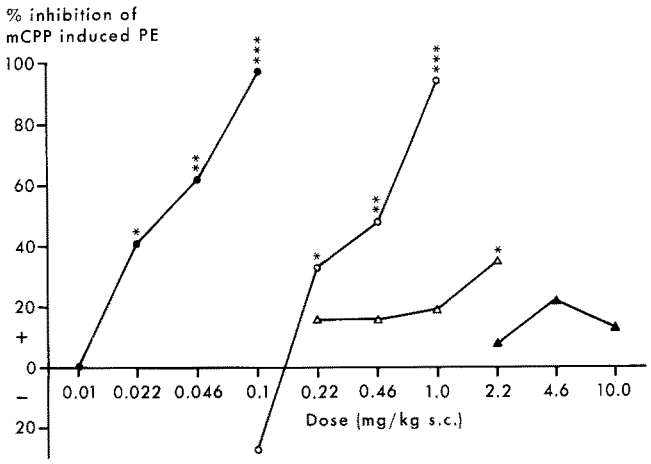

Fig. 3. Effect of 5-HT-agonists on mCPP (0.46 mg/kg SC)-induced penile erections (*PE*). Effects are expressed as percentage inhibition relative to saline plus mCPP groups. Agonists were injected simultaneously with mCPP. Ten animals per group were tested. ●– – –● 8-OH-DPAT; ○– – –○ 5MeODMT; △– – –△ DOI; ▲– – –▲ CGS 12066B. * $P<0.05$; ** $P<0.01$; *** $P<0.001$ if compared to control group

CGS 12066 B did not induce PE, nor did DOI. However in spiperone- or pirenperone-pretreated rats DOI did induce PE (Fig. 2). DOI by itself induced head shakes. These head shakes were dose dependently blocked by spiperone and pirenperone.

Blockade of PE by 5-HT agonists

The effects of 5-HT agonists on mCPP-induced PE are presented in Fig. 3. mCPP (0.46 mg/kg)-induced PE were potently antagonised by the 5-HT agonists 8-OH-DPAT and 5MeODMT. Their ID_{50}s were 0.03 and 0.4 mg/kg, respectively. DOI weakly antagonised mCPP-induced PE: at 2.2 mg/kg the effect of mCPP was reduced by 35%. CGS 12066 B up to 10 mg/kg had no effect.

The animals treated with the combination of mCPP and 8-OH-DPAT 0.1 mg/kg SC were restless, showed forepaw treading, lower lip retraction and a flat body posture.

After treatment with mCPP and 5MeODMT at all doses tested, the animals showed some forepaw treading and Straub tail and after 1 mg/kg 5MeODMT also a flat body posture. Some forepaw treading was also seen after mCPP + DOI treatment.

Blockade of PE by 5-HT antagonists

mCPP 0.46 mg/kg induced PE could be antagonised by metergoline, cyproheptadine, mesulergine, mianserin and ritanserin. Their ID_{50}s were 0.04, 0.4, 0.03, 0.06 and 0.4 mg/kg, respectively (Tables 1 and 2). Ketanserin was less active in this respect, its ID_{50} being about 2 mg/kg. The potency of these antagonists to block mCPP-induced PE was found to be related to their selectivity for 5-HT_{1C} versus 5-HT_2 receptors in binding (Table 2). The potency of 5-HT agonists to induce PE was similarly related to their preference for $5HT_{1C}$-receptors in binding. This preference was calculated from the affinity of the compounds for $5HT_2$ and $5HT_{1C}$-receptors (see note to Table 2). Spiperone and GR 38032 F were not able to antagonize mCPP-induced PE. Rats treated with spiperone were hypoactive.

Table 1. Effect of 5-HT antagonists on mCPP (0.46 mg/kg SC)-induced penile erections (PE). Antagonists were injected 30 min before mCPP. Ten animals per group

Drug	Dose mg/kg SC	PE mean ± SE	% Change
Metergoline	Plac	3.1 ± 0.2	
	0.022	3.3 ± 0.4	+6
	0.046	1.6 ± 0.2	−48[b]
	0.1	0.5 ± 0.2	−84[c]
	0.22	0.2 ± 0.1	−94[c]
Cyproheptadine	Plac	3.0 ± 0.5	
	0.1	2.5 ± 0.4	−17
	0.22	1.9 ± 0.2	−37
	0.46	1.2 ± 0.3	−60[a]
	1.0	0.8 ± 0.3	−73[b]
Mesulergine	Plac	2.9 ± 0.2	
	0.022	1.7 ± 0.2	−41[b]
	0.046	0.9 ± 0.2	−67[c]
	0.1	0.5 ± 0.3	−81[c]
	0.22	0.1 ± 0.1	−95[c]
Mianserin	Plac	2.9 ± 0.7	
	0.022	1.8 ± 0.5	−38
	0.046	1.9 ± 0.4	−34
	0.1	1.2 ± 0.3	−59[a]
	0.22	0.6 ± 0.3	−79[a]
Ritanserin	Plac	3.6 ± 0.5	
	0.046	3.2 ± 0.5	−11
	0.1	2.0 ± 0.3	−44[a]
	0.22	2.4 ± 0.4	−33
	0.46	1.6 ± 0.3	−56[b]
Ketanserin	Plac	3.2 ± 0.7	
	0.46	3.1 ± 0.7	−3
	1.0	3.4 ± 0.8	+6
	2.2	1.4 ± 0.5	−56
	4.6	1.1 ± 0.4	−66[a]
Spiperone	Plac	3.1 ± 0.4	
	0.1	3.0 ± 0.4	−3
	0.22	2.8 ± 0.7	−10
	0.46	3.2 ± 0.4	+3
	1.0	2.2 ± 0.6	−29
GR 38032 F	Plac	4.5 ± 0.4	
	1.0	5.4 ± 1.3	+19
	2.2	2.9 ± 0.5	−36
	4.6	5.1 ± 0.8	+14
	10.0	4.5 ± 0.9	0

If compared to Plac + mCPP-treated group (two-tailed)
[a] $P<0.05$; [b] $P<0.01$; [c] $P<0.001$

Discussion

Although mCPP and TFMPP have been claimed before to have some selectivity for the 5-HT_{1B} receptor (Sills et al. 1984), there is now in vitro as well as in vivo evidence that these drugs also have potent 5-HT_{1C} affinity

Table 2. Comparison of the effects of 5-HT compounds on PE with their affinity to the 5-HT_{1C} and 5-HT_2 receptors

	ED_{50} mg/kg for antagonism of mCPP-induced PE	Affinity values: (pK_d)			$5HT_{1C}$ preference ratio[e]
		5-HT_{1B}[a] receptor	5-HT_{1C}[a] receptor	5-HT_2[a] receptor	
Mesulerine	0.027	4.88	8.79	8.42	2.34
Metergoline	0.042	7.39	9.19	9.03	1.44
Mianserin	0.06	5.21	8.00	8.08	0.83
Cyproheptadine	0.36	5.32	7.86	8.46	0.25
Ritanserine	0.35	4.00	8.64	9.25	0.24
Ketanserin	2	5.72	7.01	8.86	0.014
Spiperone	⩾1 induced number of PE at optimal dose	5.27	5.94	8.76	0.0015
MK 212	4.7	5.03	6.16	4.76	25
mCPP	2.6[b]	6.58	7.68	6.70	10
TFMPP	1.8	6.36	7.21	6.57	4.4
Quipazine	1.3[b,c]	6.51	6.73	6.20	3.4
DOI	0.4[c]	5.9[d]	7.73	7.84	0.8

[a] Affinity values for 5-HT_{1B}, 5-HT_{1C} and 5-HT_2 receptors are from Hoyer 1988a. Those of DOI are from Hoyer (1988b)
[b] From Berendsen and Broekkamp (1987)
[c] Not different from placebo
[d] Calculated from Titeler et al. (1988)
[e] the $5HT_{1C}$ preference ratio represents the ratio of dissociation constants for $5HT_2$ and $5HT_{1C}$-receptors. Dissociation constants were the antilogs of the pK_d values as given in the table

(Hoyer 1988a; Kennett and Curzon 1988a, b). Both compounds induce PE (Berendsen and Broekkamp 1987; this paper). MK 212, which has very poor affinity for the 5-HT_{1B} receptor but binds more potently to the 5-HT_{1C} receptor (Hoyer 1988a), also induced PE, whereas the recently described selective 5-HT_{1B} agonist CGS 12066 B (Neale et al. 1987) was ineffective in this respect. Therefore it seems that the 5-HT_{1C} rather than the 5-HT_{1B} receptors are mediating the induction of PE. This is further supported by the effects obtained with DOI which binds potently to the 5-HT_2 and 5-HT_{1C} (Hoyer 1988b) and only weakly to the 5-HT_{1A} and 5-HT_{1B} receptors (Titeler et al. 1988); DOI induces PE after blockade of the 5-HT_2 receptors with spiperone or pirenperone, indicating that its 5-HT_{1C} properties were probably responsible for its PE-inducing effect. The 5-HT antagonists metergoline, cyproheptadine, mesulergine, mianserin and ritanserin potently inhibited mCPP-induced PE. These compounds have high affinity for the 5-HT_{1C} and 5-HT_2 receptor in common (Hoyer 1988a). Ketanserin, which has a somewhat lower affinity for the 5-HT_{1C} receptor, also less potently antagonized mCPP-induced PE, whereas spiperone, which hardly binds to the 5-HT_{1C} receptor, but strongly to the 5-HT_{1A}, 5-HT_2 and dopamine receptors, did not affect mCPP-induced PE up to 0.46 mg/kg. At higher doses there may be some effect, but these doses also induce catalepsy. This suggests that blockade of the 5-HT_{1C} receptor might be the most probable explanation for the PE-inhibiting effect of the 5-HT antagonists.

An influence of 5-HT_2 receptor activation or blockade on both induction and inhibition of PE cannot be excluded: DOI only induced PE after blockade of the 5-HT_2 receptor. The headshakes which are thought to be the result of 5-HT_2 receptor activation (Yap and Taylor 1983; Heaton et al. 1988) disappear after blocking the 5-HT_2 receptor. It has been reported before that quipazine also induced more PE in 5-HT_2 antagonist-pretreated rats (Berendsen and Broekkamp 1987). The influence of the 5-HT_2 receptor may also explain why the effect of MK 212 on PE is stronger than those of mCPP or TFMPP, whereas the latter two compounds show a higher affinity for the 5-HT_{1C} receptor than MK212 (Hoyer 1988a). If selectivity ratios for 5-HT_{1C} versus 5-HT_2 receptors are calculated then the sequence for 5-HT_{1C} selectivity is MK 212 > mCPP > TFMPP > quipazine > DOI and this is also the sequence of potency to induce PE (Table 2). When the selectivity ratios for the 5-HT_{1C} versus 5-HT_2 receptors of the antagonists are calculated, then their selectivity for the 5-HT_{1C} receptor is also closely parallel to their potency to antagonise the mCPP-induced PE (Table 2). This suggests that 5-HT_2 agonistic properties prevent or counteract induction of PE and that concomitant 5-HT_2 antagonistic properties makes the antagonist less effective. Indeed DOI-induced PE in rats pretreated with a $5HT_2$ antagonist and at 2.2 mg/kg some antagonism of mCPP-induced PE was seen. Interaction studies have also been done with the 5-HT_{1A} agonist 8-OH-DPAT and the mixed 5-HT_{1A}/5-HT_2 agonist 5MeODMT (Middlemiss and Fozard 1983; Tricklebank et al. 1984; Sills et al. 1984). Both compounds potently antagonise mCPP-induced PE, indicating that 5-HT_{1A} receptor activation interferes with expression of 5-HT_{1C} receptor activation. Flat body posture induced by these compounds could possibly influence induction of PE but this cannot ex-

plain the disappearance of PE by 8-OH-DPAT and 5MeODMT. These drugs inhibit PE already at doses at which flat body posture was not yet seen.

This functional interplay of the 5-HT receptor subtypes has been seen before in other experiments: mCPP and DOI prevented induction of lower lip retraction by 8-OH-DPAT (Berendsen et al. 1988, 1989b) and antagonised 8-OH-DPAT-induced hypoactivity and hypothermia (Berendsen et al. 1989a). A similar functional interplay of the 5-HT_{1C} receptor with the 5-HT_{1B} receptor is less likely, since simultaneous injection of mCPP with the purported selective 5-HT_{1B} agonist CGS 12066 B (Neale et al. 1987) did not change the effect of mCPP.

The lack of effect of spiperone on mCPP-induced PE excludes a role for dopamine receptors. In agreement with this, it was previously found that haloperidol at doses which block yawning and penile erections induced by the dopamine receptor agonist apomorphine (Gower et al. 1984) did not block mCPP-induced PE (Berendsen and Broekkamp 1987).

A role for the 5-HT_3 receptors is not likely, since GR 38032 F, a 5-HT_3 antagonist (Brittain et al. 1987), had no effect on mCPP-induced PE. A functional interplay with 5-HT_{1C} and 5-HT_3 receptors as seen for the 5-HT_{1C} with the 5-HT_{1A} and 5-HT_2 receptors cannot be excluded as yet, since a selective 5-HT_3 agonist is not available to date. Induction of PE is not the only consequence of activation of 5-HT_{1C} receptors, since it was found that mCPP- and TFMPP-induced hypoactivity and hypophagia are probably also 5-HT_{1C} receptor-mediated effects (Kennett and Curzon 1988a, b). Our data support the suggestion that the 5-HT_{1C} receptors play an important role in the control of behaviour. The finding that 5-HT releasers and 5-HT uptake inhibitors induce PE further indicates a postsynaptic location of the responsible 5-HT_{1C} receptors. A further implication of these findings is that the 5-HT_{1C} receptors should be studied in the context of depression. The putatively 5-HT_{1C} receptors mediated penile erections are not only induced by the 5-HT uptake inhibitors but also by mCPP the main metabolite of the antidepressant compound trazodone (Yamamoto et al. 1974) and 5HTP. The 5-HT_{1C} receptor could very well be the common point of action for these antidepressants.

Acknowledgement. We thank Mr. J. van Schadewijk for his contribution and Mrs. P. van Haalen for preparation of the manuscript. The generous gifts of test compounds are gratefully acknowledged.

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