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Synergistic actions of the 5-HT_{1A} receptor antagonist WAY-100635 and citalopram on male rat ejaculatory behavior

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Abstract

The selective serotonin re-uptake inhibitor citalopram (0–40 mg kg^{-1}, s.c., — 60 min) did not affect the male rat ejaculatory behavior, and there were no statistically significant effects of the 5-HT_{1A} receptor antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexane carboxamide 3HCl (WAY-100635) (0.04–0.08 mg kg^{-1}, s.c., — 30 min). When combined, there was a marked, and statistically significant, prolongation of the ejaculation latency in comparison with saline treated controls, as well as in comparison with either drug by itself. This citalopram (10.0)/WAY-100635 (0.04)-induced effect was fully antagonized by the administration of the 5-HT_{1B} receptor antagonist isamoltane (4.0 mg kg^{-1}). There were no consistent effects on other aspects of the male rat sexual behavior, i.e., number of mounts and intromissions preceding ejaculation and the post-ejaculatory interval. Finally, the intromission latency was also markedly enhanced in animals receiving both citalopram and WAY-100635, and at the higher dose of WAY-100635 (0.08 mg kg^{-1}) 7 out of 18 animals failed to initiate copulation. It is suggested that blockade of inhibitory 5-HT_{1A} autoreceptors discloses inhibitory effects of the selective serotonin re-uptake inhibitor citalopram on male rat ejaculatory behavior mediated via stimulation of 5-HT_{1B} receptors.

Keywords: 5-HT (5-hydroxytryptamine, serotonin); Ejaculation; 5-HT_{1A} receptor; Serotonin re-uptake inhibitor, selective; Rat, male

1. Introduction

It is well known that an enhanced synaptic availability of 5-hydroxytryptamine (5-HT) in the central nervous system (CNS) results in an inhibition of ejaculation, as reported in several clinical and laboratory studies (see Ahlenius and Larsson, 1991). In fact, interference with ejaculation, and other aspects of sexual functions, is a prominent side effect of the widely used selective serotonin re-uptake inhibitor antidepressants (see Modell et al., 1997). Evidence from laboratory studies suggests that stimulation of 5-HT_{1B} receptors is of particular importance for these effects (Ahlenius and Larsson, 1998; Hillegaart and Ahlenius, 1998).

A current topic of great interest is the increased clinical efficacy of selective serotonin re-uptake inhibitors, as well as a faster onset of antidepressant actions, by the addition of the β-adrenoceptor antagonist pindolol (Perez et al., 1997; Bordet et al., 1998; see Artigas et al., 1996). Pindolol is also an antagonist at 5-HT_{1A} receptors (see Hoyer et al., 1994), and this property appears to be of particular importance for its interactions with selective serotonin re-uptake inhibitors. Thus, laboratory studies have shown that facilitation of forebrain 5-HT release by selective serotonin re-uptake inhibitors is enhanced by the administration of selective antagonists at this 5-HT receptor subtype (Gartside et al., 1995; Arborelius et al., 1996; Dawson and Nguyen, 1998).

In a recent study (Ahlenius and Larsson, 1998), it was shown that the 5-hydroxytryptophan (5-HTP)-induced inhibition of male rat ejaculatory behavior was enhanced in animals also administered the 5-HT_{1A} receptor antagonist WAY-100635 (Forster et al., 1995). These observations prompted the present study where we have examined the effects of this 5-HT_{1A} receptor antagonist, and the highly selective serotonin re-uptake inhibitor citalopram (see

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Owens et al., 1997), alone and in combination, on male rat ejaculatory behavior.

2. Methods

2.1. Animals

Adult male and female Wistar rats (B&K Universal, Sollentuna, Sweden) were used. The animals arrived in the laboratory at least 10 days prior to start of the experiments, in order to adapt to the laboratory environmental conditions of controlled light–dark cycle (12:12 h, lights off 1000 h), relative humidity (55–65%) and temperature (21.0 ± 0.4°C). The animals were housed by sex, five per cage (Makrolon® IV). Food (R36, Ewos, Södertälje, Sweden), and tap water were available ad libitum in the home cage.

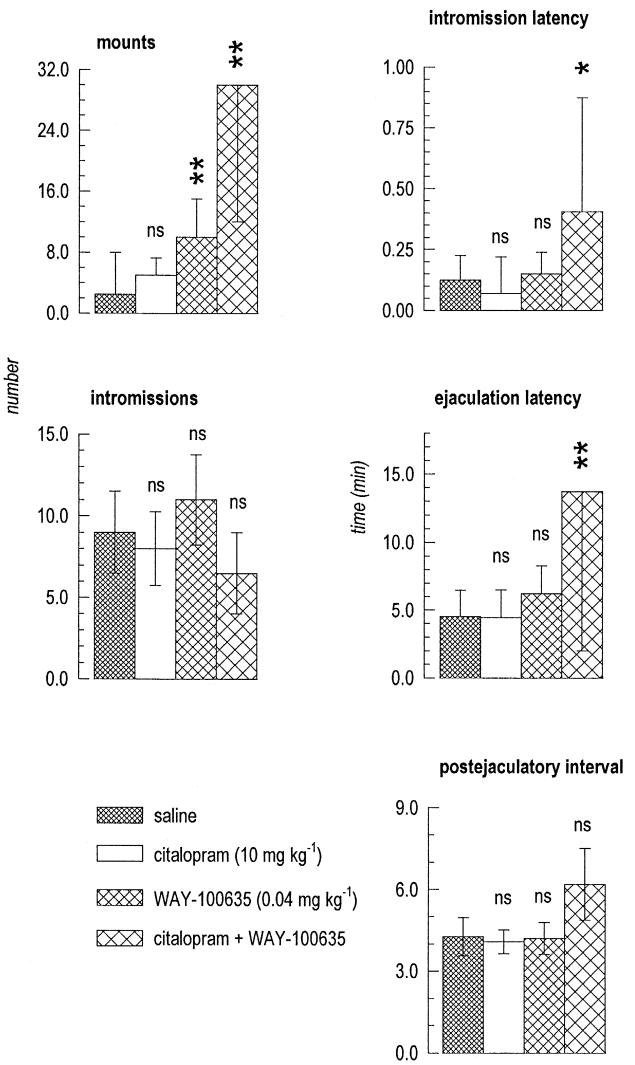

Fig. 1. Effects of citalopram and a sub-threshold WAY-100635 dose on male rat ejaculatory behavior. Citalopram (10 mg kg^{-1} s.c.) was administered 60 min, and WAY-100635 (0.04 mg kg^{-1} s.c.) 30 min, before observations started. Statistical comparisons with saline treated controls, or as indicated by brackets, are shown in the figure. $^{ns}P > 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$.

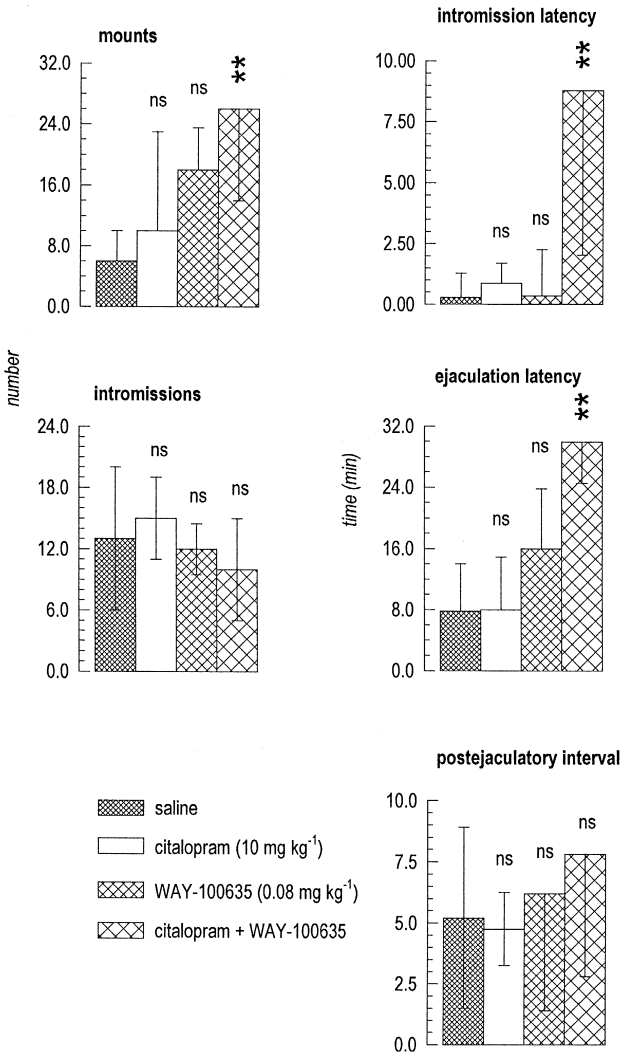

Fig. 2. Effects of citalopram and a threshold WAY-100635 dose on male rat ejaculatory behavior. Citalopram (10 mg kg^{-1} s.c.) was administered 60 min, and WAY-100635 (0.08 mg kg^{-1} s.c.) 30 min, before observations started. Statistical comparisons with saline treated controls, or as indicated by brackets, are shown in the figure. $^{ns}P > 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$.

The studies were approved by the Gothenburg Local Ethical Committee on Animal Experiments.

2.2. Drugs

N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexane carboxamide 3HCl (WAY-100635), mol wt. 549.97 (Wyeth-Ayerst, Princeton, NJ); citalopram HBr, mol wt. 405.30 (Lundbeck, Copenhagen, Denmark); isamoltane HCl, mol wt. 250.70 (Novartis, Basel, Switzerland). The drugs were dissolved in 0.9% NaCl and controls were given the saline vehicle. The route of administration was subcutaneous in a volume of 2 ml kg^{-1}. Females were brought into estrus by sequential treatment with estradiol benzoate (Fluka, Buchs, Switzerland) 12.5 μg per animal given at 48 h, followed by progesterone (Fluka) 0.5 mg per animal given at 6 h, before the observations. The hormones were dissolved in fractionated coconut oil

(Miglyol®-812, Nobel Chemicals, Karlskoga, Sweden), and injected s.c. in a volume of 0.1 ml per animal.

2.3. Behavioral observations

Male rats, sexually experienced in at least four pretests over a 2-week period, were presented with a receptive female in a circular perspex arena (∅ = 500 mm), the floor covered with wood shavings, in a dimly lit room. The following items of the male rat sexual behavior were recorded: Mounts (M), number of mounts without vaginal penetration; Intromissions (I), number of mounts with vaginal penetration; Intromission latency (IL), time from presentation of the female to the first intromission; Ejaculation latency (EL), time from the first intromission to ejaculation; Postejaculatory interval (PEI), time from ejaculation to the following intromission. The observations were ended when one of the following conditions was fulfilled. (1) If, after the first ejaculation, the animals had initiated a new copulatory series by an intromission; (2) If the male made an intromission, but no ejaculation occurred within 30 min; (3) If the male did not initiate copulation by an intromission within 15 min upon presentation of the female.

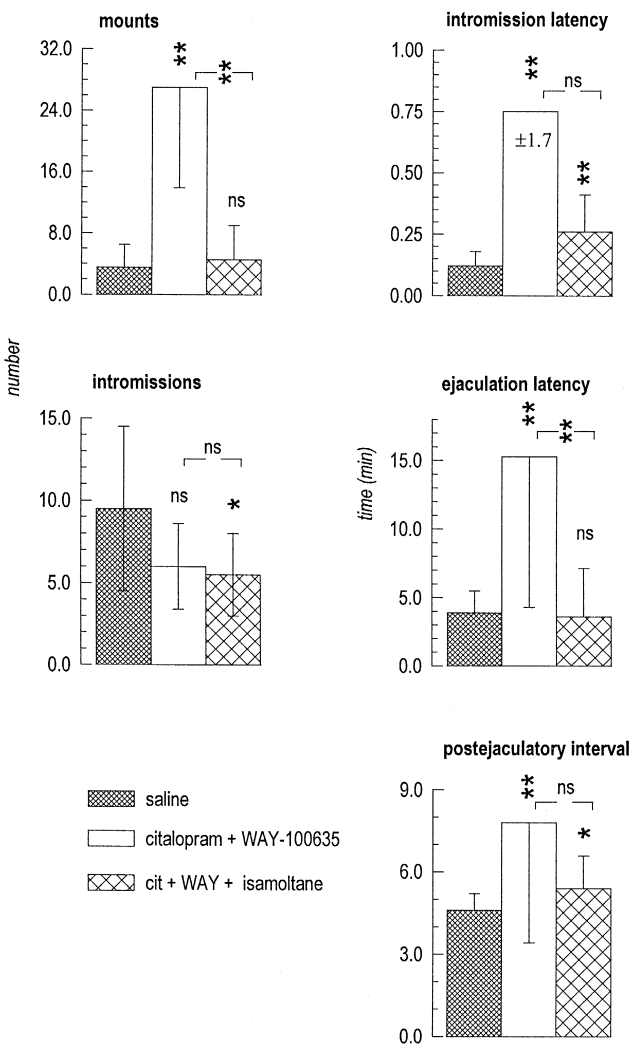

Fig. 3. Antagonism by isamoltane of the citalopram/WAY-100635-induced inhibition of male rat ejaculatory behavior. Citalopram (10 mg kg^{-1} s.c.) was administered 60 min, isamoltane (4.0 mg kg^{-1} s.c.) 30 min, and WAY-100635 (0.04 mg kg^{-1} s.c.) 20 min, before observations started. Statistical comparisons with saline treated controls, or as indicated by brackets, are shown in the figure. $^{ns}P > 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$.

Table 1
Outcome of the Friedman two-way ANOVA for results presented in Figs. 1–3. The table shows χ^2 values and associated statistical probabilities

	citalopram + WAY(0.04)	citalopram + WAY(0.08)	isamoltane/citalopram + WAY(0.04)
Intromission latency	12.81[c]	13.88[c]	9.59[c]
Ejaculation latency	15.68[c]	12.25[c]	7.62[b]
Post-ejaculatory interval	6.75[a]	8.32[b]	6.89[b]
Mounts	18.38[c]	4.28[a]	16.03[c]
Intromissions	15.66[c]	10.99[b]	9.90[c]
df	3	3	2

[a] $P > 0.05$.
[b] $P < 0.05$.
[c] $P < 0.01$.

2.4. Experimental design

A separate group of animals were used for each of the experiments presented in Figs. 1–3 ($n = 16$–18). Repeated observations of the same animals were performed by means of a change-over design (Li, 1964). The animals thus served as their own controls and were observed twice a week (Rat #1: abcd; Rat #2 bcda; Rat #3 cdab, etc.).

2.5. Statistical procedures

Non-parametric statistical procedures were used throughout. Thus, the results are presented as medians ± semi-interquartile range, and statistical analysis was performed by means of a Friedman two-way analysis of variance (see Table 1), followed by the Wilcoxon matched-pairs signed-ranks *T*-test for comparisons between individual groups (Siegel, 1956).

3. Results

3.1. Effects of citalopram or WAY-100635 on male rat sexual behavior

By itself, citalopram (0–40 mg kg^{-1} s.c.) did not significantly affect any aspect of the copulatory behavior (Figs. 1 and 2 and Table 2). As regards WAY-100635, there were no statistically significant effects, except for an increase in number of mounts at the lowest dose (0.04 mg kg^{-1} s.c.).

Table 2
Effects of citalopram on the male rat sexual behavior. The table shows medians ± semi-interquartile range, based on repeated observations of 12 rats

	Citalopram (mg kg^{-1})				
	0	2.5	10.0	40.0	$\chi^2(3)$
Intromission latency	0.13 ± 0.11	0.13 ± 0.05	0.17 ± 0.10	0.13 ± 0.03	0.18^{ns}
Ejaculation latency	2.60 ± 1.65	2.25 ± 1.52	2.74 ± 2.21	1.61 ± 2.41	1.30^{ns}
Post-ejaculatory interval	4.39 ± 0.86	4.51 ± 0.95	4.37 ± 0.75	4.61 ± 0.54	0.57^{ns}
Mounts	2.5 ± 2.0	4.0 ± 2.5	4.5 ± 5.0	4.5 ± 7.0	4.90^{ns}
Intromissions	6.5 ± 3.0	5.0 ± 2.0	5.5 ± 3.0	4.0 ± 2.5	3.78^{ns}

$^{ns}P > 0.05$.

3.2. Effects of combined treatment with citalopram and WAY-100635 on male rat sexual behavior

All animals receiving the combination of a low dose WAY-100635 (0.04 mg kg^{-1}) and citalopram treatment initiated copulation, although 6 of the 16 animals failed to ejaculate within the 30 min allowed following the first intromission. As seen in Fig. 1, all aspects of the copulatory behavior observed, except for the post-ejaculatory interval, were affected by this combination treatment. Furthermore, the number of mounts was increased, whereas number of intromissions decreased, suggesting less copulatory efficiency in terms of vaginal penetration per mount. Finally, the increases in ejaculation latency produced by the combined treatment was significantly elevated also by direct comparison with WAY-100635 or citalopram treated animals ($P < 0.01$, Wilcoxon matched-pairs signed-ranks *T*-test).

The combination of citalopram and a higher dose of WAY-100635 (0.08 mg kg^{-1}) produced a marked increase in intromission latency, and in fact 7 of the 18 animals failed to initiate copulation. The most conspicuous effect in the remaining 11 animals was a marked increase in the ejaculation latency (Fig. 2) and this increase was statistically significant also in comparison with the WAY-100635 or citalopram treatment ($P < 0.01$, Wilcoxon matched-pairs signed-ranks *T*-test). Except for a statistically significant increase in number of mounts, as compared to controls (but not in comparison with WAY-100635 or citalopram treated animals), there were no other statistically significant effects of this combination.

3.3. Antagonism by isamoltane of the citalopram / WAY-100635-induced inhibition of male rat ejaculatory behavior

As expected from the results presented above, the combination of citalopram (10 mg kg^{-1} s.c.) with WAY-100635 (0.04 mg kg^{-1} s.c.) produced a marked and statistically significant increase in the ejaculation latency. In further agreement with the above results, there was also an increase in the intromission latency and an increased number of mounts preceding ejaculation. In addition, there was also a statistically significant increase in the post-ejaculatory interval. The increase in ejaculation latency, as well as in the number of mounts, was fully antagonized by treatment with the 5-HT$_{1B}$ receptor antagonist isamoltane (4 mg kg^{-1} s.c.), and there was a similar tendency for antagonism of the other effects produced by the citalopram/WAY-100635 combination (Fig. 3). Isamoltane, by itself, does not affect the male rat sexual behavior as shown in recent parallel experiments (Ahlenius and Larsson, 1998; Hillegaart and Ahlenius, 1998).

4. Discussion

The present results clearly demonstrate synergistic actions of the 5-HT$_{1A}$ receptor antagonist WAY-100635 and the selective serotonin re-uptake inhibitors citalopram, on male rat ejaculatory behavior. Thus, when combined in sub-threshold doses, a marked enhancement of their inhibitory effects is seen. In fact, also the efficacy appears stronger by the combination, since higher doses of either drug by itself produced no, or very modest, increase in ejaculation latency, as shown in the present and other studies (Ahlenius and Larsson, 1998; Hillegaart and Ahlenius, 1998). It is interesting to note that similar synergistic interactions recently were reported for effects of WAY-100635 and a selective serotonin re-uptake inhibitor on feeding behavior. Thus, the hypophagia produced by selective serotonin re-uptake inhibitors in rats was markedly enhanced by WAY-100635 treatment (Trillat et al., 1998).

It has previously been shown that the combination of sub-threshold doses of 5-HTP and the selective serotonin re-uptake inhibitor zimeldine results in increased ejaculation latency (Ahlenius et al., 1980). There is both direct and indirect evidence that this effect is mediated via stimulation of 5-HT$_{1B}$ receptors. Thus, the 5-HTP-induced prolongation of ejaculation latency is antagonized by co-treatment with the 5-HT$_{1B}$ receptor antagonist isamoltane (Waldmeier et al., 1988), and the inhibitory effects of 5-HTP are further enhanced by co-treatment with the 5-HT$_{1A}$ receptor antagonist WAY-100635 (Ahlenius and Larsson, 1998). Since stimulation of 5-HT$_{1A}$ receptors facilitates the male ejaculatory behavior (see Ahlenius and Larsson, 1991), blockade of this receptor leaves the 5-HT$_{1B}$ receptor stimulation unopposed by of the 5-HT$_{1A}$ receptor

stimulation. This contention receives strong support from the present observation that the citalopram/WAY-100635-induced inhibition of the male rat ejaculatory behavior was fully antagonized by isamoltane.

There is evidence that also stimulation of 5-HT_2 receptors is inhibitory to male rat sexual behavior. This inhibition is not selective for ejaculation, however, and is primarily expressed as a decrease in number of copulating animals, whereas the ejaculation latency is not affected in those individuals initiating copulation (Watson and Gorzalka, 1991; Fernandez-Guasti and Rodriguez-Manzo, 1992; Fernandez-Guasti et al., 1992; Klint et al., 1992; Ahlenius and Larsson, 1998). This appears to apply primarily to the 5-HT_{2A} receptor, whereas the 5-HT_{2C} receptor primarily has been associated with mechanisms of penile erection (Berendsen et al., 1990; Millan et al., 1997). Effects on penile erections, however, are not directly related to ejaculatory behavior, as observed here. Thus, for example, the prototypic 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), which markedly facilitates ejaculation in the rat, inhibits the display of penile erections (Simon et al., 1993; Protais et al., 1995; see Ahlenius and Larsson, 1991). Nevertheless, is would be of great interest to compare directly the effects of selective 5-HT_{2A} and 5-HT_{2C} receptor agonists and antagonists on male rat ejaculatory behavior.

As mentioned in Section 1, there is presently a great interest in the possibility of increasing clinical efficacy of selective serotonin re-uptake inhibitors by the use of a 5-HT_{1A} receptor adjuvant. The present result suggests that sexual side effects of selective serotonin re-uptake inhibitors would be prominent. It should be noted, however, that this concept is based on the ability of (−)-pindolol to enhance the antidepressant efficacy of selective serotonin re-uptake inhibitors. There is a strong possibility that the mechanism whereby (−)-pindolol produces this effect is unrelated to antagonism of 5-HT_{1A} receptors by (−)-pindolol (Kaur and Ahlenius, 1997; Clifford et al., 1998). In any case, the present interactions in the effects of WAY-100635 and citalopram on male rat ejaculatory behavior, not only appear related to potency, but also efficacy. Thus, the combination of 5-HT_{1A} receptor antagonists with a selective serotonin re-uptake inhibitor could have therapeutic utility in the field of urogenital pharmacology, as for example in the treatment of *ejaculatio praecox*.

As shown here, and in previous studies, WAY-100635 or citalopram by themselves have a weak tendency to enhance ejaculation latency in rats. When combined at sub-threshold doses a marked and statistically significant prolongation of time to ejaculation is obtained. This effect was sensitive to isamoltane treatment, suggesting mediation via 5-HT_{1B} receptors. Other effects by citalopram and/or WAY-100635 on the male rat sexual behavior, such as number of mounts and intromissions, as well as the post-ejaculatory interval, were weak and inconsistent.

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