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Opposite Effects of 5-Methoxy-N,N-di-Methyl-Tryptamine and 5-Hydroxytryptophan on Male Rat Sexual Behavior

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AHLENIUS, S. AND K. LARSSON. *Opposite effects of 5-methoxy-N,N-di-methyl-tryptamine and 5-hydroxytryptophan on male rat sexual behavior.* PHARMACOL BIOCHEM BEHAV **38**(1) 201–205, 1991.—The administration of 5-methoxy-N,N-di-methyltryptamine (5-MeODMT), 0–2.0 mg·kg^{-1} SC −15 min, produced a dose-dependent facilitation of the male rat sexual behavior, as evidenced by a decrease in the number of intromissions to ejaculation and in the ejaculation latency. The effects produced by 5-MeODMT (1 mg·kg^{-1}) were antagonized by pindolol (4 mg·kg^{-1} SC −30 min), but not pirenperone (0.25 mg·kg^{-1} SC −30 min) or metergoline (1 mg·kg^{-1} SC −30 min), administration. As expected, 5-HTP (25 mg·kg^{-1} SC −60 min) produced an increased number of mounts and intromissions to ejaculation and an increase in the ejaculation latency in benserazide (25 mg·kg^{-1} SC −90 min) pretreated animals. Pindolol (4 mg·kg^{-1}) by itself produced the same effects as seen after 5-HTP administration, and the combination of these compounds produced additive effects. Betaxolol (8 mg·kg^{-1} SC −30 min) had no effects of its own and did not interact with 5-HTP. The results suggest that stimulation of brain 5-HT$_1$ or 5-HT$_2$ receptors produces facilitation and inhibition, respectively, of the male rat sexual behavior.

Male sexual behavior 5-HT receptors 5-MeODMT 5-HTP Rat

IT has been suggested that central serotonergic mechanisms are inhibitory in neuronal pathways mediating male rat sexual behavior [see (24)]. In agreement with this contention, the administration of the 5-hydroxytryptamine (5-HT) precursor 5-hydroxytryptophan (5-HTP) produces a delay in the time to ejaculation, and an increase in the number of mounts and intromissions preceding ejaculation in rats pretreated with an inhibitor of peripheral aromatic amino acid decarboxylase (1). These effects are enhanced by additional treatment with zimelidine, a selective inhibitor of neuronal 5-HT reuptake (7). In contrast, the administration of the 5-HT$_{1A}$ receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (21,26) produces a facilitation of the male rat sexual behavior (8, 18, 25). In further support for a specific role of 5-HT$_1$ receptors, a number of compounds with affinity for this 5-HT receptor subtype also facilitate the male rat sexual behavior. These other compounds include buspirone, 5-OH-DPAC (an aminochroman analogue of 8-OH-DPAT), ipsapirone and 5-methoxy-N,N-*di*-methyltryptamine (5-MeODMT) (5, 13, 14, 18).

In the present experiments we examined, in more detail, a possible specific involvement of 5-HT$_1$ and 5-HT$_2$ receptors in the mediation of male rat sexual behavior. In order to obtain selective 5-HT$_2$ receptor stimulation, 5-HTP-treated rats were also given the β-adrenoceptor blocking agent pindolol, which has been shown also to block 5-HT receptors (12). As a 5-HT receptor blocking agent, pindolol has preferential affinity for the 5-HT$_1$ receptor subtype [see (27)]. A β-blocker with no affinity for 5-HT receptors, betaxolol, was used as a control (10). In order to limit the effects of 5-HTP to the CNS, the animals were pretreated with benserazide, an inhibitor of peripheral 5-HTP decarboxylase (9). 5-MeODMT was chosen as a 5-HT$_1$ receptor agonist [see (28)] and the effects of this compound were studied after pretreatment with pindolol or with the 5-HT$_2$ receptor-blocking agents pirenperone or metergoline (11,16).

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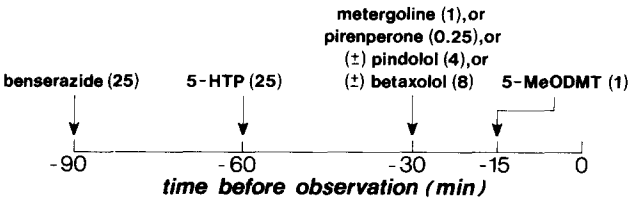

FIG. 1. Schedule of drug injections in relation to behavioral observations. The different compounds were administered SC in the doses indicated ($mg \cdot kg^{-1}$).

METHOD

Animals

Adult male (350–400 g) and female (240–260 g) Wistar rats were used (Möllegaard, Vejle, Denmark). The animals, 5 per cage, were kept under controlled conditions of temperature (22°C), relative humidity (50–60%) and light-dark cycle (12:12 h, lights off 10.00 h). The animals arrived in the laboratory at least two weeks before being used experimentally. Food (R3; Ewos, Södertälje, Sweden) and tap water were available at all times in the home cage.

Drugs

The following drugs were used: 5-hydroxy-*L*-tryptophan (5-HTP) (Sigma, St Louis, MO), benserazide HCl (Roche,* Basel, Switzerland), 5-methoxy-N,N-*di*-methyltryptamine oxalate (5-MeODMT) (RBI, Natick, MA), (±)pindolol (Shiratori,* Tokyo, Japan), (±)betaxolol HCl (Synthelabo,* Paris, France), metergoline (Farmitalia,* Milan, Italy) and pirenperone (Janssen,* Beerse, Belgium). Metergoline was dissolved in a few drops of ethanol and 0.9% saline was added to final volume. The other drugs were dissolved in 0.9% saline only. All drugs were administered SC in a volume of $2\ ml \cdot kg^{-1}$.

Behavioral Observations

Male rats were presented with a female brought into estrous by sequential treatment with estradiol benzoate ($12.5\ \mu g \cdot rat^{-1}$ SC in sesame oil, −54 h), and progesterone ($0.5\ mg \cdot rat^{-1}$ SC in sesame oil, −6 h). The following items of the male rat sexual behavior were observed: Mounts (M) (number of mounts without penile intromission), Intromissions (I) (number of mounts with penile intromission), Intromission latency (IL) (time from the presentation of the female to the first intromission), Ejaculation latency (EL) (time from the first intromission until ejaculation), Postejaculatory interval (PEI) (time from ejaculation until the following intromission). The observations were terminated (A) when no intromission had occurred within 15 min after presentation of the female. These animals were excluded in the further analysis of the results; (B) If the male had not ejaculated within 30 min from the first intromission. These animals were assigned an EL of ≥30 min and ≥ the number of intromissions and mounts displayed up to this point; (C) At the first intromission following ejaculation; (D) 15 min after ejaculation if no intromission had occurred at this time. These animals were assigned a PEI of ≥15 min in the data processing.

The animals were observed in circular perspex boxes (∅ = 500 mm) lit by a 15-W bulb above the arena, and the observations were performed between 13.00–16.00 h. The animals were given at least four pretests, and only sexually active animals were used in the experiments.

Experimental Design and Statistics

Separate groups of animals served as their own controls in the three experiments presented in Figs. 2–3, and in Table 1. A change-over design was used [see (22)], and statistical evaluation was performed by means of the Friedman nonparametric ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test for comparisons with appropriate controls [see (30)].

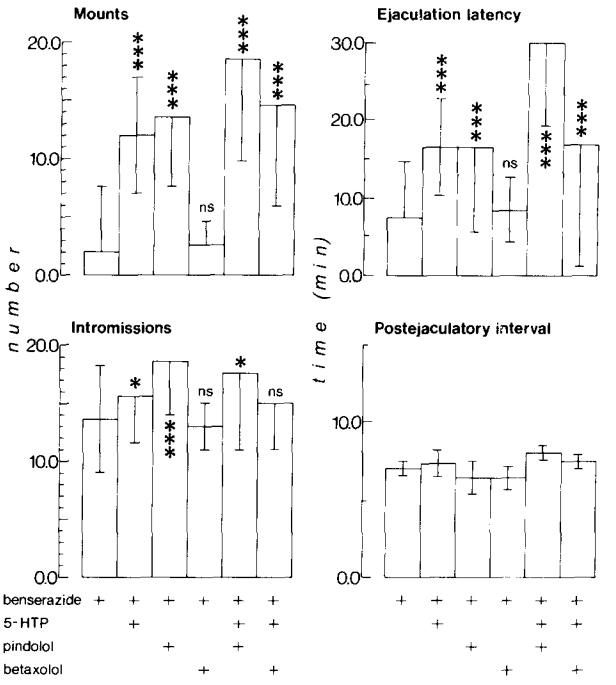

FIG. 2. Effects of pindolol and betaxolol on 5-HTP-induced inhibition of male rat sexual behavior. For schedule of drug injections see Fig. 1. The figure shows medians ± semi-interquartile range, based on observations of 22 animals. Mounts: $\chi^2_5 = 41.20$, $p \leq 0.01$; Intromissions: $\chi^2_5 = 16.14$, $p \leq 0.01$; Ejaculation latency: $\chi^2_5 = 41.14$, $p \leq 0.01$; Postejaculatory interval: $\chi^2_5 = 11.07$, n.s. Statistical comparisons with benserazide-treated controls, as indicated in the figure. $^{ns}p > 0.05$, $^{*}p < 0.05$, $^{***}p < 0.01$.

RESULTS

The injection schedules for the various treatments in the two experiments on effects of 5-HTP and 5-MeODMT, as described below, are summarized in Fig. 1.

Effects of Pindolol and Betaxolol on 5-HTP-Induced Inhibition of Male Rat Sexual Behavior

The IL was significantly prolonged in animals receiving 5-HTP, as compared to benserazide-treated controls (0.35 vs. 0.05 min, $p \leq 0.01$). No other statistically significant effects were noted and the median IL was in all other groups between 0.05 and 0.1 min. Treatment with 5-HTP or pindolol produced an inhibition of the male rat sexual behavior, as evidenced by an increase in mounts, intromissions and in time to ejaculation (Fig. 2). Combined, 5-HTP and pindolol produced a further inhibition of the behavior, as evidenced by an increase in time to ejaculation as compared to the EL after treatment with either compound alone ($p \leq 0.025$). Betaxolol by itself had no effects on the male rat sexual behavior and did not change the effects produced by 5-HTP (Fig. 2). There were no statistically significant changes by any of the treatments on the PEI.

TABLE 1

EFFECTS OF 5-MeODMT ON MALE RAT SEXUAL BEHAVIOR

	5-MeODMT ($mg \cdot kg^{-1}$)			
	0.0	0.5	1.0	2.0
Intromission latency (min)	0.15 ±0.20	0.33^{ns} ±0.38	0.75* ±1.10	6.47† ±4.29
Mounts (number)	3.5 ±4.3	1.5* ±2.3	7.0^{ns} ±5.0	4.0^{ns} ±4.3
Intromissions (number)	12.0 ±4.5	7.5^{ns} ±2.0	6.0† ±1.0	3.0† ±1.5
Ejaculation latency (min)	6.1 ±2.8	3.9^{ns} ±3.9	3.7† ±2.6	2.1† ±1.6
Postejaculatory interval (min)	5.3 ±0.8	6.1^{ns} ±0.8	6.3^{ns} ±0.7	5.5^{ns} ±0.6
Number of ejaculating animals	15	16	15	9

5-MeODMT was administered SC, 15 min before behavioral observations. The table shows medians ± semi-interquartile range. The animals (n = 17) served as their own controls in a change-over design (22). Statistical anlaysis was performed by means of the Wilcoxon matched-pairs signed-ranks test for comparisons with saline-treated controls, as indicated in the table.

$^{ns}p>0.05$, $*p<0.05$, $\dagger p<0.01$.

Effects of Pirenperone, Metergoline and Pindolol on the Facilitation of Male Rat Sexual Behavior Produced by 5-MeODMT

The administration of 5-MeODMT, 0–2.0 $mg \cdot kg^{-1}$ SC, by itself produced a facilitation of the male rat sexual behavior as evidenced by a dose-dependent decrease in the number of intromissions preceding ejaculation and in time to ejaculation. Except for a dose-dependent increase in the IL, no other consistent effects were noted. At the highest dose, however, some animals failed to initiate copulation (Table 1).

There was no antagonism by pirenperone or metergoline administration of the effects produced by 5-MeODMT, 1 $mg \cdot kg^{-1}$. The administration of pindolol not only antagonized the facilitation of the behavior as observed after 5-MeODMT but also produced an inhibition of the behavior as compared to both 5-MeODMT- and saline-treated animals (see Fig. 3 for details).

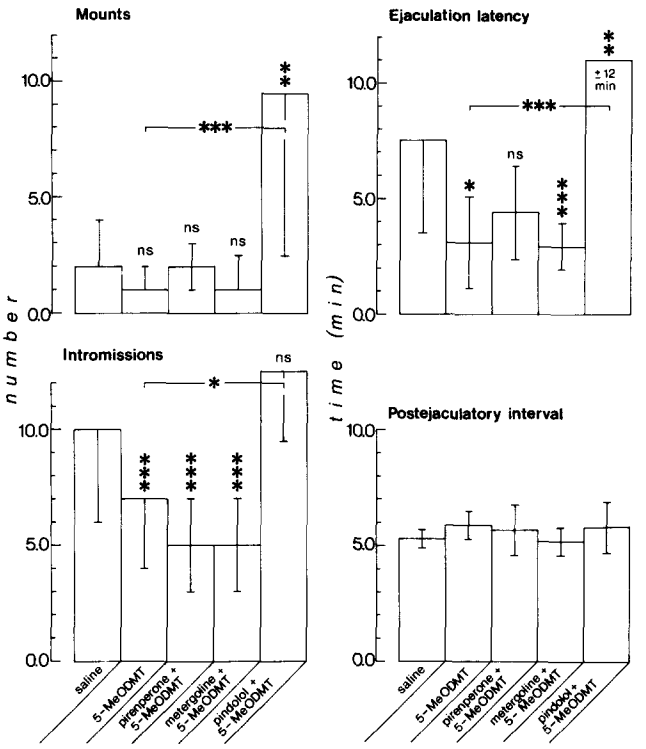

FIG. 3. Effects of pirenperone, metergoline and pindolol on 5-MeODMT-induced facilitation of male rat sexual behavior. For schedule of drug injections see Fig. 1. The figure shows medians ± semi-interquartile range, based on observations of 16 animals. Mounts: $\chi^2_4 = 18.72$, $p \leq 0.01$; Intromissions: $\chi^2_4 = 19.43$, $p \leq 0.01$; Ejaculation latency: $\chi^2_4 = 21.37$, $p \leq 0.01$; Postejaculatory interval: $\chi^2_4 = 9.49$, n.s. Statistical comparisons with saline-treated controls, as indicated in the figure. Other group comparisons, as indicated by brackets. $^{ns}p>0.05$, $*p<0.05$, $**p<0.025$, $***p<0.01$.

DISCUSSION

In agreement with previous observations, the present results demonstrate an inhibition and a facilitation of the male rat sexual behavior by the administration of 5-HTP and 5-MeODMT, respectively (1, 7, 14). 5-MeODMT is a direct-acting 5-HT_{1A} receptor agonist (17, 23, 32). The effects produced by 5-HTP are in all probability also due to postsynaptic 5-HT receptor stimulation since (a) 5-HTP-induced effects are potentiated by pretreatment with the selective 5-HT reuptake inhibitor zimelidine (7), and (b) the same effect, inhibition of the male rat sexual behavior, is obtained by the local application of 5-HT into terminal areas of serotonergic projections in the limbic forebrain of the rat, whereas the local application of 5-HT onto cell bodies in the brainstem raphe nuclei, produces facilitation of the sexual behavior (19,20).

The inhibition of the male rat sexual behavior produced by 5-HTP should be due to postsynaptic 5-HT_2 receptor stimulation since it can be blocked by the administration of pirenperone (2), but not by pindolol treatment as shown here. In fact, pindolol by itself produced an inhibition of the sexual behavior in the present study, and the combined 5-HTP/pindolol treatment further inhibited the behavior in an additive manner. In contrast to the antagonism by pirenperone, or metergoline, of 5-HTP-induced inhibition of the male rat sexual behavior, there was no antagonism by either of these compounds of the 5-MeODMT-induced facilitation of the sexual behavior. This latter observation is in agreement with results from experiments on 8-OH-DPAT (2), and support the contention that stimulation of brain 5-HT_{1A} receptors is responsible for the facilitation produced by 5-MeODMT, or 8-OH-DPAT. Furthermore, the effects produced by 5-MeODMT were completely blocked by pindolol treatment, as previously shown for effects produced by 8-OH-DPAT (4). Together with other observations (15), these results suggest that brain 5-HT_1 and 5-HT_2 have a facilitatory and inhibitory role, respectively, in the mediation of male rat sexual behavior. Considering remaining problems, however, of 5-HT receptor classification (29), and the lack of selective pharmacological tools, we can safely conclude that continued research will disclose further details regarding the involvement of presumed receptor subtypes in complex functions like male rat sexual behavior.

We have previously noted the apparent 5-HT receptor-blocking properties of 8-OH-DPAT and lisuride (3). Thus, 5-HTP-induced effects on male rat sexual behavior are blocked by low, per se inactive, doses of these compounds. It is not immediately clear how these findings relate to the balance between the 5-HT_1 and 5-HT_2 receptor mechanisms involved in the mediation of male rat sexual behavior discussed above. It should also be noted that although depletion of brain 5-HT by means of the tryptophan hydroxylase inhibitor *p*-chloro-phenylalanine produces a facilitation of the male rat sexual behavior, this does not appear to be the case by treatment with pirenperone, alone or in combination with 5-HTP, nor does pirenperone treatment appear to enhance the facilitation produced by 5-MeODMT or 8-OH-DPAT, as shown here and in previous studies [see (6)]. These apparent discrepancies are probably related to the fact that the present taxonomy of 5-HT receptors, primarily based on affinity of receptor ligands to various animal tissues, does not necessarily correspond to pharmacologically and physiologically distinct receptors. It should also be important to know the involvement of the different serotonergic pathways described in detail [see (31)]. Thus, although there is no doubt that central serotonergic mechanisms are of great importance in the mediation of male rat sexual behavior, future developments in this field will be closely related to the functional mapping of brain serotonergic pathways and the characterization of new selective pharmacological tools.

In conclusion, the present results demonstrate that stimulation of brain 5-HT_2 receptors, by means of combined 5-HTP and pindolol treatment, inhibits the performance of male rat sexual behavior. Stimulation of 5-HT_1 receptors by 5-MeODMT treatment produced a facilitation of the sexual behavior, and this effect was blocked by pindolol, but not pirenperone or metergoline, treatment. Together with other recent findings (15), these observations suggest the existence of central facilitatory 5-HT_1, and inhibitory 5-HT_2, receptor mechanisms in the mediation of male rat sexual behavior.

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