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Partial antagonism of 8-OH-DPAT'S effects on male rat sexual behavior with a D_2, but not a 5-HT_{1A}, antagonist

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Abstract

The serotonin agonist 8-hydroxy-di-propylaminotetralin (8-OH-DPAT), injected systemically or directly into the medial preoptic area (MPOA), reduces the ejaculatory threshold in male rats. While 8-OH-DPAT has been characterized as an agonist at the 5-HT_{1A} receptor, it also acts at other receptor sites including the dopamine D_2 receptor. The current experiments investigated whether 8-OH-DPAT injected into the MPOA facilitates male sexual behavior through stimulation of the 5-HT_{1A} receptor or the dopamine D_2 receptor. Experiment 1 co-administered 8-OH-DPAT (6 μg) with either the 5-HT_{1A} antagonist 4-iodo-*N*-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-benzamide hydrochloride (MPPI) (10 μg) or the D_2 antagonist raclopride (10 μg). Raclopride blocked 8-OH-DPAT's facilitative effects on ejaculation frequency and latency, while the 5-HT_{1A} antagonist was ineffective. In Experiment 2, 8-OH-DPAT (500 μM), retrodialyzed into the MPOA through a microdialysis probe, enhanced male copulatory behavior similarly to the microinjection, increasing ejaculation frequency and decreasing ejaculation latency, postejaculatory interval and mount frequency. Retrodialyzing 8-OH-DPAT through a microdialysis probe in the MPOA had been previously shown to increase extracellular levels of dopamine and serotonin. The data from the present studies suggest that the effects of 8-OH-DPAT in the MPOA on male rat copulatory behavior may be mediated, at least in part, either directly through 8-OH-DPAT's activity at D_2 receptors or indirectly through 8-OH-DPAT's ability to increase extracellular dopamine.

Keywords: Male sexual behavior; 8-OH-DPAT; Medial preoptic area; Dopamine; Serotonin; Raclopride; MPPI

1. Introduction

The expression of masculine sexual behavior by rats has been shown to be enhanced by dopamine (DA) and inhibited by serotonin (5-HT) neurotransmission in the brain (reviewed in Refs. [9,18,30,42]). Although most behavioral experiments support this generalization, an exclusively inhibitory role for 5-HT has been challenged by observations that 8-hydroxy-di-propylaminotetralin (8-OH-DPAT), a 5-HT_{1A} agonist, facilitates ejaculation. When administered systemically, 8-OH-DPAT decreases the number of intromissions before ejaculation, ejaculation latency, and the post ejaculatory interval in male rats [1,3–6,15,31,34]. Similar behavioral effects occur following central infusion of 8-OH-DPAT into the cerebral ventricles, the intrathecal space, the medial preoptic area (MPOA), nucleus accumbens and median raphe nucleus [14,21,40].

Stimulation of both auto and postsynaptic 5-HT_{1A} receptors has been suggested to mediate the effects of 8-OH-DPAT on male sexual behavior. Consistent with the findings that 5-HT in general inhibits sexual behavior, 8-OH-DPAT may enhance sexual behavior by decreasing 5-HT activity in terminal regions. Indeed, stimulation of

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5-HT_{1A} autoreceptors located on serotonergic cell bodies in the raphe decreased 5-HT cell firing and terminal release [11,20,36,37,39]. On the other hand, 8-OH-DPAT may exert its behavioral effects by stimulating forebrain 5-HT_{1A} postsynaptic receptors. Evidence for a postsynaptic receptor effect derives from experiments in which the 5-HT neurotoxin 5,7-DHT abolished presynaptic 5-HT input, but did not prevent 8-OH-DPAT's effects on sexual behavior [12]. Furthermore, stimulation of raphe 5-HT_{1A} autoreceptors cannot be responsible for the decreased ejaculation threshold of 8-OH-DPAT when it is infused into specific forebrain sites, such as the MPOA.

The putative 5-HT_{1A} agonist has been shown to interact with neurotransmitter systems besides 5-HT, including dopaminergic systems. For example, 8-OH-DPAT has moderate affinity for the DA D_2 receptor [38,41]. Similarly to 8-OH-DPAT, stimulation of the D_2 receptor by a selective D_2 agonist reduces the ejaculatory threshold by decreasing the number of intromissions prior to ejaculation [25]. Recently, we have observed that 8-OH-DPAT, reverse dialyzed into the MPOA, increased extracellular levels of DA and 5-HT; these effects were not blocked by a 5-HT_{1A} antagonist [29]. While 5-HT_{1A} receptor stimulation is thought to be responsible for 8-OH-DPAT's effects on male copulatory behavior, to date there have been no reports showing that administration of a 5-HT_{1A} antagonist into 5-HT terminal regions of the brain can prevent 8-OH-DPAT's effects on male rat sexual behavior. The first objective of the following pharmacological investigation was to determine whether 8-OH-DPAT influences sexual activity through stimulation of 5-HT_{1A} or D_2 receptors located in the MPOA. The second objective was to test whether reverse dialysis of 8-OH-DPAT into the MPOA, at a dose shown to increase both DA and 5-HT, would enhance copulation in a manner similar to microinjections of 8-OH-DPAT.

2. Materials and methods

2.1. Animals

Adult male Long–Evans/Blue Spruce rats (300–350 g) were used for all experiments. They were singly housed in large plastic cages in a temperature and humidity controlled room, on a reverse light cycle (off at 1100 h and on at 2100 h). Food and water were available ad libitum. All subjects were weighed daily to monitor their health and adapt them to handling procedures. For the copulation tests, ovariectomized females of the same strain were used. The stimulus females were brought into receptivity with a subcutaneous injection of 20 μg estradiol benzoate in oil, 48 h before behavioral testing. All procedures followed the guidelines of, and were approved by, the local Institutional Animal Care and Use Committee.

2.2. Stereotaxic surgery

Each subject received a unilateral guide cannula while under ketamine hydrochloride (75 mg/kg) and xylazine hydrochloride (3 mg/kg) anesthesia. A Kopf stereotaxic frame, with the incisor bar at +5 mm, was used to implant the 23 gauge guide cannula, 17 mm in length, aimed 3 mm above the left MPOA (from bregma AP: +2.4 mm; ML: +0.2; DV: −6.3 from top of skull) [33]. Dental acrylic was applied around the cannula and three metal screws were used to anchor the cannula to the skull. A metal obturator fashioned from 27 gauge stainless steel was inserted into the guide cannula following surgery until the test day.

2.3. Infusions and drugs

Drug solutions were prepared freshly in saline (microinjection) or a modified Ringer's solution (reverse dialysis) before each copulatory test. All drugs were purchased from Research Biochemicals International. For microinjections, each subject received saline or 6 μg/μl of 8-OH-DPAT hydrobromide alone, or in combination with 10 μg/μl of either the 5-HT_{1A} antagonist 4-iodo-*N*-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-benzamide hydrochloride (MPPI) or the dopamine antagonist *S*(−)-raclopride L-tartate (raclopride). Drug treatments were given in a counterbalanced order with 1 week separating behavioral test sessions.

Microinjections of drug were accomplished by removing the metal obturator and replacing it with a 27 gauge injection cannula, 18 mm in length. The injection cannula was connected to a Harvard (model 22) infusion pump by a length of PE 20 tubing. Each rat received 1 μl of the appropriate solution delivered at a rate of 0.5 μl/min. The injection cannula was left in place for an additional 60 s, and then the obturator was reinserted. Subjects completed a 30-min copulatory behavioral test immediately following microinjection.

For reverse dialysis, subjects were briefly anesthetized with ether to allow for insertion of a concentric microdialysis probe through the implanted guide cannula. The subjects were then placed individually into a circular Plexiglas test arena. Ringer's solution (147 mM NaCl, 1.2 mM $CaCl_2$, and 4 mM KCl) flowed through the probes at a rate of 0.5 μl/min. After a 4-h period, Ringer's solution was exchanged for a solution of 500 μM 8-OH-DPAT in Ringer's solution. A 15-min delay between switching the solutions and the behavioral test allowed the drug to travel to the active dialysis surface of the membrane and perfuse

the surrounding tissue. The 8-OH-DPAT solution was perfused for the entire 60-min behavioral test.

2.4. Behavioral testing

Seven days after intracranial surgery, males were given a postoperative copulation test with a receptive female for a 30 min period or until the first ejaculation. Males failing to ejaculate within 30 min were given a second postoperative test 1 week later. All subjects successfully ejaculated by the end of the second session.

Experimental behavioral tests lasted 30 min (microinjections) or 60 min (reverse dialysis) after the first intromission, or 30 or 60 min after the introduction of the female, if the male failed to intromit. The following copulatory measures were recorded: latency to first mount and intromission following the introduction of the female; latency from the first intromission to the first ejaculation;

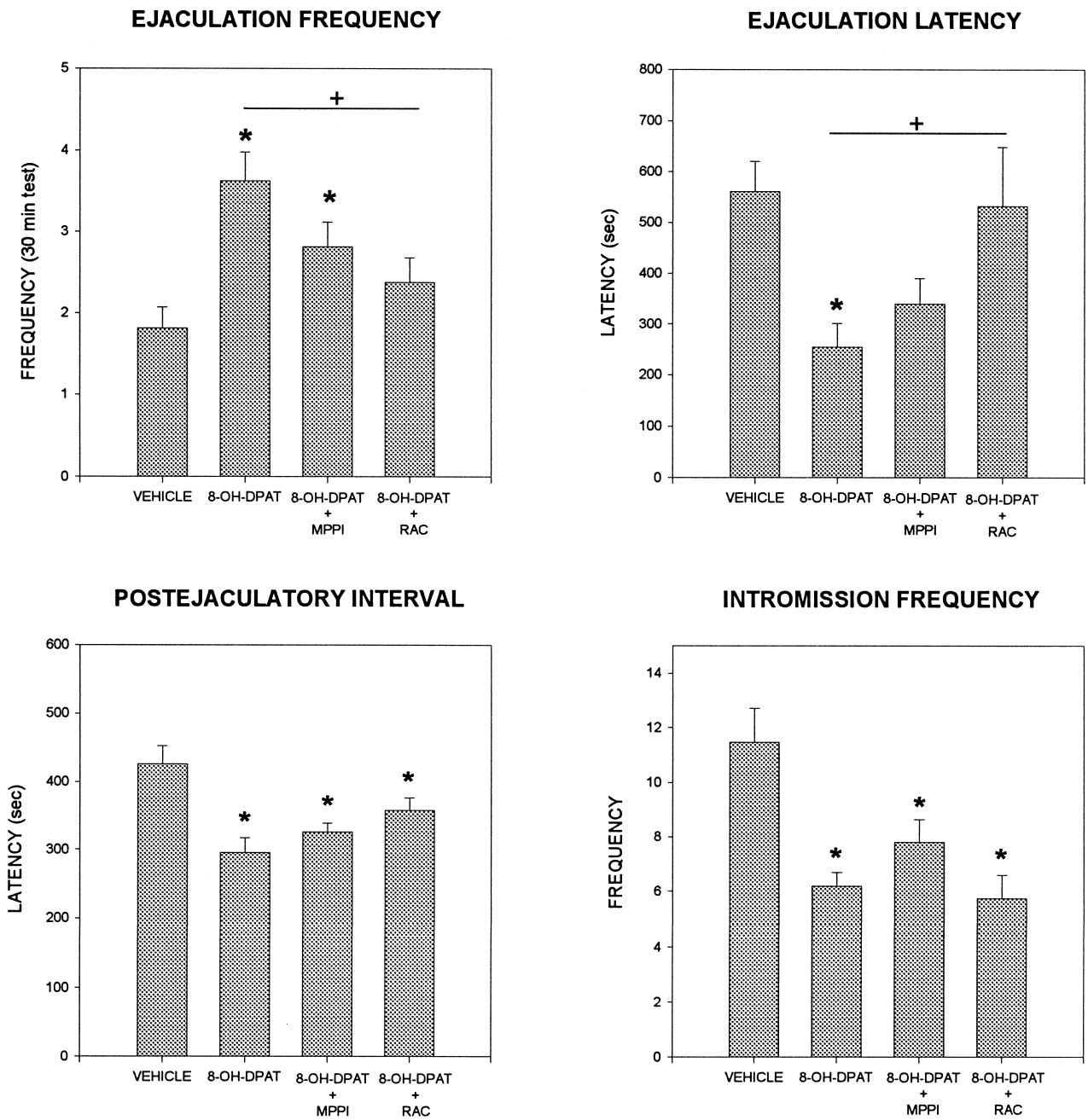

Fig. 1. Copulatory measures following microinjection of vehicle, 8-OH-DPAT (6 μg), 8-OH-DPAT + MPPI (10 μg), or 8-OH-DPAT + raclopride (10 μg) into the MPOA. Co-administration of 8-OH-DPAT + raclopride blocked the increase in ejaculation frequency and the decrease in ejaculation latency by 8-OH-DPAT ($+p < 0.05$ relative to 8-OH-DPAT alone; $*\ p < 0.05$ relative to vehicle). All three drug combinations decreased the first post-ejaculatory interval and the number of intromissions preceding the first ejaculation ($*\ p < 0.05$).

time interval from ejaculation to the ensuing intromission (post-ejaculatory interval); number of mounts and intromissions during each ejaculatory series; and frequency of ejaculations during the 30- or 60-min test.

2.5. Histology

After completing all behavioral tests, animals were sacrificed, and their brains were removed, frozen, and sliced immediately, using a cryostat. Coronal sections (40 μm) were mounted on glass slides and were left to dry for 1–2 days. The slides were then stained with a Cresyl violet solution, cover-slipped and examined for proper cannula location using Pellegrino et al. [33] as a reference.

2.6. Data analysis

All subjects with correctly positioned cannulae ending above the MPOA were used in the data analysis. In Experiment 1, three subjects were excluded from data analysis because their guide cannulae were located outside the MPOA. Of the remaining 16 subjects, each copulated during at least three of the four drug conditions. Three subjects in the vehicle, two in the 8-OH-DPAT + MPPI, and one in the 8-OH-DPAT + raclopride conditions failed to ejaculate. Data from these animals were not included in the analysis of ejaculation latency, numbers of mounts and intromissions preceding ejaculation, or post-ejaculatory interval (PEI). Separate repeated measures analysis of variance (ANOVA) tests were used to examine the effect of treatment on each copulatory measure outlined in Section 2.4. Post hoc comparisons followed, using Neuman–Keuls pairwise tests.

For the reverse dialysis copulatory test, 10 subjects had correctly placed cannulae and were included in the experiment ($n = 5$/drug treatment). However, one subject infused with vehicle failed to ejaculate and was therefore excluded from data analysis of mounts and intromissions preceding ejaculation, ejaculation latency, and PEI. Independent *t*-tests were used to compare vehicle to 8-OH-DPAT for each copulatory measure.

3. Results

3.1. Experiment 1. Effects of MPOA microinjection of 8-OH-DPAT and two antagonists on male copulatory behavior

Consistent with previous reports, administration of 8-OH-DPAT significantly increased the number of ejaculations during the 30 min test session ($F(3,45) = 8.6$, $p < 0.001$, Fig. 1). Post hoc tests showed that this effect on ejaculation was not blocked by the co-administration of the 5-HT_{1A} antagonist MPPI, but was blocked by co-administration of the D_2 antagonist raclopride. Animals treated with 8-OH-DPAT and raclopride did not differ from vehicle controls. Microinjecting 8-OH-DPAT also decreased ejaculation latency ($F(3,39) = 4.37$, $p < 0.01$, Fig. 1). Again, the decrease was not blocked when MPPI was administered with 8-OH-DPAT, but was blocked by adding

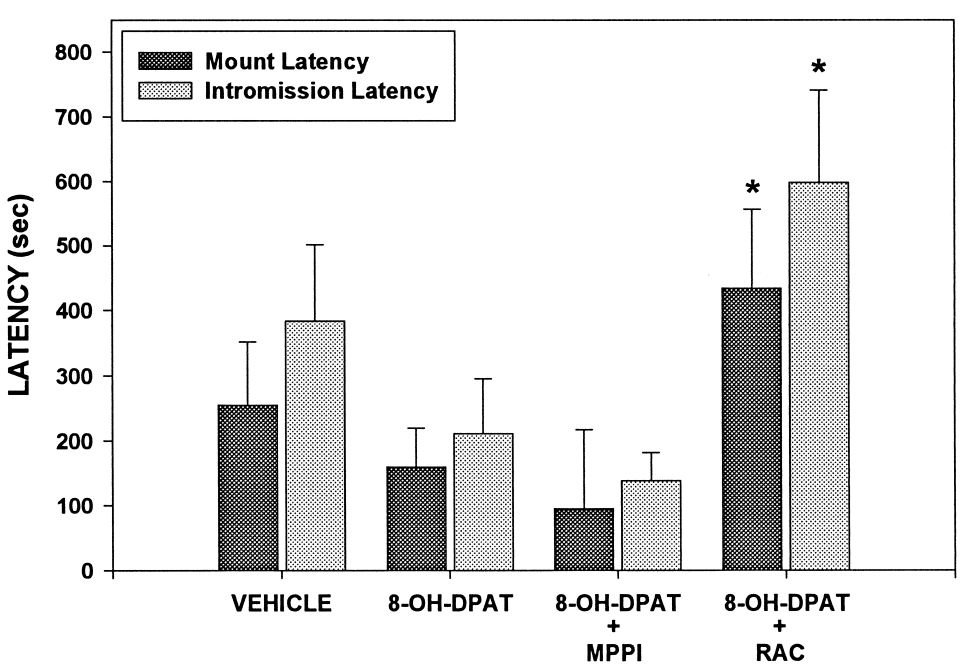

Fig. 2. Co-injection of 8-OH-DPAT + raclopride into the MPOA increased the latency to mount and intromit the female (* $p < 0.05$), relative to 8-OH-DPAT or 8-OH-DPAT + raclopride.

Table 1
Effects of reverse dialyzing 500 μM 8-OH-DPAT into the MPOA on copulatory behavior in the male rat

	Vehicle	8-OH-DPAT
Mount latency	72.86 + 38.0	122.25 + 93.6
Intromission latency	653.43 + 356.5	178.75 + 101.3
Ejaculation latency	459.00 + 87.3	158.1 + 23.9 *
Post-ejaculatory interval	527.7 + 68.1	316.0 + 13.8 *
Number of mounts before ejaculation	5.71 + 1.1	2.17 + 0.6 * *
Number of intromissions before ejaculation	5.57 + 0.5	3.27 + 0.7
Number of ejaculations during test	3.25 + 0.6	6.25 + 0.7 *

8-OH-DPAT decreased ejaculation latency, post-ejaculatory interval, frequency of mounts to the first ejaculation, and increased the number of ejaculations per 60-min test. Latencies are in seconds. * $p < 0.05$ vs. vehicle, * * $p < 0.01$ vs. vehicle.

raclopride to the 8-OH-DPAT solution. All three drug treatments significantly decreased the PEI ($F(3,39) = 10.36$, $p < 0.001$, Fig. 1), as well as the number of intromissions preceding ejaculation ($F(3,39) = 7.73$, $p < 0.001$, Fig. 1).

The latencies to the first mount and first intromission were affected by drug treatment, as revealed by the overall ANOVAs ($F(3,44) = 3.66$, $p < 0.05$; $F(3,44) = 4.29$, $p < 0.01$, respectively). Subjects given the combination of 8-OH-DPAT + raclopride had significantly longer mount and intromission latencies, compared to subjects given either 8-OH-DPAT or 8-OH-DPAT + MPPI (Fig. 2). Neither mount nor intromission latencies were affected by administration of 8-OH-DPAT alone or in combination with MPPI, compared to the vehicle group.

3.2. Experiment 2. Effects of 8-OH-DPAT dialyzed into the MPOA on male copulatory behavior

Infusion of 8-OH-DPAT into the MPOA via reverse dialysis significantly decreased ejaculation latency ($t(7) = 3.421$, $p < 0.05$), PEI ($t(7) = 3.427$, $p < 0.05$) and number of mounts preceding ejaculation ($t(7) = 4.076$, $p < 0.01$; Table 1). 8-OH-DPAT also increased the number of ejaculations ($t(8) = 2.51$, $p < 0.05$), an effect similar to Experiment 1.

4. Discussion

Delivering the 5-HT_{1A} agonist 8-OH-DPAT into the MPOA by microinjection or reverse dialysis facilitated copulation, as evidenced by decreases in ejaculation latency, PEI, and the number of mounts (reverse dialysis) or intromissions (microinjection) preceding ejaculation, while increasing the number of ejaculations. Co-injection of the D_2 antagonist raclopride blocked 8-OH-DPAT's effects on ejaculation frequency and latency. However, neither antagonist blocked 8-OH-DPAT's ability to decrease the PEI or the number of intromissions preceding ejaculation. Furthermore, the mixed infusion of 8-OH-DPAT and raclopride increased the latency to mount and intromit, compared to the 8-OH-DPAT and 8-OH-DPAT + MPPI conditions. In contrast to the partial antagonism of raclopride, co-injecting the 5-HT_{1A} antagonist MPPI did not prevent 8-OH-DPAT's effects on any copulation parameter.

The present findings concur with previous studies that reported a facilitation of the ejaculatory mechanism in male rats following administration of 8-OH-DPAT. When given systemically or into the cerebral ventricles, nucleus accumbens, median raphe nucleus or MPOA, 8-OH-DPAT reduced ejaculation latency, as well as the number of intromissions prior to ejaculation [1,5,6,15,21]. Other 5-HT_{1A} agonists, administered systemically or intrathecally, have also shown a propensity to enhance male rat copulatory behavior [6,14,16,19].

Few studies have demonstrated the pharmacological specificity of 8-OH-DPAT's effects on copulation by blocking its actions with 5-HT antagonists. Systemic administration of the general 5-HT antagonists metergoline, methiothepin or pirenperone failed to inhibit 8-OH-DPAT's behavioral effects [3]. The antagonist pindolol, which is relatively selective for the 5-HT_{1A} receptor compared to other 5-HT receptors [22], blocked the decreases in ejaculation latency and number of intromissions prior to ejaculation produced by systemic administration of 8-OH-DPAT [2]. However, pindolol acts as an antagonist at the noradrenergic β-receptor, as well as the 5-HT_{1A} receptor. Although another β-adrenoceptor antagonist, betaxolol, failed to block 8-OH-DPAT's effects on copulatory behavior [2], other studies support the interaction between the noradrenergic system and 8-OH-DPAT [13,16].

The ability of the D_2 antagonist raclopride to block 8-OH-DPAT's increase in ejaculation frequency and decrease in ejaculation latency suggest that these effects may be mediated by D_2-like receptors in the MPOA. Indeed, we have previously reported that the mixed agonist apomorphine, microinjected into the MPOA, decreased ejaculation latency and increased both the number of ejaculations per test and the copulatory rate [10,23,32]. Furthermore, the D_3/D_2 agonist quinelorane (LY163502) reduced ejaculation latency when administered systemically [17], and decreased the number of intromissions preceding ejaculation when microinjected into the MPOA [25]. Microinjection of quinelorane into the MPOA also increased the number of ex copula seminal emissions, but decreased the number of ex copula erections, again suggesting a shift of autonomic influence to favor ejaculation [8]. Consistent with the importance of D_2-like receptors in the MPOA for ejaculation threshold, microinjection of the D_2 antagonist raclopride (10 μg) by itself into the MPOA increased ejaculation latency and PEI and decreased ejaculation frequency (Hull laboratory, unpublished observations). How-

ever, it also increased mount and intromission latencies, similar to its effects in the present experiment, in which it was co-injected with 8-OH-DPAT. Lower doses (1 and 3 μg) were not effective. Thus, D_2-like receptors in the MPOA may promote the onset of copulation as well as ejaculation. Since 8-OH-DPAT alone did not affect mount or intromission latency, its effects are not completely co-extensive with those of D_2-related drugs.

In the present study, the highly selective 5-HT_{1A} antagonist MPPI [7,26,27] did not block the effects of 8-OH-DPAT when co-injected directly into the MPOA. A relatively high dose of MPPI (10 μg or 17.3 nmol) was chosen to antagonize the effects of 6 μg (18.28 nmol) 8-OH-DPAT, a dose previously reported to enhance male copulatory behavior [14,21]. MPPI has been shown to antagonize the effects of 8-OH-DPAT in a similar dose ratio when co-injected into the midbrain periaqueductal gray [35]. In that study, 1.5 and 3.0 nmol MPPI blocked the behavioral effects of 3 nmol 8-OH-DPAT. In vitro studies have demonstrated that 100 nmol MPPI completely inhibited forskolin stimulated adenlyate cyclase activity produced by 100 nmol of 8-OH-DPAT [26]. Although it is difficult to extrapolate effective antagonist doses from different in vivo or in vitro studies, the aforementioned studies of MPPI and 8-OH-DPAT suggest that the 10 μg dose of MPPI should have been an effective 5-HT_{1A} antagonist for 6 μg of 8-OH-DPAT. Nevertheless, it is possible that a higher dose of the antagonist would have been effective.

The facilitative actions of 8-OH-DPAT, when administered systemically or into the median raphe nucleus may result from stimulation of autoreceptors located on serotonergic cell bodies in the raphe. As an agonist at the autoreceptor site, 8-OH-DPAT decreases 5-HT cell firing and release at terminal regions [11,20,36,37,39]. Indeed, following systemic administration of 8-OH-DPAT, extracellular 5-HT levels decreased in several forebrain regions, including the MPOA [29,36]. However, Fernandez-Guasti and Escalante [12] reported that systemic 8-OH-DPAT maintained its behavioral effects on copulation after subjects received 5,7-DHT lesions of 5-HT cell bodies. These findings suggest that postsynaptic, instead of presynaptic, 5-HT_{1A} receptors may mediate 8-OH-DPAT's behavioral facilitation. The failure of the 5-HT_{1A} antagonist to block 8-OH-DPAT's effects in the present experiment suggests that the effects of 8-OH-DPAT may include a non-5-HT_{1A} mechanism, such as stimulation of D_2-like receptors [38].

In the same manner as the microinjection of 8-OH-DPAT, administration of 8-OH-DPAT into the MPOA via reverse dialysis facilitated components of male rat copulation. Although the pharmacological actions of 8-OH-DPAT were not tested in the present reverse dialysis experiment, a parallel microdialysis study found that the same dose of 8-OH-DPAT (500 μM), when dialyzed into the MPOA, increased extracellular levels of both 5-HT and DA [29]. The increases in 5-HT and DA were not prevented by the co-administration of the 5-HT_{1A} antagonist MPPI (500 μM), suggesting that 8-OH-DPAT may affect transmitter function through non-5-HT_{1A} receptor systems. Furthermore, microinjections of 8-OH-DPAT into the MPOA protected 5-HT neuronal content from the decreases produced by local injections of the 5-HT neurotoxin 5,7-DHT [29]. Because the neurotoxin must be transported into axonal terminals in order to deplete the neurotransmitter, the protective effect was probably mediated by an inhibition of transporter function. These findings suggest that 8-OH-DPAT may act at the 5-HT transporter to elevate 5-HT extracellular levels [29]. The mechanism by which 8-OH-DPAT elevates DA levels was not tested in that experiment. These studies suggest that 8-OH-DPAT administered into the MPOA may enhance copulation indirectly by enhancing extracellular monoamine levels.

Administration of 8-OH-DPAT, either systemically or into the MPOA, facilitates sexual behavior and increases extracellular DA levels in the MPOA; however, these two routes have opposite effects on MPOA 5-HT levels [29]. Previous research in our laboratory has suggested that 5-HT in the MPOA may have little influence on male rat sexual behavior. Increasing extracellular 5-HT levels in the MPOA with a microinjection of a 5-HT reuptake blocker did not significantly affect any parameter of male rat sexual behavior, although similar injections into the anterior lateral hypothalamus (LHA) impaired several copulatory measures [28]. Furthermore, extracellular levels of 5-HT in the MPOA did not change during copulation or following ejaculation, although 5-HT levels did increase in the LHA at the time of ejaculation [28]. On the other hand, extracellular levels of DA in the MPOA increased during copulation with an estrous female [24]. The present study provides further support for a dopaminergic role in 8-OH-DPAT's effects on male copulatory behavior. The DA antagonist raclopride, co-injected into the MPOA, blocked the increase in ejaculation frequency and decrease in ejaculation latency by 8-OH-DPAT, although it did not block the decreases in PEI or in the number of intromissions preceding ejaculation. An earlier study reported that the facilitation of sexual behavior by systemic administration of 8-OH-DPAT was not antagonized by the DA antagonist haloperidol [3]. This suggests that the dopaminergic mechanism partially underlying 8-OH-DPAT's effects reported here may be specific to the MPOA.

Together, the data presented here suggest that within the MPOA increased activity of the dopaminergic system may at least partially mediate the facilitation of male rat copulatory behavior by 8-OH-DPAT. In other brain regions, 8-OH-DPAT may produce its behavioral effects by acting at postsynaptic 5-HT_{1A} receptors, altering 5-HT neuronal firing, and/or interacting with other neurotransmitter systems. These findings may partially explain the discrepancy between the general understanding of 5-HT as inhibitory to male sexual behavior and 8-OH-DPAT's facilitation of copulation.

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References

[1] S. Ahlenius, K. Larsson, Specific involvement of central 5-HT_{1A} receptors in the mediation of male rat ejaculatory behavior, Neurochem. Res. 22 (1997) 1065–1070.
[2] S. Ahlenius, K. Larsson, Antagonism by pindolol, but not betaxolol, of 8-OH-DPAT-induced facilitation of male rat sexual behavior, J. Neural Transm. 77 (1989) 163–170.
[3] S. Ahlenius, K. Larsson, Failure to antagonize the 8-hydroxy-2-(di-*n*-propylamino)tetralin-induced facilitation of male rat sexual behavior by the administration of 5-HT receptor antagonists, Eur. J. Pharmacol. 99 (1984) 279–286.
[4] S. Ahlenius, K. Larsson, Lisuride, LY-141865, and 8-OH-DPAT facilitate male rat sexual behavior via a nondopaminergic mechanism, Psychopharmacology 83 (1984) 330–334.
[5] S. Ahlenius, K. Larsson, A. Wijkstrom, Behavioral and biochemical effects of the 5-HT_{1A} receptor agonists flesinoxan and 8-OH-DPAT in the rat, Eur. J. Pharmacol. 200 (1991) 259–266.
[6] S. Ahlenius, K. Larsson, L. Svensson, S. Hjorth, A. Carlsson, Effects of a new type of 5-HT receptor agonist on male rat sexual behavior, Pharmacol. Biochem. Behav. 15 (1981) 785–792.
[7] A.R. Allen, A. Singh, Z.-P. Zhuang, M.-P. Kung, H.F. Kung, I. Lucki, The 5-HT_{1A} receptor antagonist *p*-MPPI blocks responses mediated by postsynaptic and presynaptic 5-HT_{1A} receptors, Pharmacol. Biochem. Behav. 57 (1997) 301–307.
[8] T.J. Bazzett, R.C. Eaton, J.T. Thompson, V.P. Markowski, L.A. Lumley, E.M. Hull, Dose dependent D_2 effects on penile reflexes after MPOA injections of quinelorane and apomorphine, Life Sci. 48 (1991) 2309–2315.
[9] D. Bitran, E.M. Hull, Pharmacological analysis of male rat sexual behavior, Neurosci. Biobehav. Rev. 11 (1987) 365–389.
[10] D. Bitran, J.T. Thompson, E.M. Hull, B.D. Sachs, Quinelorane (LY163502) a D_2 agonist, facilitates seminal emission but inhibits penile erection in the rat, Pharmacol. Biochem. Behav. 34 (1989) 453–458.
[11] G. Bonvento, B. Scatton, Y. Claustre, L. Rouquier, Effect of local injection of 8-OH-DPAT into the dorsal or median raphe nuclei on extracellular levels of serotonergic projection areas in the rat brain, Neurosci. Lett. 137 (1995) 101–104.
[12] A. Fernandez-Guasti, A. Escalante, Role of presynaptic serotonergic receptors on the mechanism of action of 5-HT_{1A} and 5-HT_{1B} agonists on masculine sexual behaviour: physiological and pharmacological implications, J. Neural Transm. 85 (1991) 95–107.
[13] A. Fernandez-Guasti, G. Rodriquez-Manzo, 8-OH-DPAT and male rat sexual behavior: partial blockade by noradrenergic lesion and sexual exhaustion, Pharmacol. Biochem. Behav. 56 (1997) 111–116.
[14] A. Fernandez-Guasti, A.L. Escalante, S. Ahlenius, V. Hillegaart, K. Larsson, Stimulation of 5-HT_{1A} and 5-HT_{1B} receptors in brain regions and its effects on male rat sexual behaviour, Eur. J. Pharmacol. 210 (1992) 121–129.
[15] A. Fernandez-Guasti, A. Escalante, A. Agmo, E. Hong, Behavioral actions of indorenate, a new putative 5-HT receptor agonist, Pharmacol. Biochem. Behav. 37 (1990) 83–88.
[16] A. Fernandez-Guasti, S. Hansen, T. Archer, G. Jonsson, Noradrenaline-serotonin interactions in the control of sexual behavior in the male rat: DSp_4-induced noradrenaline depletion antagonizes the facilitatory effect of serotonin receptor agonists, 5MeODMT and lisuride, Brain Res. 377 (1986) 112–118.
[17] M.M. Foreman, J.L. Hall, Effects of D_2-dopaminergic stimulation on male rat sexual behavior, J. Neural Transm. 68 (1987) 153–170.
[18] B.B. Gorzalka, S. Mendelson, N.V. Watson, Serotonin receptor subtypes and sexual behavior, Ann. New York Acad. Sci. 600 (1990) 435–446.
[19] S. Hansen, Spinal control of sexual behavior: effects of intrathecal administration of lisuride, Neurosci. Lett. 33 (1982) 329–332.
[20] V. Hillegaart, S. Hjorth, S. Ahlenius, Effects of 5-HT and 8-OH-DPAT on forebrain monoamine synthesis after local application into the median and dorsal raphe nuclei of the rat, J. Neural Transm. 81 (1990) 131–145.
[21] V. Hillegaart, S. Ahlenius, K. Larsson, Region-selective inhibition of male rat sexual behavior and motor performance by localized forebrain 5-HT injections: a comparison with effects produced by 8-OH-DPAT, Behav. Brain Res. 42 (1991) 169–180.
[22] D. Hoyer, Functional correlates of serotonin 5-HT_1 recognition sites, J. Recept. Res. 8 (1988) 59–81.
[23] E.M. Hull, D. Bitran, E.A. Pehek, R.K. Warner, L.C. Band, G.M. Holmes, Dopaminergic control of male sex behavior in rats: effects of an intracerebrally-infused agonist, Brain Res. 370 (1986) 73–81.
[24] E.M. Hull, J. Du, D.S. Lorrain, L. Matuszewich, Extracellular dopamine in the medial preoptic area: implications for sexual motivation and hormonal control of copulation, J. Neurosci. 15 (1995) 7465–7471.
[25] E.M. Hull, R.K. Warner, T.J. Bazzett, R.C. Eaton, J.T. Thompson, L.L. Scaletta, D2/D1 ratio in the medial preoptic area affects copulation of male rats, J. Pharmacol. Exp. Ther. 251 (1989) 422–427.
[26] H.F. Kung, M.-P. Kung, W. Clarke, S. Maayani, Z.-P. Zhuang, A potential 5-HT_{1A} receptor antagonist: *p*-MPPI, Life Sci. 55 (1994) 1459–1462.
[27] M.-P. Kung, D. Frederick, Z.-P. Zhuang, H.F. Kung, 4-[2′-methoxyphenyl)-1-[2′-(*n*-2″-pyridinyl)-*p*-iodobenzamido]-ethylpiperazine ([^{125}I] *p*-MMPI) as a new selective radioligand of serotonin-1A sites in rat brain: in vitro binding and autoradiographic studies, J. Pharmacol. Exp. Ther. 272 (1995) 429–437.
[28] D.S. Lorrain, L. Matuszewich, R.D. Friedman, E.M. Hull, Extracellular serotonin in the lateral hypothalamic area increases during the postejaculatory interval and impairs copulation in male rats, J. Neurosci. 17 (1997) 9361–9366.
[29] D.S. Lorrain, L. Matuszewich, E.M. Hull, 8-OH-DPAT influences extracellular levels of serotonin and dopamine in the medial preoptic area of male rats, Brain Res. 790 (1998) 217–223.
[30] M.R. Melis, A. Argiolas, Dopamine and sexual behavior, Neurosci. Biobehav. Rev. 19 (1995) 19–38.
[31] S.D. Mendelson, B.B. Gorzalka, 5-HT_{1A} receptors: differential involvement in female and male sexual behavior in the rat, Physiol. Behav. 37 (1986) 345–351.
[32] E.A. Pehek, R.K. Warner, T.J. Bazzett, D. Bitran, L.C. Band, R.C. Eaton, E.M. Hull, Microinjection of *cis*-flupenthixol, a dopamine antagonist, into the medial preoptic area impairs sexual behavior of male rats, Brain Res. 443 (1988) 70–76.
[33] L.J. Pellegrino, A.S. Pellegrino, A.J. Cushman, A Stereotaxic Atlas of the Rat Brain, 2nd edn., Plenum, New York, 1979.
[34] D.L. Rowland, E.J. Houtsmuller, 8-OH-DPAT interacts with sexual experience and testosterone to affect ejaculatory response in rats, Pharmacol. Biochem. Behav. 60 (1998) 143–149.
[35] M.B. Shaikh, N.C. DeLanerolle, A. Siegel, Serotonin 5-HT1A and 5-HT2/1C receptors in the midbrain periaqueductal gray differentially modulate defensive rage behavior elicited from the medial hypothalamus of the cat, Brain Res. 765 (1997) 198–207.
[36] T. Sharp, R.S. Bramwell, G.D. Grahame-Smith, 5-HT_1 agonists reduce 5-hydroxytryptamine release in rat hippocampus in vivo as determined by brain microdialysis, Br. J. Pharmacol. 98 (1989) 283–290.
[37] T. Sharp, R.S. Bramwell, S. Hjorth, G.D. Grahame-Smith, Pharmacological characterization of 8-OH-DPAT-induced inhibition of rat hippocampal 5-HT release in vivo as measured by microdialysis, Br. J. Pharmacol. 98 (1989) 989–997.

[38] C.F.C. Smith, S. Cutts, Dopamine agonist activity of 8-OH-DPAT, Arch. Int. Pharmacodyn. 306 (1990) 106–113.
[39] J.S. Sprouse, G.K. Aghajanian, Electrophysiological response of serotonergic dorsal raphe neurons to 5-HT_{1A} and 5-HT_{1B} agonists, Synapse 1 (1987) 3–9.
[40] L. Svensson, S. Hansen, Spinal monoaminergic modulation of masculine copulatory behavior in the rat, Brain Res. 302 (1984) 315–321.
[41] I. Van Wijngaarden, M.T. Tupl, W. Soudijn, The concept of selectivity in 5-HT receptor research, Eur. J. Pharmacol. 188 (1990) 301–312.
[42] C.A. Wilson, Pharmacological targets for the control of male and female sexual behavior, in: A.J. Riley, M. Peet, C.A. Wilson (Eds.), Sexual Behavior, Clarendon Press, Oxford, 1993, pp. 1–58.