ELSEVIER

Brain Research 790 (1998) 217–223

BRAIN RESEARCH

Research report

8-OH-DPAT influences extracellular levels of serotonin and dopamine in the medial preoptic area of male rats

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Accepted 13 January 1998

Abstract

Serotonin (5-HT) is generally inhibitory to male rat sexual behavior. However, the 5-HT_{1A} agonist 8-hydroxy-di-propylaminotetralin (8-OH-DPAT), injected either systemically or into the medial preoptic area (MPOA), facilitates ejaculation. Three experiments were conducted to test the effects of 8-OH-DPAT on 5-HT and dopamine (DA) neurotransmission in the MPOA, a very important site for the control of male sexual behavior. In Experiment 1, systemically injected 8-OH-DPAT (0.4 mg/kg) decreased extracellular 5-HT levels in the MPOA as measured by in vivo microdialysis. In Experiment 2, 8-OH-DPAT (500 μM) administered directly into the MPOA via reverse dialysis increased extracellular levels of both DA and 5-HT; pretreatment with the selective 5-HT_{1A} antagonist 4-iodo-*N*-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-benzamide hydrochloride (p-MPPI) failed to prevent 8-OH-DPAT's stimulatory effects on DA and 5-HT levels in the MPOA. In Experiment 3, 8-OH-DPAT (8 μg) co-injected with 5,7-dihydroxytryptamine (5,7-DHT; 6 μg) prevented neurotoxic depletion of 5-HT in the site of injection (MPOA). Because systemic and MPOA injections of 8-OH-DPAT resulted in opposite effects on extracellular 5-HT in the MPOA, yet both can facilitate ejaculation, these data suggest that moderate changes in 5-HT in the MPOA may have relatively little influence on male copulatory behavior. Instead, the facilitative effects of 8-OH-DPAT in the MPOA on male copulatory behavior may result, at least in part, from stimulatory effects of 8-OH-DPAT on DA transmission. Facilitative effects of systemic injections of 8-OH-DPAT may result from decreased 5-HT release in several sites. © 1998 Elsevier Science B.V.

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

1. Introduction

The serotonin agonist 8-hydroxy-di-propylaminotetralin (8-OH-DPAT) has been used to evaluate the contribution of the 5-HT_{1A} receptor subtype in several behaviors, including sexual behavior, learning, memory and locomotion (for review, see Refs. [1,18]). In tests of male rat sexual behavior, 8-OH-DPAT, administered peripherally or centrally, decreased ejaculation latencies, decreased postejaculatory intervals of sexual quiescence, decreased the number of intromissions prior to ejaculation, and increased the number of ejaculations per test [2,3,15,23,25,33]. On the other hand 8-OH-DPAT, administered systemically [4,27,36] or into the medial preoptic area (MPOA) [35], impaired female rat sexual behavior.

Facilitative effects of 8-OH-DPAT on masculine sexual behavior have been difficult to explain in the light of prevailing evidence demonstrating that most 5-HT agonists inhibit copulation (reviewed in Refs. [10,18,40]). The facilitative effects of 8-OH-DPAT were, at first, thought to be mediated by decreased serotonergic activity, due to stimulation of inhibitory autoreceptors. Administration of 8-OH-DPAT, peripherally or centrally into 5-HT cell body regions, inhibits 5-HT neuron firing and/or release from terminal regions [12,19,29,30,32]. Among areas affected may be forebrain sites where 5-HT release would normally inhibit male rat copulatory performance [20].

These results do not, however, explain postsynaptic effects of 8-OH-DPAT on copulatory behavior. Destruction of presynaptic 5-HT_{1A} autoreceptors by neurotoxic

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lesions of 5-HT cell bodies failed to block the facilitative effects of 8-OH-DPAT microinjected into the MPOA [14]. These results have been used to support the argument that postsynaptic 5-HT_{1A} receptors mediate 8-OH-DPAT's stimulatory effects on copulation.

Alternatively, 8-OH-DPAT may influence sexual behavior by stimulating non-5-HT receptors located around the site of microinjection, or by increasing extracellular levels of neurotransmitters known to enhance copulation. These possibilities exist because: (1) 8-OH-DPAT has appreciable affinity for the dopamine (DA) D_2 receptor [31,37]; (2) local administration of 8-OH-DPAT has been shown to increase extracellular DA levels in the nucleus accumbens (NAcc), striatum and cortex [6,9,17]; and (3) microinjecting a DA agonist into the MPOA also enhances copulation [21], as do 8-OH-DPAT microinjections into the same region [15].

The current experiments were initiated to test the hypothesis that microinjecting 8-OH-DPAT into the MPOA facilitates copulation by increasing local DA transmission. Peripheral administration of this drug, on the other hand, may enhance copulation by decreasing MPOA 5-HT release. In vivo microdialysis was used during 8-OH-DPAT treatment to measure these effects. Unexpectedly, perfusing 8-OH-DPAT into the MPOA, via reverse dialysis, increased extracellular levels of both DA and 5-HT. Two additional experiments were then conducted to test: (1) whether these increases reflected 8-OH-DPAT stimulation of 5-HT_{1A} receptors in the MPOA; and (2) whether 8-OH-DPAT may interfere with the 5-HT transporter and therefore result in increased extracellular 5-HT levels.

2. Materials and methods

2.1. Animals

Adult male Long–Evans/Blue Spruce rats (300–350 g, Harlan Sprague–Dawley, Indianapolis) were used for all experiments. They were singly housed in large plastic cages in a temperature- and humidity-controlled room, on a reversed light cycle (off at 11:00 and on at 21:00 h). Food and water were available ad libitum. All subjects were weighed daily to monitor their health and adapt them to handling procedures. All procedures followed the guidelines of the Society for Neuroscience and were approved by the local Institutional Animal Care and Use Committee.

2.2. Stereotaxic surgery

Subjects were anesthetized with ketamine hydrochloride (75 mg/kg) and xylazine hydrochloride (3 mg/kg) for implantation of guide cannulae. For both microdialysis and microinjection experiments, animals were placed into a Kopf stereotaxic frame, with the incisor bar set at +5 mm, and implanted with a 23-gauge 17-mm stainless steel guide cannula aimed above the left MPOA (from bregma, in mm, AP: +2.4; ML: +0.2; DV: −6.3 [28]). The cannula was fixed in place by applying dental acrylic around the cannula and 3 metal screws anchored to the skull. A metal obturator fashioned from 27-gauge stainless steel was inserted into the guide cannula following surgery to prevent entry of unwanted material.

2.3. Microdialysis

Concentric microdialysis probes were constructed in the laboratory according to the procedures of Ref. [41]. A 3-mm length of dialysis membrane (SpectraPor 6000 MW cutoff, 210 μm o.d.) extended beyond the stainless steel shaft of the probe. Waterproof epoxy was used to seal and deactivate 2 mm of the membrane, leaving a 1-mm active surface. Dialysate samples recovered from probes were collected into 250-μl centrifuge tubes and injected immediately onto an LC Packings capillary column for high-performance liquid chromatography with electrochemical detection (HPLC-EC) analysis of DA and 5-HT concentrations.

The dialysis perfusion medium was a Ringer's buffered saline solution (138 mM NaCl, 4 mM KCl, and 1.2 mM $CaCl_2$; pH 7.4). Dialysate flowed at a rate of 0.5 μl/min, controlled by a Harvard syringe infusion pump (model 22). A length of PE 20 tubing connected an Instech single channel infusion swivel to the microdialysis probe. For microdialysis experiments, drugs were dissolved in Ringer's solution and delivered to the MPOA via reverse dialysis through the probe.

On the day of sample collection, subjects were briefly anesthetized with ether to allow for ease of insertion of the microdialysis probe. The obturator was removed from the guide cannula, and a probe was slowly inserted in its place. The flow of dialysate was started immediately after probe insertion. A 4-h stabilization period was allowed prior to sample collection. All dialysate samples were collected in 6-min intervals. For each subject, baseline values for DA and 5-HT were established by analyzing dialysate content until 3 consecutive samples showed no more than 10% variation. All data are expressed as a percentage of the average of these final three pre-drug baseline samples.

2.4. Microinjections and ex vivo tissue processing

Microinjections of 5,7-DHT, with or without 8-OH-DPAT, were accomplished by removing the obturator from the previously implanted guide cannula and inserting in its place a microinjection cannula constructed from 27-gauge stainless steel tubing. A Harvard (model 22) infusion pump delivered a 4-μl volume of 0.2 mg/ml ascorbic acid solution containing the appropriate drug at a rate 0.5 μl/min. The injection cannula was left in place for an additional 60 s. The obturator was then replaced, and

animals were returned to their colony room until tissue processing. Six hours after microinjection, the subjects were decapitated, their brains quickly removed and immediately frozen on dry ice. The MPOA was then dissected from a 1000 μm thick coronal slice (AP = +2.4 mm to +1.4 mm [28]) using a length of 18- gauge stainless steel tubing. The resulting tissue pellet was placed into a centrifuge tube containing 500 μl of 0.05 M perchloric acid, weighed, homogenized and spun in a BioAnalytical Systems (BAS) centrifuge for 30 min. The supernatant was drawn through a 0.45 μm pore filter. The resulting solution was then analyzed by HPLC-EC. The tissue's wet weight was recorded by subtracting the weight of the centrifuge tube containing 500 μl of the 0.05 M perchloric acid from the same tube after addition of the tissue pellet.

2.5. Biochemical measurement

Dialysate samples (3 μl) were assayed for 5-HT and DA concentrations using HPLC-EC. The supernatant from MPOA tissue was assayed for 5-HT only. All samples were loaded into a Rheodyne injector valve delivering a 500-nl volume to a C18 reversed phase capillary column (LC Packings, 0.32 mm × 5 cm, packed with 3 μm particles). The circulating mobile phase consisting of 30 mM citric acid, 50 mM sodium acetate, 0.027 mM Na_2EDTA, 0.25 mM octyl sodium sulfate and 2.5% acetonitrile v/v (pH, 3.8). A Gilson model 307 pump, operating at 0.5 ml/min, was equipped with an Acurate flow splitter which delivered 6 μl/min to the column. Compounds were detected with an Antec micro flowcell (11 nl), using a glassy carbon working electrode maintained at a potential of +0.7 V relative to a Ag/AgCl reference electrode.

2.6. Histology

At the end of each microdialysis experiment, subjects received 0.3 cc Somlethol, were decapitated, and the brain quickly removed and frozen. Coronal sections (40 μm) were collected onto glass slides, stained with Cresyl violet, coverslipped and examined for proper placement of microdialysis probes. Only those animals with correct placements were used for statistical analysis.

2.7. Data analysis

Microdialysis concentrations of DA and 5-HT were represented as a percentage of baseline values. A two-way repeated measures ANOVA was used to compare drug treatments (no injection, 0.2, or 0.4 mg/kg, i.p. 8-OH-DPAT) across six consecutive time points. Significant main effects were probed using Neuman–Keuls pairwise comparisons. A one-way ANOVA for independent groups was used to compare the four drug conditions in Experiment 2. The tissue levels of 5-HT in Experiment 3 were compared between groups using a one-way ANOVA.

2.8. Procedures

Three experiments were conducted. Experiment 1 tested whether systemically injected 8-OH-DPAT affects extracellular 5-HT in the MPOA. Thirteen animals with microdialysis probes in the MPOA were injected with 0.2 ($n = 5$) or 0.4 ($n = 8$) mg/kg i.p. of 8-OH-DPAT (Sigma) after collection of baseline microdialysis samples. Five consecutive samples were collected after the injection. Six control animals were allowed the same 4-h stabilization period, after which a baseline sample was collected, followed by five consecutive samples. Experiment 2 tested whether 8-OH-DPAT, retrodialyzed into the MPOA, affects extracellular levels of 5-HT and/or DA, and whether those effects can be blocked by a 5-HT_{1A} antagonist. Following collection of baseline samples, 8-OH-DPAT's effects were tested by switching the dialysate for one containing 100 ($n = 3$) or 500 ($n = 6$) μM 8-OH-DPAT. Attempts to block the effects of 8-OH-DPAT were made by switching first to 500 μM p-MPPI, followed 15 min later by a mixture of 8-OH-DPAT + p-MPPI (500/500 μM, $n = 6$). Seven subjects were randomly chosen to receive 0.0 μM 8-OH-DPAT before receiving one of the other three drug treatments, to control for any transmitter change that may occur from the switching procedure itself. In all conditions, a 15-min delay was allowed between the switch and sample collection to account for probe dead volume. Only one 6-min sample was collected, because drug administered through the probe, unlike systemic injections, would have been available to the brain tissue within the 15-min delay period. Samples were analyzed for DA and 5-HT content. Experiment 3 tested whether the increase in extracellular 5-HT observed in Experiment 2 could be explained by inhibition of 5-HT transport. The 5-HT neurotoxin 5,7-dihydroxytryptamine (5,7-DHT, 6 μg) was microinjected into the MPOA either with ($n = 5$) or without ($n = 6$) 8-OH-DPAT (8 μg). Six control animals received only vehicle (4 μl of 0.2 mg/ml ascorbic acid solution).

3. Results

3.1. Experiment 1

3.1.1. Effects of systemic 8-OH-DPAT on MPOA 5-HT release

Serotonin concentrations decreased in dialysate collected from the MPOA following an injection of 8-OH-DPAT (Dose: $F[2,80] = 6.56$, $p < 0.01$; Time: $F[5,80] = 9.58$, $p < 0.0001$; Fig. 1). Pairwise comparisons revealed that only the 0.4 mg/kg dose significantly affected 5-HT levels, relative to no injection. Levels were lower in the five samples collected after injection compared to baseline 5-HT values. Decreased 5-HT concentrations were also apparent following a 0.2 mg/kg i.p. injection, but the

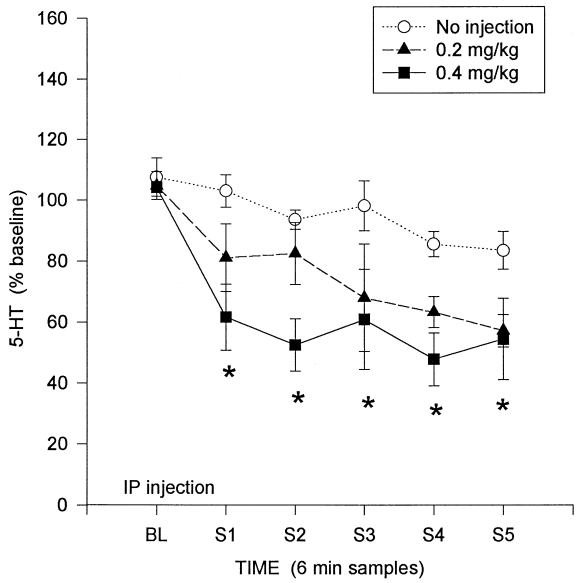

Fig. 1. Temporal changes in MPOA 5-HT following 0.2 and 0.4 mg/kg 8-OH-DPAT (i.p.) or no injection. Samples were collected every 6 min. Dialysate 5-HT decreased following the higher dose of 8-OH-DPAT, $* p < 0.05$ vs. no injection controls.

difference did not reach statistical significance. There was no significant difference in DA concentrations with either dose.

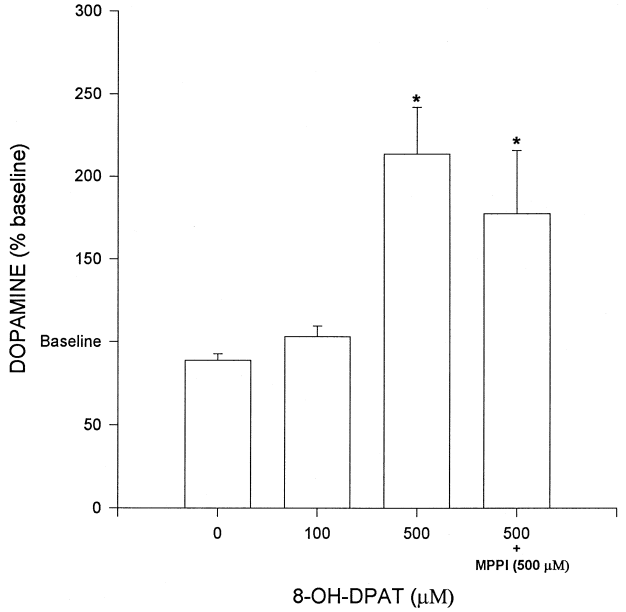

Fig. 2. Effect of reverse dialysis of 8-OH-DPAT into the MPOA on extracellular DA activity. Following collection of baseline samples, the dialysate was switched for one containing 100 ($n = 3$) or 500 ($n = 6$) μM 8-OH-DPAT, or 500 μM p-MPPI alone, followed 15 min later with a mixture of 8-OH-DPAT + p-MPPI (500/500 μM, $n = 6$). Administration of 500 μM 8-OH-DPAT increased dialysate DA concentrations, with or without administration of p-MPPI. $* p < 0.05$ vs. 0.0 μM.

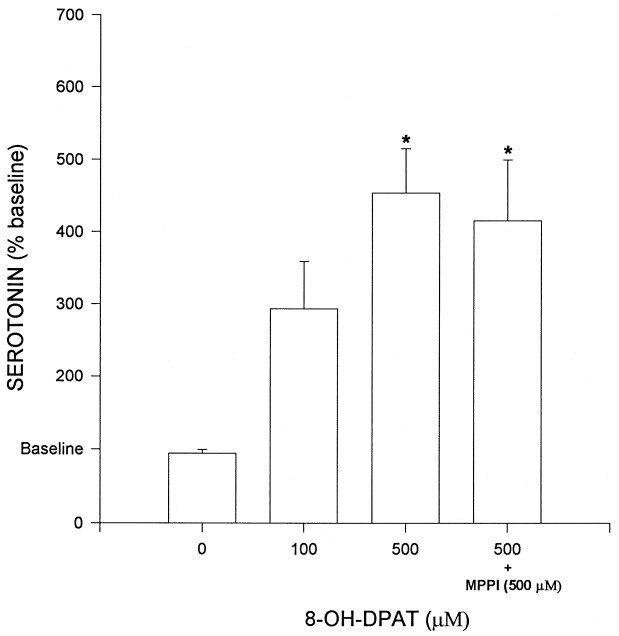

Fig. 3. Effect of reverse dialysis of 8-OH-DPAT into the MPOA on extracellular 5-HT activity. Following collection of baseline samples, the dialysate was switched for one containing 100 ($n = 3$) or 500 ($n = 6$) μM 8-OH-DPAT, or 500 μM p-MPPI alone, followed 15 min later with a mixture of 8-OH-DPAT + p-MPPI (500/500 μM, $n = 6$). Administration of 500 μM 8-OH-DPAT increased dialysate 5-HT concentrations, with or without administration of p-MPPI. $* p < 0.05$ vs. 0.0 μM.

3.2. Experiment 2

3.2.1. Effects of 8-OH-DPAT perfusion into the MPOA on extracellular DA and 5-HT

The overall ANOVA detected a difference in MPOA DA concentrations across drug treatments [$F(3,18) = 5.32$, $p < 0.01$]. Post-hoc comparisons revealed that DA increased after perfusing 500 μM 8-OH-DPAT with and without 500 μM p-MPPI, compared to the 0.0 μM drug condition ($p < 0.05$, Fig. 2). In the same animals, drug treatment also affected 5-HT levels [$F(3,18) = 8.63$, $p < 0.001$]. Similarly, post-hoc comparisons showed that 8-OH-DPAT (500 μM) alone or with p-MPPI (500 μM) increased MPOA 5-HT levels compared to the 0.0 μM condition ($p < 0.05$, Fig. 3).

Table 1
Effects of injecting vehicle, 5,7-DHT alone, or 5,7-DHT + 8-OH-DPAT into the MPOA on ex vivo 5-HT tissue content

Treatment	MPOA 5-HT
Vehicle	555.2 ± 79.6
5,7-DHT	183.7 ± 46.4 *
5,7-DHT + 8-OH-DPAT	444.5 ± 93.6

The 5-HT neurotoxin 5,7-DHT depleted MPOA 5-HT when administered alone (6 μg/4 μl), but not in the presence of 8-OH-DPAT (8 μg/4 μl). Values are pg/mg wet tissue weight.
Tissue weight was 2.4 ± 0.3 mg.
$* p < 0.05$ vs. vehicle and 8-OH-DPAT + 5,7-DHT groups.

3.3. Experiment 3

3.3.1. Effects of 5,7-DHT microinjection into the MPOA on 5-HT levels

Serotonin levels in MPOA tissue were significantly different across the three drug groups [$F(2,14) = 6.95$, $p < 0.01$]. Post-hoc comparisons showed that microinjecting the neurotoxin, 5,7-DHT significantly decreased 5-HT content when compared to 5-HT levels in MPOA tissue dissected from subjects that received vehicle injections, and those receiving both 8-OH-DPAT and 5,7-DHT ($p < 0.05$, Table 1).

4. Discussion

Systemic administration of the 5-HT_{1A} agonist 8-OH-DPAT, at a dose that has been shown to facilitate ejaculation in male rats (0.4 mg/kg [1]), decreased extracellular 5-HT in the MPOA. The more modest decrease following injection of the lower dose (0.2 mg/kg) was not statistically significant. Consistent with the present results, previous reports have demonstrated that peripheral administration of 8-OH-DPAT decreased extracellular 5-HT levels in several other forebrain regions [29,30,32]. These effects were suggested to result from stimulation of somatodendritic 5-HT_{1A} autoreceptors [32].

The decrease in MPOA 5-HT, which resulted from a dose of systemic 8-OH-DPAT that facilitates ejaculation, is consistent with the proposed inhibitory effects of MPOA 5-HT on copulation. Thus, 8-OH-DPAT may facilitate male sexual behavior by decreasing extracellular 5-HT in the MPOA. Evidence for an inhibitory influence of 5-HT in the MPOA is derived from experiments that administered 5-HT in rather high doses (10 to 40 μg) directly into the MPOA [15,38]. That evidence is also consistent with the known facilitative effects of systemically administered 5-HT synthesis inhibitors or lesions of the raphe nuclei, the main source of serotonergic input to the forebrain (reviewed in Refs. [10,40]). Furthermore, the MPOA is critical for the control of male copulatory behavior in all vertebrate species that have been studied [26]. There is evidence, however, that the facilitative effects of 8-OH-DPAT in the MPOA do not result from inhibition of 5-HT release there, but perhaps from stimulation of postsynaptic 5-HT_{1A} receptors. Specifically, neurotoxic lesions of presynaptic serotonergic neurons did not affect the facilitative effects of 8-OH-DPAT microinjected into the MPOA [14].

Administration of 8-OH-DPAT into the MPOA by reverse dialysis increased, rather than decreased, extracellular 5-HT in the MPOA and also increased extracellular DA. These 5-HT results were unexpected, and argue against an inhibitory influence of moderate increases in extracellular 5-HT on copulation. The increases in 5-HT and DA levels were not blocked by the selective 5-HT_{1A} antagonist p-MPPI, which was retrodialyzed alone for 15 min before being retrodialyzed with 8-OH-DPAT. This suggests that the increases in extracellular 5-HT and DA cannot be explained simply by activation of 5-HT_{1A} receptors, either pre- or postsynaptic.

The local effects of 8-OH-DPAT on 5-HT transport may have caused the observed increase in MPOA dialysate levels of 5-HT. In support of this explanation, results from Experiment 3 showed that microinjections of 8-OH-DPAT into the MPOA prevented the neurotoxic effects of 5,7-DHT on 5-HT tissue levels. Administration of 5,7-DHT without 8-OH-DPAT resulted in significant 5-HT depletion in MPOA tissue. Although the full cascade of events leading to 5,7-DHT induced 5-HT depletion are not known, transport of this compound into 5-HT cells is necessary for neurotoxicity [34]. Therefore, substances that block or interfere with the 5-HT transporter also prevent 5-HT depletion [16]. Whether 8-OH-DPAT prevented 5-HT depletion by blocking 5,7-DHT transport or by competing for transport is not known. 8-OH-DPAT administered into the hippocampus by reverse dialysis or into hippocampal synaptosomes was also reported to block 5-HT uptake [7].

Evidence for a lack of influence of MPOA 5-HT on copulation includes the present findings that two treatments that facilitate copulation, systemic and MPOA administration of 8-OH-DPAT, resulted in decreases and increases, respectively, in extracellular 5-HT. The relatively small dose of 8-OH-DPAT administered by reverse dialysis in this experiment has previously been shown to facilitate copulation in male rats [25]. Furthermore, a recent microdialysis experiment showed that there was no change in extracellular 5-HT in that site during copulation or after ejaculation [24]. A more likely site for serotonergic inhibition of male sexual behavior is the anterior lateral hypothalamic area, where 5-HT increases following ejaculation, and where pharmacologically induced increases in extracellular 5-HT impair male copulatory behavior [24].

Extracellular DA, as well as 5-HT, was increased by 8-OH-DPAT retrodialyzed into the MPOA in Experiment 2. Previous reports showed increases in DA levels in NAcc, striatum, and cortex resulting from retrodialysis of 8-OH-DPAT [6,9,17]. However, the factors that produce this effect are not known. A test of 8-OH-DPAT's effects on the DA transporter in the MPOA, comparable to the 5,7-DHT protection experiment here, was not deemed feasible. Previous attempts in this lab to deplete MPOA DA, using 6-hydroxydopamine (6-OHDA), resulted in only 23% depletion, which was not sufficient to induce copulatory deficits, unless a minimal dose of a DA synthesis inhibitor was administered, or unless the behavioral tests were administered within the first few hours after the neurotoxin [8,11]. The techniques used in those experiments had previously produced 80–90% depletions in striatal DA [5,39]. However, there are very few DA transporters in the MPOA to transport the toxin into the neurons [13]. Therefore, it would be difficult to produce a

sufficient depletion of DA to test the potential neuroprotective role of 8-OH-DPAT. Thus, the basis for the increase in extracellular DA in response to 8-OH-DPAT is not known. However, since increases in DA release [22] and stimulation of DA receptors [21] have been associated with enhanced copulatory ability, the behavioral facilitation by 8-OH-DPAT may result from the increase in extracellular DA in the MPOA, rather than any direct changes in 5-HT levels. On the other hand, increased DA in the MPOA cannot account for the previously observed facilitative effects of systemically administered 8-OH-DPAT [1,3]. In Experiment 1, there were no significant effects of systemic injections of 8-OH-DPAT on extracellular DA in the MPOA. Therefore, two different effects may account for the facilitation of copulation by 8-OH-DPAT administered either systemically or into the MPOA. Systemic administration may enhance copulation by reducing 5-HT release in several sites, perhaps including the anterior lateral hypothalamic area, whereas intra-MPOA administration may have similar effects on copulation by increasing extracellular DA levels.

5. Summary

Systemic administration of the 5-HT_{1A} agonist 8-OH-DPAT resulted in decreased levels of extracellular 5-HT in the MPOA, a site where 5-HT has been thought to inhibit masculine sexual behavior. However, reverse dialysis of 8-OH-DPAT into the MPOA increased extracellular levels of both 5-HT and DA. These increases were not blocked by the selective 5-HT_{1A} antagonist p-MPPI. The increase in 5-HT may have resulted from inhibition of uptake or competition for uptake sites, since 8-OH-DPAT protected MPOA tissue stores of 5-HT from the neurotoxic effects of 5,7-DHT, which must be transported into the terminal to produce its toxic effects. Finally, it is possible that the facilitative effects of 8-OH-DPAT in the MPOA result, at least in part, from increased extracellular levels of DA in that site, whereas the behavioral facilitation of systemic injections may result from decreased 5-HT release in several sites, perhaps including the anterior lateral hypothalamic area.

Acknowledgements

This research was supported by NIMH grant MH 40826 to EMH.

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