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8-OH-DPAT and Male Rat Sexual Behavior: Partial Blockade by Noradrenergic Lesion and Sexual Exhaustion

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FERNANDEZ-GUASTI, A. AND G. RODRIGUEZ-MANZO. *8-OH-DPAT and male rat sexual behavior: partial blockade by noradrenergic lesion and sexual exhaustion.* PHARMACOL BIOCHEM BEHAV **56**(1) 111–116, 1997.—As previously shown, the 5-HT_{1A} agonist 8-OH-DPAT is a potent facilitator of male rat copulatory behavior in both sexually experienced and sexually exhausted male rats. The basis of this facilitation is still not clear. Therefore, the purpose of the present study was to determine whether 8-OH-DPAT-induced sexual-behavior facilitation could be counteracted by lesioning the NA system with the noradrenergic neurotoxin DSP_4. In NA-lesioned, sexually experienced, non-exhausted rats, the facilitatory effects of 8-OH-DPAT on the number of mounts and the postejaculatory interval were reduced, the effect on the intromission latency disappeared, while the percentage of copulating rats was not significantly altered. In sexually exhausted rats bearing a lesion of the NA system, the facilitatory effects of 8-OH-DPAT on the percentage of copulating rats was blocked. Data are discussed on the basis of the interactions between the noradrenergic and serotonergic systems in the mediation of the facilitatory effect of 8-OH-DPAT in sexually exhausted and non-exhausted rats.

8-OH-DPAT DSP_4 Sexual exhaustion Rat Male Sexual behavior Noradrenaline-serotonin interactions

THE ROLE of serotonin (5-HT) in the mediation of male rat sexual behavior seems unclear (11,28). Most of the evidence suggests that endogenous serotonergic transmission plays an inhibitory role in the regulation of this behavior (2,18,19,40). However, Larsson and coworkers (4) demonstrated that 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), a 5-HT_{1A} agonist (12), induces a drastic facilitation of copulatory behavior mainly evidenced as a decrease in the number of intromissions preceding ejaculation and a shortening of the ejaculation latency. After this first discovery, several research groups have found that other 5-HT_{1A} agonists such as ipsapirone (15,21), indorenate (16), lisuride (3,24) and 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) (14) possess similar behavioral properties.

Several attempts to block the facilitatory effect of serotonergic 5-HT_{1A} agonists on rat masculine sexual behavior have been made. However, neither treatment with monoaminergic (5,6,8,16) or opioid (1) antagonists, nor with the serotonin synthesis inhibitor, p-chlorophenylalanine, had been able to completely prevent the stimulation of sexual behavior produced by these compounds (17). Ahlenius et al. (4), initially proposed that 8-OH-DPAT might be acting through the stimulation of 5-HT_{1A} somatodendritic receptors. Following this hypothesis, we tested the effects of this drug in animals in which the serotonergic system was lesioned by treatment with the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT). Again, in 5,7-DHT lesioned rats, 8-OH-DPAT still produced its facilitatory effects on male sexual behavior (17).

In contrast to the lack of effect of serotonergic lesions on 5-HT_{1A}-influenced sexual behavior, it was determined that the

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facilitatory effect of lisuride and 5-MeODMT behavior, was partially absent in animals with lesion of the noradrenergic system induced by the neurotoxin, *N*-2-chloroethyl-*n*-ethyl-2-bromobenzylamine (DSP_4) (14). These data suggest an interaction between the serotonergic and the noradrenergic systems in the facilitation, by 5-HT_{1A} agonists, of some sexual behavior parameters.

In addition, we have recently found that 8-OH-DPAT is able to reverse the sexual behavior inhibition resulting from sexual exhaustion by increasing the percentage of copulating rats (32). These rats responded with the typical reduction in the number of mounts and intromissions and the shortening of the ejaculation latency described for this compound in non exhausted animals (4).

Therefore, the purpose of the present paper was to analyse whether lesion of the noradrenergic system, produced by DSP_4 administration, alone or in combination with sexual exhaustion, could prevent the well-established stimulation of male sexual behavior induced by 8-OH-DPAT.

METHOD

Animals

Sexually experienced male Wistar rats (350–400 g b wt) were used in this study. All animals were kept, six per cage, in a room with a reversed light/dark cycle (12 h light: 12 h dark, lights on at 2200 h). Animals had ad lib access to water and Purina rat chow for the duration of the experiments.

Before the experiments were initiated, all animals received three sexual behavior tests. The sexually active males, that is, those showing an ejaculation latency (the time that elapses from the first intromission to ejaculation) shorter than 15 min., were selected for the study.

Drugs

Zimelidine and 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) were purchased from Research Biochemicals (Natick USA), *N*-2-chloroethyl-*n*-ethyl-2-bromobenzylamine (DSP_4) from Astra (Läkemedel AB, Sweden). DSP_4 and 8-OH-DPAT were dissolved in distilled water, while zimelidine was dissolved in a saline solution.

Noradrenergic Lesion

Rats were rendered noradrenaline (NA) deficient through the use of the neurotoxin DSP_4 (2 × 50 mg/kg, IP). Since it has been reported that this neurotoxin produces a small, but consistent depletion of brain serotonin (5-HT) (9,26), a selective 5-HT reuptake inhibitor, zimelidine (20 mg/kg, IP), was administered 60 min before DSP_4 in order to provide total protection against this effect. One week later the treatment was repeated. This procedure has been demonstrated in our (14) and other laboratories (26,35) to be effective in abolishing noradrenaline levels without modifying 5-HT. Nevertheless, a biochemical assay was performed to determine the extent of the noradrenergic lesion (see below).

Three weeks after the last injection, the lesioned animals were submitted to a sexual behavior test, either directly or preceded by a sexual exhaustion session (see below). The respective control groups (sham lesioned) received zimelidine (20mg/kg), 60 min before an IP injection of distilled water following the same schedule of DSP_4-lesion.

Biochemical Assay

Noradrenaline levels, after DSP_4-lesion, were determined in different brain areas by HPLC with electrochemical detection, following the technique described by Saligaut et al (36) with minor modifications. Animals were sacrificed by decapitation, the brains were removed, placed on a cold plate and the hippocampus, hypothalamus and frontal cortex dissected according to the method of Iversen and Glowinski (25). Tissue was immediately sumerged in a vial containing 1 ml of 0.1 M perchloric acid and 0.05 mM ascorbic acid, frozen in liquid nitrogen and stored at −70°C until analyzed (36 h after dissection at the most). After thawing, vials were spiked with 100 ng of 3,4-dihydroxybenzylamine (DHBA) as an internal standard. Thereafter, tissue was homogenized and the suspension centrifuged at 37013 *g* for 20 min at 4°C. Aliquots of 0.1 ml of the supernatant were injected into a liquid chromatography system (Waters Assoc., Milford, MA) coupled to an amperometric detector (Bioanalytical Systems, West LaFayette, IN). The system was equipped with a reverse phase column biophase ODS of 5 μm particle size (BAS) eluted with a mixture of 925 ml of 0.15 M monochloracetic acid buffer, pH 3.0, containing 0.86 mM of sodium octyl sulphate, 75 ml of acetonitrile and 18 ml of tetrahydrofuran. The column was kept at room temperature. Detection was carried out using a glassy carbon working electrode maintained at + 800 mV against Ag/AgCl, and the resulting current recorded. Retention time for noradrenaline was 3.13. The comparisons were performed between the DSP_4-lesioned and the sham lesioned groups. The results, shown in Table 1, are expressed as ng of NA/ g of fresh tissue.

Sexual Behavior Observation

Sexual behavior observation was conducted in a room under dim red light. The percentage of animals showing mounts, intromissions, ejaculation and resumption of copulation was calculated. The precise proportion of animals showing each of these behavioral features was also determined. Additionally, from those males ejaculating, specific sexual behavior parameters were recorded as follows: intromission latency (*IL*, time in minutes from the introduction of the female to the first intromission), number of mounts (*M*) and intromissions (*I*) preceding ejaculation, ejaculation latency (*EL*, time in minutes from the first intromission to ejaculation) and postejaculatory interval (*PEI*, time in minutes from ejaculation to the first intromission of the next series of copulation). For statistical purposes, an arbitrary value of 30 min was assigned to those animals that did not resume copulation, after ejaculation, within this period. A maximum of 30 min for intromission and ejaculation latencies was established. Thus, observations were ended either after animals completed a copulatory series or after they showed *IL*, *EL* or *PEI* values longer than 30 min.

Sexual Exhaustion Paradigm

Sexually experienced male rats were allowed to individually copulate ad lib during four consecutive h with female rats treated with oestradiol valerianate (4 μg/rat, −44 h) followed by progesterone (2 mg/rat, 0 h). Tests were performed 4 h after progesterone injection and 6 h after the onset of darkness. Twenty four h later, the sexually exhausted rats were presented to new sexually receptive females (treated as forementioned) and the masculine sexual behavior recorded (see above). This paradigm has been successfully used in our laboratory for previous pharmacological analyses (32,33,34).

TABLE 1

NORADRENALINE ASSAY (ng/g TISSUE) ON THE HIPPOCAMPUS, HYPOTHALAMUS AND FRONTAL CORTEX OF DSP_4 AND DISTILLED WATER TREATED RATS

	Noradrenaline		
	Control	DSP_4	% of Control
Hippocampus	352 ± 77	51 ± 51**	14
Hypothalamus	952 ± 209	477 ± 100*	50
Frontal cortex	568 ± 51	85 ± 47**	15

Student *t*-test, $^{**}p < 0.002$, $^{*}p < 0.05$. DSP_4 (2 × 50 mg/kg, IP) was injected 60 min after zimelidine (2 × 20 mg/kg, IP). Values are expressed as means ± S.E.

Treatments

The sexually experienced animals were randomly divided into two main groups: DSP_4-lesioned ($n = 38$) and non-lesioned ($n = 69$) rats. Each of these groups was further divided into non-sexually exhausted and sexually exhausted animals.

A. Effect of 8-OH-DPAT injection in non-exhausted animals following lesion of the noradrenergic system. In this group, the sexually experienced animals were divided into two main groups: sham-lesioned (intact) and DSP_4-lesioned rats. Three weeks after the last injection of either distilled water or DSP_4 respectively, the rats were injected with 8-OH-DPAT (0.5 mg/kg, -15 min) or distilled water (2ml/kg, -15min.) and thereafter directly submitted to the sexual behavior test.

B. Effect of 8-OH-DPAT injection in sexually exhausted animals following lesion of the noradrenergic system. In this group, the sexually experienced animals were again divided into two main groups: sham-lesioned (intact) and DSP_4-lesioned rats. Three weeks after the last injection of either distilled water or DSp_4 respectively, the rats were submitted to the sexual exhaustion paradigm. Twenty-four h later the experimental subjects received either 8-OH-DPAT (0.25 mg/kg, -15 min) or distilled water (2 ml/kg, -15 min) and were submitted to the sexual behavior test.

Doses and latencies of drug injection were selected according to previous data (32). The difference in 8-OH-DPAT dose between the sexually exhausted and non-exhausted groups was established on the basis of a reported exacerbated drug sensitivity in sexually exhausted rats (see 32).

Statistics

Proportion comparisons were made using the Fisher F test (37). The specific sexual behavior parameters were compared by means of the Kruskal-Wallis analysis of variance followed by the Mann-Whitney U test (37). Data from the neurochemical analysis were statistically analyzed by the Student t test (38).

RESULTS

The results of the biochemical assay are shown in Table 1. Statistically significant reductions in the noradrenaline levels in the hippocampus, hypothalamus and frontal cortex of DSP_4-treated rats were found, when compared to the levels of this neurotransmitter in the same areas of sham-lesioned rats.

As described in detail below, the 8-OH-DPAT-induced sexual-behavior facilitation, normally seen in sexually experienced intact male rats, was partially counteracted by DSP_4-lesion. In sexually exhausted rats, the effect of this drug was abolished, as to the percentage of copulating animals, by lesion of the noradrenergic system.

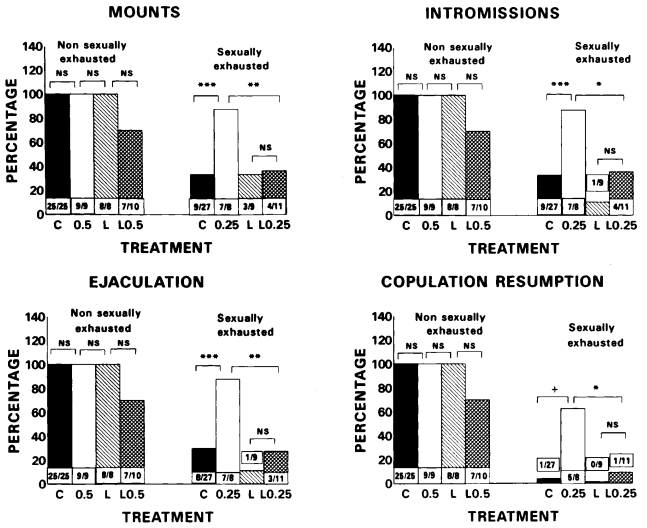

FIG. 1. Percentage of non-sexually exhausted (left) and sexually exhausted (right) copulating rats after: vehicle (C) (dark bars, $n = 25$ for non sexually exhausted and $n = 27$ for sexually exhausted), 8-OH-DPAT (0.5) and (0.25) (clear bars, 0.5 mg/kg, $n = 9$ for non sexually exhausted and 0.25 mg/kg, $n = 8$ for sexually exhausted), DSP_4-lesion (CL) (dashed bars, $n = 8$ for non sexually exhausted and $n = 10$ for sexually exhausted) and the combined manipulation of DSP_4 plus 8-OH-DPAT (L0.5) and (L0.25) (crossed-hatched bars, $n = 10$ for non sexually exhausted and $n = 11$ for sexually exhausted). Numbers on the X axes refer to the dose of 8-OH-DPAT. Fisher F test, $^{*}p < 0.05$; $^{**}p < 0.02$; $^{***}p < 0.01$; $^{+}p < 0.001$

A. Effect of 8-OH-DPAT injection in non exhausted animals following lesion of the noradrenergic system. On the left side of each panel in Fig. 1, the effect of 8-OH-DPAT treatment on the proportion of sexually experienced, non exhausted male intact and DSP_4-lesioned animals exhibiting mounts, intromissions, ejaculation and resuming copulation after ejaculation is shown.

In these rats, none of the treatments had statistically significant effects in the proportion of animals showing each of the sexual behavior components (i.e. mounts, intromissions, ejaculation and copulation resumption). A facilitatory effect of 8-OH-DPAT on these parameters cannot be observed in intact rats (0.5), due to the already maximal response exhibited by sexually experienced control animals (C). Lesion of the noradrenergic system (L) per se did not alter this maximal response, and the combined treatment of DSP_4-lesion plus 8-OH-DPAT (L0.5) provoked a small, non-statistically significant reduction (7/10) in the proportion of male rats showing each of the sexual behavior responses.

Figure 2 shows, on the left side of each panel, the specific sexual behavior parameters (*IL*, *M*, *I*, *EL* and *PEI*) of those sexually experienced, non-exhausted experimental subjects achieving ejaculation, i.e. intact rats (C, left) 25/25; intact, 8-OH-DPAT-treated rats (0.5, left) 9/9; DSP_4-lesioned rats (L, left) 8/8 and DSP_4-lesioned, 8-OH-DPAT-treated rats (L0.5, left) 7/10.

With regard to the intact animals, it is clear that treatment with 8-OH-DPAT (0.5) drastically reduced all sexual behavior

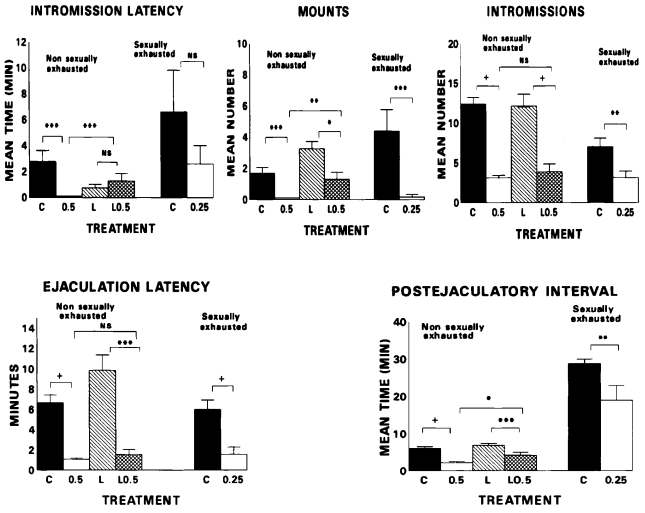

FIG. 2. Specific sexual behavior parameters (see methods) shown by non sexually exhausted (left) and sexually exhausted (right) rats after: vehicle (dark bars), 8-OH-DPAT (clear bars), DSP_4-lesion (dashed bars) and the combined manipulation of DSP_4 plus 8-OH-DPAT (cross-hatched bars). Data are based upon the number of animals achieving ejaculation in each group (see results section). Numbers on the X axis refer to the dose of 8-OH-DPAT. Kruskal-Wallis analysis of variance IL: H = 11.72, $p < 0.01$; M: H = 14.47, $p < 0.01$; I: H = 29.92, $p < 0.001$; EL: H = 33.3, $p <: 0.001$; PEI: H = 24.44, $p < 0.001$. Mann Whitney U test, $*p < 0.05$; $**p < 0.02$; $***p < 0.01$; $+p < 0.001$.

parameters. Lesion of the NA system (L) had no statistically significant effect, per se, on any of these specific parameters, when compared to the intact group (C). Interestingly, in DSP_4-lesioned rats, 8-OH-DPAT (L0.5) lost its facilitatory effect on intromission latency. Further, the reduction in the number of mounts, and in the duration of the postejaculatory interval were less potent, when compared with the effect of this drug in intact animals (0.5). However, no differences in the effect of 8-OH-DPAT between the DSP_4-lesioned (L0.5) and intact animals (0.5) were found for the number of intromissions or ejaculation latency.

B. Effect of 8-OH-DPAT Injection in Sexually Exhausted Animals Following Lesion of the Noradrenergic System. The data regarding the sexually exhausted groups appear on the right side of each panel in Figs. 1 and 2. With regard to the proportion of sexually exhausted animals (Fig.1) that exhibited the different sexual behavior responses (i.e. mounts, intromissions, ejaculation and copulation resumption), it is clear that in the vehicle control intact group (C) a low proportion of animals showed mounts (9/27), intromissions (9/27), ejaculation (8/27) and resumption of copulation (1/27). These data are in accordance with previous results showing that about one third of the male rats submitted to the sexual exhaustion paradigm are still able to ejaculate 24 h later, but that they are unable to resume copulation after ejaculation (32). Treatment with 8-OH-DPAT (0.25) effectively reversed the decrease in the proportion of animals mounting, intromitting, ejaculating (7/8) and resuming copulation (5/8). DSP_4-lesion had no statistically significant effect per se on the proportion of sexually exhausted rats capable of showing each of the sexual behavior responses at the 24-hour test (L). Finally, in DSP_4-lesioned rats treated with 8-OH-DPAT (L0.25) a statistically significant reduction -as compared with the intact, 8-OH-DPAT treated group (0.25) in the percentage of rats showing mounts (4/11), intromissions (4/11), ejaculation (3/11) and copulation resumption (1/11) was found. Thus, 8-OH-DPAT-induced reversal of the low, exhaustion-influenced proportions of copulating rats, was blocked by the NA-system lesion.

Figure 2 shows, on the right side of each panel, the specific sexual-behavior parameters of those sexually exhausted animals achieving ejaculation, i.e. intact rats (C) 8/27 and intact, 8-OH-DPAT-treated rats (0.25, right) 7/8. For the DSP_4-lesioned rats treated either with distilled water (L) or with 8-OH-DPAT (L0.25), statistical comparisons of the specific sexual behavior parameters were not possible, due to the low number of rats attaining ejaculation (1/9 and 3/11, respectively).

With regard to the intact rats, it is clear that 8-OH-DPAT treatment (0.25), nearly maintains its total stimulatory effect on sexual behavior by significantly reducing the number of mounts and intromissions, ejaculation latency and postejaculatory interval, but does not affect the intromission latency.

DSP_4-lesion (L) plus sexual exhaustion almost entirely blocked the expression of copulatory behavior (only one rat out of nine was able to ejaculate). 8-OH-DPAT (L0.25) injection could not restore sexual behavior expression in noradrenaline deficient animals.

DISCUSSION

The present data lead to the following conclusions:

a. As previously demonstrated, 8-OH-DPAT facilitates all aspects of rat masculine sexual behavior in non-exhausted, intact rats.
b. Lesion of the noradrenergic system had no effect per se on the copulatory performance of sexually experienced rats.
c. In noradrenergic-lesioned, non-exhausted animals, the stimulatory action of 8-OH-DPAT on the intromission latency disappears, while its facilitatory effect on the number of mounts and the postejaculatory interval decreases.
d. The sexual exhaustion process causes, as previously described, a severe decrease in the proportion of copulating males.
e. In sexually exhausted intact rats, treatment with 8-OH-DPAT effectively reverses the reduction in the proportion of copulating rats and maintains the majority of its facilitatory effects on male sexual behavior. Specifically, 8-OH-DPAT decreases the number of mounts and intromissions, the ejaculation latency and the postejaculatory interval, but lacks an effect on intromission latency.
f. The effect of 8-OH-DPAT in sexually exhausted animals bearing a lesion of the noradrenergic system is abolished with regard to the percentage of animals displaying sexual behavior. The specific sexual-behavior parameters of these animals could not be analyzed due to the low number of rats ejaculating.

The 5-HT_{1A} agonist 8-OH-DPAT has been known for years to be a potent facilitator of male rat copulatory behavior. This facilitation has been proposed to be mainly mediated by the stimulation of the serotonergic system (7). However, in a previous report an interaction between serotonin and noradrenaline in the mediation of the effect of 5-HT_{1A} agonists, such as lisuride and 5-MeODMT, on masculine sexual behavior was

suggested (14). The present finding that the stimulatory action of 8-OH-DPAT on copulatory behavior is partially blocked by DSP_4-treatment, supports this proposal. It is worth mentioning that for other 5-HT_{1A}-mediated behavioral actions such as influences on anxiety (29,30), hypothermia (22), nociception (9), generalization of discriminative stimulus (39,41) and the "serotonin syndrome" (39), using other pharmacological approaches, a similar conclusion has been suggested. The nature of such interaction, at this time, seems unclear although it is noteworthy that some of the behavioral actions of 8-OH-DPAT might be entirely blocked by, α for instance, or β-adrenergic antagonists (29,39,41). In contrast, the stimulation of rat masculine sexual behavior by 8-OH-DPAT has not been completely inhibited by any manipulation. In this respect, Carlsson in 1987 (12) proposed that the stimulation of the 5-HT_{1A} receptor subtype may produce non-physiological responses; more recently, we have found (17) that the action of 8-OH-DPAT on rat copulatory behavior is not mediated via the stimulation of 5-HT_{1A} somatodendritic receptors. Therefore, from the various original mechanisms proposed for the characteristic effects of 8-OH-DPAT on sexual behavior, posed by Ahlenius et al. (4), the mechanism most likely to be involved is the stimulation of a particular subgroup of postsynaptic 5-HT_{1A} receptors. However, the fact that 8-OH-DPAT may interact with adrenoceptors (13,23) and that some α-adrenergic antagonists bind to the 5-HT_{1A} receptor subtype (20,42,43) must also be considered. Independently of this direct drug interaction with adrenoceptors or 5-HT_{1A} receptors, the two neurotransmitter pathways may be involved in the regulation of masculine sexual behavior in a parallel fashion. Therefore, at least two non-exclusive interpretations could be made from the observation that some features of 8-OH-DPAT action on male sexual behavior are affected in DSP_4-lesioned rats. The first would involve the possible direct interaction of this 5-HT_{1A} compound with adrenoceptors present on adrenergic terminals. The second would relate to the possibility that 8-OH-DPAT might be interacting with 5-HT_{1A} receptors located on the noradrenergic neurones of the locus coeruleus (31). In both cases, neurotoxic lesion of the noradrenergic system would prevent some of the facilitatory actions of 8-OH-DPAT on sexual behavior. Further experiments, to clarify the nature of the direct and particularly of the parallel interactions between the diverse neurotransmitter systems in the activation of sexual behavior induced by 8-OH-DPAT should be investigated.

The present results showing that sexual exhaustion causes a drastic decrease in the proportion of copulating males, confirm previous findings of our group (32) and of other laboratories (10,27).

Interestingly, the inhibition of sexual behavior produced by sexual exhaustion can be surmounted by 8-OH-DPAT administration. The facilitatory effect of 8-OH-DPAT in sexually exhausted animals is observed both in the percentage of copulating rats (Fig.1 right), and on specific sexual behavior parameters (Fig.2, right). This drug maintains its drastic facilitatory effects on the number of mounts and intromissions, the ejaculation latency and the postejaculatory interval of sexually exhausted rats. In contrast, its facilitatory effect on the intromission latency disappears.

The present data also show that lesion of the noradrenergic system with DSP_4 had no significant effect on the proportion of sexually exhausted animals that show copulatory behavior 24 h later (Fig.1, right). However, when compared to the proportion of intact, sexually exhausted rats (C,right) capable of showing copulatory behavior, a trend towards a further decrease appears in lesioned animals (L,right). The absence of statistical significance could be due to the fact that we may be dealing with a floor effect.

Interestingly, it is clear that 8-OH-DPAT is incapable of inducing a facilitatory action in rats with combined sexual exhaustion and noradrenergic lesion (see Fig. 1, right); thus indicating that this combined manipulation blocks the stimulatory effect of 8-OH-DPAT. Such a blockade might be the result of the sum of opposite effects rather than a true pharmacological antagonism, as it is the case for (-)pindolol and (-)alprenolol which inhibit sexual behavior per se, and that also partially prevent 8-OH-DPAT actions (8).

Finally, it has been recently demonstrated (33) that the integrity of the noradrenergic system seems to be essential for the action of other drugs (yohimbine and naloxone), to reverse sexual exhaustion. The stimulatory effect of 8-OH-DPAT on rat masculine sexual behavior seems to depend upon several factors including the interaction between various neurotransmitter systems, and the stimulation of a specific 5-HT_{1A} receptor subtype that cannot be effectively antagonized by the drugs yet tested. Needless to say, further experiments are required to examine the pharmacological and putative physiological properties of this specific 5-HT_{1A} receptor subtype.

In any case, the present data show that the presence of noradrenergic neurons is necessary for the full expression of 8-OH-DPAT's facilitatory effects on male rat sexual behavior in both sexually exhausted, and sexually experienced, non-exhausted animals.

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