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Stimulation of Dopamine Autoreceptors Elicits "Premature Ejaculation" in Rats

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NAPOLI-FARRIS, L., W. FRATTA AND G. L. GESSA. *Stimulation of dopamine autoreceptors elicits "premature ejaculation" in rats.* PHARMACOL BIOCHEM BEHAV **20**(1) 69–72, 1984.—Following treatment with dopamine (DA) receptor agonists, such as apomorphine, N-n-propyl-norapomorphine, lisuride and 3-(3-hydroxyphenyl)-N-n-propyl-piperidine (3-PPP) (50, 2.5, 400 and 5000 μg/kg, respectively), male rats attain ejaculation with receptive females sooner and after fewer penile intromissions than controls. Since doses of DA agonists needed to produce "premature ejaculation" are within the low dose range needed to stimulate DA autoreceptors, it is suggested that "premature ejaculation" in rats results from inhibition of DA neurotransmission. This hypothesis is supported by the finding that 6 hr after haloperidol (1 mg/kg), rats achieve ejaculation after fewer intromissions than normal.

Dopamine receptors Premature ejaculation Copulatory behaviour Apomorphine
N-n-propyl-norapomorphine Lisuride 3-(3-hydrophenyl)-N-n-propyl-piperidine Haloperidol

MARKED lowering of ejaculation threshold may be induced in the laboratory rat by the administration of different dopamine (DA) receptor agonists, such as L-DOPA, apomorphine, N-n-propyl-norapomorphine (NPA), lisuride and pergolide [1, 2, 3, 4, 13]. The present study provides evidence that DA receptors responsible for pharmacologically induced "premature ejaculation" have similar characteristics to DA autoreceptors or may be identified with them. DA autoreceptors are a special kind of receptors located on the dopaminergic neuron itself, the stimulation of which results in decreased dopaminergic firing and reduced DA synthesis and release [5, 6, 15]. A characteristic of DA autoreceptors is that they are more sensitive to DA agonists than postsynaptic DA receptors which are responsible for stimulatory motor responses to DA agonists [18]. Recently, a rather selective stimulant for DA autoreceptors has been synthesized, 3-(3-hydroxyphenyl)-N-n-propyl-piperidine (3-PPP) [10]. This compound may be an important tool for elucidating the possible nature of the receptors involved in the sexual stimulant response to DA agonists.

METHOD

Animals

Male Sprague-Dawley CD rats (Charles River, Como, Italy), aged approximately 100 days and weighing 250–275 g at the beginning of experiments, were used. The animals were individually housed at 24°C, 60% humidity, under reversed 12 hr light-dark cycle (light on from 11.00 p.m. to 11.00 a.m.). Each rat underwent a series of mating tests at weekly intervals, with a female in estrus. At the end of this training period, a population of rats which reached at least 2 ejaculations in the last of the 4 mating tests was selected. The female rats used in the mating tests were of the same strain as the males. They were ovariectomized at least 3 weeks before the test and brought into estrus by subcutaneous injection of oestradiol benzoate (200 μg/rat, in oil) and progesterone (0.5 mg/rat, in oil), 48 and 6 hr before the mating test, respectively.

Mating Tests

Mating tests were carried out during the dark phase of the cycle, from 4.00 to 6.00 p.m. in a room lit by a dim red light. A female was introduced into the male's home cage. Then the following measures of copulatory behaviour were recorded on an event recorder (Esterline Angus) for 30 min.

Latencies. (a) Intromission latency (IL): the time which elapsed from the introduction of the female into the male's cage until the first intromission. Since our sexually experienced rats usually began copulation with an intromission, irrespective of treatment, values for mount latency are not reported in the tables. (b) Ejaculation latency (EL): the time from the first intromission until the first ejaculation.

Frequencies. (1) Mount frequency (MF) and intromission frequency (IF): the number of mounts or intromissions in a series. (b) Ejaculation frequency (EF): total number of ejaculations during 30 min observation.

Intervals. (a) Post-ejaculatory interval (PEI): the time from the first ejaculation to the next intromission. (b) "Premature ejaculation" (PE): "premature ejaculation" in rats is defined as a decrease in both the intromission frequency and the ejaculation latency: ejaculation refers to the behavioural response and not seminal emission.

Each test included an equal number of saline and drug treated rats. Each rat in a given group received each of the treatments, as reported in the tables. The animals were tested at weekly intervals, the treatment sessions being separated by one or more control session until the original level of response was exhibited. Control values were those obtained from non-treated animals on the days in which the other rats of the same group received the drug.

TABLE 1

LOWERING OF EJACULATION THRESHOLD BY DOPAMINE RECEPTOR STIMULANTS IN RATS

Treatment (No. of rats)	I.L.	E.L.	M.F.	I.F.	E.F.	P.E.I.
Group 1 (18)						
Saline	110 ± 75	989 ± 101	5.6 ± 2.5	13.1 ± 1.5	2.5 ± 0.3	386 ± 21
Apomorphine	31 ± 7	509 ± 90†	4.8 ± 1.2	5.5 ± 1.1†	2.3 ± 0.4	370 ± 41
NPA	57 ± 11	680 ± 60*	5.1 ± 2.1	4.6 ± 1.8†	2.8 ± 1.3	430 ± 53
Group 2 (18)						
Saline	57 ± 25	1226 ± 131	5.8 ± 1.2	12.2 ± 1.3	2.0 ± 0.4	425 ± 86
Lisuride	45 ± 15	520 ± 87†	4.0 ± 1.2	5.2 ± 1.8†	3.9 ± 0.2†	343 ± 17*
3-PPP	95 ± 32	844 ± 137*	7.4 ± 2.3	6.2 ± 1.3†	2.1 ± 0.8	177 ± 18*

Each rat in the same group received treatment at 15 day intervals. The doses/kg were: apomorphine 50 μg, NPA 2.5 μg, lisuride 400 μg and 3-PPP 5 mg. Values are means ± S.E. for the same rats under different treatment conditions. Measures of time as expressed in seconds.

*$p<0.01$ and †$p<0.001$ (1-way analysis of variance).

Drugs

Apomorphine·HCl (Sigma) and NPA (Research Biochem. Inc. MA) were freshly dissolved in bidistilled water containing 0.2 mg/ml ascorbic acid, (±)-3-PPP (was kindly provided by S. Hjorth, University of Göteborg) and lisuride (a gift from Schering) were dissolved in saline, haloperidol (Janssen) and domperidone (Servier) were used in the commercially available solutions.

Apomorphine, NPA and 3-PPP were administered subcutaneously and the other drugs intraperitoneally.

Statistics

The statistical significance of the results was evaluated using the 1-way analysis of variance.

RESULTS

Selected sexually experienced rats attained ejaculation with receptive females after 8–13 penile intromissions into the vagina and within 8–12 min after the first intromission.

As expected from previous results [1, 4, 13], the administration of a small dose of apomorphine, NPA or lisuride, given to the male rat 30 min prior to the mating test with a receptive female, markedly decreased the intromission frequency and shortened the ejaculation latency. NPA was the most potent DA agonist, the active dose being as low as 2.5 μg/kg, subcutaneously (Table 1).

Moreover, a dose of 5 mg/kg of 3-PPP markedly reduced intromission frequency and also caused a modest, significant decrease in ejaculation latency.

Active doses of DA agonists which produce premature ejaculation decreased motor activity in male rats in the absence of receptive females.

Since the results indicated that the decrease in ejaculation threshold was mediated by stimulation of DA autoreceptors and a secondary impariment of DA neurotransmission, we studied the effect of haloperidol and domperidone, a central and peripheral DA receptor blocker, respectively, on copulatory pattern. These results are shown in Table 2. As expected from previous results [8,20], one hour after haloperidol treatment (1 mg/kg), copulatory behaviour was suppressed in 89% of the animals. Surprisingly, however, 6 hours after treatment, in spite of the presence of marked catalepsy, almost all the animals resumed copulation and achieved ejaculation. However, similarly to the rats treated with DA agonists, ejaculation occurred after fewer intromissions than normal in haloperidol-treated rats. Domperidone treatment failed to modify copulatory behaviour at either 1 or 6 hours after treatment.

DISCUSSION

Following treatment with different DA receptor agonists, sexually experienced male rats achieve ejaculation after fewer penile intromissions and a shorter latency.

The doses of DA agonists which produced this response were within the low dose-range needed to stimulate DA autoreceptors, i.e, much lower than the doses necessary to produce motor stimulation and stereotypy. Moreover, 3-PPP, which is considered a rather selective stimulant of DA autoreceptors, also decreased ejaculation latency and intromission frequency. While the effect of 3-PPP on the latter component of copulatory behaviour was as pronounced as that of DA agonists, the compound was less effective in decreasing ejaculation latency. This difference might be explained by the fact that the racemic mixture of 3-PPP was used in our experiments. While both enantiomers of 3-PPP possess DA autoreceptor stimulatory capacity, the levorotatory enantiomer inhibits postsynaptic DA receptors as well. In contrast, the dextrorotatory enantiomer, although at much higher doses than that used in our experiments, has agonistic effects on postsynaptic DA receptors [9]. A study with separate enantiomers of 3-PPP might give further information on this matter.

These results indicate that a special kind of DA receptors regulate ejaculation threshold and suggest that they may be identified with DA autoreceptors, i.e., those receptors whose stimulation results in the inhibition of DA neurotransmission. The hypothesis that lowering of ejaculation threshold might indeed result from an impairment of DA neurotransmission in some brain area is supported by the finding that a marked decrease in intromission frequency was produced by haloperidol which, however, unlike DA agonists failed to decrease ejaculation latency. It is possible that the difference in the effect between haloperidol and DA agonists might depend on the neurological deficit produced

TABLE 2

EFFECT OF HALOPERIDOL AND DOMPERIDONE ON COPULATORY BEHAVIOUR IN THE MALE RAT

Treatment (No. rats)	hours before test	% rats achieving at least 1 ejaculation	I.L.	E.L.	M.F.	I.F.	E.F.	P.E.I.
Group 3 (18)								
Saline	1	100	21.2 ± 3.5	667 ± 60	4.2 ± 1.0	10.8 ± 1.9	2.4 ± 0.3	301 ± 13
Haloperidol	1	11†						
Haloperidol	6	88	63.1 ± 12*	681 ± 75	1.0 ± 0.3*	5.3 ± 0.2†	1.9 ± 0.5	337 ± 91
Group 4 (18)								
Saline	1	100	31.5 ± 4.1	775 ± 81	5.3 ± 2.1	11.7 ± 2.1	2.6 ± 0.4	253 ± 61
Domperidone	1	100	35.6 ± 4.5	683 ± 113	3.7 ± 4.1	10.0 ± 1.9	2.3 ± 0.3	345 ± 32
Domperidone	6	100	43.5 ± 3.7	721 ± 87	2.8 ± 3.1	9.3 ± 0.9	2.9 ± 0.2	305 ± 26

Each rat in the same group received each treatment (in the dose of 1 mg/kg) at 15 day intervals. Values are means ± S.E. for the same rats under different treatment conditions. Measures of time are expressed in seconds. Values for haloperidol were calculated from rats achieving at least one ejaculation.

*$p<0.01$, †$p<0.001$ (1-way analysis of variance).

by haloperidol, which may interfere with the animal's ability to perform the copulatory act.

Moreover, it is not clear why haloperidol suppreses copulatory behaviour during the first hour after treatment but the inhibition disappears later when the neuroleptic effect is maximal. A detailed study on the effects of the DA receptor blocker on various components of copulatory behaviour might shed some light on this problem.

The effect of lisuride on copulatory behaviour has been attributed by Ahlenius [1] to the impairment of brain serotonin (5-HT) neurotransmission secondary to the stimulation of 5-HT autoreceptors. It has been argued that a similar decrease in intromission frequency and ejaculation latency is produced by p-chlorophenylalanine (PCPA) [16], an inhibitor of 5-HT synthesis, and that lisuride is a more potent agonist for 5-HT receptors than for DA receptors [1]. Although a possible involvement of 5-HT receptors in premature ejaculation cannot be excluded at present, our studies favour the DA autoreceptor hypothesis. Accordingly, doses of lisuride needed to modify sexual pattern are far higher than those required to suppress 5-HT firing [14]. Finally, PCPA is far from selective in inhibiting the synthesis of 5-HT but effectively inhibits also that of catecholamines [11, 12, 19]. On the other hand, an interference with 5-HT neurotransmission may explain the fact that lisuride, similarly to PCPA, increases the number of ejaculations during the observation period (Table 1) and induces full copulatory behaviour in castrated male rats [1].

Apart from their nature and anatomical location, the finding that a special kind of DA receptors may be involved in premature ejaculation may offer new approaches to control such distrubances occurring in man. According to our hypothesis, drugs which preferentially block DA autoreceptors should be useful in premature ejaculation. It is possible that the therapeutic efficacy observed with thiorazine [17] and metochlopramide [7] might be due to such a mechanism.

Finally, the decrease in both ejaculation latency and intromission frequency produced by presynaptic DA agonists may represent a useful animal model of premature ejaculation.

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