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BRIEF COMMUNICATION

Possible Stimulatory Role of Brain Dopamine in the Copulatory Behavior of Male Rats

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TAGLIAMONTE, A., W. FRATTA, M. DEL FIACCO AND G. L. GESSA. *Possible stimulatory role of brain dopamine in the copulatory behavior of male rats.* PHARMAC. BIOCHEM. BEHAV. 2(2) 257–260, 1974. – Apomorphine and a combination of Ro 4-4602 with L-DOPA increase the copulatory behavior of male adult rats with a low basal level of sexual activity. This effect is prevented by haloperidol. This drug also suppresses the spontaneous copulatory behavior in rats with high basal level of sexual activity.

Sexual behavior Apomorphine L-DOPA Dopamine Haloperidol

WE HAVE REPORTED that the stimulatory effect of p-chloro-phenylalanine (pCPA) on male mounting behavior in rats is potentiated by pargyline, a monoamineoxidase inhibitor [23]. Since the administration of pargyline to rats whose serotonin synthesis is blocked by pCPA, produces a selective accumulation of brain catecholamines [23], we postulated that both brain serotonin and catecholamines control sexual behavior in male animals; with serotonin inhibiting and catecholamines enhancing this behavior. Recent reports indicating an aphrodisiac effect of L-DOPA in some Parkinsonian patients [4, 8, 15, 19, 24], might be interpreted in the light of this theory rather than as an unspecific improvement of health and function.

However, the role of brain catecholamines in male sexual behavior is controversial. Bertolini and Vergoni found that p-chloro-N-methylamphetamine, a compound which inhibits serotonin synthesis and also releases brain catecholamines [17], is more potent than pCPA in stimulating male to male mounting behavior [9]. Moreover, Benkert observed that the male to male mounting behavior produced by pCPA in rats is potentiated by L-DOPA [8] and reported that p-chloro-N-methylamphetamine has some beneficial effect in the treatment of impotence in male patients [7]. On the contrary, Hyyppa *et al.* failed to observe increased copulatory behavior in male adult rats treated with L-DOPA [14]. Finally, Butcher *et al.* [11] reported that apomorphine and amphetamine reduce ejaculatory latency but have no effect on other aspects of copulatory behavior in male rats with a high level of sexual activity.

The results of the present study show that both apomorphine and L-DOPA improve the copulatory behavior in sexually sluggish male rats. This effect is prevented by haloperidol. Moreover, haloperidol suppresses the copulatory behavior in male rats with a high basal level of sexual activity. These findings suggest that brain dopamine plays a stimulatory role in the copulatory behavior of male rats.

METHOD

Male Wistar rats, weighing 300–350 g, were housed individually in 20 × 40 cm cages starting at least one week before the beginning of the experimental period, under a reversed light–dark cycle (with light from 9:00 p.m. to 9:00 a.m.) and fed ad lib. Each rat underwent 4 mating tests with a female in oestrus, at weekly intervals, as described below. At the end of this training period two groups of rats were selected; the first group consisted of 50 rats which did not reach ejaculation in 3 out of 4 mating tests and were as such classified as sexually sluggish. The second group consisted of 40 rats which reached at least 3 ejaculations in each test and were classified as selected copulators. More than 400 rats were tested over a period of 2 months.

Female Wistar rats to be used in the mating tests were ovariectomized 3 weeks before the mating test and brought into heat by subcutaneous injections of oestradiol and progesterone in olive oil [17]. Mating tests were carried out during the dark phase of the cycle, from 10:00 a.m. to 12:00 a.m., in red light.

A female was introduced into the male's own cage and the test was terminated either if the animals failed to ejaculate within 30 min or if the postejaculatory latency exceeded 30 min. Patterns of copulatory behavior were scored according to Beach [6]. Each male rat underwent

different mating tests with and without treatments in a latin square design.

RESULTS

The effect of apomorphine and the combination of L-DOPA with Ro 4-4602, a peripherally acting decarboxylase inhibitor, was studied on the copulatory behavior of male sexually sluggish rats. Ro 4-4602 was given to prevent the decarboxylation of L-DOPA in peripheral tissues and to increase the amount of L-DOPA reaching the brain. As shown in Table 1 a dose of 0.5 mg/kg of apomorphine increased from 58 to 80, from 54 to 80 and from 14 to 62 percent, the number of rats showing mountings, intromissions and ejaculations, respectively. On the other hand, 5 mg/kg of this compound produced a marked stereotyped behavior, which prevented the occurrence of other goal-directed behaviors, including the copulatory one.

A single injection of L-DOPA to rats treated with Ro 4-4602, markedly increased the number of animals showing mountings and intromissions, while the percentage of rats ejaculating was only slightly increased. This effect was more pronounced with two doses of L-DOPA at a 30 min interval: this treatment increased to 64% the number of rats reaching ejaculation. On the other hand, no sexual stimulation was observed after L-DOPA administered alone, at doses up to 150 mg/kg i.p., given from 30 to 50 min before testing; suggesting that brain dopamine must rise above a critical level in order to elicit an aphrodisiac effect.

Table 2 shows that the aphrodisiac effect elicited by apomorphine or by the combination of L-DOPA with Ro 4-4602 was blocked by 1 mg/kg of haloperidol. This drug also suppressed the spontaneous copulatory behavior of rats with high basal level of sexual activity.

Experiments were carried out with selected copulators in order to study the effect of L-DOPA on the copulatory pattern. As Table 3 shows, two doses of L-DOPA given at a 30 min interval to animals pretreated with Ro 4-4602, shortened the ejaculation latency, the postejaculatory interval and decreased the number of mounts and intromissions prior to ejaculation. The administration of Ro 4-4602 alone modified the sexual behavior neither in sexually sluggish rats nor in selected copulators.

DISCUSSION

The present investigation has shown that the copulatory behavior of sexually sluggish male animals is stimulated by a combination of L-DOPA with Ro 4-4602 and by apomorphine. Since the administration of L-DOPA to rats treated with Ro 4-4602 has been shown not only to increase the content of brain catecholamines [5], but also to decrease that of serotonin [10], the stimulatory effect on male copulatory behavior can be ascribed to either mechanism. On the other hand, since apomorphine is considered to act as a direct stimulant of the dopamine receptors in brain [3], the finding that also this compound stimulated the copulatory behavior in male rats supports the hypothesis that brain dopamine plays a stimulatory role on male sexual behavior.

Consistently, the effect of apomorphine and L-DOPA was prevented by haloperidol, a specific inhibitor of dopaminergic receptors in brain [2]. Moreover, this drug also suppressed the spontaneous copulatory behavior of male rats with a high basal level of sexual activity.

Since this paper was submitted for publication, Malmnäs has reported data [16] concerning the effect of LSD, apomorphine disulfiran and pimozide on the copulatory behavior of male rats, castrated and treated with subliminal doses of testosterone. His results are in good agreement with our previous [23] and present data on the inhibitory and excitatory role of serotonin and dopamine respectively on male sexual behavior.

Two corollaries of this study are that sexually sluggish rats may be a useful tool for screening drugs with a potential aphrodisiac effect and that the shortening of the ejaculation latency, produced by L-DOPA, as well as that produced by reserpine [12, 13, 22] and pCPA [1, 19, 21] may be considered a possible model in animals of ejaculation praecox occurring in man.

TABLE 1

STIMULATION BY L-DOPA (WITH Ro 4-4602) AND APOMORPHINE OF THE COPULATORY BEHAVIOUR OF MALE SEXUALLY SLUGGISH RATS

Treatment	% of Animals Exhibiting at Least One		
	Mounting*	Intromission*	Ejaculation*
Saline	58	54	14
Apomorphine 0.5 mg/Kg†	80	80	62
Ro 4-4602 + L-DOPA‡	90	90	30
Ro 4-4602 + L-DOPA × 2	90	90	64

Each value was obtained from 50 rats. Each rat underwent different mating tests with and without treatment, at weekly intervals.

*Occurring within 30 min after male and female rats were paired.

†Apomorphine was given i.p. 15 min before the mating test.

‡L-DOPA (100 mg/Kg i.p.) was given 20 min after Ro 4-4602 (50 mg/Kg i.p.). The experiment was performed half an hour after the last treatment.

Two doses of L-DOPA (100 mg/Kg each) were injected i.p. 20 and 50 min after Ro 4-4602 respectively. The experiment was performed half an hour after the last treatment.

TABLE 2

INHIBITION BY HALOPERIDOL OF THE COPULATORY BEHAVIOUR OF NORMAL MALE RATS AND OF THAT INDUCED BY APOMORPHINE OR L-DOPA IN SEXUALLY SLUGGISH RATS

Rats	Treatment	Haloperidol mg/Kg	% of Animals Exhibiting at Least One Mounting*	Intromission*	Ejaculation*
Selected copulators	none	none	100	100	100
Selected copulators	none	1	0	0	0
Sexually sluggish	Apomorphine	none	80	80	62
Sexually sluggish	Apomorphine	1	20	20	12
Sexually sluggish	Ro 4-4602 + L-DOPA	none	90	90	64
Sexually sluggish	Ro 4-4602 + L-DOPA	1	10	10	0

*Occurring within 30 min after male and female rats were paired.
Values for selected copulators were obtained from 40 rats.
Values for sluggish rats were obtained from 50 rats.
These treatments were given as described in Table 1.

TABLE 3

EFFECT OF THE COMBINATION OF L-DOPA WITH Ro 4-4602 ON THE PATTERN OF COPULATORY BEHAVIOUR OF MALE, SELECTED COPULATORS

	Treatments and Number of Animals		
	base line	Ro 4-4602 + L-DOPA once	Ro 4-4602 + L-DOPA twice
Number of mounts before ejaculation	5.45	6.2	4.05*
Number of intromission before ejaculation	9.35	8.85	6.73*
Ejaculation latency (min and sec)	9.60	8.76	6.20*
Postejaculation interval (min and sec)	6.32	6.12	4.12*

Each value is the mean of at least 2 experiments carried out with 28 rats. Every rat received one mating test under each of the three conditions, according to a latin square design. The data reported refer only to the first ejaculation.
*$p<0.01$ in respect to control values.
Treatments were given as described in Table 1.

REFERENCES

1. Ahlenius, S., H. Eriksson, K. Larsson, K. Modigh and P. Södersten. Mating behavior in the male rat treated with p-chlorophenylalanine methyl ester alone and in combination with pargyline. *Psychopharmacologia* **20:** 383–388, 1971.
2. Anden, N.-E., A. Dahlström, K. Fuxe and T. Hokfelt. The effect of haloperidol and chlorpromazine on the amine levels of central monoamine neurons. *Acta physiol. scand.* **68:** 419–420, 1966.

3. Anden, N.-E., A. Rubenson, K. Fuxe and T. Hökfelt. Evidence for dopamine receptor stimulation by apomorphine. *J. Pharm. Pharmac.* **19:** 627–629, 1967.
4. Barbeau, A. L-Dopa therapy in Parkinson's disease: a critical review of nine years experience. *Can. Med. Ass. J.* **101:** 791–800, 1969.
5. Bartholini, G., J. Constantinidis, R. Tissot and A. Pletscher. Formation of monoamines from various amino acids in the brain after inhibition of extracerebral decarboxylase. *Biochem. Pharmac.* **20:** 1243–1247, 1971.
6. Beach, F. A. and L. Jordan. Sexual exhaustion and recovery in the male rat. *Q. Jl exp. Psychol.* **8:** 121–133, 1956.
7. Benkert, O. L-Dopa treatment of impotence: a clinical and experimental study. In: *L-Dopa and Behavior,* edited by Sidney Malitz. New York: Raven Press, Publishers, pp. 73–79, 1972.
8. Benkert, O., G. Crombach and G. Kockott. Effect of L-Dopa on sexually impotent patients. *Psychopharm.* **23:** 91–95, 1972.
9. Bertolini, A. and W. Vergoni. Effetto eccito-sessuale della p-chloro-N-metilamfetamine associata a testosterone, nel ratto maschio. *Riv. Farm. Ter.* **1:** 423–426, 1970.
10. Butcher, L. L. Behavioral, biochemical and histochemical analyses of the central effects of monoamine precursors after peripheral decarboxylase inhibition. *Brain Res.* **41:** 387–411, 1972.
11. Butcher, L. L., S. G. Butcher and K. Larsson. Effects of apomorphine, (+)-amphetamine, and nialamide on tetrabenazine-induced suppression of sexual behavior in the male rat. *Eur. J. Pharmac.* **7:** 283–288, 1969.
12. Dewsbury, D. A. Copulatory behavior of male rats following reserpine administration. *Psychon. Sci.* **22:** 177–179, 1971.
13. Dewsbury, D. A. Effects of tetrabenazine on the copulatory of male rats. *Eur. J. Pharmac.* **17:** 221–240, 1971.
14. Hyyppa, M., P. Lehtinen and U. K. Rinne. Effect of L-DOPA on the hypothalamic, pineal and striatal monoamines and on the sexual behavior of the rat. *Brain Res.* **30:** 265–272, 1971.
15. Jenkins, R. B. and R. H. Broh. Mental symptoms in Parkinsonian patients treated with L-DOPA. *Lancet* **II:** 177–180, 1970.
16. Malmnäs, C. O. Monoaminergic Influence on Testosterone-Activated Copulatory Behavior in the Castrated male rat. *Acta phisiol. scand. (Suppl. 395),* Uppsala 1973.
17. Meyerson, B. J. The effect of neuropharmacological agents on hormone-activated estrus behaviour in ovariectomized rats. *Archs. int. Pharmacodyn. Ther.* **150:** 4–33, 1964.
18. Miller, F. P., R. H. Cox, Jr., W. R. Snodgrass and R. P. Maickel. Comparative effects of p-chlorophenylalanine, p-chloroamphetamine and p-chloro-n-methylamphetamine on rat brain norepinephrine, serotonin and 5-hydroxyindole-3-acetic acid. *Biochem. Pharmac.* **19:** 435–442, 1970.
19. Mitler, M. M., B. Morden, S. Levine and W. Dement. The effects of parachlorophenylalanine on the mating behavior of male rats. *Physiol. Behav.* **8:** 1147–1150, 1972.
20. Mones, R. J., T. S. Elizan and G. J. Siegel. Evaluation of L-DOPA therapy in Parkinson's disease. *N. Y. State J. Med.* **70:** 2309–2318, 1970.
21. Salis, P. J. and D. A. Dewsbury. p-chlorophenylalanine facilitates copulatory behavior in male rats. *Nature* **232:** 400–401, 1971.
22. Soulairac, A. and M. L. Soulairac. Action de la reserpine sur le comportament sexuel du rat male. *C.r. Soc. Biol.* **155:** 1010 1012, 1961.
23. Tagliamonte, A., P. Tagliamonte, G. L. Gessa and B. B. Brodie. Compulsive sexual activity induced by p-chlorophenylalanine in normal and pinealectomized male rats. *Science* **166:** 1433–1435, 1969.
24. Van Woert, M. H., G. Heninger, U. Rathey and M. B. Bowers, Jr. L-DOPA in senile dementia. *Lancet* **I:** 573–574, 1970.