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BRIEF COMMUNICATION

Apomorphine and Haloperidol-Induced Effects on Male Rat Sexual Behavior: No Evidence for Actions Due to Stimulation of Central Dopamine Autoreceptors

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AHLENIUS, S. AND K. LARSSON. *Apomorphine and haloperidol-induced effects on male rat sexual behavior: No evidence for actions due to stimulation of central dopamine autoreceptors.* PHARMACOL BIOCHEM BEHAV **21**(3) 463–466, 1984.—The administration of apomorphine (0.2–0.8 mg/kg IP) or (+)3-PPP (4–8 mg/kg IP) produced a facilitation of the male rat sexual behavior. Apomorphine in lower doses, as well as the selective DA autoreceptor agonist (−)3-PPP were ineffective. Except for a decrease in number of intromissions and an increase in the postejaculatory interval at the highest dose (0.32 mg/kg IP) there were no effects after administration of haloperidol. These data indicate that activation or inhibition of the presynaptic dopamine receptor does not affect male rat sexual behavior.

Male rat sexual behavior Dopamine Autoreceptors

THE newly developed drug 3-(3-hydroxyphenyl)-N-*n*-propylpiperidine (3-PPP) has been shown to predominantly stimulate central dopamine (DA) autoreceptors [6]. The resolution of 3-PPP into its (+) and (−) enantiomers disclosed two biologically active compounds with different pharmacological profiles. (+)3-PPP appears to be an unselective DA receptor agonist, whereas (−)3-PPP selectively activates DA autoreceptors, and at increasing doses, blocks postsynaptic DA receptors as well [5]. In preliminary experiments, we found that the racemic form of 3-PPP facilitated male rat sexual behavior, as indicated by a decrease in number of intromissions preceding ejaculation and a decrease in the ejaculation latency. In order to investigate a possible role of presynaptic DA receptors in this effect we decided to study the effects of the two 3-PPP enantiomers. We have also observed the effects of apomorphine and haloperidol in doses that might be expected to produce pre- as well as postsynaptic effects at central DA receptors (see [14]).

METHOD

Animals

Male Wistar rats (Möllegaard, Vejle, Denmark), approximately 5 months old at the start of the experiments, were used. They were maintained, four per cage, under conditions of constant temperature and humidity, with food and water available ad lib. The day-light cycle was artificially maintained (dark 11.00 a.m. to 11.00 p.m.).

Behavioural Testing Procedure

Mating tests were begun 2 hr after onset of darkness. The males were presented with a female brought into sexual receptivity by sequential treatment with estradiol benzoate (20 μg/animal), followed 42 hr later by progesterone (0.5 mg/animal), which was injected 6 hr before testing. The test was ended when one of the following conditions was fulfilled: (a) 15 min after the presentation of the female to the male, if at that time no intromission had taken place; (b) 30 min after the first intromission, if no ejaculation had taken place; (c) 15 min after ejaculation, if no further intromission had occurred; (d) after the first intromission following ejaculation. All animals that did initiate copulation (b–d) were included in the statistical evaluation and, when appropriate, assigned time and frequency values obtained within the limits indicated. The animals were observed, 4 at a time, by a trained observer and the following behavioural components were recorded: (a) mount latency: time from the entrance of the female into the observation cage to the first mount, without intromission; (b) intromission latency; (c) mount frequency: mounts without intromission before ejaculation; (d)

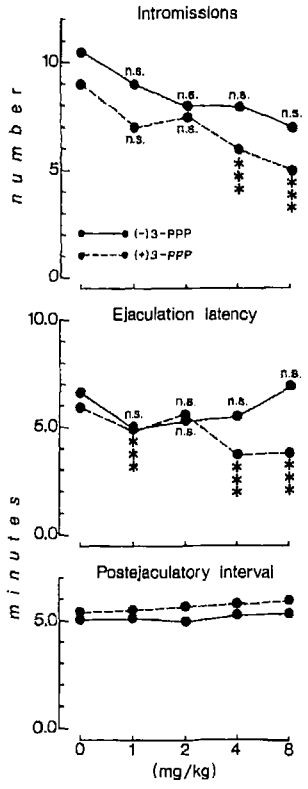

FIG. 1. Effects of 3-PPP enantiomers on male rat sexual behavior. (+) or (−) 3-PPP, 0–8 mg/kg IP, was administered 30 min before the observations. The performance after the different treatments is represented by medians in the figure. Statistical evaluation as follows: (−)3-PPP (n=18): all $\chi^2(4)$ values <9.49, n.s. (+)3-PPP (n=18): intromissions, $\chi^2(4)=23.32$, $p<0.01$; ejaculation latency, $\chi^2(4)=14.38$, $p<0.01$; postejaculatory interval, $\chi^2(4)=9.07$, n.s. The semi-interquartile range of intromissions, ejaculation latency and postejaculatory interval for controls were: 3.5, 1.18, and 0.7 respectively [(−)3-PPP] and 2.5, 2.50, and 0.65 respectively [(+)3-PPP]. ***$p<0.01$.

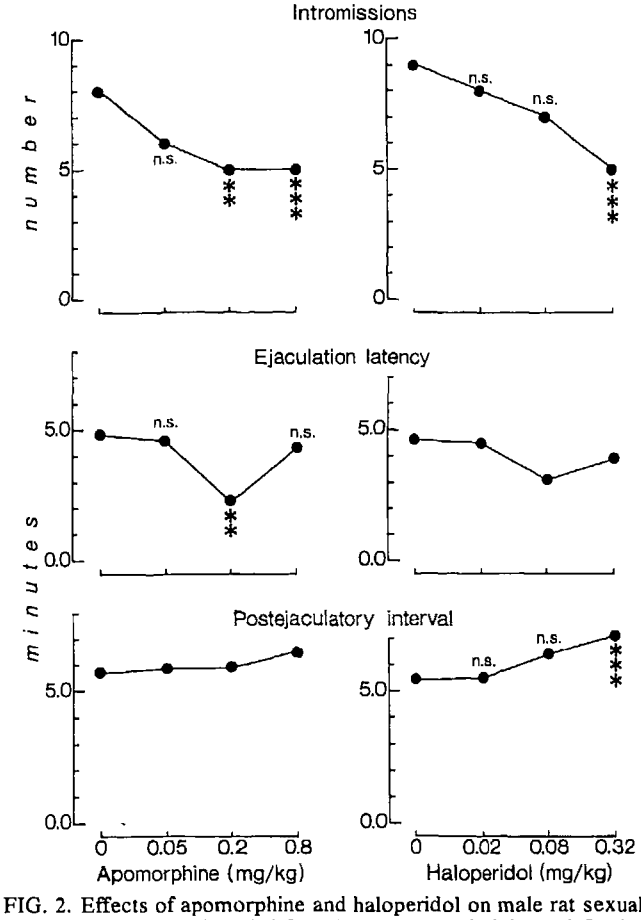

FIG. 2. Effects of apomorphine and haloperidol on male rat sexual behavior. Apomorphine, 0–0.8 mg/kg IP, was administered 5 min, and haloperidol, 0–0.32 mg/kg IP, 30 min before the observations. The performance after the different treatments is represented by medians in the figure. Statistical evaluation as follows: Apomorphine (n=18): intromissions, $\chi^2(3)=14.54$, $p<0.01$; ejaculation latency, $\chi^2(3)=8.10$, $p<0.05$; postejaculatory interval, $\chi^2(3)=6.54$, n.s. Haloperidol (n=17): intromissions, $\chi^2(3)=13.42$, $p<0.01$; ejaculation latency, $\chi^2(3)=1.03$, n.s.; postejaculatory interval, $\chi^2(3)=22.63$, $p<0.01$. The semi-interquartile range of intromissions, ejaculation latency and postejaculatory interval for controls were: 3.3, 2.69, and 0.88 respectively (apomorphine) and 1.3, 1.21, and 0.98 respectively (haloperidol). **$p<0.025$, ***$p<0.01$.

intromission frequency; (e) ejaculation latency: time from the first intromission until ejaculation; (f) postejaculatory interval: time from the ejaculation to the next intromission.

Drugs

The following drugs were used: (+) and (−) 3-(3-hydroxyphenyl)-N-*n*-propylpiperidine·HCl (3-PPP) (synthesized at Astra Läkemedel AB, Research and Development Laboratories, Södertälje, Sweden by O. Thorberg), apomorphine·HCl (Sandoz AB, Täby, Sweden) and haloperidol (Janssen Leo Farma AB, Helsingborg, Sweden). 3-PPP enantiomers and apomorphine were dissolved in physiological saline, whereas haloperidol was dissolved in a few drops of glacial acetic acid with 5.5% glucose added to final volume. Drugs were injected intraperitoneally in a volume of 2 ml/kg b.w.

Statistics

For each drug the animals received all doses serving as their own controls using a balanced design. At least two days were allowed between injections. Unless otherwise stated, statistical analysis was performed by means of the Friedman two-way ANOVA and, if overall significance was obtained, followed by the Wilcoxon matched-pairs signed-ranks test, two-tailed [13]; $p<0.05$ was considered as statistically significant.

RESULTS

No statistically significant effects were obtained when analysing mount latency, intromission latency or number of mounts and these data will not be presented further.

Effects of 3-PPP Enantiomers

Following administration of (+)3-PPP (1–8 mg/kg IP) a decrease was observed in the number of intromissions preceding ejaculation and a shortening of the ejaculation latency (Fig. 1). No statistically significant effects were found in the

number of mounts or in the postejaculatory interval. Administration of the (−) enantiomer of 3-PPP (1–8 mg/kg IP) produced no statistically significant effects.

Effects of Apomorphine

As shown in Fig. 2 apomorphine produced a statistically significant decrease in the number of intromissions (0.2–0.8 mg/kg IP) and in the ejaculation latency (0.2 mg/kg IP). At 0.2 mg/kg 1 animal failed to ejaculate and this figure was increased to 5 at 0.8 mg/kg (n=18). Particularly at the highest dose, this appeared to be due to competing behaviours like sniffing and other beginning stereotypies.

Effects of Haloperidol

Treatment with haloperidol (0.02–0.32 mg/kg IP) produced a dose-dependent decrease in the number of intromissions preceding ejaculation (Fig. 2). No statistically significant changes were observed in the number of mounts or in the ejaculation latency. However, at the highest dose, two animals failed to ejaculate (n=17) and there was a statistically significant increase in the postejaculatory interval, in all probability indicating extrapyramidal motor impairment.

DISCUSSION

In agreement with previous reports we have shown that apomorphine, like *L*-DOPA, may facilitate male rat sexual behavior by decreasing the number of intromissions preceding ejaculation and by decreasing the ejaculation latency [2, 10, 11, 15]. The effects produced by apomorphine or *L*-DOPA are in all probability due to an activation of central DA receptors since the effects are prevented by pretreatment with the DA receptor blocking agent pimozide [10,11]. In view of these findings it is not surprising that (+)3-PPP, which has been shown to be an agonist at central DA receptors [5], turned out to produce the same effects as apomorphine or *L*-DOPA.

It should also be noted that apomorphine or *L*-DOPA produce hyperactivity and, with increasing doses, stereotypies (e.g., [12]). It is obvious that these extrapyramidal effects will influence the performance of the sexual behavior by male rats. Thus, it is likely that the facilitation seen by the administration of apomorphine or *L*-DOPA as mentioned above, or *d*-amphetamine [2], at least partially is due to general alerting or activating effects. At the same time, beginning stereotypies like sniffing and chewing will interfere with the ability to perform and may explain the biphasic effects of apomorphine on the ejaculation latency in the present experiments. It should also be noted that high doses of *L*-DOPA do not facilitate male rat sexual behavior [4,7]. Furthermore, in comparison with other drugs that facilitate male rat sexual behavior, like *p*-chlorophenylalanine and some ergot derivatives, the effect by drugs that activate central DA receptors appears to be slight and less reliable (see [9]).

Haloperidol, at the highest dose used in the present experiments (0.32 mg/kg), decreased the number of intromissions without affecting the ejaculation latency. In addition, there was an increase in the postejaculatory interval and some animals failed to initiate copulation. The decrease in number of intromissions may seem paradoxical but is probably due to pharmacologically induced "enforced intervals" in the copulatory behavior due to extrapyramidal effects at this dose of haloperidol. Enforced intervals between intromissions have previously been shown to reduce the number of intromissions without affecting time to ejaculation [8]. These findings show that a blockade of central (or peripheral) DA receptors did not affect the ability to ejaculate although other measures like the postejaculatory interval and the number of intromissions were affected by the drug treatment.

In the present experiments the doses of apomorphine and haloperidol were chosen to encompass preferential pre- as well as postsynaptic agonist/antagonist activity [14]. In addition, we included (−)3-PPP since this drug has been shown to have selectivity for central presynaptic DA autoreceptors [5]. There was no evidence, however, that either apomorphine or haloperidol produced any effects due to presynaptic agonist or antagonist actions at DA receptors, respectively. The lowest dose used of either drug has in other contexts been shown to produce effects, which probably are due to actions at the autoreceptor [1, 3, 14]. Considering the fact that (−)3-PPP was also devoid of effects, these results indicate that a presynaptic modulation of dopaminergic neurotransmission does not influence the sexual behavior of the intact male rat.

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REFERENCES

1. Ahlenius, S. and J. Engel. Effects of small doses of haloperidol on timing behavior. *J Pharm Pharmacol* **23**: 301–302, 1971.
2. 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 Pharmacol* **7**: 283–288, 1969.
3. Di Chiara, G., M. L. Porceddu, L. Vargiu, A. Argiolas and G. L. Gessa. Evidence for dopamine receptors mediating sedation in the mouse brain. *Nature* **264**: 564–567, 1976.
4. Gray, G. D., H. N. Davis and D. A. Dewsbury. Effects of *L*-DOPA on the heterosexual copulatory behavior of male rats. *Eur J Pharmacol* **27**: 367–370, 1974.
5. Hjorth, S., A. Carlsson, D. Clark, K. Svensson, M. Lindberg, H. Wikström, D. Sanchez, P. Lindberg, U. Hacksell, L.-E. Arvidsson, A. Johansson and J. L. G. Nilsson. Central dopamine receptor agonist and antagonist actions of the enantiomers of 3-PPP. *Psychopharmacology (Berlin)* **81**: 89–99, 1983.
6. Hjorth, S., A. Carlsson, H. Wikström, P. Lindberg, D. Sanchez, U. Hacksell, L.-E. Arvidsson, U. Svensson and J. L. G. Nilsson. 3-PPP, a new centrally acting DA-receptor agonist with selectivity for autoreceptors. *Life Sci* **28**: 1225–1238, 1981.

7. Hyyppä, M., P. Lehtinen and U. K. Rinne. Effect of *L*-DOPA on hypothalamic, pineal and striatal monoamines and on the sexual behaviour of the rat. *Brain Res* **30:** 265–272, 1971.
8. Larsson, K. *Conditioning and Sexual Behavior in the Male Albino Rat*. Stockholm: Almqvist and Wiksell, 1956, pp. 117–144.
9. Larsson, K. and S. Ahlenius. Masculine sexual behavior and brain monoamines. In: *Psychopharmacology of Sexual Disorders*, edited by M. Segal. London: John Libbey and Co, 1984, in press.
10. Malmnäs, C-O. The significance of dopamine, versus other catecholamines, for L-Dopa induced facilitation of sexual behavior in the castrated male rat. *Pharmacol Biochem Behav* **4:** 521–526, 1976.
11. Paglietti, E., B. Pellegrini Quarantotti, G. Mereu and G. L. Gessa. Apomorphine and L-Dopa lower ejaculation threshold in the male rat. *Physiol Behav* **20:** 559–562, 1978.
12. Randrup, A. and I. Munkvad. Biochemical anatomical and psychological amphetamines. In: *Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970, pp. 695–713.
13. Siegel, S. *Nonparametric Statistics for the Behavioral Sciences*. New York: McGraw-Hill, 1956.
14. Strömbom, U. On the functional role of pre- and postsynaptic catecholamine receptors in brain. *Acta Physiol Scand* Suppl **431:** 1–43, 1975.
15. Tagliamonte, A., W. Fratta, M. del Fiacco and G. L. Gessa. Possible stimulatory role of brain dopamine in the copulatory behavior of male rats. *Pharmacol Biochem Behav* **2:** 257–260, 1974.