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Effects of selective dopamine D_1 and D_2 antagonists on male rat sexual behavior [1]

S. Ahlenius [2] and K. Larsson [3]

Department of Psychology, University of Göteborg, POB 14 158, S-400 20 Göteborg (Sweden), and Department of Neuropharmacology, Astra Research Centre, S-151 85 Södertälje (Sweden)
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Summary. The effects of selective dopamine (DA) D_1 and D_2 antagonists on male rat sexual behavior were investigated. The D_1 antagonist (+)SCH-23390, 25–100 μg kg^{-1} s.c. – 20 min, and the D_2 antagonist raclopride, 0.1–1.6 mg kg^{-1} s.c., – 20 min, decreased both the number of mounts and intromissions preceding ejaculation. No statistically significant effects in the time up to ejaculation or in the time up to the first intromission were noted, whereas both compounds produced a statistically significant increase in the post-ejaculatory interval. The effect can generally be characterized as psychomotor inhibition, and no evidence was obtained for a specific role of DA D_1 or D_2 receptors in the mediation of male rat sexual behavior.
Key words. Male rat; sexual behavior; dopamine.

It is well known that the administration of drugs that enhance brain dopamine (DA) neurotransmission, like apomorphine, N-*n*-propyl-norapomorphine, *d*-amphetamine or *L*-DOPA, results in a facilitation of male rat sexual behavior, as evidenced by a decrease in the number of intromissions preceding ejaculation and in the time up to ejaculation [4]. These effects, generally small, are probably due to psychomotor stimulation; an inhibition of brain DA neurotransmission, as produced by DA receptor blocking agents, monoamine depleting drugs like tetrabenazine or reserpine, or by lesions of ascending dopaminergic pathways, does not markedly effect the performance of male rat sexual behavior, except in the higher dose range, where the number of animals initiating copulation is diminished [4–7]. Brain DA neurotransmission is mediated via two types of DA receptors: D_1, positively coupled to adenylate cyclase formation, and D_2, not (or negatively) coupled to adenylate cyclase formation [8]. In recent years a number of selective agonists and antagonists which have their effect at these two types of brain DA receptors have been developed.

The results described above, on the role of brain DA in the mediation of male rat sexual behavior, are based on the use of treatments with poor selectivity for the DA D_1 and D_2 receptor subtypes. Therefore in the present experiments we investigated the effects of selective inhibition of brain DA D_1 and D_2 receptors by use of the selective antagonists (+)SCH-23390 [9] and raclopride [10], respectively.

Materials and methods

Animals. Adult male (350–400 g) and female (240–260 g) Wistar rats were used (Möllegaard, Vejle, Denmark). The animals were housed, 5 per cage, under controlled conditions of temperature, humidity and light-dark cycle (12:12 h, lights off 10.00 h). Food (R3, Ewos, Södertälje) and tap water was available ad libitum in the home cage. The animals arrived in the laboratory at least 2 weeks before the experiments to be described below.

Drugs. Raclopride tartrate (Astra, Södertälje, Sweden) and (+)SCH-23390 HCl (RBI, Natick, MA) were used. Both drugs were dissolved in physiological saline and injected subcutaneously in a constant volume of 2 ml kg^{-1}. Doses refer to the form given above.

Behavioral observations. Male rats were presented with a female brought into estrous by sequential treatment with estradiol benzoate (12.5 μg rat^{-1}, i.m. in sesame oil, – 54 h), and progesterone (0.5 mg rat^{-1}, i.m. in sesame oil, – 6 h). The following items of the male rat sexual behavior were recorded: Mounts (M): number of mounts without penile intromission; Intromissions (I): number of mounts with penile intromission; Intromission latency (IL): time from the presentation of the female to the first intromission; Ejaculation Latency (EL): time from the first intromission until ejaculation; Postejaculatory interval (PEI): time from ejaculation until the following intromission. The observations were terminated at the first intromission following ejaculation, but also if the IL was

≥ 15 min or if the EL was ≥ 30 min. The animals were observed in circular perspex boxes (∅ = 500 mm) lit by a 15 W bulb above the arena, and the observations were performed between 13.00 and 16.00 h. The animals were given at least four pre-tests, and only sexually active animals were used in the experiments.

Experimental design and statistics: A change-over design was used, in which the animals served as their own controls[11], and statistical evaluation was performed by means of the Wilcoxon matched-pairs signed-ranks test[12].

Results

Effects of raclopride. Administration of raclopride, 0.1–1.6 mg kg^{-1} s.c., had no statistically significant effects on IL. The median IL values were 0.2, 0.1, and 0.4 min in the animals treated with 0, 0.1, 0.4 and 1.6 mg kg^{-1}, respectively. There was a statistically significant reduction in the number of M and I before ejaculation, as shown in figure 1. Furthermore, there was a statistically significant increase in the PEI. No statistically significant changes were noted in the EL. It should be noted, however, that a number of the animals given the highest dose of raclopride (1.6 mg kg^{-1}) failed to initiate copulation, and the statistical comparison in this case is based on 11 of the 16 animals used in this experiment.

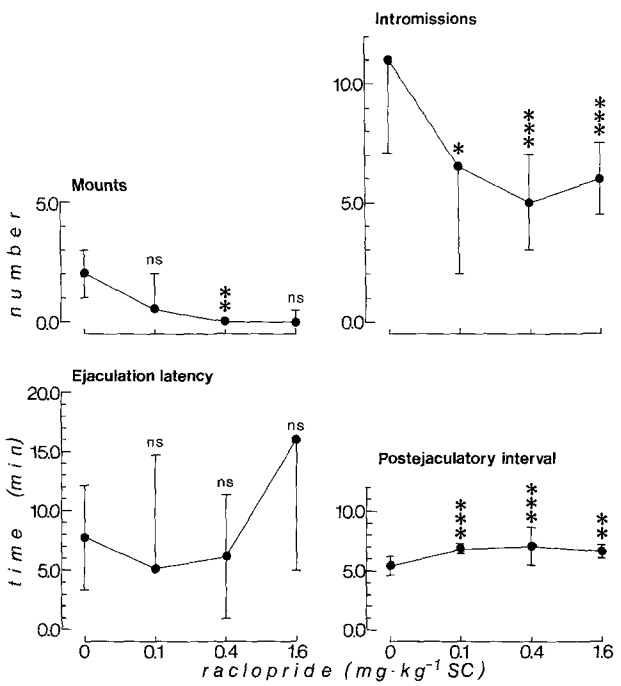

Figure 1. Effects of raclopride on male rat sexual behavior. Raclopride was administered, as indicated in the figure, 20 min before observations. Results are presented as medians ± semi-interquartile range, based on the performance of 16 rats. The animals served as their own controls in the experiments, which used a change-over design. Statistical comparison with saline-injected controls was performed by means of Wilcoxon matched-pairs signed-ranks test, as indicated in the figure. $^{ns}p > 0.05$, $^{*}p < 0.05$, $^{**}p < 0.02$, $^{***}p < 0.01$.

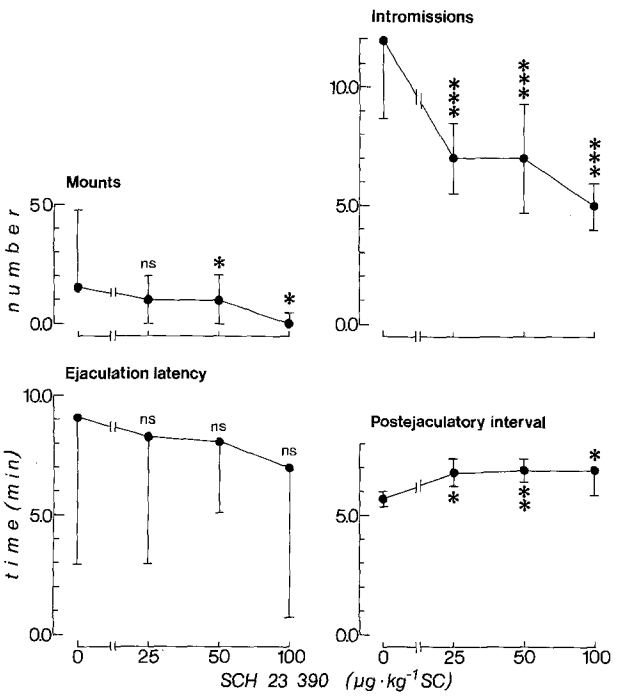

Figure 2. Effects of (+)SCH-23390 on male rat sexual behavior. (+)SCH-23390 was administered, as indicated in the figure, 20 min before observations. Results are presented as medians ± semi-interquartile range, based on the performance of 18 rats. The animals served as their own controls in experiments using a change-over design, and statistical comparisons with saline-injected controls was performed by means of Wilcoxon matched-pairs signed-ranks test, as indicated in the figure. $^{ns}p > 0.05$, $^{*}p < 0.05$, $^{**}p < 0.02$, $^{***}p < 0.01$.

Effects of (+)SCH-23390. The median IL was 0.1 min for all doses, 25–100 µg kg^{-1} s.c., of (+)SCH-23390. The numbers of M and I were statistically significantly reduced by (+)SCH-23390. No statistically significant effects were noted on the EL, whereas the PEI was increased at all doses of (+)SCH-23390, as shown in figure 2.

Discussion

There were no qualitative differences in the effects produced by the selective DA D_1 and D_2 receptor blocking agents (+)SCH-23390 and raclopride, respectively, on the performance of male rat sexual behavior. In agreement with results from previous experiments where the unselective DA receptor blocking agent haloperidol has been used, there was a decrease in the number of intromissions preceding ejaculation[13,14]. In the present experiments, there was also a decrease in mount frequency. The ejaculation latency was unchanged and the postejaculatory interval was slightly, but consistently, increased by the (+)SCH-23390 or the raclopride treatment. These observations are in good agreement with results obtained in animals with lesions of ascending dopaminergic pathways[6]. Thus, although higher doses produced an increasing number of failures to initiate copulation, there was little evidence for an inhibition of the

performance as such, except for an increase in the inter-intromission or inter-mount time.

A blockade of brain DA receptors produces a dose-dependent increase in Parkinson-like extra-pyramidal motor effects[15]. This applies to haloperidol, as well as to raclopride or (+)SCH-23390, in approximately the dose-range used here[16-18]. A possible explanation for the fact that a blockade of DA receptors produces a reduction in intromission frequency, an effect also seen after DA receptor stimulation (see introduction), is that developing extrapyramidal effects produce pharmacologically induced 'enforced intervals'. Enforced intervals between intromissions, by physically separating the male from the female during copulation, have previously been shown to reduce the number of intromissions without affecting time to ejaculation[19]. The effect is apparently not related to a specific mechanism, since the full DA agonists (+)3-PPP and apomorphine produce qualitatively the same effect, a decrease in intromission frequency, as the partial DA agonist (−)3-PPP, which in turn shares this effect with the DA receptor blocking agent haloperidol[13].

Under the present experimental conditions, with sexually highly experienced male rats, and a relatively limited mating arena where the male and the receptive stimulus female are immediately brought into close contact, there was no statistically significant decrease in the latency up to initiation of copulation. It should also be noted that the animals which did not initiate copulation within 15 min were excluded from the calculations (cf. methods). However, an increase in intromission latency brought about by the administration of a number of DA receptor blocking agents was recently reported by Pfaus and Phillips[14], in support of the contention that the major effect of such intervention is psychomotor inhibition of behavior. It is probable that the effects produced by drugs causing stimulation of brain DA receptors, like apomorphine or *d*-amphetamine, are also to a large extent of a psychomotor nature, rather than specific effects on the sexual behavior as such[4]. However, the fact that no difference was found between the effects produced by the selective DA D_1 and D_2 receptor blocking agents in the present experiments does not exclude the possibility of more specific effects by selective stimulation of DA D_1 and D_2 receptors.

In the report by Pfaus and Phillips[14] only the so-called typical antipsychotics, haloperidol and pimozide, produced a decrease in intromission frequency and an increase in post-ejaculatory interval, whereas no effects, except for the increased intromission latency, were observed after administration of the atypical antipsychotics clozapine and sulpiride. According to this interpretation, both raclopride and (+)SCH-23390 behaved as typical antipsychotic compounds in the present study. It should be noted, however, that pharmacological properties other than the dopaminergic effects may explain the different profiles of clozapine and sulpiride. For example, sulpiride penetrates poorly across the blood-brain barrier and clozapine has anticholinergic and α-blocking properties. These properties alone may directly or indirectly cause inhibition of the display of sexual behavior before effects on central dopaminergic neurotransmission can be expressed.

In conclusion: The selective DA D_1 and D_2 receptor antagonists (+)SCH-23390 and raclopride both decreased the intromission frequency and increased the post-ejaculatory interval in male rats. The time up to ejaculation was not altered. Thus, no inhibition of the sexual behavior was noted, other than an increased post-ejaculatory interval, up to doses which inhibited the performance altogether. In view of these observations, it is concluded that a blockade of brain DA D_1 or D_2 receptors primarily affects the performance of male rat sexual behavior indirectly via psychomotor inhibition.

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2 Address for reprint requests: Department of Neuropharmacology, Astra Research Centre, S-151 85 Södertälje, Sweden.
3 Department of Psychology.

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