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BRIEF COMMUNICATION

Effects of the Dopamine D_3 Receptor Ligand 7-OH-DPAT on Male Rat Ejaculatory Behavior

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AHLENIUS, S. AND K. LARSSON. *Effects of the dopamine D_3 receptor ligand 7-OH-DPAT on male rat ejaculatory behavior.* PHARMACOL BIOCHEM BEHAV 51(2/3) 545–547, 1995.—As previously shown, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) produces a marked and highly characteristic facilitation of male rat ejaculatory behavior, and this effect is not sensitive to dopamine (DA) receptor antagonists of the D_1 or D_2 receptor families. The structural congener 7-OH-DPAT, primarily characterized as a DA D_3 receptor selective ligand, produced a facilitation of male rat ejaculatory behavior, as evidenced by a dose-dependent decrease in the number of intromissions preceding ejaculation and in time to ejaculation. These effects could be antagonized by pretreatment with the DA D_2/D_3 receptor antagonist, raclopride. Thus, 7-OH-DPAT-induced effects on male rat ejaculatory behavior can be pharmacologically differentiated from effects produced by 8-OH-DPAT.

Dopamine receptors 7-OH-DPAT Sexual behavior Male rat

THE 5-HYDROXYTRYPTAMINE (5-HT) 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (9,14) has specific effects on male rat ejaculatory behavior. Thus, 8-OH-DPAT produces a marked reduction in the number of penile intromissions preceding ejaculation and in the time needed to reach ejaculation [see (5)]. These specific effects are shared by some ergot-related compounds such as lisuride, pergolide, and quinpirole. Lisuride has 5-HT receptor agonist properties (10) and displays high affinity for the 5-HT_{1A} receptor site (11), but no such effects have been described for pergolide or quinpirole, commonly regarded as dopamine (DA) D_2 receptor selective agents [e.g., (7)]. The facilitation of male rat ejaculatory behavior produced by 8-OH-DPAT, lisuride, or quinpirole is not sensitive to treatment with DA D_2-preferring receptor antagonists such as haloperidol or raclopride (2,5).

Recently, a new DA D_3 receptor site was described for which quinpirole and pergolide display high affinity (18). Interestingly, the DA receptor agonist bromocriptine, which according to Sokoloff et al. (18) has little selectivity for the new DA D_3 affinity site, displayed no, or only slight, effects on male rat ejaculatory behavior in comparison with effects produced by quinpirole or pergolide (1,2). Furthermore, an aminotetralin closely related to 8-OH-DPAT, 7-OH-DPAT, has recently been described as a prototype DA D_3 receptor ligand with about 70-fold selectivity over DA D_2 receptors (12). 8-OH-DPAT itself has some, albeit weak, affinity for the DA D_3 receptor (12); and this receptor site cannot be excluded as a common denominator for effects of 8-OH-DPAT and these ergot-related compounds on male rat ejaculatory behavior. It should also be noted that in vivo, with increasing doses 7-OH-DPAT produces decreased brain 5-HT synthesis (6), an effect characteristic for 5-HT_{1A} receptor agonists [e.g., (9)]. In view of these considerations, the present study had two objectives: first, to observe possible effects of 7-OH-DPAT on male rat ejaculatory behavior and, second, to examine to what extent effects thus induced would be sensitive to raclopride treatment.

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METHOD

Adult male and female Wistar rats were used (Möllegaard, Vejle, Denmark). The animals arrived in the laboratory at least 10 days before use in experiments and were housed, five per cage, under controlled conditions of temperature (approximately 21°C), relative humidity (55–65%), and 12 L : 12 D cycle (lights off 1000 h). Food (R36; Ewos, Södertälje, Sweden) and tapwater were available ad lib in the home cage.

(±)-7-hydroxy-2-(di-*n*-propylamino)tetralin HBr, 328.3 mol. wt. (RBI, Natick, MA) and raclopride tartrate, 497.4 mol. wt. (Astra, Södertälje, Sweden) were dissolved in physiologic saline. The injection route was SC and the volume of injection was kept constant at 2 ml/kg.

The males were presented with a female brought into estrous by sequential treatment with β-estradiol-3-benzoate (Sigma, St Louis, MO) (12.5 μg/animal, -54h) and progesterone (Sigma) (0.5 mg/animal, -6h). The hormones were dissolved in sesame oil and injected SC in a volume of approximately 0.3 ml/kg. The following items of male rat sexual behavior were observed: 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). All males in the present series of experiments ejaculated, and the observations were terminated when a second copulatory series was initiated by an intromission. The animals were observed in circular Perspex boxes (Ø 500 mm), lit by a 15-W bulb above the arena. Observations were performed between 1300 and 1600 h. The animals included in the experiment had ejaculated in at least three of four pretests.

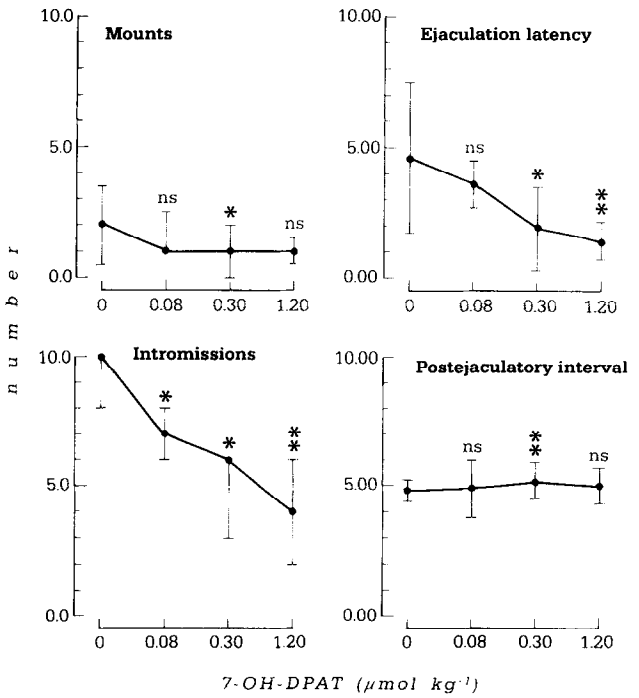

FIG. 1. Effects of 7-OH-DPAT on male rat sexual behavior. 7-OH-DPAT (or the saline vehicle) was administered SC, 20 min before the observations started. The medians ± semi-interquartile range are shown. The animals (n = 11) served as their own controls in a changeover design (13). Statistical comparisons with saline-treated controls, as indicated in the figure, were performed by means of the Wilcoxon matched-pairs signed-ranks t-test (17). ns, $p > 0.05$; *$p < 0.05$; **$p < 0.01$.

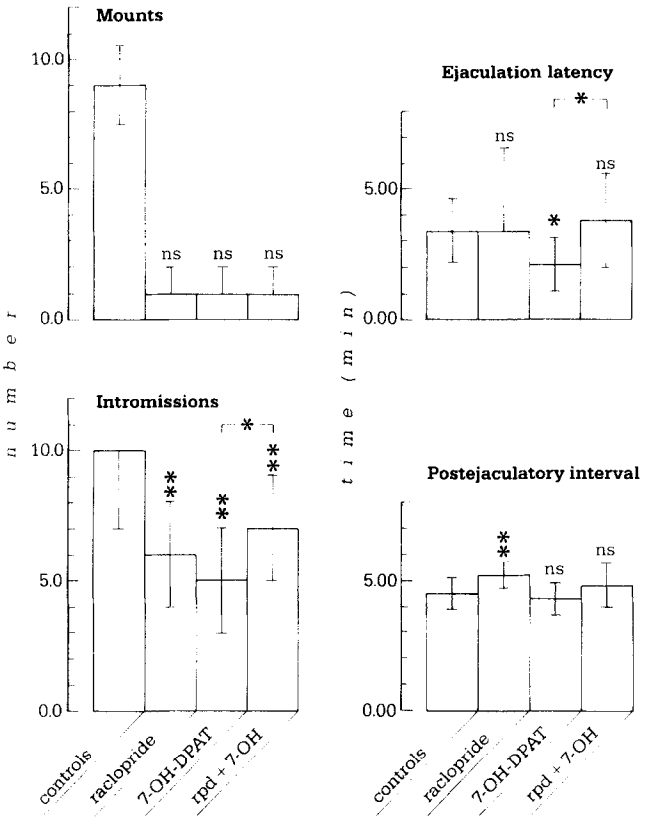

FIG. 2. Antagonism by raclopride administration of 7-OH-DPAT-induced facilitation of male rat ejaculatory behavior. Raclopride (0.5 μmol/kg, SC) was administered 30 min, and 7-OH-DPAT (0.3 μmol/kg, SC) 20 min, before observations started. The medians ± semi-interquartile range are shown, based on the performance of 15 rats. For further details, see Fig. 1. ns, $p > 0.05$; *$p < 0.05$; **$p < 0.01$.

RESULTS

As shown in Fig. 1, 7-OH-DPAT produced a dose-dependent decrease in the number of intromissions preceding ejaculation and in the ejaculation latency. There were smaller and variable effects on the number of mounts and the postejaculatory interval. The effects of 7-OH-DPAT, 0.3 μmol/kg, on the male ejaculatory behavior was fully (EL) or partially (I) antagonized by pretreatment with raclopride 0.5 μmol/kg (Fig. 2). In agreement with previous observations, raclopride alone produced a significant decrease in the number of intromissions preceding ejaculation and a slight but statistically significant increase in the postejaculatory interval (4).

DISCUSSION

As previously shown for 8-OH-DPAT, 7-OH-DPAT administration facilitated the male rat ejaculatory behavior. In contrast to effects produced by 8-OH-DPAT, however, the 7-OH-DPAT-induced facilitation of ejaculatory behavior was sensitive to pretreatment with the DA D_2/D_3 receptor antagonist, raclopride [cf. (5)]. Thus, by the use of raclopride, the

effects of 7-OH-DPAT and 8-OH-DPAT on in copula male rat ejaculatory behavior can be pharmacologically differentiated. In addition, there appears to be a qualitative difference in the effects produced by 8-OH-DPAT and 7-OH-DPAT. Thus, in the 7-OH-DPAT-treated rats, we never observed the markedly reduced number of intromissions characteristic for 8-OH-DPAT (some animals ejaculating on the very first intromission), and in this regard 7-OH-DPAT behaves as a DA D_2 receptor agonist [see (5)].

Although raclopride has preferential affinity for the DA D_2 receptor, it cannot be excluded that affinity for the DA D_3 receptor site also contributes to the antagonism of 7-OH-DPAT-induced effects. Furthermore, there is recent evidence by use of 7-OH-DPAT for functional effects specifically mediated via DA D_3 receptors (15). Taken together with previous results from this laboratory, this possibility serves to strengthen the dissociation between effects produced by 8-OH-DPAT, not related to effects at DA receptors of the D_1 or D_2 receptor families and effects by 7-OH-DPAT, 5-OH-DPAT, and other DA receptor agonists [e.g., (5,8)]. In fact, considering qualitative aspects of behavioral change and sensitivity to a range of DA antagonists of the DA D_2 receptor family, there is a strong possibility that stimulation of DA D_2 and D_3 receptors produce an indistinguishable pattern of effects on male rat sexual behavior. Needless to say, a conclusive separation of effects mediated via DA D_2 and D_3 receptors must await the further development of selective pharmacologic tools.

Raclopride and haloperidol, which both display preferential affinity for the DA D_2 over the DA D_3 receptor site (16), produce the same pattern of effects on male rat sexual behavior. Thus, the administration of either compound results in a moderate, dose-dependent, decrease in the number of intromissions and a slight, dose-independent increase in the post-ejaculatory interval, whereas the ejaculation latency is not significantly affected in doses as high as 3.2 and 0.8 μmol/kg, respectively (3,4). The dose of raclopride (0.5 μmol/kg) in the present study was based on effects in those and other studies from this laboratory (19). Despite the expected slight decrease in number of intromissions after the raclopride treatment, this dose significantly antagonized the suppression induced by 7-OH-DPAT. Naturally, this antagonism could not be expected to exceed the effects produced by raclopride alone.

In general agreement with effects previously reported for 8-OH-DPAT, the administration of 7-OH-DPAT resulted in a facilitation of male rat ejaculatory behavior. In contrast to 8-OH-DPAT [see (5)], however, effects produced by 7-OH-DPAT were sensitive to raclopride treatment. The present observations suggest that the effects of 7-OH-DPAT on male rat ejaculatory behavior are mediated via agonist actions at DA receptors of the DA D_2 receptor family, primarily DA D_2 receptors.

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