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Effects of Stereoselective 5-HT_{1A} Agonists on Male Rat Sexual Behavior

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AHLENIUS, S., K. LARSSON AND L.-E. ARVIDSSON. *Effects of stereoselective 5-HT_{1A} agonists on male rat sexual behavior.* PHARMACOL BIOCHEM BEHAV **33**(3) 691–695, 1989.—The effects on male rat sexual behavior of some new stereoselective 5-HT agonists, related to 8-OH-DPAT, are presented. It was found that (+)*cis*-8-hydroxy-1-methyl-2-(di-*n*-propylamino) tetralin (8-OH-MeDPAT), as well as (−)*trans*-2-(2-hydroxyphenyl)-N,N-di-*n*-propylcyclopropylamine (2-OH-DCPA), and its 3-hydroxyphenyl analog (3-OH-DCPA), stereoselectively facilitated the male rat sexual behavior, as evidenced by a decrease in the number of intromissions preceding ejaculation, and a shortening of the ejaculation latency. For the former two compounds, studied in further detail, the potency and efficacy appear to be of the same magnitude as previously found for 8-OH-DPAT. The results demonstrate specific 5-HT receptor involvement in the mediation of male rat sexual behavior.

Male sexual behavior 5-HT agonists Stereoselectivity Rat

THE 5-hydroxytryptamine (5-HT) agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (10,21), has previously been shown to produce a marked facilitation of the male rat sexual behavior (6). This behavioral facilitation, characterized by a decrease in number of intromission and in time to ejaculation, is specific for 8-OH-DPAT, and some related ergot compounds [see (4)]. The precise mechanism of action of 8-OH-DPAT is unknown. Results from initial pharmacological and biochemical experiments showed that 8-OH-DPAT both decreases 5-HT synthesis, and produces signs of the "5-HT syndrome" in reserpine-treated rats, indicating that the compound is a centrally active, direct acting, 5-HT receptor agonist (21). Furthermore, results from receptor binding experiments show interactions at a particular receptor site, tentatively labelled 5-HT_{1A} (26).

In a recent series of experiments, Arvidsson *et al.* (11–13) examined structure-activity relationships for N-substituted 8-hydroxy-2-aminotetralins, a group of agents to which 8-OH-DPAT belongs, and for monophenolic N,N-dialkylated *trans*-2-phenylcycloproylamines. In both these groups of agents, highly stereoselective effects were found on brain 5-HT synthesis. 8-OH-DPAT itself displays a poor stereoselectivity in its effects on brain 5-HT synthesis (9,10).

Stereoselective agonists (or antagonists) provide indispensible tools for proper receptor identification. The facilitation of male rat sexual behavior is specific for 8-OH-DPAT, and related compounds, and this in turn indicates specific receptor interactions. The aim of the present study was to investigate if the stereoselectivity in biochemical effects, as demonstrated for these new serotonergic compounds, also holds for effects on male rat sexual behavior.

METHOD

Animals

Adult male and female Wistar rats (Möllegaard, Vejle, Denmark) were used. The age of the animals was in the range of 2–4 months. They were housed by sex, 3–5 per cage, under conditions of controlled temperature and relative humidity, with food (E3, Ewos, Södertälje, Sweden) and tap water available ad lib. The light-dark cycle (12:12 hr) was artificially maintained (lights off 10:00 hr).

Behavioral Observations

Mating tests were begun 2 hr after the lights went off. The males were presented with a female brought into estrous by sequential treatment with estradiol benzoate (12.5 $\mu g \cdot animal^{-1}$), followed 42 hr later by progesterone (0.5 $mg \cdot animal^{-1}$), 6 hr

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before testing. The following components of the male rat sexual behavior were recorded: Intromission latency (IL), time from the entrance of the female into the observation cage to the first intromission; Mount frequency (M), number of mounts, without penile intromission, before ejaculation; Intromission frequency (I), number of mounts with penile intromission; Ejaculation latency (EL), time from the first intromission until ejaculation; Postejaculatory interval (PEI), time from ejaculation to the following intromission. The test was ended when one of the following conditions was fulfilled: 1) 15 min after the presentation of the female to the male, if at that time no intromission had occurred, 2) 15 min after ejaculation, if no further intromission had occurred, or 3) at the time of the first intromission after ejaculation.

Drugs

The (+) and (−) enantiomers of the following compounds were used: *cis*-8-Hydroxy-1-methyl-2-(di-*n*-propylamino)tetralin HCl (8-OH-MeDPAT), *trans*-2-(2-hydroxyphenyl)-N,N-di-*n*-propylcyclopropylamine HBr (2-OH-DPCA), and *trans*-2-(3-hydroxyphenyl)-N,N-di-*n*-propylcyclopropylamine HBr (3-OH-DPCA). In addition, racemic *trans*-2-(4-hydroxyphenyl)-N,N-di-*n*-propylcyclopropylamine HBr (4-OH-DPCA) was tested. The compounds were synthesized at The Department of Organic Pharmaceutical Chemistry, University of Uppsala, Uppsala, Sweden, and at The Unit of Organic Chemistry, Department of Pharmacology, University of Göteborg, Sweden. Doses were calculated on the salts given above. The drugs were dissolved in 0.9% NaCl and injected subcutaneously in a volume of 2 $ml \cdot kg^{-1}$.

Experimental Procedures and Statistics

Before the experiments started, the males were observed twice a week for 2 weeks, i.e., tests were separated by 2–3 days. Only animals which displayed sexual behavior, as evidenced by ejaculation in at least 3 of these pretests, were included in the experiment. The animals were observed on the same time schedule in the respective experiments, and served as their own controls in a change-over design. As an example, three treatments a,b and c are given to rat No. 1 abc, to rat No. 2 bca, and to rat No. 3 cab, etc. [see (24)]. Statistical evaluation was performed by means of appropriate nonparametric methods as indicated in figure legends (28).

RESULTS

Effects of cis*-8-OH-MeDPAT Enantiomers on Male Rat Sexual Behavior*

The (+) enantiomer of 8-OH-MeDPAT produced a statistically significant decrease in number of mounts, and in time to ejaculation (Fig. 1). There were no statistically significant effects on the number of intromissions, or on the postejaculatory interval. The (−) enantiomer did not produce any changes in the male rat sexual behavior, as measured here.

In order to further study the potency and efficacy of the (+) enantiomer, a separate group of animals was given lower doses of this compound. As seen in Fig. 4, the number of intromissions was significantly decreased by 0.13–0.5 $mg \cdot kg^{-1}$, and the ejaculation latency was significantly decreased in the dose range of 0.03–0.5 $mg \cdot kg^{-1}$. There were no statistically significant effects on the number of mounts or on the postejaculatory interval (data not shown).

Effects of N,N-Dialkylated Monophenolic trans*-2-Phenylcyclopropylamines on Male Rat Sexual Behavior*

The (−) enantiomer of both 2-OH- and 3-OH-phenyl-N,N-di-*n*-propylcyclopropylamine produced a statistically significant decrease in the number of intromissions, and in the ejaculation latency. In addition, the 3-OH compound also produced a statistically significant decrease in the number of mounts, and (−) 2-OH-DPCA a statistically significant decrease in the postejaculatory interval (Figs. 2 and 3). The (+) enantiomer of either compound was inactive in the present test system. In this series of experiments we also tested racemic 4-OH-DPCA in a dose of 2 $mg \cdot kg^{-1}$, which was found to be inactive (data not shown).

Further evaluation of the dose-effect curve of (−)2-OH-DPCA indicated that there was a dose-dependent decrease in the number of intromissions, and in time to ejaculation (Fig. 4). Statistically significant effects were obtained from 0.13 $mg \cdot kg^{-1}$ (EL) and 0.5 $mg \cdot kg^{-1}$ (I). In addition, there was a statistically significant reduction in the postejaculatory interval by the administration of 0.13 and 0.5 $mg \cdot kg^{-1}$ ($p<0.01$ in comparison with the saline control condition) (data not shown). No statistically significant effects were noted in the number of mounts.

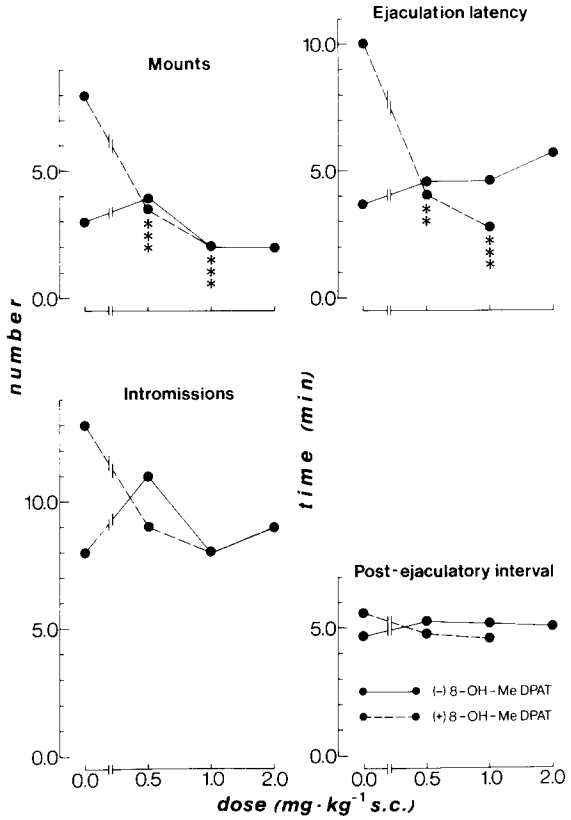

FIG. 1. Effects of *cis*-8-OH-1-methyl-2-(di-*n*-propylamino)tetralin enantiomers on male rat sexual behavior. The respective enantiomer was injected SC 20 min before the observations started. The animals in the respective experiment, (+) (n = 17) and (−) (n = 15), served as their own controls in a change-over design. Results are presented as medians and statistical evaluation was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test for individual comparisons with the saline control condition. (+)8-OH-MeDPAT. Mounts: $\chi^2(2) = 12.12$, $p<0.01$; Intromissions: $\chi^2(2) = 3.29$, n.s.; Ejaculation latency: $\chi^2(2) = 6.50$, $p<0.05$; Postejaculatory interval: $\chi^2(2) = 3.16$, n.s. (−)8-OH-MeDPAT. All χ^2 values were found to be below the critical level for statistical significance $\chi^2(2)<5.99$. n.s.$p>0.05$, *$p<0.05$, **$p<0.025$, ***$p<0.01$.

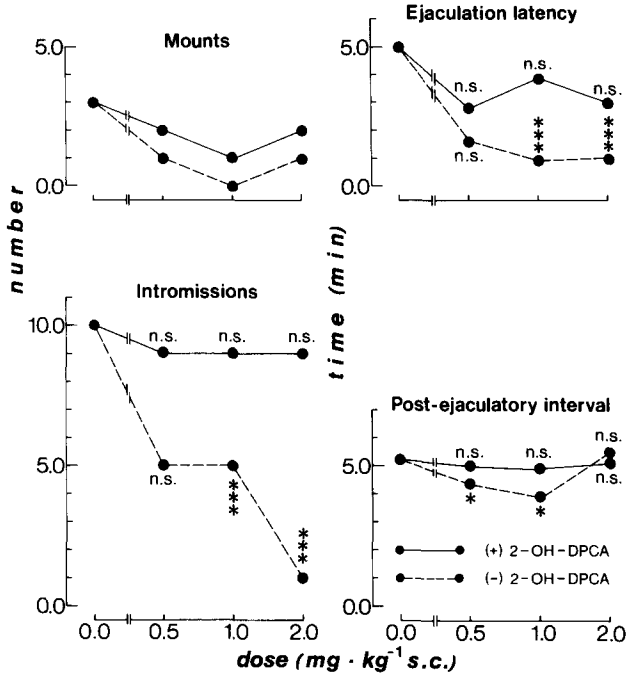

FIG. 2. Effects of *trans*-2-(2-hydroxyphenyl)-N,N-di-*n*-propylcyclopropylamine enantiomers on male rat sexual behavior. The two enantiomers were administered SC 20 min before the observations started. The animals (n = 15) served as their own controls in a change-over design. Results are presented as medians, and statistical evaluation was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test for comparisons with the saline control condition. Mounts: $\chi^2(6) = 7.74$, n.s.; Intromissions: $\chi^2(6) = 38.21$, $p<0.001$; Ejaculation latency: $\chi^2(6) = 35.42$, $p<0.001$; Postejaculatory interval: $\chi^2(6) = 12.66$, $p<0.05$. n.s.$p>0.05$, *$p<0.05$, ***$p<0.01$.

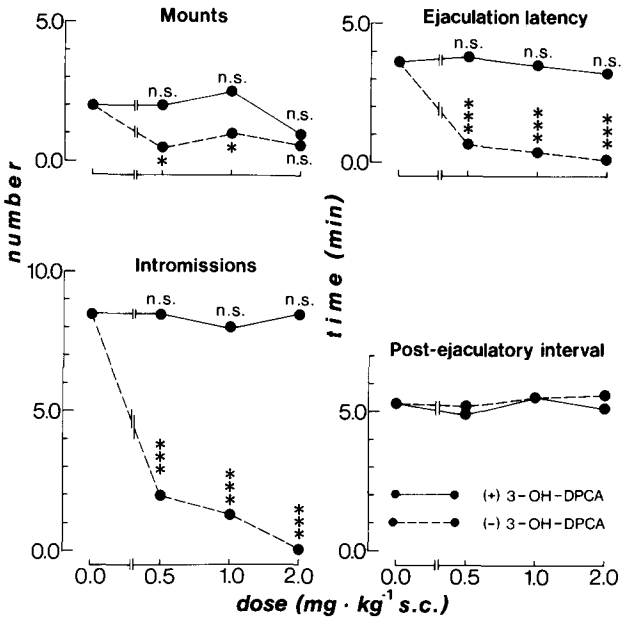

FIG. 3. Effects of *trans*-2-(3-hydroxyphenyl)-N,N-di-*n*-propylcyclopropylamine enantiomers on male rat sexual behavior. The two enantiomers were administered SC 20 min before the observations started. The animals (n = 18) served as their own controls in a change-over design. Results are presented as medians, and statistical evaluation was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test for comparisons with the saline control condition. Mounts: $\chi^2(6) = 14.61$, $p<0.05$; Intromissions: $\chi^2(6) = 60.42$, $p<0.001$; Ejaculation latency: $\chi^2(6) = 56.94$, $p<0.001$; Postejaculatory interval: $\chi^2(6) = 7.17$, n.s. n.s.$p>0.05$, *$p<0.05$, ***$p<0.01$.

DISCUSSION

In our original report on the effects of 8-OH-DPAT on male rat sexual behavior, we only studied the effects of racemic 8-OH-DPAT (6), since biochemical experiments indicated that the compound possessed poor stereoselectivity (9,10). Our behavioral experiments with the enantiomers of the related compound 8-MeO-DPAT, were in line with this finding (6). The resolution of 8-OH-MeDPAT, 2-OH-DPCA and 3-OH-DPCA into their respective enantiomers, however, resulted in compounds with a high degree of stereoselectivity in their effects on brain 5-HT synthesis (11,12). The present results demonstrate that this also holds true for their effects on the male rat sexual behavior. The (+) enantiomer of 8-OH-MeDPAT, and the (−) enantiomers of 2- and 3-OH-DPCA, were all highly efficacious, whereas their steric antipod, as well as racemic 4-OH-DPCA were inactive. For two of these compounds, (+)8-OH-MeDPAT and 2-OH-DPCA, the potency and efficacy were studied in some detail and found to be comparable to what has been described for 8-OH-DPAT. For further discussion on structural requirements for 5-HT receptor affinity see (13).

In standard pharmacological models of 5-HT receptor interactions [see (7,22)], 8-OH-DPAT behaves as a 5-HT receptor agonist (21), but in a few situations 8-OH-DPAT produces effects opposite to what would be expected by a 5-HT agonist. Thus, manipulations with the availability of 5-HT in the CNS consistently show that a decrease is associated with a facilitation, and an increase with an inhibition, of male rat sexual behavior [see (23,25)]. To account for the facilitation of the sexual behavior produced by 8-OH-DPAT we postulated a new type of 5-HT agonist, (A) activating a subgroup of postsynaptic receptors, (B) stimulating 5-HT autoreceptors, or (C) blocking 5-HT receptors (6). These, not mutually exclusive, possibilities have been investigated in turn, and resulted in the suggestion that 8-OH-DPAT is a partial 5-HT agonist, as detailed elsewhere [see (4)]. Basically, we found that 5-HTP-induced inhibition of male rat sexual behavior was antagonized by 8-OH-DPAT in a dose-dependent manner, and receptor blocking properties of 8-OH-DPAT were thus disclosed in this situation. Together with other observations, as discussed above, this demonstrates that 8-OH-DPAT, like lisuride, is a mixed agonist/antagonist at central 5-HT receptors. This explanation may apply also to other situations where 8-OH-DPAT produces effects not expected by a 5-HT agonist. These other functions include feeding (16), and body temperature (1, 18, 20). It would also be very interesting to know if these functions are stereoselectively affected by the new 5-HT agonists now available.

It should be noted that some ergot compounds, structurally related to 8-OH-DPAT, like lisuride and quinpirole, with prominent dopaminomimetic actions, produce 8-OH-DPAT-like effects on the male rat sexual behavior (3,5). These effects, as well as the effects produced by the DA agonist RSD-127 (8,15), are probably not fully accounted for by serotoninergic actions [but see (14)]. In further support of a dopaminergic link, in some of the effects produced by 8-OH-DPAT, we recently described region-selective effects by this compound on striatal DA synthesis (2).

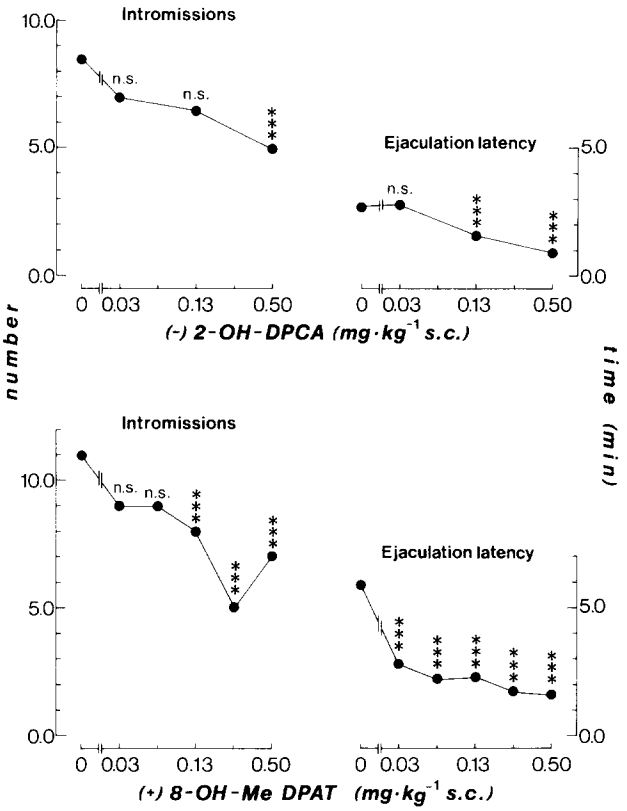

FIG. 4. Effects of (−)*trans*-2-(2-hydroxyphenyl)-N,N-di-*n*-propylcyclopropylamine and (+)cis-8-OH-1-methyl-2-(di-*n*-propylamino)tetralin on male rat sexual behavior. The two compounds were administered SC 20 min before the observations started. The animals (n = 18 and n = 15, respectively) served as their own controls in a change-over design. Results are presented as medians and statistical evaluation was performed by means of the Friedman two-way ANOVA, followed by the Wilcoxon matched-pairs signed-ranks test, for comparisons with the saline control condition. (−)2-OH-DPCA. Intromissions: $\chi^2(3) = 13.28$, $p<0.01$; Ejaculation latency: $\chi^2(3) = 24.95$, $p<0.001$. (+)8-OH-MeDPAT. Intromissions: $\chi^2(5) = 13.04$, $p<0.05$; Ejaculation latency: $\chi^2(5) = 30.67$, $p<0.01$. n.s. $p>0.05$, *** $p<0.01$.

A note of caution is in place here, however, when comparing results obtained from different samples of animals. Several of the components of the male rat sexual behavior show much variation due to age and experience as well as a number of other factors. This is, for example, valid for the number of intromissions preceding ejaculation and the ejaculation latency, both measures which have been found to be particularly sensitive to the drug treatments of the present study. Direct comparisons between different samples, as expressed by ED_{50} values, are often not possible under these conditions. This problem is well illustrated in Fig. 1. In this particular experiment, the difference in control level of performance was about as great as the maximal effect produced by (+)8-OH-MeDPAT. This does not influence the conclusion, however, that the one enantiomer is active and the other not. To make quantitative estimates, further experiments, as described in Fig. 4, have to be carried out. It should also be noted that even in the case of a short ejaculation latency in controls, this measure remains a highly sensitive indicator of behavioral effects of 8-OH-DPAT-induced effects. Thus, statistically significant effects by 8-OH-DPAT can be detected from 25–50 $\mu g \cdot kg^{-1}$ SC [see (4)].

Receptor binding experiments indicate that 8-OH-DPAT has high affinity for a receptor site designated 5-HT_{1A} (26). In addition, some β-receptor blocking agents, like pindolol and propranolol, which also block central 5-HT receptors (19), have affinity for this binding site (27). Indeed, many of the behavioral effects produced by 8-OH-DPAT in rats, like hypothermia, hyperphagia or the facilitation of male sexual behavior, can be antagonized by administration of such agents (4, 17, 19). It is not immediately clear how these observations relate to other observations on the mechanism of action of 8-OH-DPAT, as discussed above. The availability of new stereoselective 5-HT agonists and, hopefully in the near future, antagonists, will greatly enhance the possibilities of defining the receptor site mediating effects produced by 8-OH-DPAT, and related compounds. In further support of specific receptor interactions, the present experiments demonstrate stereoselective effects of some new agents related to 8-OH-DPAT.

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