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The Effects of 8-Hydroxy-2-(di-*n*-propylamino)tetralin and Other Serotonergic Agonists on Performance in a Radial Maze: A Possible Role for 5-HT_{1A} Receptors in Memory

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WINTER, J. C. AND D. T. PETTI. *The effects of 8-hydroxy-2-(di-n-propylamino)tetralin and other serotonergic agonists on performance in a radial maze: A possible role for 5-HT_{1A} receptors in memory.* PHARMACOL BIOCHEM BEHAV 27(4) 625–628, 1987.—A group of ten rats was trained to obtain food pellets in an 8-arm radial maze. The effects of pretreatment with (+)-Lysergic acid diethylamide (+)-tartrate (LSD), *m*-trifluoromethylphenylpiperazine (TFMPP), 5-methoxy-N,N-dimethyltryptamine oxalate (5-MeO-DMT), racemic 8-hydroxy-2-(di-*n*-propylamino)tetralin HBr (8-OH-DPAT), and 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole succinate (RU 24969) were then evaluated. All drugs were administered IP 15 min before testing. With the exception of an increased rate of responding at a dose of 0.1 mg/kg of 8-OH-DPAT, all drugs produced a dose-related decline in response rate. In addition, LSD, RU 24969, and 8-OH-DPAT caused a statistically significant decrease in efficiency of responding. Of the three, 8-OH-DPAT was clearly the most active. Doses of 0.3, 1.0, and 3.0 mg/kg resulted in efficiencies of 61%, 53%, and 44%, respectively. The present results taken in light of 8-OH-DPAT's preferential binding to 5-HT_{1A} receptors, the high density of these receptors in hippocampus, and the observation that the number of 5-HT_{1A} receptors is decreased in Alzheimer's disease, suggest a possible role for this serotonergic receptor subtype in memory.

Radial maze 8-OH-DPAT LSD TFMPP RU 24969 5-MeO-DMT 5-HT_{1A} receptors Memory

THE radial maze was originally described by Olton and Samuelson in 1976 [20]. Since then the effects upon maze performance of drugs from several different pharmacological classes have been examined (see [15] for references). In view of the generally acknowledged importance of cholinergic systems in memory, it is not surprising that agents which interact with these systems have often been studied. In contrast, little is known of the role, if any, which serotonin (5-hydroxytryptamine, 5-HT) plays in the mechanisms of memory in general [27] or in radial maze performance in particular. Beatty and Rush [2] found methysergide, an ergot which has both anti-serotonergic and anti-histaminergic effects, to be inactive in a test of spatial working memory. We are unaware of any other studies of serotonergic agents in the radial maze.

In the thirty-five years since the discovery of serotonin, thousands of chemicals with activity at serotonergic receptors have been reported. In the past these drugs have been categorized on the basis of function: agonistic, antagonistic, or mixed. More recently, radioligand binding studies have suggested the existence of serotonergic receptor subtypes [14, 23–25]. Thus an opportunity has been provided for receptor-based as well as function-based classification and for the correlation of the two.

The drugs chosen for study were lysergic acid diethylamide (LSD), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), *m*-trifluoro-methylphenylpiperazine (TFMPP), 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), and the piperidinyl indole, RU 24969. Each produces behavioral effects which have been attributed to agonistic activity at serotonergic receptors and each has significant affinity for at least one serotonergic receptor subtype.

METHOD

Animals

A group of 10 male Fischer 344 rats as obtained from Charles River Breeding Laboratories, Inc., Wilmington

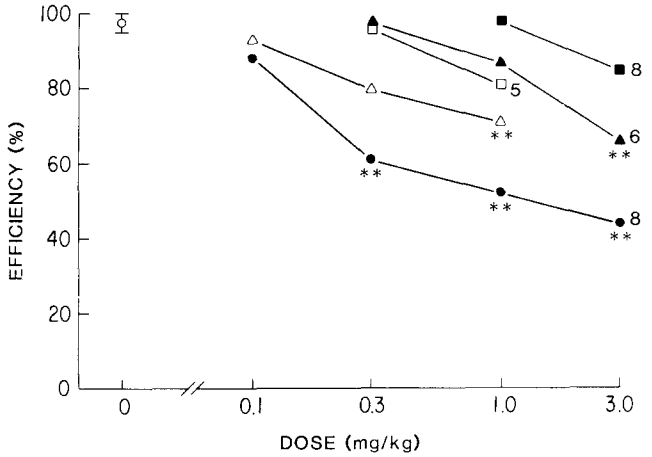

FIG. 1. Dose response relationship for 8-OH-DPAT (circles), LSD (open triangles). TFMPP (open squares), RU 24969 (closed triangles), and 5-MeO-DMT (closed squares). Unless otherwise noted, each point represents the mean of 1 determination in each of 10 subjects. Points representing fewer than 10 subjects are indicated by a number adjacent to them and reflect the fact that subjects whose total number of arm entries and reentries was less than 8 were not included in the data. The data point at zero dose is the mean and 95% confidence limits of saline control values. *Abscissa*: Doses of drugs expressed on a log scale. *Ordinate*: Efficiency. $^{**}p<0.01$.

MA. They were housed in pairs under a natural light-dark cycle and allowed free access to water in the home cage. Subjects were maintained at 75–80% of their expected free-feeding weight by limiting access to food to 2 hours per day.

Apparatus

The radial maze consisted of a central hub, 34 cm in diameter, with eight 86 cm by 9 cm arms radiating from it. The sides were 10 cm high at the center of the maze and sloped to a height of 6 cm at the end of the arms. The maze was constructed entirely of aluminum with the exception of the food wells which were plastic cups, 1.5 cm deep with a diameter of 2 cm. The entire device was elevated 46 cm from the floor.

Procedure

a. Training. At the start of a session, a 45 mg Noyes food pellet was placed in a well at the end of each arm and, on the first day only, a pellet was placed a short distance from the starting point to encourage exploration of the maze. A session lasted until all eight food pellets were obtained or 10 minutes had elapsed. An entry into an arm was scored whenever a rat had all four paws in an arm. Performance during each session was scored by visual observation in terms of (a) efficiency of responding (number of non-repeated arm entries before all eight arms were entered or 10 minutes had elapsed divided by total entries; expressed as a percentage) and (b) rate of responding (arm entries per minute until all eight arms were entered or 10 minutes had elapsed).

b. Drug tests. Rats performed in the maze Monday through Friday. The effects of saline or drug injection were determined on Wednesdays and Fridays. All tests were terminated after all eight arms had been entered or 10 minutes had elapsed. Tests were conducted only if efficiency on the immediately preceding day was at least 89%. Performance in the maze over the four-month period of this study was quite stable; fewer than 5% of test sessions were postponed because of inefficient performance. Test sessions in which fewer than 8 arms were entered were considered to be incomplete and were not included in the data. All injections were made 15 minutes before testing. Drugs were tested in the following sequence: LSD, 5-MeO-DMT, 8-OH-DPAT, TFMPP, and RU 24969. The lowest dose of each drug was based upon the drug discrimination literature; doses were then increased at half log unit intervals. Doses of each drug were tested in ascending order and for each drug a zero-dose (saline) session was included.

Drugs

(+)-Lysergic acid diethylamide (+)-tartrate (LSD) was provided from the National Institute on Drug Abuse, Rockville, MD. *m*-Trifluoromethylphenylpiperazine (TFMPP) was purchased from Aldrich Chemical Co., Milwaukee, WI. 5-Methoxy-N,N-dimethyltryptamine oxalate (5-MeO-DMT) and racemic 8-hydroxy-2-(di-*n*-propylamino)tetralin HBr (8-OH-DPAT) were purchased from Research Biochemicals Inc., Wayland, MA. 5-Methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole succinate (RU 24969) was generously provided by Roussel UCLAF, Romainville, France. All drugs were dissolved in saline and injected IP 15 minutes before testing in a constant volume of 1 ml/kg of body weight.

Statistics

Values for efficiency and rate of responding were compared with the immediately preceding control session by means of individual applications of Student's *t*-test for paired data. Differences were considered to be significant if they would be expected to arise by random sampling alone with a probability less than 0.05.

RESULTS

The figure shows a significant dose-related decrease in efficiency following LSD, RU 24969, and 8-OH-DPAT. Although a trend toward decreased efficiency is also seen with TFMPP and 5-MeO-DMT, the values did not reach statistical significance. The zero dose value together with its 95% confidence interval represents the mean of two determinations in each of the animals. These data were obtained in exactly the same manner as were the drug data, i.e., following a preceding control session. With the exception of LSD, the highest dose of each drug caused at least 2 subjects of the group to fail to enter eight arms during the 10-minute session. Following a dose of 3 mg/kg of TFMPP and a dose of 10 mg/kg of 5-MeO-DMT, none of the group entered or reentered a total of eight arms.

At the lowest dose of 8-OH-DPAT tested (0.1 mg/kg), response rate increased to 173% of control ($p<0.01$). Other than this, all drugs produced a dose-related decline in response rate. The lowest doses to produce a significant decrease in response rate were 8-OH-DPAT: 3 mg/kg, LSD: 0.3 mg/kg; TFMPP: 1.0 mg/kg; RU 24969: 3.0 mg/kg; 5-MeO-DMT: 3.0 mg/kg.

DISCUSSION

A massive amount of evidence indicates that LSD and 5-MeO-DMT act at least in part via serotonergic receptors. For the more recently discovered drugs, 8-OH-DPAT [1,9],

RU 24969 [4, 6, 17], and TFMPP [5, 16, 22], the data in support of a serotonergic mechanism are less voluminous but are convincing nonetheless. Estimates of the affinities of these drugs at the various 5-HT receptor subtypes and the role which each subtype plays in behavioral effects remain uncertain. Potentially significant variables include species and brain area from which the receptors are derived, the radioligand employed, and the specific conditions of the assay [12].

With respect to 5-HT_1 and 5-HT_2 receptors there is general agreement that LSD is nonselective, displaying nanomolar affinities at each [13,24]. In contrast, the affinities of RU 24969 and 8-OH-DPAT are at least a thousand fold greater at 5-HT_1 than at 5-HT_2 sites [3,7]. With respect to the 5-HT_{1A} and 5-HT_{1B} subtypes, LSD is again non-selective but 5-MeO-DMT and 8-OH-DPAT have higher affinities at 5-HT_{1A} while TFMPP and RU 24969 have higher affinities at 5-HT_{1B} [7, 10, 18, 26]. In preparations derived from rat frontal cortex, 8-OH-DPAT appears to be the most selective of the drugs with an affinity for the 5-HT_{1A} receptor at least 1,000 fold greater than for the 5-HT_{1B} site. Affinity ratios for 5-MeO-DMT, TFMPP, and RU 24969 are on the order of 50 to 1. However, Heuring *et al.* [8] have recently presented evidence that RU 24969 has, in addition, significant interactions at non-5-HT_{1A} sites. These sites have not as yet been pharmacologically characterized.

For each of the drugs shown in the figure, there is a trend toward decreased efficiency. However, only for LSD, RU 24969, and 8-OH-DPAT did that decrease reach statistical significance. Of the three, 8-OH-DPAT was clearly the most active over the range of doses tested.

In a previous study in this laboratory [15], it was observed that an increase in rate of responding was not a necessary concomitant of decreased efficiency in the radial maze. Specifically, it was found that a dose of phencyclidine which decreased efficiency also increased rate. In contrast, N-allyl-N-normetazocine (SKF-10-047) produced a comparable decrement in efficiency without any significant effect on rate of responding. This lack of correlation between efficiency and response rate is confirmed by the present data. Doses of 0.3 and 1.0 mg/kg of 8-OH-DPAT resulted in obvious impairments of efficiency without any significant effect upon rate.

Decreased efficiency following 8-OH-DPAT is particularly interesting in that 5-HT_{1A} receptors are especially numerous in the in rat hippocampus [11], a region widely held to be crucial in spatial memory [20,21]. Possible clinical relevance is suggested by the recent observation by Middlemiss *et al.* [19] that binding of radio-labeled 8-OH-DPAT is decreased in membranes from frontal cortex of patients with Alzheimer's disease as compared with age-matched controls. A pressing need at this time is the identification of a specific antagonist at the 5-HT_{1A} receptor.

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