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The 5-HT_2 Receptor Activation Enhances Impulsive Responding Without Increasing Motor Activity in Rats

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KOSKINEN, T., S. RUOTSALAINEN, AND I. SIRVIÖ. *The 5-HT_2 receptor activation enhances impulsive responding without increasing motor activity in rats*. PHARMACOL BIOCHEM BEHAV **66**(4) 729–738, 2000.—The effects of 5-HT_2 receptor ligands on the performance of rats were investigated using a 5-choice serial reaction time (5-CSRT) task. Systemic administration of DOI (0.03 to 0.3 mg/kg subcutaneously [SC]), a 5-HT_2 receptor agonist, did not impair choice accuracy of well-performing rats under either baseline conditions or more demanding conditions of the task, in which the stimulus duration or intensity were reduced or the intertrial interval (ITI) was decreased. DOI (0.1 mg/kg or 0.15 mg/kg) increased premature responding (the probability of intertrial interval hole pokes) in all testing conditions, except under conditions of a short ITI when the rats did not make any hole responses. Ketanserin (0.1 to 0.3 mg/kg SC), a 5-HT_{2A} receptor antagonist, had no marked effect on performance. When combined with ketanserin (0.2 mg/kg SC), however, DOI (0.1 mg/kg) did not increase premature responding. The lowest doses of DOI (0.05 and 0.1 mg/kg) that increase premature responding had no effect on open-field performance. Further, the effects of systemically administered DOI were not reproduced by bilateral administration of DOI into the anterior cingulate cortex. These data indicate that excessive activation of 5-$HT_{2A/2C}$ receptors interferes with response control rather than visual attention. Furthermore, the DOI-induced enhancement of impulsive responses are not due to locomotor hyperactivity, and the anterior cingulate cortex is not the primary site of action for this enhancement of premature responding. © 2000 Elsevier Science Inc.

5-HT_{2A}receptors Attention Impulsiveness Arousal Rat Hyperactivity

ATTENTION-DEFICIT hyperactivity disorder (ADHD) is a common behavioral disorder among school-age children. Patients with ADHD have difficulty controlling their attentional and activity levels (5). The neurobiologic background of ADHD has not been established, but is thought to involve a functional disorder of the monoaminergic system (12,41). Central nervous system (CNS) stimulants, e.g., methylphenidate and d-amphetamine, are commonly used in the treatment of ADHD (5,41). There is also some clinical data suggesting a role for the serotonin (5-HT) system in this disorder (2,8), although its role in eliciting the specific symptoms of ADHD is unclear.

Results of previous experiments suggest that the 5-choice serial reaction time (5-CSRT) task (6) is helpful for identifying animals with attentional deficits in conjunction with impulsivity (37,38). This task, adapted from Leonard's reaction time task for humans (52), requires a rat to detect and respond to brief flashes of light presented randomly in one of five spatially diverse locations (6). This discrimination task makes it possible to separate drug effects on motor activity or food motivated behavior (7) and can be made more challenging by manipulating the parameters, e.g., decreasing the stimulus duration (thought to place a greater demand on attentional capacity) or reducing the intensity of the visual stimulus (taxing visual discrimination; 10).

Puumala and coworkers (38) reported that the measure of

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attention (percent correct responses) is inversely correlated with the probability of premature responses, a reflection of impulsiveness. Therefore, the subpopulation of rats performing poorly (rats with low choice accuracy and high number of premature responses) in the 5-CSRT task might represent the rat equivalent of ADHD. Puumala and Sirviö (39) further reported that poorly performing rats have an elevated 5-HT utilization ratio (5-HIAA/5-HT) in the frontal cortex compared with well-performing rats.

The present study investigated whether activation of 5-HT_2 receptors impaired the performance of rats in the 5-CSRT task. 5-HT_2 receptors were selected for the present study because 5-HT_2 receptors are tonically inactive (43), exist in a supersensitive state under normal basal conditions, and are found in the frontal cortex and striatum (22) areas, which are also important in attentional processes (31). In the present study, DOI, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride, was used to activate 5-HT_2 receptors. The specific questions addressed were 1) does DOI impair the performance of rats (by reducing the choice accuracy and increasing premature responses) in an attentional task? 2) Are these effects exacerbated under more demanding conditions, to dissociate impairments in attentional performance from visual discrimination? 3) Can the effects of DOI on the performance of rats be blocked by the 5-HT_{2A} selective antagonist ketanserin.

As pilot studies indicated that DOI enhances premature responding, the second aim of this study was to examine whether premature responding is paralled by locomotor hyperactivity. In this part of the study, the effect of DOI on the ambulation of rats in an open-field was tested and we examined 4) whether the same doses of DOI that elicit premature responding in the 5-CSRT task affect locomotion in the open-field.

Because anterior cingulate cortex lesions increase premature responses in the 5-CSRT task (31) and serotonergic projections extend to this area (34,35), the effect of DOI on 5-CSRT task performance might be attributable to disruption in the function of the anterior cingulate cortex. Therefore, the involvement of the anterior cingulate cortex, corresponding to Zilles's areas Cg 1 and Cg 2 caudal to the genu of the corpus callosum (59), was examined to determine whether this is the brain area that mediates the effects of DOI on premature responses. The specific question addressed was 5) is the systemic-DOI-induced premature responding reproduced by bilateral administration of DOI into the anterior cingulate cortex?

METHOD

Animals

The present study was approved by the provincial government of Kuopio (approval numbers 127 Zd and 12 Zd, 1997). All studies were performed according to the Declaration of Helsinki and with the Guide for the Care and Use of Laboratory Animals. Male Han:Wistar rats were used. The rats were 8-weeks old at the beginning of behavioral training and 22-weeks old at the beginning of behavioral testing. The rats were singly housed in stainless steel shoe-box cages in a controlled environment (temperature 20°C, humidity 50% to 60%, lights on from 0700 to 1900 h). During training and testing, the rats were deprived of food for 14 to 16 h before daily training or testing. After daily behavioral training or testing, the rats received 15 to 17 g of food pellets (Special Diet Service, Stockholm, Sweden), and were maintained at 85% of their free-feeding weight. Water was available ad libitum except in the test apparatus. Rats ([Experiment I: $n = 12$; Experiment II: $n = 14$; Experiment III: $n = 12$ [from which 6 were analyzed]), were selected to be tested from a larger group of 46 (Experiment I) and 50 (Experiment II and III) rats. This subgroup of rats was experimentally naïve and had better than average choice accuracy scores in the 5-CSRT task.

Chemicals

DOI, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (Research Biochemicals), a 5-HT_2 receptor agonist was dissolved in distilled water (Experiment I and II: 0.03, 0.1, 0.3 mg/kg; 0.05, 0.1, 0.2 mg/kg) or saline (pH 6; Experiment III: 1, 3, 10 μg/side) in the brain injection experiments. DOI is reported to have a similar (22), or up to 40-fold higher affinity (50), for 5-HT_{2A} sites than for 5-HT_{2C} sites.

Ketanserin, (Research Biochemicals), a 5-HT_{2A} receptor antagonist (0.1, 0.2, 0.3 mg/kg) was dissolved in a drop of acetic acid and then diluted in water (pH 5-6). Water or water with a drop of acetic acid was used as a vehicle. The dose of ketanserin (0.2 mg/kg) to be used in the blocking experiment was chosen to have no effect on its own. Ketanserin was selected because it is highly selective for 5-HT_{2A} receptors. It is approximately 1000-fold more selective for 5-HT_{2A} receptors than for 5-HT_1 receptors, and is 100-fold more selective for 5-HT_{2A} receptors than 5-HT_{2CA} receptors. Ketanserin also binds to a minor extent to H_1 histamine and α_1 adrenergic receptors (29,22).

Behavioral Training and Testing

5-CSRT Task.

Apparatus. The apparatus consisted of a 25 cm × 25 cm aluminium chamber with a curved rear wall. Nine 2.5-cm square holes, 4-cm deep, were set 2.5-cm above floor level in the curved wall. Each hole had an infrared photocell beam crossing the entrance vertically that illuminated a photoelectric cell. A standard 2-W bulb at the rear of each hole provided illumination. The entrances to holes 2, 4, 6, and 8 were blocked with metal caps. Food pellets (45 mg, dustless, Bioserv Inc., NJ, USA) were dispensed automatically into a magazine at the front of the chamber. Access was gained to the magazine through a Perspex door (= panel). The distances from the panel to the illuminated holes at the rear of the box were all 25 cm. The chamber was illuminated by a 2-W houselamp mounted in the roof. The animals were introduced to the chamber through a Perspex door in the upper half of the front wall. The apparatus was housed in a dark, soundproof compartment. On-line control of the apparatus and data collection were performed using microprocessors that had been programmed using Spider (Paul Fray Ltd, Cambridge, UK).

Training: Rats were trained to spatially discriminate a brief visual stimulus presented randomly by the computer in one of the five holes (from left, holes 1, 3, 5, 7, and 9). In the first phase of behavioral training, all rats were magazine-trained by being placed in a chamber for 15 min (with the house-light off) and the magazine containing 20 to 30 food pellets. In the next phase, the rats were placed in the chamber for 15 min (with the house-light on) and a food pellet was delivered every 15 s into the magazine. In the third phase, one of the holes was illuminated all the time during the 15-min training period and each time a rat made a response (nose-poke)

in the illuminated hole it was reinforced by delivery of a food pellet into the magazine.

After reaching the training criteria, rats entered the next phase, which was started by the delivery of a single food pellet. The first trial was started when the rat opened the panel to collect the food pellet. After a fixed delay (intertrial interval, ITI = 5.0 s), the light in one of the holes was illuminated for a short period (stimulus duration = 0.5 s). A response by a rat into the illuminated hole or a response in that particular hole for a short period of time after the illumination (the limited hold = 3.5 s) was rewarded with the delivery of a food pellet and a correct response was recorded. The light stimulus was presented in each of the holes for an equal number of times during each complete session, and the order of presentations was randomized by the computer. The next trial was initiated when the rat opened the panel to collect the food pellet. A response in any other hole (incorrect response) or a failure to respond at all during the limited hold (omission) resulted in a period of darkness (time out). Therefore, if the rat was facing in the wrong direction when the visual stimulus was presented on a hole it would not have detected the stimulus and consequently this trial resulted in an omission and period of time-out. Any response made during the time-out period restarted the time-out. Responses made in the holes during the ITI were recorded as premature (or anticipatory) responses, and these responses resulted in a period of time-out. Responses made into the magazine during the ITI (perseverative responses) were also recorded, but they did not result in a time-out. After a time-out, the next trial was initiated when the rat opened the panel (the magazine was empty). The latency between the onset of the stimulus and response (whether correct or incorrect) was measured, as well as the latency to collect the earned food pellet after completion of a correct response. Each daily training session (five sessions/week) consisted of 20 to 30 min of training. During the first session of training, the stimulus duration and limited hold periods were set at 4.0 s and 0.5 s, respectively. These durations were then progressively altered to 0.5 s and 3.5 s, respectively, during the training. The ITI and time-out were set at 5.0 s and 4.0 s, respectively, and kept constant during training. Each rat was trained on this schedule depending on its performance until a stable level of performance was reached. This required normally about 40 to 60 training sessions.

Parametric manipulations: To detect possible drug-induced visual deficits, the intensity of the visual stimulus was reduced to half of normal by adding resistors in series with the stimulus bulbs. In addition, the duration of the visual stimulus was decreased (0.5 s to 0.25 s) in order to load attentional processes of rats during the drug treatment. Furthermore, the ITI period was decreased (5 s to 1 s) to selectively study the effects of DOI on accuracy. All of the tests were run every third day and there was always one habituation session to each new condition before each testing series, which lasted for four consecutive sessions.

Behavioral variables: The following parameters were selected for statistical analysis: 1) choice accuracy (%CORRECT) = percent correct responses [correct/(correct + incorrect)] × 100; 2) response control (%ITI hole) = the proportion of premature responses on the holes [ITI hole responses/(trials completed + omissions + ITI hole responses)] × 100; 3) response tendency (%OMISSION) = the proportion of times when rats failed to respond at all to the visual stimulus [omissions/(trials completed + omissions)] × 100; 4) trials completed = the total number of trials completed (correct + incorrect) made during a 30-min testing session; 5) response latency = the mean latency for correct response (CORRECT LATENCY); 6) motivation for food = the latency to collect earned food pellets from the magazine after correct responses (PANEL LATENCY). The number of trials completed and response latency indicate motor activity. If there were no completed trials, %CORRECT and latencies could not be calculated and those rats were excluded from the analysis of %CORRECT, CORRECT LATENCY, and PANEL LATENCY (series 1).

Open-field

Twenty-four days after behavioral testing in the 5-CSRT task, the rats (n = 14) were tested in the open-field to assess their exploratory behavior and motor activity. The open-field test was performed in a black open arena (85 × 85 cm) with walls (30 cm in height) placed under a camera that was linked to a computer through an image analyzer (HVS Image, UK). The room in which the open-field was situated was dimly illuminated by four reflector lamps (80 W each). Before the start of testing in the open-field, the rats (n = 14) were habituated to the open-field testing board and environment for 9 min each day for 3 days. During the experiment the animals were placed in the open-field for a 9-min period (3 × 3 min session interrupted by a 10-s period to load the computer). The floor and the walls of the open-field board were cleaned between animals. Locomotor activity, expressed by DISTANCE walked, was recorded for each animal by the computer. The number of times the rat reared up on its hind legs (REARINGS), the number of GROOMINGS, and the number of FECAL BOLI were counted by the experimenter.

Surgical Procedure

Two months after behavioral testing in the 5-CSRT task, chronic cannulae were implanted into the rats (n = 12). Before the operation, food was available without restriction. Cannulae were implanted under pentobarbital anesthesia (MEBUNAT: 70 mg/kg IP). Two stainless steel guide cannulae (21 gauge; 0.81-mm external diameter, 0.50-mm internal diameter, 2.3-mm long) were implanted stereotaxically bilaterally with a 20° angle into the anterior cingulate cortex (AP −1.3; L ± 1.3). Guide cannulae were fixed to the skull with two screws and dental acrylic cement. The tip of injection cannulae (26 gauge; 0.46-mm external diameter, 0.24-mm internal diameter, 3.3-mm long) and the dummy cannulae (0.46-external diameter) reached 1 mm below the guide cannulae. Seven to 10 days after surgery, restricted access to food was initiated and the rats were subjected to behavioral testing and trained until consistent performance was attained (5 times).

Histology

All animals with chronic injection cannulae in the anterior cingulate cortex were sacrificed after the final testing day. Their brains were removed and stored at −80°C. The frozen tissue was sliced (30 μm) using a cryostat. After drying, the slices were defatted in chloroform/absolute ethanol, rehydrated in a graduated series of ethanol, stained with thionin, and dehydrated through a series of ethanol and xylene.

Experiments

Drugs were injected subcutaneously (SC) (1 ml/kg) or intracerebrally (IC) (1.0 μl/side) every third day in a pseudorandom order. The drugs were administered 30 min (SC) or 10 min (IC) before behavioral testing according to a re-

peated-measurement test design. IC injections of DOI were administered using Hamilton microsyringes via polyethylene tubing with two metal needles. The injection needles were lowered 1.0 mm below the guide cannulae and the solution was administered bilaterally over 2 min plus 1 additional min with the injection cannulae remaining in place before they were removed and the dummy cannulae replaced. When ketanserin and DOI were tested in combination, the antagonist was injected 2 min prior to DOI. For controls, two vehicle injections were used. The test series was carried out as shown in Table 1. Wash out periods before the next time series are presented.

Statistical Analysis

A multivariate analysis of variance (MANOVA) was used to analyze the treatment effects (vehicle and different doses of drugs) and interactions between these effects on different parameters reflecting attention and behavioral activity. Before MANOVA analysis, data were normalized using appropriate transformations (%CORRECT, %ITI hole, and %OMISSION were transformed using an arcsine transformation; trials completed using the square root transformation; data for latencies using a logarithmic transformation). A two-tailed pair-wise *t*-test (*p*-values corrected using Bonferroni's equation) was used to compare different doses of drug to vehicle treatment if the MANOVA revealed a significant main treatment effect. The treatment effect and the testing effect (three 3-min periods) and their interactions with the data of the open-field test (distance, number of rearings, groomings, and fecal boli) were analyzed using MANOVA for repeated measurements.

RESULTS

Experiment I

In the first series of DOI (0.1 and 0.3 mg/kg) testing, DOI treatment decreased the number of completed trials in a dose-dependent manner ($F(2, 22) = 22.29$, $p < 0.001$; Table 2). The higher dose of DOI (0.3 mg/kg) severely disrupted the performance of rats in the 5-CSRT task and many rats did not complete any trials. Thus only the probability of omissions could be reliably used for statistical analysis of all the treatments. DOI (0.3 mg/kg) increased the probability of omissions ($F(2, 22) = 6.68$, $p < 0.01$; Table 2). When the 0.3 mg/kg dose was excluded from the analysis, 0.1 mg/kg DOI increased premature responses (%ITI hole) and probability of omissions as compared with vehicle treatment (Table 2), whereas there was no statistically significant effect on choice accuracy (%CORRECT). In this series, 0.1 mg/kg DOI increased the latency for food reward (Table 2).

In the next series, DOI was tested at doses of 0.03 and 0.1 mg/kg (Table 2). DOI in a dose of 0.1 mg/kg, but not 0.03 mg/kg, increased premature responding ($F(2, 22) = 4.11$, $p < 0.05$; Table 2). In this series, DOI had no significant effect on choice accuracy, correct latency, panel latency, or the probability of omissions (Table 2).

When 0.15 mg/kg DOI was tested under the different manipulations of the task (normal parameters, reduced stimulus duration and reduced stimulus intensity; Fig. 1A), there was a significant reduction in the choice accuracy (%CORRECT) following manipulation of the visual stimulus ($F(3, 33) = 11.65$, $p < 0.01$). There was no significant treatment effect ($F(1, 11) = 0.12$, $p > 0.1$), however, nor any interaction between the drug treatment and the stimulus manipulation effects ($F(3, 33) = 0.55$, $p > 0.1$). The treatment effect of 0.15 mg/kg DOI on premature responses was significant ($F(1, 11) = 9.75$, $p < 0.01$), but there was no interaction with the effect of stimulus manipulation ($F(3, 33) = 2.22$, $p > 0.1$). The parametric manipulations of the visual stimulus had only a minor effect on %ITI hole responses ($F(3, 33) = 2.39$, $p = 0.086$; Fig. 1B).

When the intertrial interval (ITI) was reduced to 1.0 s, 0.15 mg/kg DOI decreased the number of trials completed, increased the latencies for correct responses, but had no effect on choice accuracy, the probability of omissions, or latency to

TABLE 1

TREATMENTS PERFORMED IN EACH EXPERIMENT

Treatment	Condition	Wash-out
Experiment I, $n = 12$		
1. Vehicle, DOI 0.1, 0.3 mg/kg,	Baseline	9 d
2. Vehicle, DOI 0.03, 0.1 mg/kg,	Baseline	6 d
3. Vehicle, DOI 0.15 mg/kg,	Baseline I	6 d
4. Vehicle, DOI 0.15 mg/kg,	half intensity	6 d
5. Vehicle, DOI 0.15 mg/kg,	25-s stimulus duration	6 d
6. Vehicle, DOI 0.15 mg/kg,	Baseline II	12 d
7. Vehicle, DOI 0.15 mg/kg,	1.0 s intertrial interval	12 d
8. Vehicle, Ketanserin 0.1, 0.3 mg/kg,		3 d
9. Vehicle + vehicle, vehicle + DOI 0.1 mg/kg, Ketanserin 0.2 mg/kg + vehicle, Ketanserin 0.2 mg/kg + DOI 0.1 mg/kg,		
Experiment II, n = 14		
1. Vehicle, DOI 0.05–0.2 mg/kg	Baseline	24 d
2. Vehicle, DOI 0.05–0.2 mg/kg	Open-field	
Experiment III		
1. Vehicle, DOI 0.05–0.2 mg/kg,	Baseline; $n = 5$.	60 d
2. Vehicle, DOI 1, 3 μg/brain side	Baseline; $n = 6$.	3 d
3. Vehicle, DOI 10 μg/brain side	Baseline; $n = 4$.	

TABLE 2

THE EFFECTS OF SUBCUTANEOUS DOI ON THE PERFORMANCE OF RATS IN A 5-CHOICE SERIAL REACTION TIME TASK

	TRIALS COMPLETED	%CORRECT	%ITI HOLE	%OMISSION	CORRECT LATENCY	PANEL LATENCY
VEHICLE I	56.0 ± 7.9	71.1 ± 4.7	12.3 ± 2.4	33.3 ± 3.8	0.91 ± 0.06	1.86 ± 0.23
DOI 0.1 mg/kg	22.0 ± 6.1†	66.1 ± 6.0	26.4 ± 5.3*	48.6 ± 6.9	0.82 ± 4.33	4.95 ± 1.52*
DOI 0.3 mg/kg	6.3 ± 1.7†	—	—	64.1 ± 5.8†	—	—
VEHICLE II	64.5 ± 6.8	79.2 ± 2.4	13.6 ± 2.1	29.1 ± 2.9	0.91 ± 0.05	2.1 ± 0.31
DOI 0.03 mg/kg	57.4 ± 6.9	77.6 ± 2.0	14.0 ± 2.6	30.6 ± 3.4	0.92 ± 0.05	1.9 ± 0.38
DOI 0.1 mg/kg	52.3 ± 5.0	73.0 ± 2.4	20.9 ± 3.8‡	25.2 ± 3.3	0.89 ± 0.05	2.9 ± 0.90

Results are expressed as group mean ± SEM. $n = 12$. —values are not reliable because the rats completed so few trials.
*two-tailed $p < 0.05$.
†two-tailed $p < 0.01$.
‡two-tailed $p = 0.078$. (after Bonferroni correction) using paired t-test when compared to vehicle. (Two rats deleted from analysis of %CORRECT, correct latency, and panel latency in series I, because they did not complete any trials in one of the treatment conditions).

collect the earned food pellet (Table 3). The rats did not make any hole responses during the short ITI.

Ketanserin (0.1 or 0.3 mg/kg) alone had no effect on choice accuracy, premature responding, probability of omissions, latency to respond to the stimulus (correct latency), or latency to collect earned food pellets (panel latency). The higher dose, however, decreased the number of trials completed ($F(2, 22) = 4.86, p < 0.05$; Table 4).

When ketanserin was combined with DOI (0.1 mg/kg), ketanserin at a dose of 0.2 mg/kg was used because it was expected to have no effect on its own. In this experiment, DOI did not increase premature responses when administered with ketanserin ($F(3, 33) = 5.21, p < 0.01$; Table 4). DOI alone (0.1 mg/kg) and ketanserin alone (0.2 mg/kg) decreased the number of trials completed, but their effects were not additive ($F(3, 33) = 3.27, p < 0.05$). Furthermore, DOI did not decrease the number of trials completed in the presence of ketanserin (Table 4). DOI and ketanserin treatments had no effect on the probability of omissions, correct latency, or panel latency as compared with vehicle treatment.

Experiment II

The results of experiments in which DOI (0.05, 0.1, and 0.2 mg/kg) was investigated in 5-CSRT task are shown in Table 5. DOI (0.05 to 0.2 mg/kg) increased the probability of premature responding ($F(3, 39) = 7.58, p < 0.001$; %ITI HOLE). Systemically administered DOI affected choice accuracy (%CORRECT) only modestly [MANOVA ($F(3, 39) = 4.50$, $p < 0.01$), but t-tests did not differ from vehicle]. DOI (0.05 to 0.2 mg/kg) dose-dependently decreased the number of trials completed ($F(3, 39) = 47.4, p < 0.001$), partly due to the increased number of premature responses. The highest dose of DOI (0.2 mg/kg) probably depressed the behavioral activity of the rats because it slightly increased the probability of omissions ($F(3, 39) = 4.79, p < 0.05$) and increased the la-

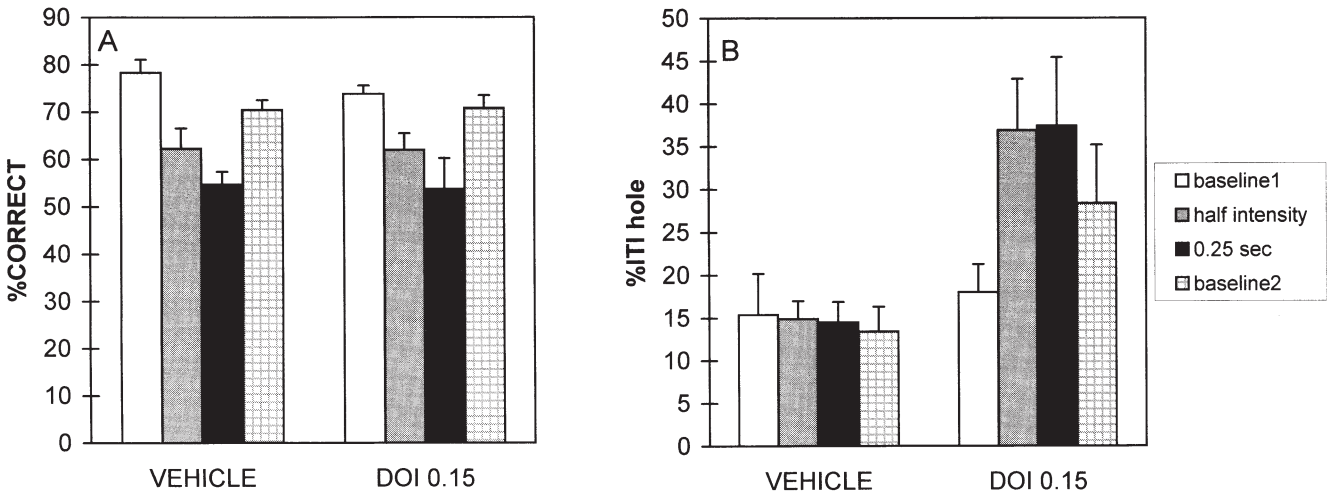

FIG. 1. The effects of DOI (0.15 mg/kg SC) on choice accuracy (%CORRECT) (A) and impulsivity (% ITI hole) (B) of rats tested under different conditions (intensity of the visual stimulus was reduced by 50%; and the stimulus duration was decreased to half: 0.25 s). Baseline 1 was performed under normal conditions before the parametric manipulations, and Baseline 2 was performed after these tests. The results are expressed as group means ± SEM. Note that in the Baseline1 testing one rat made an abnormal number of premature responses during vehicle treatment, which increased the mean. Median values for %ITI hole responses are: Vehicle:8.4; DOI:15.3.

TABLE 3

THE EFFECTS OF SUBCUTANEOUS DOI WHEN THE INTERTRIAL INTERVAL (ITI) WAS REDUCED TO 1.0 s, (THUS, RATS HAD NO TIME TO MAKE PREMATURE RESPONSES); %ITI HOLE = 0

	TRIALS COMPLETED	%CORRECT	%OMISSION	CORRECT LATENCY	PANEL LATENCY
VEHICLE	63.0 ± 10.9	71.4 ± 4.4	55.4 ± 4.9	0.99 ± 0.05	1.52 ± 0.18
DOI 0.15 mg/kg	42.8 ± 9.4*	62.6 ± 3.9	52.1 ± 4.2	1.17 ± 0.09*	1.63 ± 0.13

Results are expressed as group mean ± SEM. $n = 12$.
*two-tailed $p < 0.05$ using paired t-test when compared to vehicle.

tency for food collection ($F(3, 36) = 5.62$, $p < 0.01$; PANEL LATENCY; Table 5). DOI had no effect on latency to correct responses (CORRECT LATENCY).

DOI (0.2 mg/kg) decreased the total distance rats walked during the 9-min testing period ($F(3, 39) = 19.35$, $p < 0.01$). The distance was also decreased for each 3-min testing period ($F(2, 26) = 35.98$, $p < 0.01$) so that during the third testing session, the distance walked was less than that of the first testing session (only the summary data for the entire 9-min period are shown in Table 6). There was no interaction between the DOI treatment effect and the testing effect. DOI (0.2 mg/kg) also decreased the number of rearings ($F(3, 39) = 33.32$, $p < 0.01$), and rearings were also decreased by the end of testing ($F(2, 26) = 12.99$, $p < 0.01$), but there was no interaction between DOI treatment and the testing effect. DOI (0.05 to 0.1 mg/kg) had no effect on distance or rearings. DOI (0.05 to 0.2 mg/kg) or testing had no effect on grooming. DOI (0.05 to 0.2 mg/kg) had no effect on fecal boli (Table 6).

Experiment III

There were only 6 of 12 rats with correct placement of their cannulae and these were included in the analysis. The injection site is shown in Fig. 2. From these six rats, five were used in the experiment of systemically administered DOI (data from one rat was not saved due to a computer failure) and four rats were used in the analysis of DOI 10 μg vs. vehicle (injection failure in two rats). Systemically administered DOI (0.05 to 0.2 mg/kg) dose-dependently increased the number of premature responses ($F(3, 12) = 5.2$, $p < 0.05$; Fig. 3; %ITI hole) but had no effect on choice accuracy (%CORRECT). Intracerebrally administered DOI (1 and 3 μg bilaterally) had no effect on the performance of rats in the 5-CSRT task whereas 10 μg of DOI slightly improved the accuracy of responding (%CORRECT; Fig. 3). DOI (10 μg bilaterally) had no statistically significant effect on premature responding or any other variables in the 5-CSRT task (Fig. 3; only the data of premature responses and choice accuracy are shown).

DISCUSSION

The main finding of the present study is that activation of 5-HT_2 receptors, especially the DOI-sensitive 5-HT_{2A} subtype, impairs response control as assessed by the ability of rats to withhold premature responding. On the other hand, DOI had no effect on choice accuracy under baseline conditions or under more demanding testing conditions (a reduced stimulus duration or reduced stimulus intensity), indicating that activation of 5-HT_2 receptors does not affect selective visual attention or visual discrimination. The same doses of DOI that enhance premature responding did not increase locomotor activity. Furthermore, the anterior cingulate cortex is not the primary site of action for DOI to increase premature responding.

Carli and Samanin (7) suggested that activation of 5-HT_2 receptors causes attentional disturbances at doses that have no effect on motivation for food or speed of responding. Both lysergic acid diethylamide (LSD) and quipazine decrease cor-

TABLE 4

THE EFFECTS OF KETANSERIN AND COMBINED ADMINISTRATION OF KETANSERIN (0.2 mg/kg) AND DOI (0.1 mg/kg) ON PERFORMANCE OF THE RATS IN THE 5-CSRT TASK

	TRIALS COMPLETED	%CORRECT	%ITI hole	%OMISSION	CORRECT LATENCY	PANEL LATENCY
VEHICLE	83.6 ± 9.1	77.3 ± 2.7	8.3 ± 1.4	28.0 ± 4.0	0.87 ± 0.03	2.00 ± 0.02
KET 0.1 mg/kg	74.6 ± 8.5	79.5 ± 1.5	10.1 ± 1.8	30.2 ± 4.1	0.90 ± 0.04	2.20 ± 0.03
KET 0.3 mg/kg	69.8 ± 6.9*	78.9 ± 1.8	6.9 ± 1.4	33.3 ± 3.2	0.90 ± 0.02	2.20 ± 0.03
VEH + VEH	84.6 ± 9.1	79.4 ± 2.1	6.8 ± 1.1	28.3 ± 3.1	0.88 ± 0.04	2.03 ± 0.13
VEH + DOI 0.1	62.1 ± 9.6*	75.9 ± 2.1	26.8 ± 7.0†	25.8 ± 3.7	0.81 ± 0.03	3.04 ± 0.98
KET 0.2 + VEH	64.7 ± 9.8‡	80.0 ± 1.1	7.3 ± 2.9	31.0 ± 4.1	0.86 ± 0.04	3.52 ± 1.47
KET + DOI	70.8 ± 9.4	81.7 ± 2.0	7.2 ± 2.0	34.2 ± 4.7	0.88 ± 0.03	1.91 ± 0.25

Results are expressed as group means ± SEM. $n = 12$.
*two-tailed $p = 0.05$.
†two-tailed $p = 0.035$. using paired t-test when compared to vehicle. In this case the large deviation in VEH + DOI 0.1 decreases the significance and, after Bonferroni correction, it is not statistically significant.
‡two-tailed $p = 0.069$. (after Bonferroni correction) when compared to vehicle or to vehicle + vehicle treatment.

TABLE 5

THE EFFECTS OF DOI (0.05, 0.1, AND 0.2 mg/kg) ON PERFORMANCE OF RATS IN 5-CHOICE SERIAL REACTION TIME TASK

	TRIALS COMPLETED	%CORRECT	%ITI hole	%OMISSION	CORRECT LATENCY	PANEL LATENCY
VEHICLE	68.6 ± 6.9	76.5 ± 2.5	10.8 ± 1.6	26.7 ± 2.7	0.86 ± 0.02	0.99 ± 0.06
DOI 0.05	61.7 ± 6.0	78.5 ± 2.8	20.3 ± 3.7†	23.1 ± 2.1	0.82 ± 0.02	1.03 ± 0.06
DOI 0.1	45.3 ± 5.6*	76.5 ± 1.9	22.8 ± 2.8†	26.2 ± 2.6	0.82 ± 0.03	1.10 ± 0.08†
DOI 0.2	14.8 ± 4.0†	62.3 ± 6.8	17.3 ± 1.5†	45.9 ± 6.5*	0.98 ± 0.07	1.63 ± 0.34*

The results are expressed as group mean ± SEM. $n = 14$. (one deleted from the analysis of latencies because it had %CORRECT = 50% with 0.2 mg/kg of DOI).

*$p < 0.05$.

†$p < 0.01$. when compared to vehicle treatment (paired t-test after Bonferroni correction).

rect responses without affecting the number of premature responses. The reason for this conflicting result is unclear. Carli and Samanin (7) used nonselective 5-HT agonists and blocked the effect of LSD and quipazine on choice accuracy with ritanserin, a 5-$HT_{2/7}$ antagonist. The ability of ritanserin to block these effects does not necessarily indicate that only 5-HT2 is involved because, like LSD, ritanserin also has some affinity for other 5-HT subtypes, e.g., 5-$H_{2C,6,7}$ receptors (22,45,44). Furthermore, LSD has a high affinity for 5-$HT_{1A,1B,1D}$ receptors and quipazine for 5-$HT_{1B,1D,2C,3}$ receptors (22). Thus, involvement of other 5-HT receptors cannot be excluded in the effects of LSD and quipazine. In a parallel study (Neuropharmacology, in press), we concluded that 5-HT_{2A} receptor activation by DOI increases premature responding.

Like LSD, DOI is a hallusinogenic agent. It has been suggested that 5-HT_2 receptors mediate the hallucinogenic effect of phenylethylamine hallucinogens and LSD in humans (16,50). Therefore, it is interesting that DOI did not have effect on choice accuracy, even when the intensity of visual stimulus was reduced. On the other hand, a low dose of DOI had a marked and specific effect on premature responding. It is not clear whether putative hallusinogenic effect of DOI is involved in the remarkable 5-CSRT task behavior disruptive effects of relative higher doses of DOI (0.3 mg/kg).

The effects of DOI on attentional processes were previously studied using different prepulse inhibition (PPI) paradigms assessing sensory-motor gating and latent inhibition (LI) which measure the ability to ignore irrelevant information. DOI (>0.5 mg/kg) disrupts auditory PPI (33,47,48), but it does not consistently impair visual PPI (33). In an LI task using an auditory stimulus, 0.3 mg/kg DOI was not effective, whereas higher doses (≥1.0 mg/kg) disrupted LI, though the involvement of state-dependent learning could not be ruled out (20). Those results are consistent with the present findings indicating preserved sustained visual attention.

It is important to note that there is much experimental and clinical data linking low levels of serotonin with increased impulsivity (see 49,4,21). Impulsivity is considered to be the inability to wait before acting, to delay voluntary behavior, or to tolerate delayed gratification (4; 21), or it can be viewed as the choice to accept a smaller, less delayed reinforcer over a larger, more delayed reinforcer (30). Rats with lesions of the ascending 5-HT pathway have a shorter delay to a larger reinforcer compared with a control group in the adjusting-delay paradigm and produce a higher proportion of short inter response times (IRT) on an IRT schedule greater than 15 s, suggesting reduced capacity to inhibit positively reinforced operant behavior (55,56). Serotonin-lesioned rats also have increased premature responding in the 5-CSRT task (17,18). Thus it remains to be determined how serotonin lesion-induced impulsivity is mediated. To our knowledge, there are no studies reporting that serotonin antagonists increase the anticipatory responses in a 5-CSRT task. In the present study, ketanserin alone did not influence premature responding. Furthermore, none of the 5-HT receptor antagonists tested by Evenden induced impulsivity (13). Consistent with the present results, systemic administration of DOI (0.1 to 1.0 mg/kg) was suggested to increase impulsivity by reducing the average response length that the rats would continue to press a lever in order to receive delayed reinforcement in the fixed-paced consecutive-number paradigm (13).

In an operant delayed nonmatching to position task used to assess working memory, DOI (0.1 and 0.3 mg/kg) interferes with noncognitive performance of rats by increasing response

TABLE 6

THE EFFECTS OF DOI (0.05, 0.1, AND 0.2 mg/kg) ON RAT PERFORMANCE IN THE OPEN FIELD. SUMMARY DATA OF 3 × 3 MIN

	DISTANCE	REARING	GROOMING	FECAL BOLI
VEHICLE	5504 ± 253	52.5 ± 3.8	1.92 ± 0.32	0 ± 0
DOI 0.05	5675 ± 320	52.8 ± 2.8	1.79 ± 0.28	0.42 ± 0.29
DOI 0.1	5344 ± 374	47.3 ± 4.3	2.50 ± 0.36	0.64 ± 0.46
DOI 0.2	3754 ± 409*	27.2 ± 4.5*	2.07 ± 0.32	0.43 ± 0.31

The results are expressed as group mean ± SEM. $n = 14$.

*$p < 0.01$. when compared to vehicle treatment (paired *t*-test after Bonferroni correction).

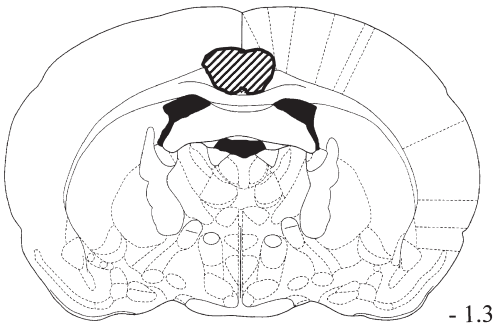

FIG. 2. The area (shown as black shaded) of the tips of implanted injection cannulae. Coordinates from bregma AP: − 1.30 mm (± external diameter of the injection canulae tip 0.46 mm); L: ± 1.30 mm in 20° angle.

latencies and the probability of omissions. It also decreases the number of trials completed, but does not significantly affect choice accuracy (% correct responses across the delays, 0 to 30 s) of rats in this task (42). This is consistent with the present results, as the highest dose of DOI (0.3 mg/kg) markedly interfered with the organization of behavior of rats in the 5-CSRT task. This could be partly due to a reduced motivation in the food-rewarded task. In addition, we observed that many rats treated with the highest dose (0.3 mg/kg) of DOI seemed to make nose pokes into holes irrespective of the stage of the task. The repetition of the main element of autoshaped behavior in a 5-CSRT task could reflect hyperrigidity or failure in organization of responding as related to serotonin overactivity, which has been proposed by Spoont (49).

Furthermore, DOI tended to increase food collection latency. This is not unexpected, because the activation of 5-HT_2 receptors reduces food consumption (57,1,26). It does not, however, account for the increase in premature responding, as reduced motivation (e.g., by prefeeding) reduces the tendency for premature responding (7). At high doses, DOI (>1mg/kg) elicits active behaviors, such as head twitches, and increases feeding by response competition (11, 26). In the present study, DOI did not elicit any head twitches at the doses used.

The open-field test is useful for recording the spontaneous activity of animals and has been extensively reviewed and critiqued elsewhere (40,25). DOI (>0.2 mg/kg), decreases locomotor and investigatory behavior in a novel environment (54) and also decreases hole pokes in a behavioral pattern monitor (27,28). Furthermore, DOI induces stereotyped forward locomotion at doses over 0.1 mg/kg in an open-field arena (24,19) and also depresses motor activity by slowing performance as assessed by swim time in the water maze (23). In the present experiment, rats were well habituated to the open-field before testing. DOI (0.05 to 0.1 mg/kg) had no effect on open-field behavior, but the highest dose of DOI (0.2 mg/kg) significantly reduced motor activity, as indicated by a decrease in ambulation distance and the number of rearings. These results are consistent with previous experiments performed in other laboratories in which DOI depressed locomotor activity with doses over 0.2 mg/kg (36, 27,28,54,19,24). As the same doses of DOI that increase premature responding in a 5-CSRT task had no effect on open-field behavior, impulsivity-like behavior induced by DOI is not explained by locomotor hyperactivity.

When administered directly into the anterior cingulate cortex, DOI had only minor effects on the performance of rats in the 5-CSRT task. The doses examined should have been high enough to induce the same effect as systemic administration of 100 μg/kg DOI (see also 36, 53,15,46). Therefore, it seems that the anterior cingulate cortex is not the primary site for DOI to induce premature responding. Systemic and intra-accumbens administration of amphetamine also increases premature responding and the speed of correct responding to the visual targets, without affecting the accuracy of discrimination (9). DOI infused into the nucleus accum-

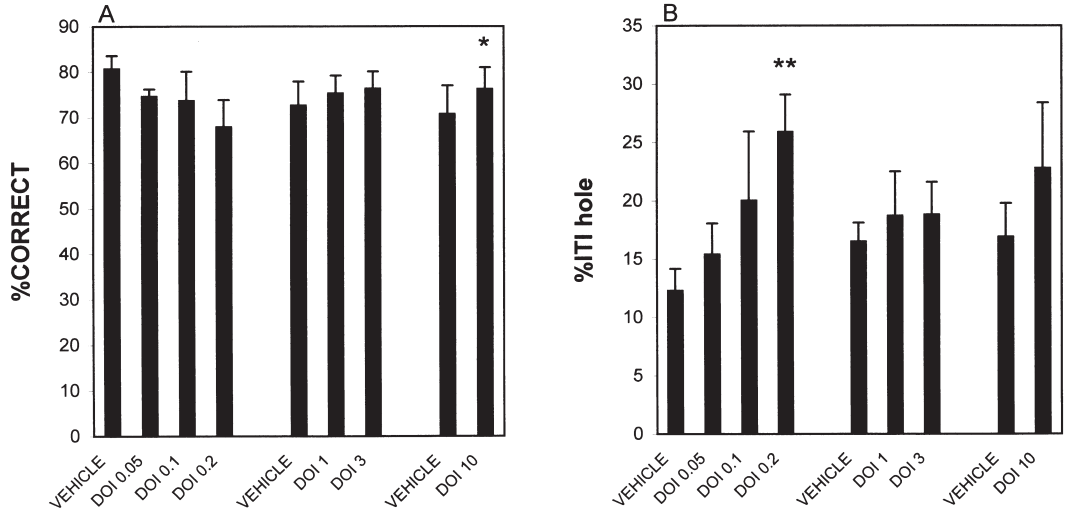

FIG. 3. The effects of DOI (0.05 to 0.2 mg/kg SC and 1 to 10μg bilaterally to anterior cingulate cortex) on choice accuracy (%CORRECT) (A) and impulsivity (%ITI hole) (B) of rats. The results are expressed as group means ± SEM. $n = 5$ in systemically administered DOI series, because of a computer error; $n = 6$ in DOI (1 to 3 μg series); and $n = 4$ in DOI (10 μg series), because of injection failure.

bens elicits extracellular dopamine in the nucleus accumbens (58). Changes in the dopamine 5-HT interaction might explain why DOI impairs performance of rats in our attentional test paradigm. The peripheral effects of DOI, however, cannot be excluded.

The relevance of the present results to the neurobiology of ADHD is a subject for speculation at the moment. ADHD is more common among boys than girls (5), and it can persist beyond adolescence. Furthermore, males are considered to be more impulsive than females (51,14), and adult men have a higher mean rate of serotonin synthesis than females (32). Moreover, Biver et al. (3) reported that men have a higher 5-HT_2 receptor binding capacity than women, especially in the frontal cortex and cingulate cortices.

In conclusion, the present study demonstrates that systemic administration of the 5-HT_2 agonist, DOI, increases premature responding without affecting choice accuracy in the 5-CSRT task. This DOI-induced enhancement in premature responding is not due simply to locomotor hyperactivity of the rats. The anterior cingulate cortex is not the primary site of action for DOI to increase this impulsive-like behavior.

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