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Spontaneous Alternation Behavior: An Animal Model for Obsessive-Compulsive Disorder?

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YADIN, E., E. FRIEDMAN AND W. H. BRIDGER. *Spontaneous alternation behavior: An animal model for obsessive-compulsive disorder?* PHARMACOL BIOCHEM BEHAV **40**(2) 311–315, 1991.—This study entailed the adoption of a well-established behavioral paradigm, spontaneous alternation, as a possible animal model for some of the symptoms observed in obsessive-compulsive disorder (OCD) in humans. Food-deprived rats were run in a T-maze in which both a black and a white goal box were equally baited with a small amount of chocolate milk. Each rat was given 7 trials every other day during which it was placed in the start box and allowed to make a choice. The mean number of choices until an alternation occurred was recorded. After a stable baseline of spontaneous alternation was achieved the effects of manipulating the serotonergic system were tested. Both the nonselective 5-HT agonist 5-MeODMT (1.25 mg/kg) and the more selective 5-HT_{1A} agonist 8-OH-DPAT (2 mg/kg) disrupted spontaneous alternation. A course of chronic treatment (2 × 5 mg/kg for 21 days) with the selective 5-HT uptake blocking agent fluoxetine had a protective effect on the 5-MeODMT-induced disruption of spontaneous alternation behavior. Serotonergic manipulations of spontaneous alternation may be a simple animal model for the perseverative symptoms or indecisiveness seen in people diagnosed with OCD.

Obsessive-compulsive disorder Spontaneous alternation Serotonin 5-MeODMT 8-OH-DPAT Fluoxetine

SPONTANEOUS alternation behavior (SAB) is the natural tendency of most species of animals to successively explore both arms of a T-maze, provided the two goal boxes are not differentially reinforced (2,10). Numerous manipulations and agents have been tested in the spontaneous alternation task, some of which have been shown to produce marked deficits (13). A deficit in this paradigm is seen as an increased tendency to repeat a choice of the same goal arm. Thus, for example, septal and hippocampal lesions consistently reduce SAB, presumably by affecting cue salience (14,16). Among pharmacological agents that have been shown to affect SAB are amphetamine and scopolamine (7).

The spontaneous alternation paradigm possesses some 'design features' that might make it suitable as an animal model for obsessive-compulsive disorder. Obsessive-compulsive disorder (OCD) is a debilitating disease characterized by obsessional thoughts, repetitive ritualistic behaviors, and indecisiveness which can seriously affect normal functioning. As mentioned earlier, spontaneous alternation consists of a choice situation which, under certain drug conditions, can result in perseverative tendencies. The purpose of this study was to evaluate the adequacy of this paradigm as a possible animal model for some aspects of the human disorder.

METHOD

Subjects

Male albino Sprague-Dawley rats obtained from Zivic-Miller, weighing 250–300 g at the start of the experiment, were housed in groups of 3 in a climate-controlled colony with the 12-h light portion of the dark/light cycle beginning at 7:00 a.m. They had free access to water and were maintained on a food-deprivation schedule of 24 h every other day. Testing was carried out between 1:00 and 4:00 p.m. on alternate days.

Apparatus

The testing apparatus for spontaneous alternation was a black Plexiglas T-maze with distinctive white and black goal boxes (10). All arms (including the start box and the two goal boxes) measured 50 × 10 cm. Black guillotine doors separated the start box and the goal boxes from the main body of the maze. Small plastic cups were placed in the corners of both goal boxes. The maze was covered with clear Plexiglas lids.

The apparatus used for testing cognitive function was a water-maze (11). It measured 130 cm in diameter, with a 50 cm rim and contained a clear glass platform, 10 cm in diameter, which was submerged 3 cm below water level.

Drugs

The nonselective serotonin agonist 5-methoxy-N,N-dimethyl tryptamine (5-MeODMT, Sigma) was dissolved in saline containing a few drops of glacial acetic acid. The selective 5-HT_{1A} agonist 8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide (8-OH-DPAT, RBI) was dissolved in saline. The serotonin uptake blocking agent fluoxetine (FLX, a gift from Eli Lilly) was dissolved in distilled water.

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Procedure

Spontaneous alternation training. Animals were first exposed to chocolate milk in their home cages in order to acquaint them with the novel food, thus reducing neophobia. They were then habituated to the T-maze for 20 min during which they were allowed to explore the entire area. They were then confined for 5 min in each goal box (counterbalanced for order of placement) where chocolate milk was available. During the following session rats were placed in the start box, the guillotine door was lifted and they were allowed to choose either of the goal arms, both of which were baited with chocolate milk. After drinking the milk they were removed, placed in a holding cage for an average of 10 s, the empty milk cup refilled and the same procedure repeated. After two or three of these 2-choice sessions were administered the same procedure was used for a total of 7 runs per session. Both the latency to reach the goal box (in s, up to a maximum of 90 s) and the choice made by the animal (right or left) were recorded. The measure taken was the mean number of goal arm choices made until an alternation occurred. According to this method, proficient spontaneous alternators would score a 1.0 and perseverators would score a 7.0.

Acute drug testing. After a stable baseline of alternation was achieved animals were injected in one experiment with 5-MeODMT (1.25 mg/kg, IP) and in another experiment with 8-OH-DPAT (2 mg/kg, IP), and their behavior monitored in the maze 5 and 15 min later, respectively.

Chronic drug testing. Naive animals were trained in the maze and then injected daily with two doses of 5 mg/kg fluoxetine or its distilled water vehicle (DW), for 21 days. They were tested in the maze every other day. On day 22, all animals were challenged in one experiment with 5-MeODMT (1.25 mg/kg, IP) and in another experiment with 8-OH-DPAT (2 mg/kg, IP), and tested in the maze.

Water-maze testing. Naive animals were trained in a water maze to reach a submerged platform. Each daily session consisted of 6 trials, with a 10-min intertrial interval. After 3 such sessions a drug session was run in which, after the first 3 trials, the animals were injected with either 5-MeODMT (1.25 mg/kg, IP) or 8-OH-DPAT (2 mg/kg, IP), and tested for another 3 trials. The time (in s) to reach the platform as well as the swimming course to the platform were recorded. After resuming their normal baseline behavior the same animals were subjected to a reversal procedure, during which the location of the submerged platform was shifted, and tested under the influence of either 5-MeODMT or 8-OH-DPAT. Both the time spent at the old platform location and the time to reach the new platform location were recorded.

Statistics. *t*-Tests were used to compare the animals' behavior to their own baseline performance (dependent samples) or to compare the behavior of the experimental group to its matched control group (independent samples).

RESULTS

SAB: Acute Drug Effects

The nonselective serotonin agonist 5-MeODMT significantly increased the number of repetitive choices in the T-maze compared to the same animals' behavior in an earlier baseline session, $t(10)=2.99$, $p<0.05$ (Fig. 1A). A similar effect was seen with the more selective 5-HT_{1A} agent 8-OH-DPAT, $t(11)=2.60$, $p<0.05$ (Fig. 2A). The latency measure in this experiment was the number of seconds elapsing from the time the guillotine door of the start box was lifted to the crossing of the animal's hind limbs into the goal box. The variability between individual animals on this measure was great, even during the baseline sessions, perhaps because of the necessity for constant handling of the animals in this paradigm. Therefore, the gross latency measure did not yield significant differences between the drug and the baseline conditions. It is possible that if the time spent at the choice point area itself is recorded separately, significant differences would emerge.

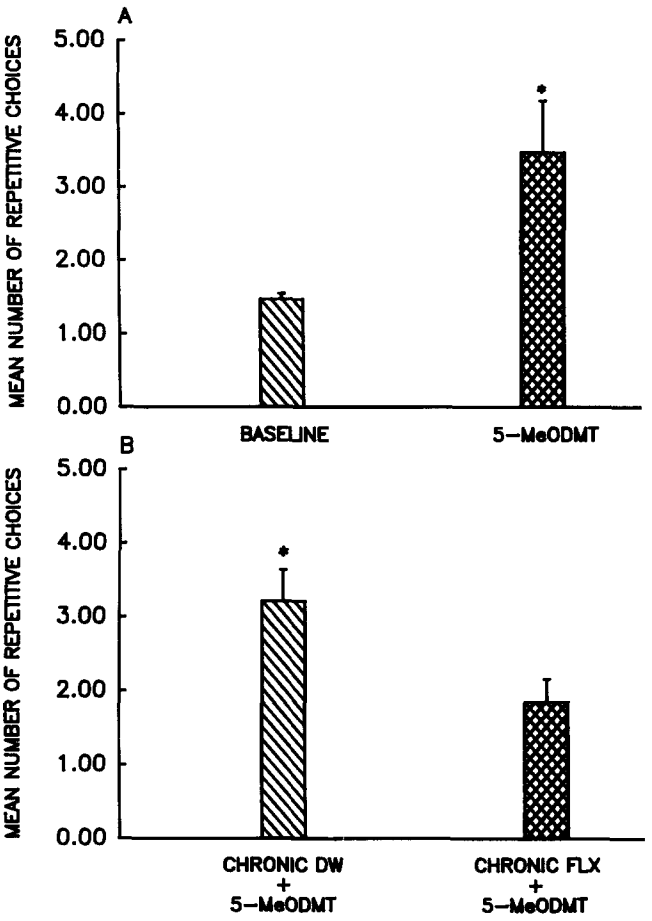

FIG. 1. (A) Spontaneous alternation behavior (the mean number of repetitive choices until an alternation occurred) in the same animals during a vehicle session (saline + a few drops of glacial acid) and during a drug treatment session (5-MeODMT, 1.25 mg/kg). *Denotes a significant difference between the two sessions. (B) Spontaneous alternation in two groups of animals, one of which was treated chronically with distilled water, the other with fluoxetine (21 days, 2×5 mg/kg), during a challenge session with 5-MeODMT (1.25 mg/kg). *Represents a significant difference between the two groups.

SAB: Chronic Drug Effects

The first dose of fluoxetine completely disrupted spontaneous alternation behavior (Fig. 3). The animals arrived at the choice point and did not proceed further into either goal box, within the set criterion for completion of a trial (90 s or even when that time was extended). As can be seen from Fig. 3, during the next few sessions, more and more animals resumed their pre-drug baseline performance. That behavior consisted of completed

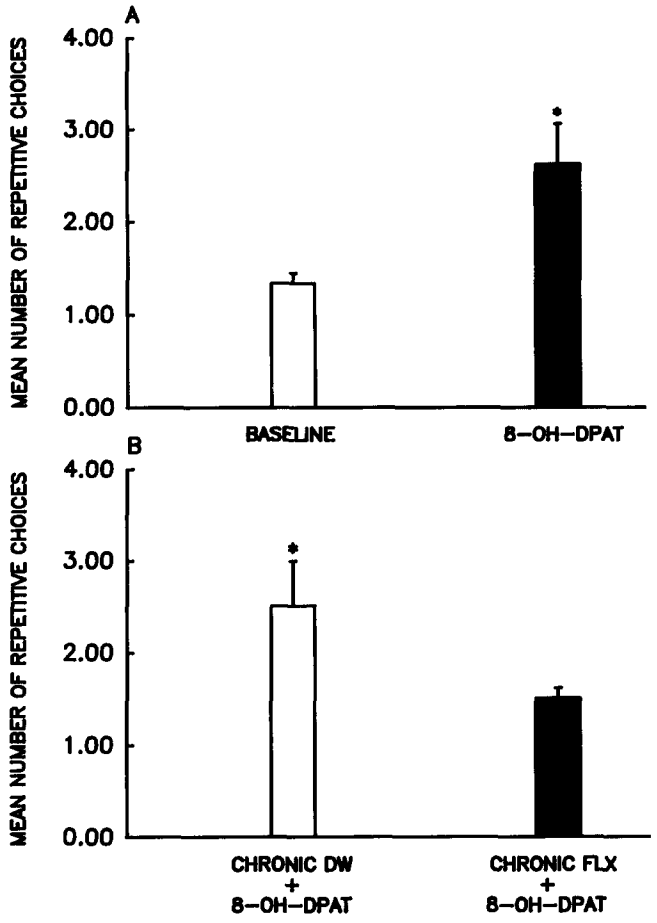

FIG. 2. (A) Spontaneous alternation in a group of animals during a vehicle session (saline) and during a drug treatment session (8-OH-DPAT, 2 mg/kg). *Marks a significant difference between the two sessions. (B) Spontaneous alternation in two groups of animals, one of which was treated chronically with distilled water, the other with fluoxetine (21 days, 2×5 mg/kg), during a challenge session with 8-OH-DPAT (2 mg/kg). *Represents a significant difference between the two groups.

trials and proficient alternation (namely, achieving a low perseveration score), a pattern that was maintained for the duration of the chronic treatment (21 days). By the end of three weeks, SAB in the fluoxetine-treated animals was no different from that of their vehicle controls. Challenged with a dose of the nonselective serotonergic agonist 5-MeODMT (Fig. 1B) or of the selective 5-HT_{1A} agonist (Fig. 2B), the animals receiving chronic vehicle injections were significantly impaired on the spontaneous alternation task while those animals receiving chronic fluoxetine injections were not, 5-MeODMT: $t(13)=2.51$, $p<0.05$; 8-OH-DPAT: $t(14)=2.26$, $p<0.05$. Once again, the latency measure did not produce significant differences between groups.

Water-Maze: Acute Drug Effects

The nonselective 5-HT agonist 5-MeODMT affected neither retention of a learned platform location nor acquisition of a new platform location (reversal). The more selective agonist 8-OH-DPAT impaired performance in the water-maze as manifested by a longer latency to reach the submerged platform 10 and 20 min

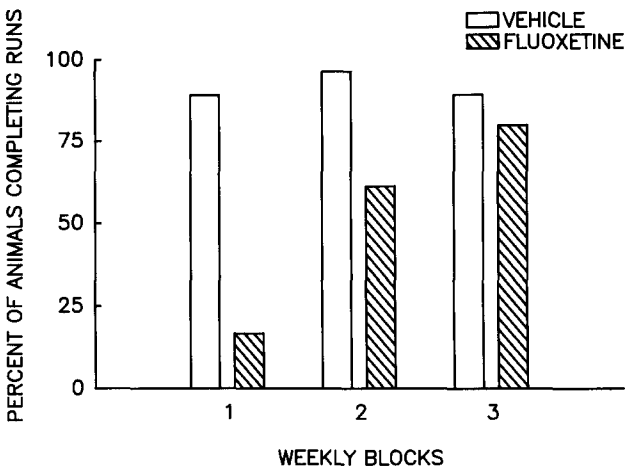

FIG. 3. The number of animals in each group, expressed as a percent of the total per group, that were able to complete the session. Each bar represents the mean of three sessions.

after the injection, >10 min: $t(12)=3.86$, $p<0.01$; >20 min: $t(12)=2.39$, $p<0.05$. In the reversal phase of the experiment animals treated with 8-OH-DPAT spent significantly more time at the old platform location than did their saline controls, $t(12)=2.78$, $p<0.05$. They were not significantly impaired in their ability to reach the new platform location.

DISCUSSION

Spontaneous alternation behavior is disrupted by serotonergic agonists injected acutely. This impairment does not appear to result from a cognitive deficit, as the animals' performance in the water-maze was either normal (with 5-MeODMT) or reflected a perseverative tendency rather than a cognitive deficit per se (with 8-OH-DPAT). Chronic treatment with the serotonin uptake blocking agent fluoxetine protected animals from the disruptive effects of the serotonergic agonists on spontaneous alternation, while the acute effect of this agent was to interfere with the performance of this task. These results seem to recommend this type of behavioral paradigm as a first approximation of an animal model for the perseverative activities and indecision seen in humans diagnosed with obsessive-compulsive disorder.

This disorder is currently estimated to afflict as many as 2% of the general population. Recent evidence has suggested that the disorder can be ameliorated in some patients by certain antidepressant drugs. Among the agents that have been most effective in reducing the symptoms of OCD are clomipramine (1, 3, 5, 17, 19) and, more recently, fluoxetine (4) and fluvoxamine (12). All these agents are potent blockers of the uptake mechanism of serotonin.

In proposing a particular paradigm (e.g., spontaneous alternation) as a candidate for an animal model of a human disorder (e.g., OCD), at least three general criteria should be met. First, the model should have some degree of face validity, namely, it should share some of the properties of the human syndrome. Deficits in spontaneous alternation are manifested as perseverative behaviors that would appear to be analogous to the repetitive motor patterns seen in human OCD patients. In addition, an increase in vicarious trial-and-error in animals with deficits would seem to mimic the apparent indecisiveness at critical decision points seen in OCD patients. Vicarious trial-and-error (VTE) is the tendency to hesitate, vacillate, and compare the alternative

stimuli by an animal arriving at a choice point (18). Rat pups treated with the dopamine (D1) agonist SKF38393 displayed increased 'vacillatory behavior' in a spontaneous alternation task, a deficit that was effectively blocked by SCH23390, buspirone and ipsapirone, and clomipramine (9,21). In the present study VTEs were observed but were not recorded and quantified. In future experiments of this sort, the behavioral patterns of the animals will be videotaped so that the total number of VTEs at the choice point can be accurately measured. Previous studies with SAB in animals found a deficit with 5-HT depletors, such as p-chloroamphetamine or p-chlorophenylalanine, or with the antagonist methysergide, only in combination with amphetamine (15). On their own these agents were without effect on SAB.

Secondly, the model should possess common etiological features with the human syndrome. Obsessive-compulsive disorder has been strongly linked to a dysfunction of the serotonergic system. Thus acutely increasing 5-HT function in OCD patients with the agonist m-CPP has been demonstrated to markedly increase obsessional symptoms, while the 5-HT receptor antagonist metergoline was associated with a decreased severity of the symptoms (23). Moreover, as mentioned earlier, the pharmacological agents that have been most successful in alleviating OC symptoms are selective serotonin uptake blockers (3).

Thirdly, the model should have predictive value. It should be able to discriminate those agents and procedures which are effective in the human disorder from those which are ineffective. So, for example, drugs such as fluoxetine and clomipramine, which have been shown to be therapeutically efficacious in human OCD, should also be effective in diminishing the deficits seen in the animal model. Other antidepressant drugs which have been shown to be ineffective in humans against this disorder (e.g., imipramine, clorgyline) should be without effect in the animal model. In humans the drugs for OCD are only effective after considerable chronic administration and, in fact, have been reported to exacerbate the symptoms during the first few days of administration (22). The time-course for the clinical effect of these agents suggests that some sort of neuronal reorganization is necessary for therapeutic action, perhaps in terms of receptor regulation. It is, therefore, particularly important that the model be able to discriminate the acute effects of the drug from its chronic effects. The drug would be expected to ameliorate the deficits produced by the serotonergic challenge dose in the model after chronic treatment and not after acute administration.

There are sporadic reports in the clinical literature of success with the 5-HT_{1A} agonist buspirone in treatment of OCD, either on its own (8), or as an augmentation to fluoxetine (20), though the rate of success is still controversial (6). None of the studies, however, reports the consequences of the acute effects of buspirone. According to the results from the animal work reported here, the acute effects of buspirone would be expected to make OC symptoms more severe at first. A therapeutic action on these symptoms would be expected after a chronic course of treatment, which is the course used in the human tests of buspirone in OCD (8,20).

The results presented here satisfy some of the criteria outlined above. Acute serotonergic activation in this behavioral task produced some features in common with the human disorder that it was designed to model, such as repetitive patterns of behavior. Moreover, chronic treatment with a selective serotonin uptake blocker protected the animals from the deficits induced by the challenging 5-HT agonists, whereas acute treatment with the blocker itself actually disrupted the spontaneous alternation. The predictive value of this model, specifically for OCD, as well as the effects of activation of the serotonergic system and its receptor subtypes on a similar behavioral task are currently being focused on. It is important to emphasize that the relationship of serotonergic manipulations on spontaneous alternation behavior in rats to OCD in humans is, by the nature of animal models, speculative. However, as a first stab at such a model it may prove to be a useful tool for further exploration. Such exploration will include the testing of agents that have been tried in humans and found to be less effective or not effective at all. These controls are necessary for the establishment of a viable model of OCD, with the capacity to predict the efficacy of newly-developed, more selective therapeutic agents that are separate from their antidepressant actions.

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