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Involvement of 5-HT_{1A} Activity in the Discriminative Stimulus Effects of Imipramine

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BARRETT, J E AND L ZHANG *Involvement of 5-HT_{1A} activity in the discriminative stimulus effects of imipramine* PHARMACOL BIOCHEM BEHAV **38**(2) 407–410, 1991 —Pigeons were trained to discriminate the tricyclic antidepressant imipramine (3.0 or 5 6 mg/kg) from saline The selective 5-HT_{1A} agonist 8-OH-DPAT (0 03–1 0 mg/kg) resulted in dose-dependent increases in responding on the key correlated with imipramine administration Doses of 8-OH-DPAT from 0 3 to 1 0 mg/kg substituted completely for imipramine NAN-190 (0 3–3 0 mg/kg), a putative 5-HT_{1A} antagonist with affinity for both 5-HT_{1A} and α_1 receptors, blocked the discriminative stimulus effects of imipramine and resulted in saline-key responding The discriminative stimulus effects of imipramine were also blocked by administration of the α_1-adrenoreceptor antagonist prazosin, suggesting a dual mediation of imipramine through both 5-HT_{1A} and α_1-adrenoreceptor systems Although antidepressants have not been used frequently as stimuli in drug discrimination studies, it may be possible to arrive at a more complete understanding of their neurochemical and behavioral effects using this procedure

5-HT_{1A} activity Imipramine Discriminative stimulus 8-OH-DPAT NAN-190 Pigeons Drug discrimination

A number of studies have suggested that the serotonin (5-HT) receptor subtype classified as 5-HT_{1A} may be involved in the action of antidepressant drugs. For example, electroconvulsive shock (ECS) and tricyclic antidepressants have been shown to decrease the hypothermic response to the 5-HT_{1A} agonists 8-OH-DPAT in rats (10) and ipsapirone in humans (13). In rats, both ECS and antidepressant administration also attenuate the behavioral syndrome produced by 8-OH-DPAT (11). Newman and Lerer (14) have shown that the degree of inhibition of forskolin-stimulated adenylate cyclase by 5-HT, a measure of 5-HT_{1A} receptor activity (6), was also reduced by chronic antidepressant administration and by ECS. These investigators suggested that the 5-HT_{1A} receptor may be a common site of action for antidepressant treatment. Other studies have demonstrated an increase in [^{3}H]8-OH-DPAT binding in the dorsal hippocampus after chronic treatment with amitriptyline (17)

Several other studies with animal models of depression have indicated that 5-HT_{1A} compounds may have antidepressant activity For example, Kennett et al. (12) observed that 8-OH-DPAT reversed stress-induced deficits in locomotor activity and Giral et al. (7) have shown that the 5-HT_{1A} compounds 8-OH-DPAT, buspirone, gepirone and ipsapirone eliminated escape failures in a learned helplessness model of depression. These studies using in vitro and in vivo methods have been supported by clinical research that implicates a role for the 5-HT_{1A} receptor in depression. Gepirone, an analog of the clinically effective anxiolytic buspirone, has been shown to exert antidepressant actions (5). Unlike buspirone, which affects dopamine, serotonin and norepinephrine neurotransmitter systems, gepirone shows selectivity for the 5-HT_{1A} receptor subtype

The purpose of the present study was to use another model to examine the possible 5-HT_{1A} effects of imipramine Previous work in which imipramine has been established as a discriminative stimulus has shown that its effects are mediated by at least NE and 5-HT (18) In pigeons trained to peck one key following imipramine administration and a different key following saline, it was found that NE uptake inhibitors (e.g , tomoxetine) and the 5-HT_{1A} compound gepirone substituted for imipramine, although gepirone did not substitute in all animals. Further, other tricyclic antidepressants such as amitriptyline and doxepin also resulted in drug-key responding. In the present study, imipramine-trained pigeons were tested with the specific 5-HT_{1A} agonist 8-OH-DPAT and with the putative 5-HT_{1A} antagonist NAN-190 (8,9) in an effort to provide further information on the possible 5-HT_{1A}-mediated actions of tricyclic antidepressants.

METHOD

Subjects

Adult male White Carneau pigeons (N = 4) were obtained from Palmetto Pigeon Plant (Sumter, SC) and maintained in individual stainless steel cages with water and crushed oyster shells continuously available. Temperature, humidity and lighting (lights on between 6 00 a.m.–8.00 p.m.) were kept constant Pigeons were maintained at 85% of their free-feeding body weights by postsession supplemental feeding of Purina Pigeon Checkers. All pigeons

had previously been trained to discriminate imipramine from saline and had been tested with a number of drugs.

Apparatus

Experiments were conducted in a two-key operant conditioning chamber that was placed inside a ventilated and sound-attenuated acoustical shell. Two response keys mounted on the front aluminum panel could be transilluminated by white lights; centered below the keys was an opening through which mixed grain could be obtained from a solenoid-operated feeder. During grain presentation, which lasted 4 s, the key lights were extinguished and the hopper area was illuminated.

Procedure

On days when saline was administered 20 min prior to the session, 30 consecutive pecks on the right key produced grain, when imipramine was administered 20 min before the session, 30 consecutive pecks on the left key produced grain. Imipramine- and saline-training sessions were arranged in a mixed sequence with never more than three drug- or saline-injection sessions occurring in a row. Two pigeons were trained with 3.0 mg/kg and two other pigeons were trained with 5.6 mg/kg imipramine. Key pecking of pigeons at the lower training dose was suppressed by the higher dose of imipramine. Different doses of imipramine, drug substitution or antagonism studies were initiated when the percentage of correct key pecks reached 90% for three consecutive sessions and, in each of those sessions, the first 30 responses occurred on the appropriate key Once these criteria were reached, substitution tests occurred on Tuesdays and Fridays, given that performance on the preceding day met the 90% correct criterion and the first 30 responses occurred on the correct key. During test days, 30 consecutive pecks on either key resulted in food delivery. When combinations of NAN-190 or prazosin with imipramine were studied, or when these drugs were administered alone, they were given 30 min before the session; 8-OH-DPAT was administered 20 min before the session. After receiving injections of appropriate compounds, animals were placed in the experimental chamber which remained dark until the session began.

Drugs

Imipramine HCl (CIBA/GEIGY Corp.) and 8-OH-DPAT HBr (RBI, Inc.) were dissolved in 0.9% saline solution. Prazosin (Pfizer) and NAN-190 (furnished by Dr. Erik Nielsen, NOVO Industri) were dissolved in water; a few drops of dilute lactic acid, sonication and gentle warming were necessary to dissolve NAN-190.

Data Analysis

The percentage of responses made on the drug-appropriate key, together with overall response rates (responses/s), was obtained for each session. These data were averaged for all four subjects to obtain measures of percent correct drug key responses and response rates at each dose and drug combination. Control values for these measures for the training drug and saline sessions were taken from successive Thursdays when either the imipramine training dose or saline was administered. There were at least 8 control sessions each for saline and imipramine.

RESULTS

Imipramine doses from 3 0–10 0 mg/kg resulted in 97–100% responding on the key correlated with imipramine administration (upper portion, Fig. 1) There were no differences in the doses at which generalization occurred, among animals trained with different doses of imipramine. The 3.0 mg/kg dose of imipramine occasioned between 87–100% responding on the drug key and all pigeons tested at the 5.6 and 10.0 mg/kg dose also responded entirely on the drug-appropriate key. One pigeon was not tested at 10.0 mg/kg because responding was markedly reduced at the 5.6 mg/kg dose. Imipramine also produced a dose-dependent decrease in response rates (lower portion, Fig. 1) compared to rates of responding after the injection of saline (open unconnected circle).

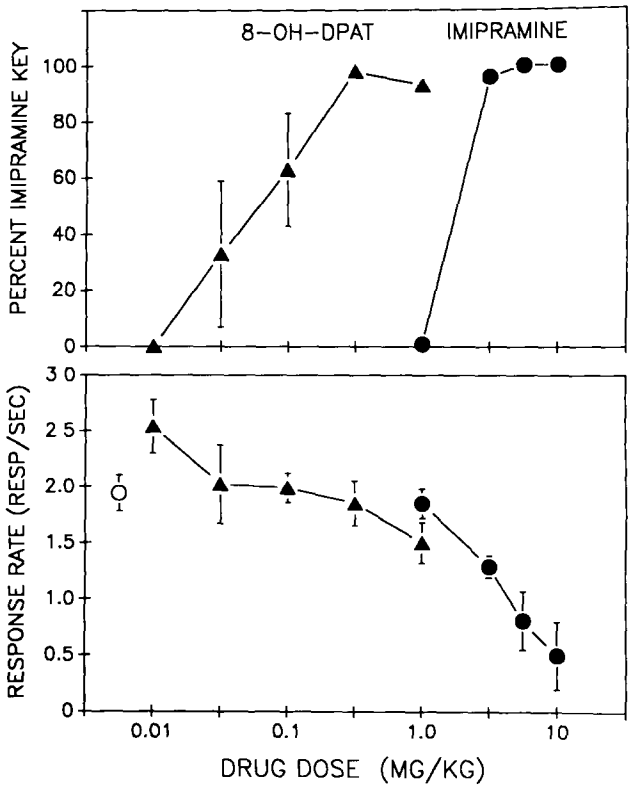

FIG 1 Dose-response curves showing percent responding on the key correlated with imipramine following different doses of imipramine or 8-OH-DPAT (top half) and effects of these drugs on rates of responding (lower half) Vertical bars denote ±1 S E , when there are no vertical lines, variability was encompassed by the point The open unconnected circle in the lower figure represents response rates following saline

Administration of 8-OH-DPAT produced dose-dependent increases in imipramine-key responding (upper portion, Fig. 1) with doses of 0.3 and 1.0 mg/kg occasioning between 93–98% drug-appropriate responding. Pigeons trained at the 3.0 mg/kg dose of imipramine were slightly more sensitive to imipramine in that the 0.1 dose of 8-OH-DPAT yielded 97–98% drug-key responses, whereas the two pigeons trained at 5.6 mg/kg imipramine made 0 and 56% imipramine- key responses at this dose of 8-OH-DPAT Higher doses of 8-OH-DPAT produced consistent responding on the drug-appropriate key that exceeded 96% in all animals.

Rates of responding with 8-OH-DPAT are shown in the lower portion of Fig 1 At doses of 8-OH-DPAT that resulted in imipramine-key responding (0 3–1 0 mg/kg), response rates were not different from those obtained following the administration of saline

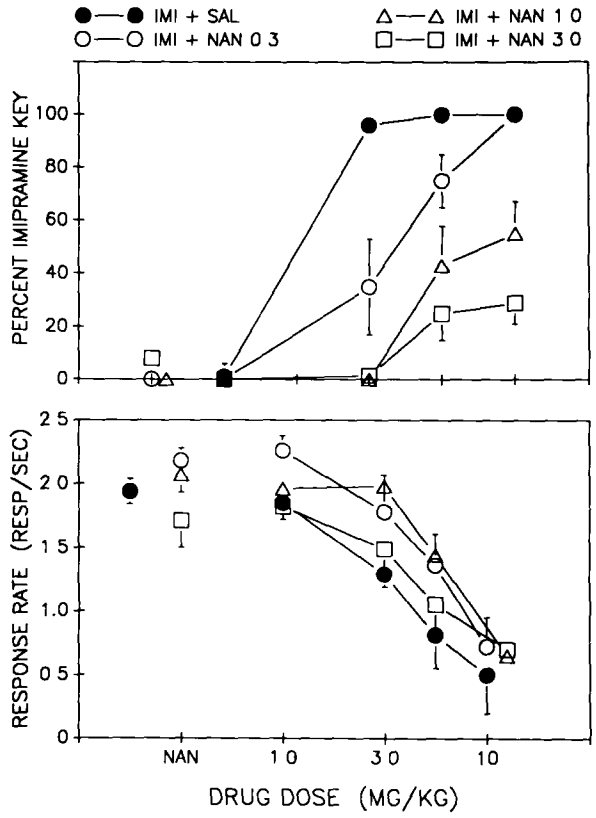

FIG 2 Antagonism of the discriminative stimulus effects of imipramine by NAN-190 Top half Percent imipramine-key responding with 3 doses of NAN-190, lower half effects on response rate of imipramine alone and in combination with NAN-190 The open unconnected symbols on the left represent effects of NAN-190 alone, the filled unconnected circle represents effects of saline on response rate Vertical bars represent ±1 S E

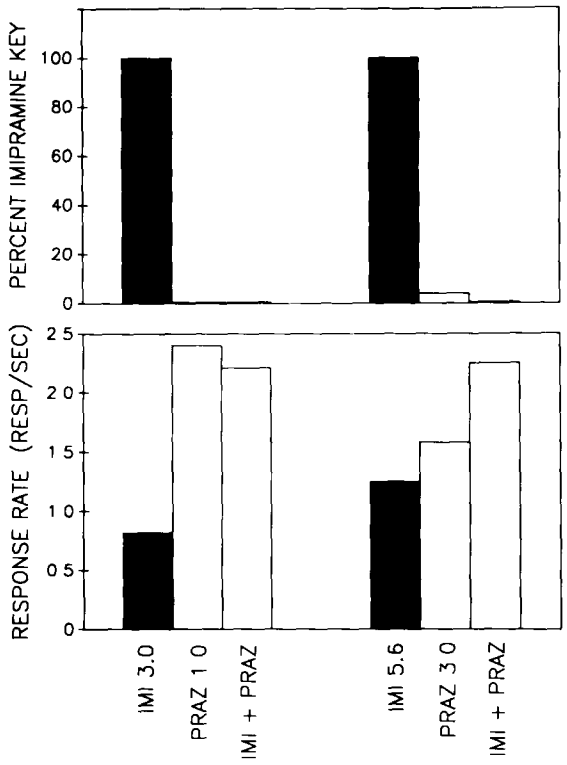

FIG 3 Effects of prazosin 1 0 (left) or 3 0 (right) mg/kg on discriminative stimulus effects (top) and response rate (bottom) of 3 0 and 5 6 mg/kg imipramine

Antagonism Studies

Doses of NAN-190 between 0 3–3.0 mg/kg did not result in more than 8% responding on the drug-appropriate key (Fig. 2, top half). Administration of NAN-190 in combination with imipramine resulted in a dose-dependent reduction in responding on the imipramine key. The 3.0 mg/kg dose of NAN-190 in combination with imipramine resulted in, at most, 25% imipramine-appropriate responding

NAN-190 also attenuated the rate-decreasing effects of imipramine (lower portion, Fig 2). Administered alone, NAN-190 did not markedly alter response rates, although the highest dose of 3.0 mg/kg resulted in a slight reduction in responding. The lower doses of 0 3 and 1.0 mg/kg NAN-190 produced a more effective reversal of the rate-decreasing effects of intermediate doses of imipramine than the highest dose of NAN-190.

Figure 3 shows effects of 1.0 mg/kg prazosin alone and in combination with 3.0 and 5.6 mg/kg imipramine Prazosin completely blocked the discriminative stimulus and rate-decreasing effects of imipramine at doses of prazosin that, when given alone, had no effect. Response rates were completely restored to saline control levels with prazosin-imipramine combinations.

DISCUSSION

In the present experiment imipramine was an effective discriminative stimulus in controlling key-pecking. Responding on the drug-appropriate key was related to dose and the discrimination was maintained at high levels throughout the course of the study Previously, the imipramine discriminative stimulus was shown to be related to NE and, possibly, to 5-HT in that the NE reuptake inhibitor tomoxetine completely substituted for imipramine, and gepirone, a 5-HT$_{1A}$ agonist, occasioned imipramine-key responding in 3 of 4 animals (18). In the present study, the selective 5-HT$_{1A}$ agonist 8-OH-DPAT substituted completely in all pigeons, suggesting a clear role for 5-HT$_{1A}$ in mediating the discriminative stimulus effects of imipramine As such, these results support previous studies implicating an involvement of the 5-HT$_{1A}$ receptor in the action of antidepressant drugs (10–12, 14)

Blockade of the imipramine stimulus by NAN-190 also supports a role for the 5-HT$_{1A}$ receptor in the actions of imipramine since this compound has also been shown to block the discriminative stimulus effects of 8-OH-DPAT (3,8). Although NAN-190 has high affinity for α_1-adrenergic binding sites (9), prazosin did not block the discriminative control of behavior by 8-OH-DPAT (1,8), suggesting that the blockade of 8-OH-DPAT by NAN-190 was through the 5-HT$_{1A}$ mechanism. Results obtained in the present study, although clearly identifying a role of 5-HT$_{1A}$ in imipramine's discriminative stimulus effects, also strongly implicate α_1-adrenergic receptor activity. Prazosin completely blocked the discriminative stimulus and rate-decreasing effects of imipramine, this antagonism of response rate was more effective than occurred with NAN-190. On the basis of the substitution by 8-OH-DPAT and the antagonism by prazosin, it seems clear that

the effects of imipramine are mediated through both the 5-HT_{1A} and α_1-systems.

Considerable biochemical evidence exists for the role of 5-HT in the actions of antidepressant drugs. Evidence also exists for supersensitivity of the α_1-adrenergic system in long-term effects of antidepressant administration (4). A number of suggestions have also been made concerning the complex interactions between 5-HT and NE and the role such interactions may play in affective disorders (15,16). The data obtained in the present study support these views and suggest that this procedure with pigeons may provide a valuable behavioral means for evaluating the neurochemical bases of action of antidepressant drugs. It has been difficult using rodents to establish a reliable, long-term discrimination based on most antidepressant drugs (1). Training doses have typically been high, resulting in toxicity, and little information is currently available on this important drug class using drug discrimination methods. The results of the present study, together with previous related work (18), suggest that the pigeon may be as useful an animal model for detailed behavioral and neuropharmacological analysis of antidepressant drugs as it has been with novel anxiolytic compounds (2).

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