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Interactions of Clozapine With the Stimulus Effects of DOM and LSD

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PALUMBO, P. A. AND J. C. WINTER. *Interactions of clozapine with the stimulus effects of DOM and LSD.* PHARMACOL BIOCHEM BEHAV **49**(1) 115–120, 1994. – Two groups of rats were trained with the 5-HT_2 agonists 2,5-dimethoxy-4-methylamphetamine (DOM) or lysergic acid diethylamide (LSD) in a two-lever discrimination task. Tests of generalization and antagonism were then carried out with clozapine. DOM did not generalize to clozapine. Partial antagonism of DOM was observed with 0.3, 1, and 2 mg/kg clozapine and statistically significant full antagonism with 3 mg/kg. LSD did not fully generalize to clozapine. Partial antagonism of LSD was observed with 3 and 4 mg/kg clozapine. Because clozapine is known to block muscarinic as well as 5-HT_2 receptors, atropine was studied in DOM-trained rats. DOM partially generalized to 3 mg/kg atropine. Partial attenuation of DOM stimulus effects was observed with 3 mg/kg atropine, and no attenuation with 5 mg/kg. A combination of 2 mg/kg clozapine and 3 mg/kg atropine vs. DOM produced response suppression in five of seven rats. The atropine test results do not exclude the possibility of an antimuscarinic component in the observed attenuation of DOM and LSD stimulus effects by clozapine.

Clozapine DOM LSD Atropine Stimulus control Rats Serotonin receptors

CLOZAPINE, an atypical antipsychotic drug, is known to affect multiple central neurotransmitter systems. All antipsychotics, including clozapine, have been believed to produce their therapeutic effects primarily by blockade of the dopamine D_2 receptor (19,20,29). The superior efficacy of clozapine and its reduced liability for causing extrapyramidal side effects (EPS) have been attributed to either activity at D_1 receptors in conjunction with D_2 effects (1,2,6), or blockade of 5-HT_2 receptors together with D_2 effects (3,28). In particular, with regard to the latter possibility, 5-HT_2 antagonism apparently alleviates the negative symptoms of schizophrenia (autism, dysphoria, depression, etc.), and may be responsible for the lower incidence of extrapyramidal side effects (5,11). Blockade of D_2 receptors seems to be more effective in the relief of the positive symptoms of schizophrenia (delusions, hallucinations, thought disorders, etc.) (11).

Clozapine also binds to muscarinic receptors, acting as an antagonist (8,21,31). It has been suggested that this action explains the reduced incidence of EPS observed with clozapine therapy (8,21,31). In a drug discrimination study, clozapine-trained rats generalized to the antimuscarinics atropine, scopolamine, and fluperlapine, but not to the 5-HT_2 antagonist ketanserin (25). These results were interpreted as evidence that muscarinic antagonism is the primary component of the clozapine discriminative cue (25).

The stimulus effects of 2,5-dimethoxy-4-methylamphetamine (DOM) generalized to those of quipazine and lysergic acid diethylamide (LSD) (13,30) in drug discrimination studies. Because the stimulus effects produced by LSD, DOM, and quipazine are blocked by the 5-HT_2 antagonists pirenpirone (7,13) and ketanserin (13,26), it appears that these effects are dependent upon the 5-HT_2 site. The discriminative stimulus effects of quipazine in rats were antagonized by clozapine, and it was concluded by Friedman and co-workers (10) that clozapine was acting as a serotonin antagonist. However, it is interesting to note that although the stimulus effects of quipazine were blocked by both clozapine and ketanserin (10,13), clozapine-trained rats did not generalize to ketanserin (25). Also, clozapine did not block the LSD discriminative cue in monkeys (24).

In the present study, an attempt was made to block the discriminative stimulus effects of DOM and LSD with cloza-

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pine, and to investigate whether 5-HT_2 blockade, rather than blockade at muscarinic receptor types, is, indeed, responsible for any observed attenuation of the discriminative stimulus effects. To this end, atropine, the prototypic muscarinic antagonist, was also administered as a potential antagonist in DOM-trained rats.

METHOD

Animals

Male Fischer-344 rats were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA). They were housed in pairs under a natural light : dark cycle and allowed free access to water in the home cage. Subjects were food deprived, and maintained at weights ranging from 280–380 g.

Apparatus

Two small animal test chambers (Colbourn Instruments model E 10-10) were used for all experiments. These were housed in larger light-proof, sound insulated boxes, which contained a house light and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper, which delivered 0.1 ml of sweetened condensed milk diluted 3 : 1 with tap water.

Procedure

Training. After learning to drink from the dipper, subjects were trained to depress first one and then the other of the two levers. The number of responses required before reinforcement was given was gradually increased from 1 to 10, and all subsequent training and testing involved a fixed-ratio 10 schedule of reinforcement. Subjects were then assigned to one of two groups, and discrimination training was begun. Prior to a 10-min training session, animals received either an intraperitoneal (IP) drug injection or no treatment. Following drug administration, every tenth response on the lever designated as drug appropriate was reinforced. Similarly, responses on the opposite lever were reinforced in the absence of treatment. For one-half the subjects in each group, the left lever was designated as the drug-appropriate lever. The right lever was drug appropriate for the remaining animals. Each rat was subjected to one training session per day for 5 consecutive days per week. Training conditions were alternated on this basis: no treatment on Monday, Wednesday, and Friday, and drug treatment on Tuesday and Thursday. For groups I and II, the training drugs were DOM and LSD, respectively. Drug injections were given 15 min before drug training sessions. The original training doses were 0.6 mg/kg DOM and 0.1 mg/kg LSD, based on reports in the literature in which these doses served as effective discriminative stimuli (16,27,34). Rats were trained to criterion performance of 83% or more of all responses prior to delivery of the first reinforcer on the appropriate lever. Stimulus control was assumed to be present when criterion performance was maintained for five consecutive training sessions. However, because of interanimal variation, a limited range of doses was employed to maintain criterion performance without response suppression. For DOM, the mean training dose was 0.5 mg/kg (range 0.3 to 0.7 mg/kg), and for LSD, the mean training dose was 0.11 mg/kg (range 0.08 to 0.15 mg/kg).

Tests of generalization. After drug-induced stimulus control was established, generalization tests or tests of antagonism were conducted in groups I and II. Tests were conducted once per week (on Thursday or Friday) in each animal as long as performance during the preceeding training sessions did not fall below a criterion of 83% correct responding. Thus, a minimum of three training sessions separated test sessions. If an animal did not perform according to the 83% correct criterion, testing was resumed only after responses were 83% correct before the first reinforcement for five consecutive training sessions. In general, tests with a given dose of drug or drug plus antagonist were balanced between Thursdays (following no treatment training sessions) and Fridays (following drug training sessions). During test sessions, no responses were reinforced, and the session was terminated after the emission of ten responses on either lever. The distribution of the responses between the two levers was expressed as the percentage of the total responses emitted on the drug-appropriate lever.

In order to ascertain that the injection procedure itself was not the basis for the observed discrimination, animals received vehicle generalization tests. Animals were injected with 0.9% saline solution and tested 15 min later. For clozapine and atropine generalization tests, animals were injected with drug 30 min prior to test sessions. When animals were tested with DOM or LSD together with clozapine and/or atropine, the latter drugs were injected 30 min before, and DOM or LSD 15 min before the test session.

Drugs

Racemic 2,5-dimethoxy-4-methylamphetamine (DOM) and (+)-lysergic acid diethylamide(+)-tartrate (LSD) were provided by the National Institute on Drug Abuse, Rockville, MD. Atropine sulfate was purchased from the Sigma Chemical Company, St. Louis, MO. These drugs were dissolved in 0.9% saline solution. Clozapine was obtained from Sandoz Pharmaceuticals, East Hanover, NJ. This was dissolved in a minimum amount of 85% lactic acid and diluted to volume with distilled water.

Statistics

Comparisons were made between data from test sessions and data from immediately preceeding training sessions. Paired *t*-tests were used to determine the statistical significance of observed differences in response distribution (15). A difference was considered to be significant when the calculated value of t exceeded the tabulated value of t at the 5% level.

RESULTS

Generalization tests with the potential antagonist clozapine were conducted in DOM-trained rats. This was done to approximate a dosage range for use in tests of antagonism and to determine whether there were any similarities between the stimulus effects of DOM and those of clozapine that might influence results of tests of antagonism. As shown in Fig. 1, rats trained to discriminate DOM did not generalize to clozapine. Because 3 mg/kg clozapine suppressed responding in the first five animals tested, no further tests were conducted at this dose. Doses of 1 and 2 mg/kg clozapine produced no treatment-appropriate responding.

Results of tests of antagonism conducted in DOM-trained rats are also shown in Fig. 1. Clozapine doses of 0.3, 1, and 2 mg/kg produced intermediate responding, i.e., responding that was significantly different from both drug- and no treatment-appropriate responding. This suggests that partial antagonism of DOM stimulus effects occurred at these doses. At 3 mg/kg clozapine, 37.6% of responses were emitted on the DOM-appropriate lever. This was significantly different from DOM-appropriate responding, and was not different from no

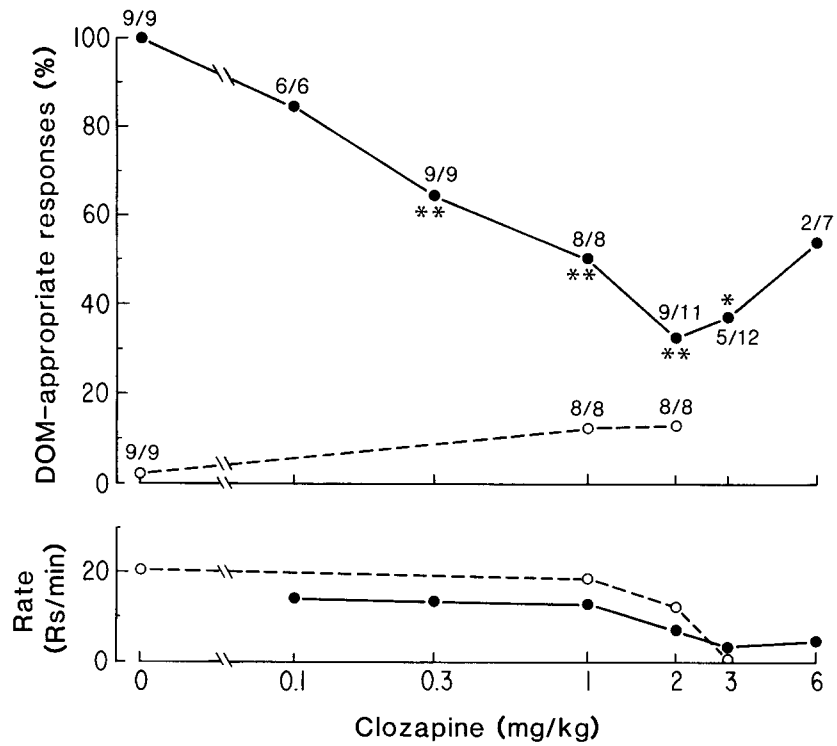

FIG. 1. The effects of clozapine alone (open circles) and in the presence of the DOM training dose (closed circles) in rats trained with DOM as a discriminative stimulus. Clozapine and DOM were injected 30 min and 15 min, respectively, before testing. Abcissa: dose of clozapine plotted on a log scale. Ordinate, upper panel: Mean percentage of responses on the DOM-appropriate lever. n/N next to each point is the number of animals completing test sessions out of the number of animals tested. Each point is the mean of one determination in each of n animals. The open circle shown at the 0 dose level is the result of tests with saline alone. The closed circle shown at the zero dose level is the result obtained during drug training sessions that immediately preceeded saline generalization tests. A double asterisk denotes significant difference from both drug-appropriate and no treatment-appropriate responding ($p < 0.05$). A single asterisk denotes significant difference from drug-appropriate responding ($p < 0.05$) and no difference from no treatment-appropriate responding. Ordinate, lower panel: Number of responses per minute. Each point is the mean of one determination in each of N animals.

treatment-appropriate responding. Thus, a statistically significant "full" antagonism of DOM stimulus effects occurred at this dose. Because only two of seven animals were able to complete test sessions after the combination of DOM and 6 mg/kg clozapine, no statistically significant differences between test results and DOM-appropriate or no treatment-appropriate responding could be detected.

The results of generalization tests with the potential antagonist clozapine in LSD-trained rats are shown in Fig. 2. Once again, this was done to determine an approximate dosage range for tests of antagonism, and to determine whether similarities between the stimulus effects of LSD and those of clozapine might influence results of tests of antagonism. Responding after 3, 4, and 6 mg/kg was not significantly different from no treatment-appropriate responding. After 2 mg/kg, intermediate responding was observed. However, the 12.3% LSD-appropriate response level after 2 mg/kg was lower than the criterion for no treatment-appropriate responding (no more than 17% LSD-appropriate responding).

When tests of antagonism were conducted with clozapine in LSD-trained rats, intermediate results were observed at 3 and 4 mg/kg (Fig. 2). This seems to indicate partial antagonism of LSD stimulus effects. Response levels after 2 and 6 mg/kg were not significantly different from LSD-appropriate responding, indicating no antagonism at these doses. Although the response level after 6 mg/kg was 95.5% on the LSD lever, only two animals out of seven completed test sessions.

Because statistically significant "full" antagonism of DOM stimulus effects was produced by clozapine, atropine was used as a "control" antagonist vs. DOM. This was done to determine whether this prototypic muscarinic antagonist could also block DOM stimulus effects, because clozapine is known to produce antimuscarinic effects (8,21,25,31). Prior to tests of antagonism, generalization tests with atropine were conducted in DOM-trained rats. The results are shown in Fig. 3. At 10 mg/kg atropine, responding was completely suppressed in the first three animals tested, and no further tests were carried out at this dose. A dose of 3 mg/kg produced a mean DOM-appropriate response level of 31% in nine of nine animals tested, an intermediate result. A dose of 5 mg/kg produced a mean of 41.8% DOM-appropriate responses, which would

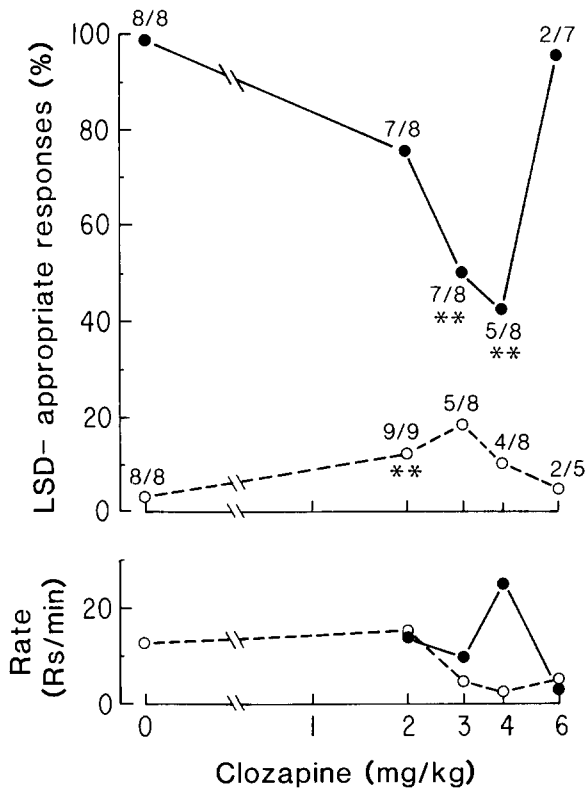

FIG. 2. The effects of clozapine alone (open circles) and in the presence of the LSD training dose (closed circles) in rats trained with LSD as a discriminative stimulus. Clozapine and LSD were injected 30 min and 15 min, respectively, before testing. Ordinate, upper panel: mean percentage of responses on the LSD-appropriate lever. Ordinate, lower panel: number of responses per minute. All other details are as in Fig. 1.

also seem to be an intermediate result. However, because only four of seven animals completed tests at this dose, no statistically significant differences could be detected between test results and DOM-appropriate and no treatment-appropriate responding.

A dose of 3 mg/kg atropine administered with the DOM training dose resulted in a mean of 60.4% DOM-appropriate responses in eight of eight animals tested, which was an intermediate result (Fig. 3). Thus, a partial attenuation of DOM stimulus properties by atropine occurred at this dose. At 5 mg/kg atropine, no antagonism was observed. A mean of 98% DOM-appropriate responses was observed in five of eight animals tested.

In an attempt to produce a more profound attenuation of DOM stimulus effects than that observed with clozapine or atropine alone, a combination of clozapine and atropine was administered along with DOM. A 2 mg/kg dose of clozapine was chosen for this experiment because at this antagonistic dose, the lowest percentage of DOM-appropriate responding was observed, and most animals were able to complete test sessions. For the same reasons, a 3 mg/kg dose of atropine was chosen. With this combination of 2 mg/kg clozapine and 3 mg/kg atropine vs. DOM, only two of seven animals were able to complete tests, and the mean response rate was 0.6 per minute. DOM-appropriate response percentages were 56% and 0%, with a mean of 28%. However, statistical conclusions could not be drawn because so few animals responded.

Administration of saline alone to DOM-trained and LSD-trained rats produced responding appropriate for the no treatment training condition (Figs. 1, 2, and 3). Points that are means of the response levels (prior to delivery of the first reinforcer) for drug training sessions that immediately preceeded the saline generalization tests are also included in Figs. 1, 2, and 3. These points serve to illustrate typical criterion levels of responding under the drug training condition.

DISCUSSION

DOM did not generalize to clozapine in DOM-trained rats. This was expected, because the stimulus effects of DOM are believed to be primarily mediated by stimulation of central 5-HT_2 receptors (7,13), although those of clozapine may largely involve central antimuscarinic effects (25) and clozapine is known to block 5-HT_2 receptors (3,28). The response suppression produced by 3 mg/kg clozapine contrasts with the results of Nielsen (25), in which eight of eight rats completed 32 lever presses after 5.76 mg/kg clozapine with a mean reaction time of only 20 s, and with the results of Friedman and co-workers (10), in which 3 mg/kg clozapine had no effect on lever pressing rates in nine rats during 20-min test sessions. These differences could be due to pharmacokinetic factors. In

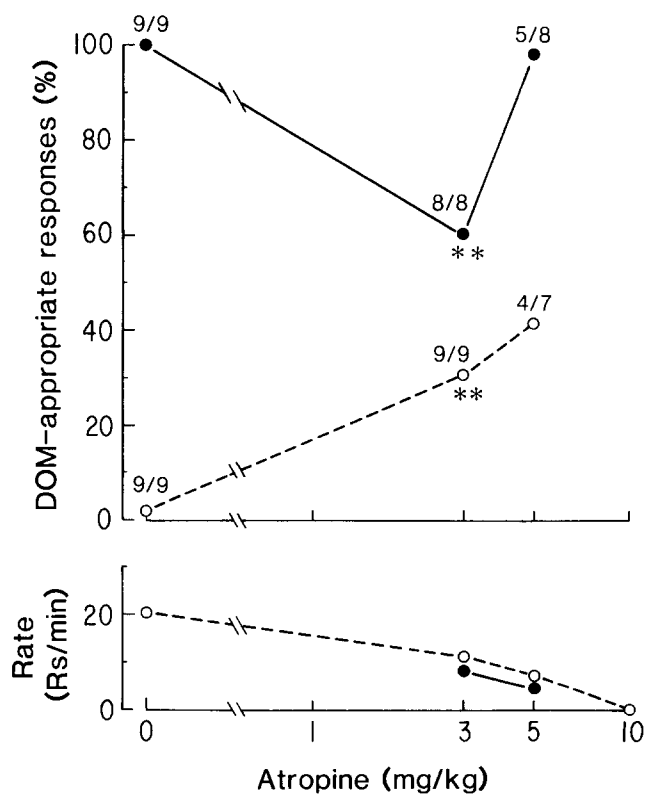

FIG. 3. The effects of atropine alone (open circles) and in the presence of the DOM training dose (closed circles) in rats trained with DOM as a discriminative stimulus. Atropine and DOM were injected 30 min and 15 min, respectively, before testing. Ordinate, upper panel: mean percentage of responses on the DOM-appropriate lever. Ordinate, lower panel: number of responses per minute. All other details are as in Fig. 1.

both studies, clozapine was dissolved in 0.2 N HCl rather than in water and lactic acid. However, in three animals tested with lactic acid solution alone vs. LSD, response rates were at least as high as rates after saline administration alone. The observed response suppressant effects of the clozapine injections were counteracted somewhat by DOM injections (Fig. 1). At 3 mg/kg clozapine plus the DOM training dose, about half of the animals (5 of 11) completed test sessions, and at 6 mg/kg clozapine plus DOM two of seven animals completed test sessions.

When 3 mg/kg clozapine was administered along with DOM, DOM-appropriate responding was reduced from 99.3% to 37.6%. Although this is a statistically significant full antagonism, it may not in reality be a full or complete antagonism of DOM stimulus effects. The antagonism is less profound than that observed with other 5-HT_2 antagonists in drug discrimination studies. Winter and Rabin (34) used pizotyline and pirenpirone to attenuate DOM-appropriate responding from approximately 100% to less than 30% and 10%, respectively. DOM response levels that were greater than 90% were reduced to 20% by ritanserin (14), to 5% by 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-s-triazolo-4,3-alpyridin-3(2H)-1-hydrochloride (THT) (14), and to 11% by methysergide (30). The observed antagonism of DOM stimulus effects by clozapine is in agreement with other reports in which the effects of 5-HT_2 agonists have been blocked by clozapine. The discriminative stimulus effects of quipazine in rats (10), the suppressant effects of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) on the firing of rat medial prefrontal cortical neurons (3), and the effects of DOM on the activity of rat locus coereleus neurons (28) were all antagonized by clozapine.

In order to investigate whether the antimuscarinic properties of clozapine might play a role in the attenuation of DOM stimulus effects, atropine was used as a potential antagonist vs. DOM. In generalization tests with atropine alone, an intermediate result was observed at 3 mg/kg (Fig. 3). Because the unique stimulus properties of a particular drug probably result from the stimulation of more than one pharmacological receptor type (4,33), intermediate responding may indicate partial similarity between the test drug and the training drug (9,32). Therefore, unexpectedly, partial similarity between the stimulus effects of DOM and atropine is suggested by this result. We are unaware of studies demonstrating interactions of DOM with muscarinic receptors or of atropine with 5-HT_2 receptors. It could be that atropine does, indeed, produce some stimulation at 5-HT_2 receptors. A second possible explanation for this result is suggested by studies on cyclohexamide-induced amnesia in mice. Cyclohexamide-induced amnesia is reversed by the nonselective 5-HT antagonist methysergide, by the selective 5-HT_2 antagonist ritanserin (22), and by the muscarinic agonist physostigmine (23). The antiamnesic effects of ritanserin were antagonized by scopolamine and by 5-HT (22). It is suggested that cholinergic and serotonergic systems may be closely linked in memory processes (22), and it seems that central muscarinic block and central 5-HT stimulation may produce similar physiological effects in the brain. In light of these studies, it does not seem surprising that DOM and atropine may have some central actions in common that may be responsible for the observed partial similarity between their stimulus effects.

Atropine produced partial antagonism or attenuation of the DOM training dose at 3 mg/kg. This contrasts with the above reported partial generalization of DOM to atropine, and suggests that DOM may produce, directly or indirectly, some degree of central muscarinic activity. Thus, it may be that the attenuation of DOM stimulus effects by clozapine is caused by a combination of 5-HT_2 receptor antagonism and physiological antagonism mediated by muscarinic receptor blockade. Alternatively, atropine may produce agonistic effects at 5-HT_2 receptors, with a lower affinity and/or intrinsic activity at these receptors as compared to DOM. This could explain the partial attenuation of DOM-appropriate responding by 3 mg/kg atropine, and the rebound to DOM-appropriate responding when 5 mg/kg atropine is given with the DOM training dose. This possibility is supported by the partial generalization of DOM to 3 mg/kg atropine. The lack of attenuation of DOM stimulus effects by atropine at a dose of 5 mg/kg is consistent with the partial similarity observed between the stimulus effects of DOM and atropine, and with the results of the cyclohexamide-induced amnesia studies discussed above.

When 3 mg/kg atropine and 2 mg/kg clozapine were administered together vs. DOM, too few animals (two out of seven) responded for any concrete conclusions to be drawn. The mean response level on the DOM-appropriate lever, 28%, was similar to the mean after 2 mg/kg clozapine alone (32.9%).

In LSD-trained rats, doses of 3, 4, and 6 mg/kg clozapine produced response suppression in three of eight, four of eight, and three of five animals, respectively. Once again, this contrasts with the lack of effect of clozapine on lever pressing response rates observed by Nielsen (25) and by Friedman and co-workers (10). The intermediate result observed with 2 mg/kg clozapine would seem to indicate partial similarity between the stimulus effects of LSD and clozapine. Although the difference between the test and no treatment control response levels is statistically significant, the 12.3% response level was lower than the criterion for no treatment-appropriate responding (no more than 17% of responses on the LSD lever). It may be that the intermediate result is merely an artifact, perhaps due to the excellent no treatment control results.

LSD is believed to produce its stimulus effects primarily by 5-HT_2 agonistic activity (12), and its stimulus effects in rats are blocked by the 5-HT_2 antagonists pizotyline (34), pirenpirone (7,34), ketanserin (13), and ritanserin (18). Because clozapine is a 5-HT_2 antagonist (3,28), full antagonism of LSD by clozapine was predicted. The observed partial antagonism of LSD by clozapine does not quite agree with the above-mentioned studies. The present results in rats contrast in the opposite respect with the results of Nielsen (24) in monkeys. In Nielsen's study, clozapine, and also pizotyline, did not antagonize the stimulus effects of LSD. Furthermore, pirenpirone and ketanserin produced only partial antagonism of LSD stimulus effects. Nielsen (24) concluded that LSD stimulus effects may be primarily mediated by 5-HT_1 receptor types, because MDMT, which binds with higher affinity at 5-HT_1 than at 5-HT_2 sites (17,34), substituted for LSD.

In summary, clozapine produced a statistically significant full antagonism of DOM stimulus effects, and a partial antagonism of the stimulus effects of LSD. Antagonism was expected because DOM and LSD are agonists at 5-HT_2 and clozapine is a 5-HT_2 antagonist. However, because atropine also partially attenuated the stimulus effects of DOM, and clozapine is known to block muscarinic receptors, an antimuscarinic component in the observed antagonistic actions of clozapine cannot be ruled out.

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