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BEHAVIORAL EFFECTS OF (±)-1-(2,5-DIMETHOXY-4-IODOPHENYL)-2-AMINOPROPANE, (DOI) IN THE ELEVATED PLUS-MAZE TEST

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Summary

The serotonin (5-hydroxytryptamine, 5-HT) system has consistently been implicated in the actions of (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and other hallucinogens. Recent evidence suggest that the 5-$HT_{2A/2C}$ receptor subtypes may be major targets for such drugs in the CNS. DOI-treated hooded rats (0.1-5.0 mg/kg) and DOI treated ICR mice (0.1-2.0 mg/kg), displayed aversions at lower doses and anti-aversions at higher doses to the open arms of the plus-maze. Mianserin (0.5 mg/kg) and ketanserin (0.1 mg/kg) blocked the anti-aversive behavior, but only mianserin was effective at reversing the aversions produced by the higher doses of DOI in the ICR mice. DOI produced an intense aversion in the DBA/2 and anti-aversion in the C57/BL6 mice to the open arms of the plus-maze. These opposing actions of DOI in the plus-maze may be exploited in studying the neurobehavioral effects of hallucinogens. Since flumazenil was ineffective at blocking the DOI induced changes, it was concluded that the mechanism of DOI induced anxiolysis or anxiogenesis may not involve an action at the benzodiazepine receptors.

Key Words: DOI, behavior, mice strains, elevated plus-maze, 5-$HT_{2A/2C}$, hallucinogen

The mechanism(s) by which (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and other hallucinogens exert their behavioral effects in animals and man is not well-understood.

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However, a number of experimental evidence have consistently implicated the neuronal serotonergic systems as major targets of hallucinogenic activity in the central nervous system (1-4). The serotonin (5-hyroxytrptamine, 5-HT) receptors have been the subject of intense investigations and the complexity revealed by the application of molecular biology techniques has resulted in the reclassification of 5-HT receptors based on their operational, transductional and structural characteristics (for a review, see 5). Activation of the central serotonin 5-HT_{2A} (formerly 5-HT_2) receptor subtype is believed to be the primary mechanism whereby hallucinogens induce their psychotomimetic effects (6). Recent research on the action of DOI has focused on the 5-$HT_{2A/2C}$ receptor subtypes (3) since the 5-HT_{2B} receptor gene is poorly expressed in the brain (7). The 5-$HT_{2A/2C}$ receptor subtypes have also been associated with a variety of disease states, including depression and schizophrenia (8) and anxiety (9). Thus, the use of 5-$HT_{2A/2C}$ receptor antagonists have been suggested for the treatment of CNS disturbances such as schizophrenia (10), affective diseases (11), hallucinations (12) and anxiety disorders (9). We and others have extensively used the elevated plus-maze to study anxiolysis and anxiogenesis induced by a number of abused substances including cannabinoids (13), benzodiazepines (14, 15), alcohol (16) and psychostimulants (17). The elevated plus-maze exploits the aversions generated in the mouse or rat by a novel test situation. This aversion is induced by placing the animals on an elevated open arm with the appropriate novelity and openness crucial for generating the behavioral and physiological changes. Anxiolytics, such as diazepam, increase the time spent and number of entries into the open arms, whereas the converse is true for anxiogenic drugs (18). The use of the elevated plus-maze may be prone to false positives and false negatives, particularly when the drug also affects motor function.

In the present study, we have evaluated the performance of rats and mice in the elevated plus-maze test system following acute treatment with the phenylalkylamine hallucinogen, DOI. The results indicate that the hallucinogenic drug elicited aversive and anti-aversive behavior to the open arms of the plus-maze which was dose, species and strain dependent. The ability of mianserin and ketanserin which show some differential selectivity for 5-$HT_{2A/2C}$ receptors to antagonize the effects of DOI was investigated. Furthermore, the involvement of the benzodiazepine receptors in the behavioral effects of DOI in the elevated plus-maze test was determined. The results suggest that an action at 5-$HT_{2A/2C}$ receptors mediates these effects.

Methods

Subjects

Male hooded rats weighing 200-250 g (Charles River, Long Evan strain) and three mouse strains 20-30g (Charles River Laboratories, ICR, DBA/2 and C57BL/6) were used as subjects for these experiments. The rats were housed in pairs in stainless steel cages while the mice were housed in groups of five according to their strains on a 12-h L : 12-h D cycle at a room temperature of 22 ± 1°C. Animals had free access to Purina Rat Chow and water at all times. The animals were habituated to the testing room which was dimly illuminated with a 60-W red bulb. After 1 h of habituation to the new environment, drug or vehicle administration commenced, followed by behavioral testing. All experiments were performed between 0830 and 1700 h.

Apparatus

The elevated plus-mazes for mice and rats were of different dimensions as the weight and size of the mouse is usually ten times smaller than the rat. Both the rat and mouse mazes are similar to that validated and described by Pellow *et al.*, (19) and by Lister, (20), respectively. The plus-maze test system has been automated and its use in the evaluation of changes in anxiolytic- and anxiogenic- like profile in rats and mice has been widely documented in a number of test conditions (13, 14, 15, 16, 21 and 22). Briefly, the apparatus consisted of two open arms (50 X 10 cm for rats; 30 X 5 cm for mice) and two enclosed arms (50 X 40 X 10 cm for rats; 30 X 15 X 5 cm for mice) linked by a central platform (10 X 10 cm for rats; 5 X 5 cm for mice) and arranged in a "plus sign" (+). The apparatus was made of a dark vinyl plexiglass material and mounted on a clear plastic base with 50 or 30 cm elevation above the floor for rats and mice mazes, respectively. The system was adapted for automation by including 12 pairs of infrared photocell units. The pairs of the photocells and their receivers were located (3 and 5 cm for the rat and 1 and 2 cm for the mice) above the test platform at the entrances to each of the open and closed arms and also on the diagonal medians of the central platform. Interruptions of the photocell beams by the animals were monitored via an interface (D-max 54, Newark) connected to an IBM PC. With this arrangement the movement and location of the animals during the 5-min test were continuously displayed, monitored and recorded. Testing was initiated 10 min after vehicle or agonist administration by placing each animal in the center of the plus-maze facing an open arm. The number of entries and the amount of time spent on the center platform were recorded. All measurements were performed with animals not previously used in any tests (18).

Experimental protocol

The experimental procedures were similar to those described by Pellow *et al.*, (19) according to our recent modification (22). After administration of vehicle, drug, or drug combinations, testing was initiated by placing each animal in the center of the plus-maze facing an open arm. The number of entries and time spent in the open, closed and center of the arms were recorded in the 5-min test session. Previously, the time spent in the center was usually ignored. In the present study, the time and number of entries in the center was included in the analysis of the data to present a complete profile of the behavior of the animals in the plus-maze. In the first series of experiments, the acute effects of DOI (0.1-5.0 mg/kg in rats) and (0.1-2.0 mg/kg in mice) on the performance of the animals in the plus-maze were determined. In the second set of experiments using the ICR mice, DOI (either 0.1 and 1.0 mg/kg) was administered in combination with selected doses of ketanserin, mianserin or flumazenil to determine whether pretreatment with subtype selective receptor antagonists could block the differential profile of responses produced by DOI. These doses were selected based on our preliminary experiments as effective doses. Throughout this study, the control data were obtained from the behavioral profile of animals that were injected with normal saline. There were a total of 6-20 animals per treatment group depending on the species. The drug pretreatment period and the testing depended on the onset of action of the different drugs. DOI and flumazenil treated animals were tested after 10 min (23 and 24) while the antagonists ketanserin and mianserin were administered 30 mins before testing or before combination with DOI (25 and 26). All drugs and vehicle were administered intraperitoneally in a volume of 1 ml/kg body weight.

Drugs used and statistical analysis

(±)-1-(2,5,-dimethoxy-4-iodophenyl)-2-amino-propane HCl (DOI), ketanserin tartrate, mianserin HCl and flumazenil were obtained from RBI, Natick, MA.

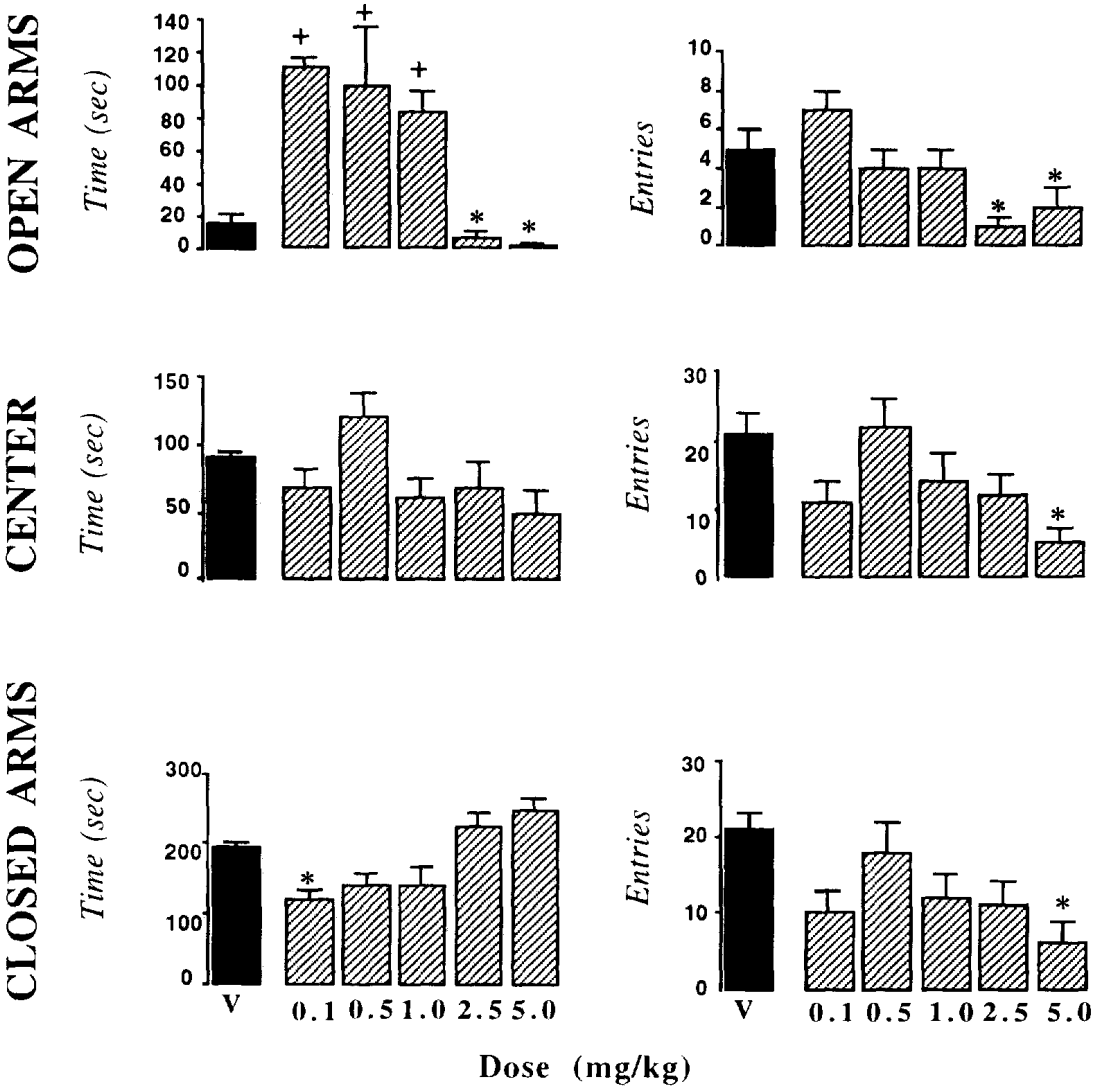

FIG. 1.

The effects of DOI on the performance of rats in the elevated plus-maze test system. The time spent and number of entries into the open, central platform and closed arms of the plus-maze in the 5 min test session are shown. Vehicle (V), and DOI were administered acutely for 10 min before the test. Significant differences from controls ($p < 0.05$, calculated from a one-way ANOVA followed by Dunnett's *t*-test for multiple comparispon with vehicle-treated groups) are indicated with an asterisk or a + sign, N=6-10 rats per group.

The behavioral results were analyzed using one-way analysis of variance (ANOVA) with multiple comparisons and the drug treatment as the independent factor. Dunnett's *t*-test was used to assess treatment differences. A p value < 0.05 was necessary to acheive statistical significance.

Results

Index of anxiolytic- and anxiogenic-like profile

Naive rats and mice demonstrate aversions to the open arms of the elevated plus-maze and enter more frequently into the closed arms (13, 19 and 20). The index of an anxiolytic-like profile after drug treatment is indicated by one or a combination of the following activities of the animals in the plus-maze: (1) increase in time and/or number of entries into the open arms, (2) reduction in the time and/or number of entries into the closed arms. The converse of (1) and (2) holds for an anxiogenic-like profile following drug administration. Drugs without an effect in this model will not be different from the vehicle response. Thus, the closed arm entries alone does not indicate an anxiolytic profile. However, the preference shown by the vehicle treated rats for the closed arms is known to reflect an aversion toward the open arms caused by "fear" or anxiety induced by the height and openness (19 and 27). The arm entries were therefore considered a part of the anxiolytic index. The total number of entries following drug treatments is an important measure of the animal's locomotor activity. A decrease in total entries may reflect sedative or CNS depressant effects of a drug which may confound interpretation of any possible anxiolytic- or anxiogenic-like profile as assessed by the criteria listed above.

Acute effects of DOI in rats and mice

The acute effects of DOI on the behavioral profile of rats evaluated in the plus-maze are shown in Fig. 1. DOI produced an increase ($p<0.05$) in the time spent in the open arms at doses less than 2.5 mg/kg. At doses equal to or higher than 2.5 mg/kg a reduction in the time spent in the open arms was apparent. Lower doses of DOI were not significantly different from the response of the control rats (data not shown). It is important to note that at 5.0 mg/kg, the highest dose of DOI utilized in this study, the total entries was significantly reduced. There was no change in the time spent in the central platform in the doses of DOI used in the rats. Similarly there were no significant alterations in the number of entries into the center of the maze except at the highest dose. The increased time spent in the open arms was mirrored by the decrease ($p<0.05$) in time spent in the closed arms at the low dose of 0.1 mg/kg.

Figure 2 shows the effects of DOI (0.1-2.0 mg/kg) on the performance of three mouse strains, ICR, DBA/2 and C57/BL6, in the elevated plus maze. In the ICR mice lower doses of DOI (0.1-0.5 mg/kg) caused significant increase while higher doses (1.0-2.0 mg/kg) caused significant reduction in the time spent in the open arms of the maze. There was little or no change in the time spent in the center and closed arms and the number of entries into the open, center and closed arms were also unaltered by acute DOI treatment in the ICR mice. In the C57/BL6 mice DOI caused a significant increase in the time spent and number of entries into the open arms and a concomitant decrease in the time spent in the closed arms. The time spent in the central platform and the number of entries into the center and the closed arms by the C57/BL6 mice remained unaltered. In contrast to the ICR and C57/BL6 mice, DOI caused a decrease in the time spent in the open arms and center, accompanied by an

increase in time spent in the closed arms ($p<0.05$) in the DBA/2 mice. The number of entries into the open, center and closed arms by the DBA/2 mice were also significantly reduced in contrast to the ICR and C57/BL6 strains.

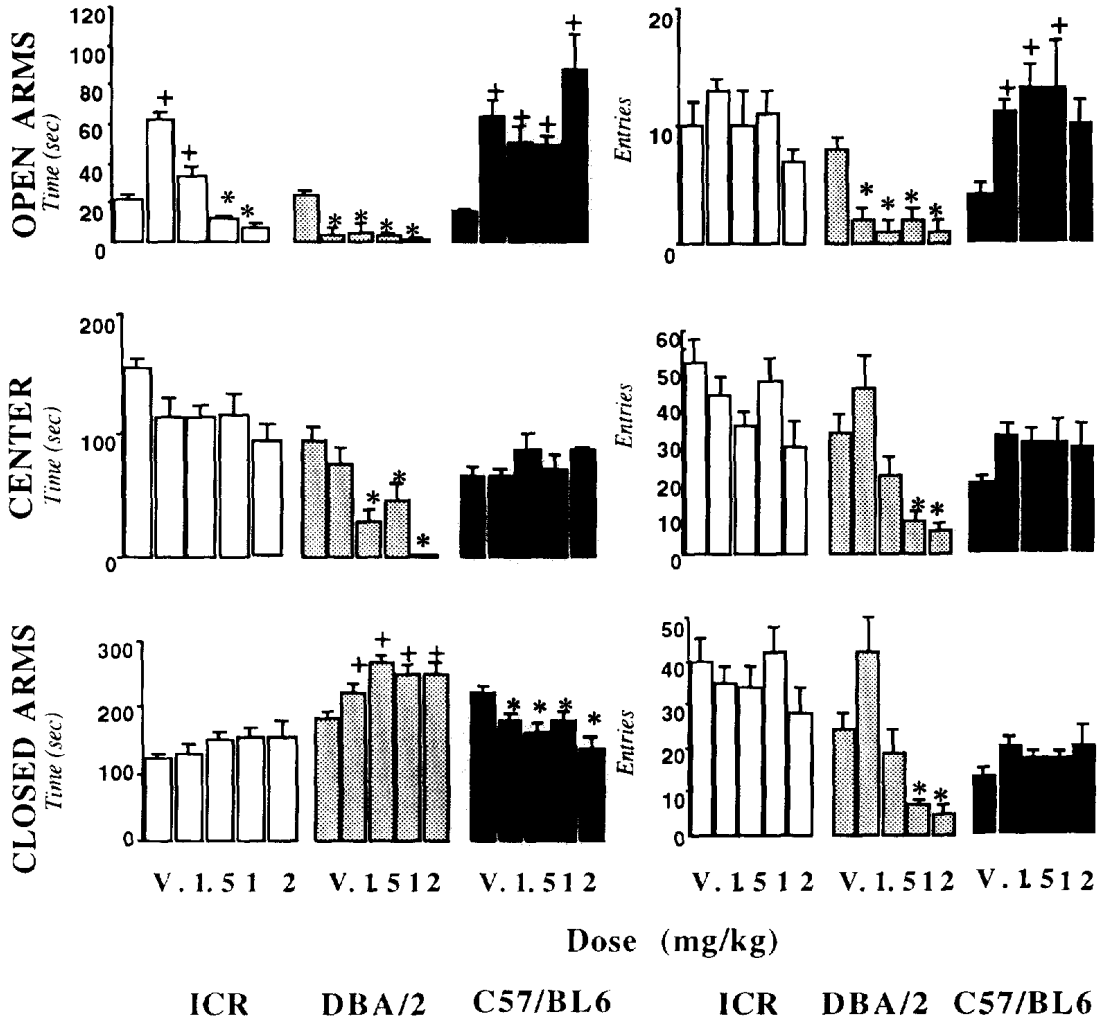

FIG. 2.

Performance of three mouse strains, ICR, DBA/2 and C57BL6 mice and the effect of DOI (0.1-2.0 mg/kg), in the elevated plus-maze test system. The time spent and the number of entries into the open, central platform and closed arms of the elevated plus-maze during the 5 min test session are shown. Vehicle (V), and DOI were administered acutely for 10 min before the test. Values are expressed as means ± SEM. The significant differences from vehicle treated animals are indicated as $^{*}p < 0.05$ or $^{+}p < 0.05$ (one-way ANOVA followed by Dunnett's *t*-test N=6-10 animals per group.

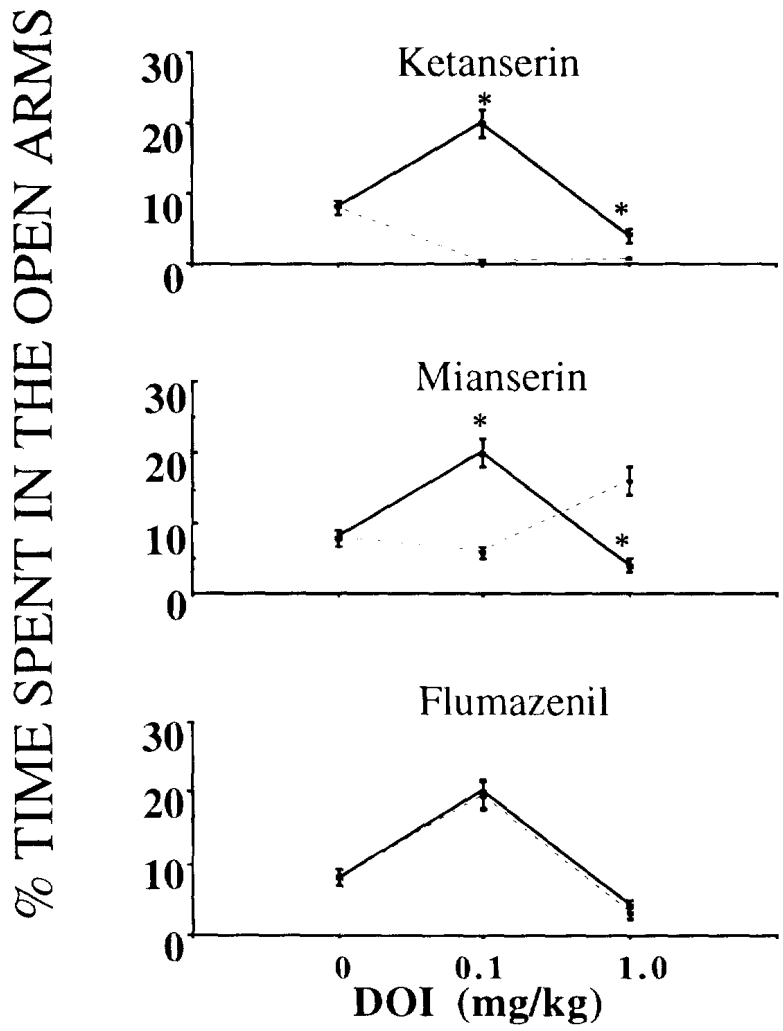

FIG. 3.

Influence of pretreatment with putative antagonists on the aversions and antiaversions induced by DOI to the open arms of the elevated plus maze in the ICR mice. A 30-min pretreatment with either vehicle, V, (solid lines), ketanserin (0.1 mg/kg), mianserin (0.5 mg/kg) or flumazenil (10 mg/kg) (broken lines) was followed by the administration of DOI 10-min before the 5-min test. *Significantly different from the vehicle treated controls at $p<0.05$ (ANOVA and post hoc analysis by Dunnett's t-test. There were at least six animals per group.mg/kg and flumazenil, 10.0 mg/kg were administered before DOI. The pretreatment time for ketanserin and mianserin was 30 min and for flumazenil 5 min.

TABLE 1

The influence of ketanserin, mianserin and flumazenil on the performance of ICR mice in the elevated plus-maze test.

Treatment	Open arms		Center		Closed arms		Total Entries
Dose mg/kg	Time	Entries	Time	Entries	Time	Entries	
Vehicle	25±4	10±1	144±18	41±4	131±17	35±3	86±11
Ketanserin							
0.1	28±3	12±1	120±8	23±4*	152±19	26±4	61±6
0.5	18±3	16±2*	107±7*	20±1*	178±7*	26±3	62±5
1.0	9±2*	10±2	102±5*	15±3*	177±7*	22±3*	47±5*
Mianserin							
0.05	21±3	9±1	130±8	28±5	150±7	26±4	63±7
0.5	31±3	7±1	107±9*	37±8	164±8*	40±8	84±12
1.0	38±4*	10±2	105±6*	48±5	155±6	51±6*	109±16
2.0	19±5	6±1*	100±15*	46±8	176±16	48±8*	100±10
Flumazenil							
1.0	26±7	11±2	136±17	37±8	141±27	39±9	87±9
10.0	29±8	12±3	140±16	42±5	136±14	34±6	88±5
20.0	24±3	9±1	148±20	39±4	133±12	37±8	90±11

* Significantly different from animals treated with vehicle at $p<0.05$ (ANOVA and *post hoc* analysis by Dunnett's *t* test).

Antagonism of the behavioral effects of DOI

ICR mice were selected for the antagonism studies since both anxiolytic- and an anxiogenic-like responses could be demonstrated clearly in this strain following the acute administration of DOI. Table 1 shows the influence of the antagonists that were used in this study. Ketanserin (0.1-1.0 mg/kg) caused a reduction in the time spent in the open arms and the central platform with corresponding increase in the time spent in the closed arms. The highest dose of ketanserin caused a reduction of total entries at ($p<0.05$). Mianserin (0.05-2.0 mg/kg) on the other hand produced a variable anxiolytic-like response with significant reductions in the time spent in the center for all but the lowest dose. Flumazenil, the benzodiazepine antagonist with relatively short half-life was administered 5 min prior to the test and did not alter the behavior of the mice in the plus-maze. Selected doses of ketanserin, 0.1 mg/kg, mianserin, 0.5 mg/kg and flumazenil, 10.0 mg/kg were administered before DOI. The pretreatment time for ketanserin and mianserin was 30 min and for flumazenil 5 min. These doses of the antagonists did not overtly modify the performance of the animals in the open arms of the maze. But as shown in fig. 3. ketanserin and mianserin blocked the anxiolytic-like effects of DOI while flumazenil had no effect. Mianserin reversed the

anxiogenic-like effects of DOI while ketanserin enhanced it and flumazenil did not alter the performance of mice treated with DOI.

Discussion

The present study demonstrates that the behavioral profile of rodents following the administration of the hallucinogen, DOI in the elevated plus-maze test system was dependent on the species and strain used. Hooded rats and ICR mice exhibited a similar profile of aversive and antiaversive behavior to the open arms of the plus-maze depending on the dose of DOI used.In contrast, DOI predominantly induced an intense aversion to the open arms in the DBA/2 and antiaversion in the C57/BL6 mice.

An important finding of this study is that opposite behavioral responses can be observed in the same strain as well as in different strains and species. This is in agreement with previous clinical and anecdotal reports of individual variations in the effects of hallucinogens. Thus, in a number of species ranging from spiders to primates and humans, hallucinogens induce a myriad of behavioral and physiological changes (2, 28, 29 and 30). Although the mechanisms by which hallucinogenic drugs (e.g. DOI) modify behaviors are not clearly understood, a number of studies implicate the serotonergic systems as major targets of activity in the central nervous system (1 and 2). The current results showing that 5-HT antagonists block the effects of DOI in the plus-maze test are consistent with a role for 5-HT in this behavior. There is increasing attention to the involvement of serotonergic mechanisms in anxiety profile (31-36). Hallucinogens including DOI on the other hand activate the 5-HT_{2A} and 5-HT_{2C} receptors with similar affinities (3, 4 and 37). In the present studies an anxiolytic-like profile of response characterized by increased time spent in the open arms of the plus-maze was induced by low doses of DOI while higher doses provoked an anxiogenic-like response in the hooded rats and ICR mice. Interestingly, only an anxiogenic-like response was produced by DOI in the DBA/2 and only an anxiolytic-like response occured in the C57/BL6.

Ketanserin blocked the anxiolytic-like and enhanced the anxiogenic-like effects of DOI in the ICR mice. Mianserin was also effective at blocking the anxiolytic-like profile of DOI but unlike ketanserin, mianserin reversed the anxiogenic-like effects of DOI. Some studies have shown that ketanserin and mianserin have differential affinities for the 5-HT_{2A} and 5-HT_{2C} binding sites in the rat brain and choroid plexus. For example, [^{3}H]5-HT binding in the choroid plexus known to label predominately 5-HT_{2C} receptors was displaced potently by mianserin but poorly by ketanserin (38). More recent studies have shown that the 5-HT_{2C} receptor site recognizes ketanserin with 10 to 30 times lower affinity than does the 5-HT_{2A} receptor site (8). The ability of mianserin to reverse the anxiogenic effects of DOI support the findings of Kennett *et al.*, (9), who demonstrated that the anxiogenic effect of mCPP in the rat model, which is thought to be mediated by 5-HT_{2C} receptors could be blocked by mianserin but not ketanserin. It is therefore attractive to speculate from the results of the present studies and those of others, an anxiogenic role for the 5-HT_{2C} receptors. Additional support comes from the recent studies of Berg *et al.*, (39), who showed that fundamental differences in signal transduction systems may exist for the $5HT_{2A}$ and $5HT_{2C}$ receptor subtypes contrary to the notion that the signal transduction is

identical for the two receptor subtypes. Unfortunately, there is a lack of specificity of action of the currently known agonists and antagonists at the $5HT_2$ receptor subtypes. A-methyl-5-HT and the phenylalkylamines (2, 5-dimethoxy-4-methylamphetamine (DOM), 2, 5-dimethoxy-4-bromoamphetamine (DOB) and DOI), the agonists frequently used all display poor selectivity with regard to the three 5-HT_2 receptor subtypes, and none alone can be relied to define unequivocally any of the $5HT_2$ receptor subtypes (5). It is also logical to determine whether the $5HT_{2A}$ and $5HT_{2C}$ receptors are interacting with benzodiazepine receptors, since these receptors have been shown to be important in the anxiolytic action of the benzodiazepines. The present studies showed that pretreatment with flumazenil a benzodiazepine antagonists failed to block the DOI effects. We have previously shown that pretreatment with 10 mg/kg flumazenil was effective at blocking benzodiazepine receptors in mice and rats (13 and 14).

It is not known whether there are differences in the expression of 5-HT receptors genes in the different mouse strains. The $5HT_{2A}$ and $5HT_{2C}$ receptors are differentially expressed in the regions of the brain. Similar or additional regulatory processes may lead to a strain difference in the expression of $5HT_{2A}$ and $5HT_{2C}$ receptors. A strain difference in response is not unique to DOI. We have recently shown for example that the C57BL/6 mice are less sensitive to the hypothermic and antinociceptive effects of Δ^9-THC than the DBA/2 and ICR mice strains (40). Others have documented differences in alcohol drinking in the C57BL/6, DBA/2 and BALB/c mice (41 and 42). The C57BL/6J strain has been shown to initiate morphine, cocaine, methamphetamine and pentobarbital self administration while the DBA/2J mice do not self administer these drugs.

Although the mechanism by which DOI alters the performance of the animals in the elevated plus-maze remains to be established, it appears that there is a link with the 5-HT_{2A} and the 5-HT_{2C} receptors. In ICR mice, DOI elicited behavior consistent with both anxiogenesis and anxiolysis. Since neither of these behaviors was sensitive to a benzodiazepine antagonist, it appears that the mechanism does not involve an action at the benzodiazepine receptors. The possibility that the 5-HT_{2A} and 5-HT_{2C} receptors mediate the opposing actions of DOI in the elevated plus-maze is intriguing. DOI elicits opposite behavioral effects in DBA/2 and C57/BL6 mice, providing a useful model for studying the mechanisms of the neurobehavioral effects of hallucinogens.

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