Effects of Psychoactive Drugs in the Vogel Conflict Test in Mice

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Received October 7, 1998 Accepted February 25, 1999

ABSTRACT—This study examined effects of various psychoactive drugs on the Vogel conflict test, where drinking behavior is punished by electric shocks, in ICR mice to clarify the pharmacological features of this method in mice. A benzodiazepine anxiolytic diazepam and a barbiturate pentobarbital produced significant anticonflict effects, which mean that these drugs increased the number of electric shocks mice received during 40-min test session. On the other hand, yohimbine (α2-receptor antagonist), caffeine (adenosine-receptor antagonist), scopolamine (muscarinic cholinergic antagonist), cyclazocine (σ-receptor antagonist), cimetidine (H2-receptor antagonist), baclofen (GABAβ-receptor agonist), MK-801 (NMDA-receptor antagonist), buspirone (5-HT1A-receptor agonist), chlorpromazine (dopamine-receptor antagonist) and haloperidol (dopamine-receptor and σ-receptor antagonist) all did not produce anticonflict effects in this test using ICR mice. The results suggest that the Vogel conflict test is applicable to ICR mice and that this test in mice is appropriate as a screening method for drugs that have apparent anti-anxiety actions.

Keywords: Vogel conflict test (mouse), Psychoactive drug, Anxiety

The Vogel conflict test (1) is a well-known method by which to examine the anti-anxiety-like action of various psychoactive drugs. This test is extensively used for preclinical evaluation of putative anxiolytics, and the methodology of the test has been investigated in detail. However, because rats are usually used in this test, only few studies tried to apply the test to other species.

Of potential interest are mice. One of the important advantages of mice over rats as subjects for behavioral pharmacology is that a great deal more information about mouse genetics and mouse strains are currently available. In addition, recent advances in molecular biology have enabled the production of various kinds of transgenic and knock-out mice, which in turn have enabled investigation of the genetic factors associated with the response to psychoactive drugs as well as molecular mechanisms underlying the effects of these drugs. Thus, if the Vogel conflict test were applied to mice, it would be possible to examine the molecular mechanisms of action of anxiolytics, thereby providing important information for understanding anxiety in humans.

In a recent study, the author applied the Vogel conflict test to mice and examined the effects of various experimental conditions on the anticonflict effect of diazepam (DZ), a benzodiazepine anxiolytic (2). Subsequently, the method developed in that study was used to evaluate the psychoactive effects of organic solvents such as trichloroethylene and tetrachloroethylene (3). These studies revealed that the anticonflict effect of these substances can be evaluated using ICR mice. Although these studies have been made, the pharmacological characteristics of the Vogel conflict test in mice have not been established yet. Thus, more systematic studies on this test in mice were required.

The present study was conducted to characterize the pharmacological features of the Vogel conflict test in mice to elucidate whether this test in mice is appropriate as an evaluation method for putative anxiolytics or not. The specific aim was clarification of the pharmacological specificity of this test in mice to be determined using a variety of psychoactive drugs.

MATERIALS AND METHODS

Animals

The animals used in this study were male, 8-week-old ICR strain mice (Clea Japan, Tokyo), that weighed 30–40 g at the start of each experiment. The mice were housed in Plexiglas cages (10 mice/cage) that had stainless steel wire mesh tops with wooden-flake bedding.
Commercial solid food (Clea Japan) was available ad libitum. Prior to each experiment, the mice were deprived of water in order to induce thirst, as described below. The animals were housed in a room artificially illuminated by fluorescent lamps on a 12-hr light-dark schedule (light period: 7 a.m. - 7 p.m.), and the room was maintained at 25±1.0°C.

All experiments in this study were performed with the approval of the Ethics Committee for Experimental Animals of the National Institute for Environmental Studies, Japan.

Drugs
The drugs used in this study were DZ (benzodiazepine agonist; Cercine Inj.®; Takeda Chem. Ind., Osaka); pentobarbital (PENT) (barbiturate; Nembutal Inj.®; Abbott Lab., North Chicago, IL, USA); buspirone (BUS) (5-HT₁A receptor agonist), MK-801 (MK) (NMDA-receptor antagonist), yohimbine (YO) (α₂-receptor antagonist), scopalamine (SCOP) (muscarinic cholinergic antagonist), chlorpromazine (CHLOR) (dopamine-receptor antagonist), haloperidol (HAL) (dopamine receptor and α-receptor antagonist), cynamocine (CYC) (α-receptor antagonist), cimetidine (CIM) (H₂-receptor antagonist), baclofen (BAC) (GABA₁-receptor agonist) and caffeine (CAF) (adenosine-receptor antagonist) (Research Biochemicals, Natic, MA, USA). DZ and PENT were diluted in 10% propylene glycol solution; and BUS, MK, SCOP, YO, CHLOR, CAF, CIM and BAC were dissolved in 0.9% NaCl solution (saline). CYC was mixed with a few drops of Tween 80 (Nacalai Tesque, Kyoto) and then diluted in saline. HAL was dissolved in 0.1% acetic acid solution. Various doses of the drugs were administered subcutaneously (s.c.) in a fixed volume of 1 ml/kg body weight, regardless of dose.

Apparatus
Five Plexiglas chambers [180 (W) × 100 (D) × 120 (H)] and a recorder (VC-3002-L and VC-2050-L; O’hara & Co., Tokyo) were used (2, 3). A water bottle was placed on top of each chamber, with water being available from the bottle spout, which penetrated the chamber. The number of licks of the spout was counted simultaneously in each chamber. Every 20th lick was punished by an electric shock (30 V, ca. 0.1 mA, 50 Hz AC, duration=0.3 sec) through the grid, which constituted the floor of the chamber.

Procedure
On the 1st day, individual animals that had been deprived of water for 2 days were put into separate chambers, and they were allowed to drink water freely for 40 min (the habituation procedure). One week later, the same animals, which had again been deprived of water for 2 days prior to the test, were put into the chambers 10 min after administration of the drugs or their vehicle. The mice had ad libitum access to water from the spout in the chamber, and the number of licks of the spout was counted simultaneously in each chamber for 40 min. Every 20th lick was punished by an electric shock.

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Fig. 1. Effects of the benzodiazepine agonist diazepam (DZ) (a) and barbiturate pentobarbital (PENT) (b) on the Vogel conflict test in ICR mice. Horizontal axis shows the doses administered 10 min prior to the Vogel conflict test. Number of animals used for each column was 14–15 for DZ (N=14–15) and 25 for PENT (N=25). 10%PG=10% propylene glycol solution. *P<0.05, **P<0.01, compared to the vehicle-treated control by Dunnett’s test.
through the grid, and the number of electric shocks during the 40 min was recorded.

Statistical analyses

Overall differences among averages of all treatments (all doses and the vehicle-treated control) for each drug were analyzed by one way analysis of variance (ANOVA). Comparisons between the vehicle-treated control and each dose of each drug were performed by Dunnett’s test (two-tailed). Five percent was used as the statistical significance level.

All data are shown as the mean ± S.E.M.

RESULTS

The benzodiazepine anxiolytic DZ produced a significant effect in the Vogel conflict test in ICR mice \((F(5, 83)=5.053, P<0.01)\) (Fig. 1a). A 1 mg/kg dose of DZ caused a significant increase in the number of electric shocks mice received (i.e., anticonflict effect). Similarly PENT also produced a significant effect in the test \((F(3, 99)=9.768, P<0.01)\) (Fig. 1b). PENT caused a significant increase at 20 mg/kg and a significant decrease at 30 mg/kg in the number of electric shocks mice received.

YO \((\alpha_2\)-receptor antagonist) did not show any significant effects in the Vogel conflict test of mice at doses examined \((F(4, 84)=1.956, P>0.05)\) (Fig. 2a). Neither CAF (adenosine-receptor antagonist) nor SCOP (muscarinic cholinergic antagonist) produced any effects on the Vogel conflict test in mice \((CAF: F(4, 74)=0.013, P>0.05)\) (Fig. 2b), SCOP: \(F(4, 85)=0.897, P>0.05\) (Fig. 2c). The sigma-receptor antagonist CYC showed a tendency to increase the number of electric shocks mice received; however, such a change was not statistically significant \((F(4, 74)=1.583, P>0.05)\) (Fig. 2d).

CIM \((H_2\)-receptor antagonist) did not produce any effects on the Vogel conflict test in mice at doses examined in this study \((F(4, 75)=0.271, P>0.05)\) (Fig. 3a). BAC (GABA\(_W\)-receptor agonist) did not exhibit any significant effect on the test, although 3 mg/kg tended to induce a

![Graphs](image)

**Fig. 2.** Effects of the \(\alpha_2\)-agonist yohimbine (YO) \((N=17-18)\) (a), adenosine antagonist caffeine (CAF) \((N=16)\) (b), muscarinic cholinergic antagonist scopolamine (SCOP) \((N=18)\) (c) and \(\delta\)-antagonist cyclazocine (CYC) \((N=15-16)\) (d) on the Vogel conflict test in ICR mice.
decrease in the number of electric shocks mice received ($F_{(4, 73)}=0.625, P>0.05$) (Fig. 3b). MK (NMDA-receptor antagonist) tended to increase the number of electric shocks mice received; however, the change was not statistically significant ($F_{(4, 85)}=0.792, P>0.05$) (Fig. 3c).

The 5-HT_{1A}-receptor agonist BUS induced a significant effect on the Vogel conflict test in mice ($F_{(7, 11)}=3.987, P<0.01$) (Fig. 4a). BUS at 8 mg/kg significantly decreased the number of electric shocks mice received. The neuroleptic HAL showed a tendency to decrease the number of electric shocks mice received; however, the effect was not statistically significant ($F_{(4, 75)}=2.216, P>0.05$) (Fig. 4b). On the other hand, another neuroleptic, CHLOR, induced an apparent effect on the test ($F_{(4, 84)}=4.041, P<0.01$) (Fig. 4c). CHLOR at 1 and 2 mg/kg significantly reduced the number of electric shocks mice received.

DISCUSSION

A preliminary study on the Vogel conflict test in mice revealed that various parameters, such as strains of mice and voltage of electric shock as punishment, affect the anticonflict effect of the benzodiazepine anxiolytic DZ. Further investigation of the effects of experimental procedure on the anticonflict effect of DZ revealed that in the Vogel conflict test of naive ICR mice, DZ does not exhibit any anticonflict effect; that is, the number of the electric shocks mice received in the test does not increase (2). On the other hand, DZ produces an anticonflict effect in animals that have been housed in an experimental chamber, with free access to water, for 40 min 1 week before the test (habituated animals). Thus, the present study examined the effects of various drugs on the Vogel conflict test using habituated ICR mice.

As expected, DZ and PENT produced significant effects in the Vogel conflict test; that is, both drugs increased the number of electric shocks mice received (i.e., anticonflict effect) in this study. Therefore, it is possible to conclude that the Vogel conflict test in ICR mice can detect anticonflict effects of those drugs, which exhibit anticonflict effects in the Vogel conflict test in rats (1, 4).

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Fig. 3. Effects of the H$_2$ antagonist cimetidine (CIM) (N=16) (a), GABA$_A$ agonist baclofen (BAC) (N=16) (b) and NMDA antagonist MK-801 (MK) (N=18) (c) on the Vogel conflict test in ICR mice.
PENT decreased the number of electric shocks mice received at the highest dose, which is close to the dose that cause anesthesia in mice. At this dose, PENT caused remarkable suppression of behaviors, suggesting that decrease of the number of electric shocks come from the action as a general depressant.

In the present study, many kinds of drugs were tested to examine the specificity of the Vogel conflict test in ICR mice as a screening method for putative anxiolytics.

Previous studies suggest that $\alpha_2$-receptors may be involved in anxiety (5, 6). Thus, I examined whether the $\alpha_2$-receptor antagonist YO had any effect on the test in mice. The results indicated that YO did not produce any effects on the test in this study. It has been reported that adenosine receptor antagonist CAF showed anticonflict effects in rodents (7, 8). However, CAF did not show any effects on the Vogel conflict test in mice in this study. CAF increases motor activity in ddY mice at 10 mg/kg (9). Thus 30 mg/kg of CAF is enough to produce psychoactive effects, suggesting that the Vogel conflict test in ICR mice may not be good for evaluating if CAF has an anticonflict effect. The muscarinic cholinergic antagonist SCOP induces drinking in rodents (10), suggesting that SCOP induces thirst. However, SCOP did not produce an anticonflict effect in the Vogel test of mice. Therefore, the anticonflict effect in the Vogel conflict test in mice is not a product of increased thirst. It has been suggested that $\sigma$-receptors may be involved in anxiety because a $\sigma$-receptor antagonist relieved the conditioned suppression of motility in mice (11). The present study examined effects of the $\sigma$-receptor antagonist CYC on the Vogel conflict test. CYC tended to increase the number of electric shocks mice received, but it was not statistically significant. One possible reason why CYC did not show any significant anticonflict effect in this test is that the dose of CYC used was not enough to produce significant effect. Further studies will be required to establish the effect of CYC on the Vogel conflict test in mice.

Roles of $H_2$ and $\gamma$-aminobutyric acid receptors in anxiety have not been well defined. The present study examined effects of the $H_2$-receptor antagonist CIM and $\gamma$-aminobutyric acid receptor agonist BAC in the Vogel conflict test in mice. The results

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**Fig. 4.** Effects of the 5-HT$_{1A}$ agonist buspirone (BUS) (N=15) (a), dopamine antagonist and $\sigma$-agonist haloperidol (HAL) (N=16) (b) and dopamine antagonist chlorpromazine (CHLOR) (N=17–18) (c) on the Vogel conflict test in ICR mice. *P<0.05, **P<0.01, compared to the vehicle-treated control by Dunnett's test.
Table 1. Summary of effects of psychoactive drugs in the Vogel conflict test, elevated plus-maze test and light/dark choice test in mice

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mediating receptor</th>
<th>Vogel conflict test</th>
<th>Elevated plus-maze test</th>
<th>Light/dark choice test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>increase of No. of shock</td>
<td>increase of open arm</td>
<td>increase of time spent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mice received (anticongflict)</td>
<td>entry/spent time (21, 24)</td>
<td>in the lit area (33 – 37)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>GABA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>increase of No. of shock</td>
<td>increase of open arm</td>
<td>increase of time spent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mice received (anticongflict)</td>
<td>entry/spent time (25)</td>
<td>in the lit area (37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>GABA</td>
<td>increase of No. of shock</td>
<td>decrease of open arm</td>
<td>decrease of time spent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mice received (anticongflict)</td>
<td>entry/spent time (36, 38)</td>
<td>in the lit area (36, 38, 39)</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>α2</td>
<td>no effect</td>
<td>decrease of open arm</td>
<td>decrease of time spent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>entry/spent time (25, 27 – 29)</td>
<td>in the lit area (36, 38, 39)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Adenosine</td>
<td>no effect</td>
<td>—</td>
<td>no effect (36)</td>
</tr>
<tr>
<td>Scorpolamine</td>
<td>Muscarinic</td>
<td>no effect</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cyclazocine</td>
<td>α</td>
<td>increase of No. of shock</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mice received (?)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>H3</td>
<td>no effect</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Baclofen</td>
<td>GABA</td>
<td>no effect</td>
<td>no effect (30)</td>
<td>—</td>
</tr>
<tr>
<td>MK-801</td>
<td>NMDA</td>
<td>no effect</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5-HT1A</td>
<td>decrease of No. of shock</td>
<td>increase of open arm</td>
<td>increase of time spent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mice received at high dose</td>
<td>entry/spent time (21, 31)</td>
<td>in the lit area (36, 40, 41)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Dopamine, α</td>
<td>decrease of No. of shock</td>
<td>no effect (32)</td>
<td>no effect (42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mice received (?)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Dopamine</td>
<td>decrease of No. of shock</td>
<td>—</td>
<td>no effect (43)</td>
</tr>
</tbody>
</table>

The numbers within parentheses show reference numbers of the original papers (see the reference list).

showed that these drugs did not produce anticonflict effects in the test, suggesting that these drugs may not possess anticonflict action. It has been reported that MK exhibited anticonflict effects in rodents (12, 13). However, the present study showed that MK did not produce an anticonflict effect in the Vogel conflict test in ICR mice. Although the reason for the discrepancy is not clear, the differences of animal species and/or strains used and methods may account for the differences of these results.

BUS is known to have an anticonflict effect in rodents (14 – 18). On the other hand, other studies reported that BUS failed to produce an anticonflict effect (19, 20) in mice. In this study, BUS did not show an anticonflict effect in ICR mice and that it suppressed the number of electric shocks mice received at higher doses. Therefore, the Vogel conflict test in ICR mice may not be appropriate for evaluation of the anticonflict effect of BUS. BUS is a partial 5-HT1A agonist (21), and it was a candidate for a non-benzodiazepine anxiolytic. On the other hand, it is known that the anti-anxiety action of BUS is of low order in comparison with that of benzodiazepines in humans (22). In addition, it is well known that repeated administration of BUS is needed to produce its anti-anxiety action. Since the present study examined an acute effect of BUS by a single administration, it may be a reason why the Vogel conflict test in mice did not show an anticonflict effect. BUS caused a decrease of the number of electric shocks mice received at higher dose. General sedation was observed at that dose, suggesting that the decrease might come from a suppressive effect of BUS on general behaviors. Decrease of water intake in water-deprived mice have been reported (19).

Neuroleptic HAL and CHLOR have been reported to have an anticonflict effect in rodents (14, 21, 23). Thus the present study examined the effects of these drugs in the Vogel conflict test in mice. The results revealed that HAL and CHLOR decreased the number of electric shocks mice received; that is, these drugs did not produce anticonflict effects in this test in mice.

Other methods, the elevated plus-maze test and light/dark choice test, for evaluation of effects of drugs on anxiety have been developed in mice already, and effects of various psychoactive drugs on them have been examined. The major results of previous studies are summarized in Table 1 and compared with the results of the Vogel conflict test that was used in the present study (Table 1). This comparison revealed several points about the characteristics of each method in mice.

First, for the psychoactive drugs that were used in the present study, effects of SCP, CYC, CIM, MK and CHLOR have not been examined by the elevated plus-maze test in mice, and those of CYC, CIM, BAC and MK have not been examined by the light/dark choice test in mice. Therefore, it is not possible to compare effects of those drugs in the elevated plus-maze test and light/dark choice test in mice with those in the Vogel conflict test in
mice. Alternatively, the present study examined the effects of drugs in the Vogel conflict test throughout. Effects of drugs that are described above in the elevated plus-maze test and light/dark choice test in mice should be examined in the future.

Second, YO and high dose of CAF, which have been known to cause an anxiogenic effect, did not show any apparent effects in the Vogel conflict test in mice, although those drugs caused effects opposite to those of DZ and PENT in both the elevated-plus-maze test and light/dark choice test in mice. Decrease of the number of electric shocks in the Vogel conflict test might indicate an anxiogenic effect of drugs (i.e., pro-conflict effect). On the other hand, many drugs can non-specifically cause a decrease in the number of electric shocks in the Vogel conflict test, as in the case of HAL and CHLOR, because of suppression of a drinking behavior by the drugs. Therefore, it is not possible to separate the suppressive effects of drugs on a drinking behavior from an anxiogenic-like effect in the Vogel conflict test. Thus, the Vogel conflict test is not appropriate for evaluating the anxiogenic effect of psychoactive drugs. This opinion is further supported by the present study because YO and a high dose of CAF, which possess an anxiogenic action, did not show any apparent effects in the present study. There is a large difference on this point between the Vogel conflict test and elevated plus-maze test and/or light/dark choice test in mice.

The third point is the effect of BUS, a 5-HT1A partial agonist (21). In the present study, BUS did not produce an increase in the number of electric shocks mice received (i.e., anticonflict effect) and caused a decrease of it at higher doses. On the other hand, BUS has been reported to increase open arm entry and/or spent time in the open arm in the elevated plus-maze test and to increase the time spent in the lit area in the light/dark choice test (Table 1). As described above, the anti-anxiety action of BUS is of low order in comparison with that of the benzodiazepine in humans (22). In addition, it has been known that BUS produces an anti-anxiety action after repeated administration for about one week. Therefore, it is probable that BUS hardly produces an apparent anti-anxiety like effect in animal experiments by a single administration. It has been reported that BUS did not produce an anti-conflict effect in another conflict paradigm, the Geller conflict test, in mice (19, 20). I also confirmed that BUS did not exhibit an anti-conflict effect in the Geller conflict test in ICR mice (unpublished data). Thus, it is reasonable that the Vogel conflict test in mice may be insensitive to BUS. Alternatively, the Vogel conflict test in mice can detect anticonflict effects of drugs such as DZ and PENT, which produce an apparent anti-anxiety effect in humans.

In summary, the present study revealed that only DZ and PENT, which produce apparent anti-anxiety effects in humans, exhibited anticonflict effects in the Vogel conflict test using ICR mice. The results suggest that the Vogel conflict test is applicable to ICR mice and that this test in mice is appropriate as a screening method for drugs that have apparent anti-anxiety actions.

REFERENCES

15. Schreiber R and De Vry J: Neuronal circuits involved in the anxiolytic effects of 5-HT1A receptor agonists 8-HO-DPAT, ipsapirone and buspirone in the rat. Eur J Pharmacol 249,
341–351 (1993)
16 Seidel WF, Cohen SA, Bliswe NG and Dement WC: Buspi-
rone: An anxiolytic without sedative effect. Psychophar-
macology (Berl) 87, 371–373 (1985)
17 Stefanski R, Paleiko W, Kostowski W and Plaznik A: The
comparison of benzodiazepine derivatives and serotonergic
agonists and antagonists in two animal models of anxiety.
Neuropharmacology 31, 1251–1258 (1992)
18 Stefanski R, Paleiko W, Bidzinski A, Kostowski W and Plaznik
A: Serotonergic innervation of the hippocampus and nucleus
accumbens septi and the anxiolytic-like action of midazolam
and 5-HT1A receptor agonists. Neuropharmacology 32, 977–
985 (1993)
19 Kuribara H: Comparison of the effects of 5-HT1A agonist
buspirone and benzodiazepine anxiolytic diazepam on conflict
in English)
20 Kuribara H: Effects of SUN8399, a potent and selective
5-HT1A agonist, on conflict behavior and ambulatory activity in
mice: Comparison with those of buspirone, tandospirone and
21 Garrett KM, Niekrasz I, Haque D, Parker KM and Seale TW:
Genotypic differences between C57BL/6 and A inbred mice in
anxiolytic and sedative actions of diazepam. Behav Genet 28,
22 Kudo Y and Kudo T: Recent progress in development of
cholinergic drugs (1)-anti-anxiety drugs. Jpn J Psychophar-
macol 15, 75–86 (1995)
23 Wiley JL, Compton AD and Porter JH: Effects of four anti-
psychotic on punished responding in rats. Pharmacol Biochem
Behav 45, 263–267 (1993)
24 Helton DR, Tizzano JP, Monn JA, Schoepf DD and Kallman
MJ: Anxiolytic and side-effect profile of LY354740: A potent,
highly selective, orally active agonist for group II metabotropic
glutamate receptors. J Pharmacol Exp Ther 284, 651–660
(1998)
25 Lister RG: The use of a plus-maze to measure anxiety in the
26 Bhattacharyya SK and Mitra SK: Anxiogenic activity of quin-
ze –an experimental study in rodents. Indian J Exp Biol 30,
33–37 (1992)
27 Jain N, Kemp N, Adeyemo O, Buchanan P and Stone TW:
Anxiolytic activity of adenosine receptor activation in mice.
28 Lapin IP: Anxiogenic effect of phenylethylamine and amphet-
amine in the elevated plus-maze in mice and its attenuation
29 Lapin IP and Politi V: Anxiolytic effect of indol-3-pyruvic acid
30 Dalvi A and Rodgers RJ: GABAergic influences on plus-maze
behavior in mice. Psychopharmacology (Berl) 128, 380–397
(1996)
31 Cao BJ and Rodgers RJ: Comparative behavioral profiles of
buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine
(1-PPP) in the murine elevated plus-maze. Neuropharmacology
36, 1089–1097 (1997)
32 Cole JC and Rodgers RJ: Ethological evaluation of the effects
of acute and chronic buspirone treatment in the murine elevated
plus-maze test: comparison with haloperidol. Psychopharma-
coology (Berl) 114, 288–296 (1994)
33 Hascoet M and Bourin M: A new approach to the light/dark
test procedure in mice. Pharmacol Biochem Behav 60, 645–653
(1998)
34 Griebel G, Perrault G and Sanger DJ: A comparative study of
the effects of selective and non-selective 5-HT2 receptor subtype
agonists in rat and mouse model of anxiety. Neuropharmacology
36, 793–802 (1997)
35 Griebel G, Sanger DJ and Perrault G: Further evidence for
differences between non-selective and BZ-1 (omega 1) selective,
benzodiazepine receptor ligands in murine models "state" and
36 Shimada T, Matsumoto K, Osanai M, Matsuoka H, Terasawa K
and Watanabe H: The modified light/dark transition test in
mice: evaluation of classic and putative anxiolytic and anxi-
37 Imaiizumi M, Suzuki T, Machida H and Onodera K: A fully
automated apparatus for a light/dark test measuring anxiolytic
or anxiogenic effects of drugs in mice. Jpn J Psychopharmacol
14, 83–91 (1994)
38 Lapine IP: Antagonism of kynurenic acid to anxiogens in mice.
39 Imaiizumi M, Miyazaki S and Onodera K: Effects of xanthine
derivatives in a light/dark test in mice and the contribution of
adenosine receptors. Methods Find Exp Clin Pharmacol 16,
639–644 (1994)
40 Griebel G, Perrault G and Sanger DJ: Characterization of the
behavioral profile of the non-peptide CRF receptor antagonist
CP-154,526 in anxiety models in rodents. Comparison with
diazepam and buspirone. Psychopharmacology (Berl) 138,55–66
(1998)
41 Onalv ES and Martin BR: Neuropharmacological and physio-
logical validation of a computer-controlled two-compartment
black and white box for the assessment of anxiety. Prog
42 Costall B and Naylor RJ: Behavioural interactions between
5-hydroxytryptophan, neuroleptic agents and 5-HT receptor.
43 Young R and Johnson DN: A fully automated light/dark
apparatus useful for comparing anxiolytic agents. Pharmacol
Biochem Behav 40, 739–743 (1991)