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The effects of abused inhalants on mouse behavior in an elevated plus-maze [1]

Scott E. Bowen, Jenny L. Wiley, Robert L. Balster *

Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298-0613, USA

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Abstract

Previous research has shown that abused inhalants (i.e., the volatile solvents) share some of the pharmacological properties of drugs used in the treatment of anxiety. In an attempt to further examine commonalities in the effects of inhalants and central nervous system depressant drugs, the behavioral effects of inhaled 1,1,1-trichloroethane, toluene, methoxyflurane and the convulsant vapor flurothyl were examined and compared to those of diazepam in the elevated plus-maze, a test used to predict antianxiety effects. After inhalant exposure or diazepam injection, mice were placed in the center of an elevated plus-maze and the number of entries and time spent in each type of arm (open versus closed) were measured during 5-min tests. Exposure to increasing concentrations of toluene produced concentration-related increases in the total number of open arm entries and the total time spent on the open arms, a pattern of behavioral effects similar to that produced by diazepam. A similar pattern was observed for increasing concentrations of 1,1,1-trichloroethane and methoxyflurane but changes in open arm activity were only observed at concentrations that increased locomotor activity. Conversely, only decreases in open arm time and number of entries were observed for flurothyl. The increasing evidence for commonalities in the behavioral effects of volatile solvents and depressant drugs may provide a foundation for understanding the neurobehavioral basis of inhalant abuse.

Keywords: Toluene; 1,1,1-Trichloroethane; Methoxyflurane; Flurothyl; Anxiolytic; Plus-maze; Inhalant abuse; (Mouse)

1. Introduction

Inhalant abuse is a worldwide public health problem (Arif et al., 1988; Beauvais, 1992; Marjot and McLeod, 1989). The self-administration of certain volatile chemicals found in common household products such as adhesives ('glue-sniffing'), cleaning fluids and various solvents leads to acute effects on the central nervous system that result in changes in mood and behavior. Evidence is beginning to accumulate that many of the abused inhalants produce a profile of acute effects that resembles that produced by classical central nervous system depressant drugs such as ethanol, barbiturates and benzodiazepines (Evans and Balster, 1991). It is therefore likely that the abuse potential of inhalants is related to their ability to produce these depressant drug-like effects (Balster, 1987).

In addition to the ability of some abused inhalants to produce behavioral effects similar to those produced by abused depressant drugs, including biphasic effects on locomotor behavior (e.g., Bowen and Balster, 1994, 1996), anticonvulsant effects (Wood et al., 1984), discriminative stimulus effects (Rees et al., 1987a,b) and impaired coordinated movement (Bowen et al., 1996; Moser and Balster, 1985; Moser et al., 1985), there is also some evidence that they have anxiolytic effects in animal tests of anxiety. For example, toluene has been shown to increase punished responding in rats to a similar magnitude as does administration of diazepam (Geller et al., 1983; Wood et al., 1984). More recently, Emmanouil et al. (1994) demonstrated that the abused gas nitrous oxide produced concentration-dependent anxiolytic-like activity in rats when tested in an elevated plus-maze.

Although many volatile substances produce a depressant-like profile of acute central nervous system effects, not all vapors do. For example, the fluorinated ether, flurothyl, is known to produce myoclonic jerks and tremor-like movements at lower concentrations and to induce clonic convulsions as concentration levels rise (Ad-

* Corresponding author. Tel.: (804) 828-2067; fax: (804) 828-2117.

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ler, 1975). In addition, flurothyl fails to produce pentobarbital-like discriminative stimulus effects in rats (Rees et al., 1987a) while substituting for the stimulant pentylenetetrazole in a similar drug discrimination procedure (Evans and Balster, 1992).

The purpose of the present study was to examine the potential anxiolytic-like effects of a variety of vapors in an elevated plus-maze procedure and to compare their effects to those of diazepam. The elevated plus-maze is a widely used screening procedure that has been shown to be sensitive to drugs that produce anxiolytic and anxiogenic effects in humans (Pellow and File, 1986; Pellow et al., 1985). We hypothesized that, like the benzodiazepines, the abused solvents toluene and 1,1,1-trichloroethane and the anesthetic methoxyflurane would produce concentration-dependent increases in open arm time and open arm entries. We also hypothesized that the convulsant vapor flurothyl would not produce these anxiolytic-like effects. Because flurothyl may have anxiogenic effects similar to pentylenetetrazole, we predicted that this vapor would produce concentration-dependent decreases in open arm time and open arm entries.

2. Materials and methods

2.1. Subjects

Experimentally naive, male albino mice (CFW, Charles River) weighing 15–20 g were used for this research. Upon arrival, mice were housed in groups of 5–7 in clear plastic cages (18 × 29 × 13 cm) containing wood chip bedding and fitted with steel wire tops. All animals were allowed free access to food and water in their home cages. The animal housing facility had a controlled temperature of 22–24°C and was maintained on a 12-h light/dark cycle; testing was done during the light cycle. Mice were weighed and handled the day before testing. Groups of 10 mice received a single dose/concentration of drug/solvent and were tested only once in the elevated plus-maze.

2.2. Apparatus

Static vapor exposures were conducted in a 29-l gas chromatography jar containing an acrylic lid as described previously (Woolverton and Balster, 1981). Each lid was equipped with injection ports and a fan which projected into the chamber above a 15-cm^2 stainless-steel mesh platform. During testing, one mouse was placed in the bottom of the chamber, the lid was replaced, and a calculated amount of liquid solvent was injected through a port onto filter paper located on the wire mesh platform. A fan, mounted on the inside of the lid, was then turned on which volatilized and distributed the agent within the jar. Nominal concentrations were confirmed by single-wavelength monitoring infrared spectrometry (Miran 1A, Foxboro Analytical). All vapor exposures were 30 min in duration and were conducted under a fume hood to vent the vapors away from laboratory personnel. Animals were removed from the exposure apparatus and placed on the plus-maze within 20 s. A similar protocol was followed during diazepam testing. Mice were injected i.p. with the appropriate dose of diazepam or vehicle, placed into the chamber, the lid replaced, and the fan turned on. This allowed the subjects in the diazepam groups to experience identical chamber conditions as those for the inhalant exposure groups. Separate control groups that did not receive vehicle injections, but were placed in the chamber, were employed in the solvent experiments.

2.3. Procedure

The elevated plus-maze consisted of two unwalled (open) arms (35 cm long × 5 cm wide) and two walled (closed) arms (35 cm × 5 cm × 15 cm deep). The entire maze was elevated to a height of 64 cm. Mice were placed in the center of the plus-maze facing one of the closed arms at the beginning of the 5-min test. A 5-min test versus the traditional 10-min test was employed in the present set of experiments because volatile agents are known to have a rapid clearance from the body. An observer (blind to test compound) recorded number of entries into each type of arm and later viewed a video-tape of the session and recorded time spent in each type of arm. An entry was defined as placing all four paws within the boundaries of the arm. Anxiolytic-like effects were indicated by increases in open arm time or in number of open arm entries. Total number of entries into either type of arm was used as a measure of overall motor activity.

2.4. Drugs and chemicals

Diazepam (Schein Pharmaceuticals, Port Washington, NY, USA) was purchased commercially at a concentration of 5 mg/ml and diluted to desired concentrations with a vehicle of ethanol (10%), propyleneglycol (40%) and sterile water (50%). Diazepam was administered intraperitoneally (i.p.) 30 min pre-testing in a volume of 10 ml/kg. The volatile agents were 1,1,1-trichloroethane (T-391, Fisher Scientific Co., Fairlawn, NJ, USA), toluene (17,996-5, Aldrich, Milwaukee, WI, USA), methoxyflurane (Pitman-Moore, Mundelein, IL, USA) and flurothyl (28-757-1, Aldrich, Milwaukee, WI, USA). Control tests were conducted in mice placed in the exposure chambers with the fans turned on and air only exposure (0 ppm).

2.5. Statistical analysis

Separate Kruskal-Wallis tests were performed on median open arm time, median number of open arm entries, and median number of total arm entries for each drug or vapor. When significant differences were indicated by

results of the Kruskal-Wallis test ($\alpha \leq 0.05$), nonparametric post hoc analyses were conducted comparing median values for each dose or concentration to median values for the corresponding control test (Daniel, 1978; Siegel and Castellan, 1988).

3. Results

As shown in Fig. 1, diazepam produced dose-dependent increases in open arm time (top panel) and in number of entries into the open arms (bottom panel). At 1 mg/kg, diazepam-treated mice entered the open arms more often than controls while the total amount of time spent in the open arms did not differ significantly from that of the control mice. At the 3 mg/kg dose, diazepam-treated mice entered the open arms more often than control mice with a significant increase in open arm time. These increases were not accompanied by significant changes in motor activity, as indicated by the total number of arm entries.

The effects of toluene in concentrations ranging from 1000 ppm to 6000 ppm are shown in Fig. 2. At 1000 ppm, toluene-exposed mice were not different from air-exposed control mice. However, toluene exposures of 2000 to 6000 ppm significantly increased both open arm time and number of open arm entries. In addition, these concentrations of toluene produced small but nonsignificant increases in the total number of arm entries.

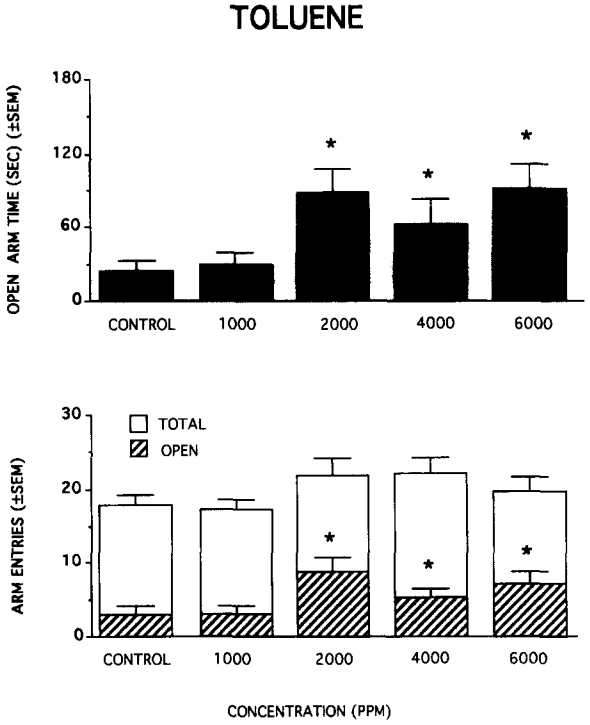

Fig. 2. Effects of toluene on mouse behavior in the elevated plus-maze. Time spent in the open arm of the maze (top panel) is shown as total number of seconds during the 300-s test. Error bars represent one standard error of the mean. All exposures were 30 min in duration and are shown as parts per million (ppm). * Significantly different from air control exposure (0 ppm).

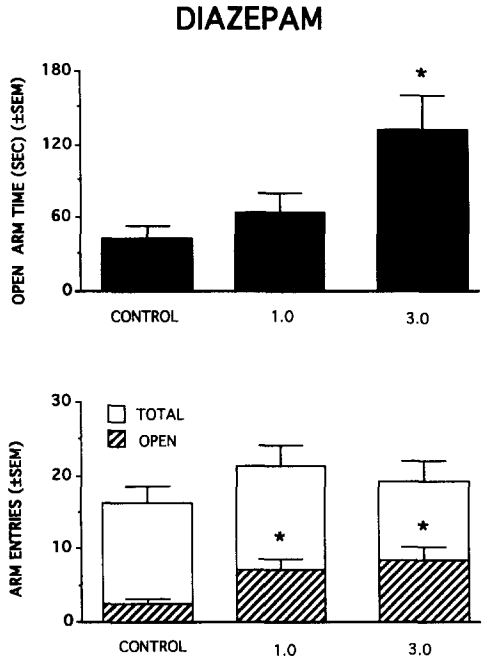

Fig. 1. Effects of diazepam on mouse behavior in the elevated plus-maze. Time spent in the open arm of the maze (top panel) is shown as total number of seconds during the 300-s test. Error bars represent one standard error of the mean. * Significantly different from vehicle/air control exposure (0 ppm).

Compared to air-exposed control mice, 1,1,1-trichloroethane-exposed mice displayed concentration-dependent increases in entries into the open arms and in total time spent in those open arms (Fig. 3). Significant effects were obtained at the two highest 1,1,1-trichloroethane exposures for number of arm entries with only the 10000 ppm exposure producing significant increases in time spent in the open arms. In addition to increased open arm activity, all 1,1,1-trichloroethane exposures produced significant increases in the total number of arm entries.

Fig. 4 shows the effects of methoxyflurane concentrations between 500 ppm and 2000 ppm. The lowest concentration of methoxyflurane produced only slight increases in open arm time and number of open arm entries which were not significantly different from control values. Compared to air-exposed control mice, methoxyflurane-exposed mice displayed concentration-dependent increases in entries into the open arms and in total time spent in those open arms at the two highest concentrations examined. All three methoxyflurane exposures significantly increased total arm entries.

In contrast to effects obtained with diazepam, toluene, 1,1,1-trichloroethane and methoxyflurane, flurothyl (300–900 ppm) produced concentration-related decreases in entries into the open arms and in total time spent in those

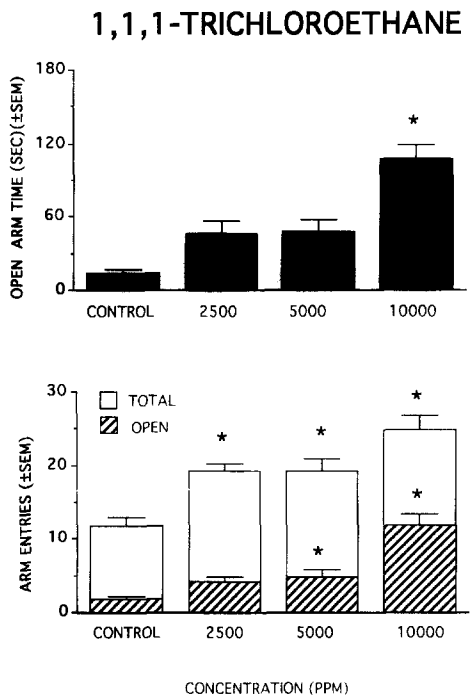

Fig. 3. Effects of 1,1,1-trichloroethane on mouse behavior in the elevated plus-maze. Time spent in the open arm of the maze (top panel) is shown as total number of seconds during the 300-s test. Error bars represent one standard error of the mean. All exposures were 30 min in duration and are shown as parts per million. * Significantly different from air control exposure (0 ppm).

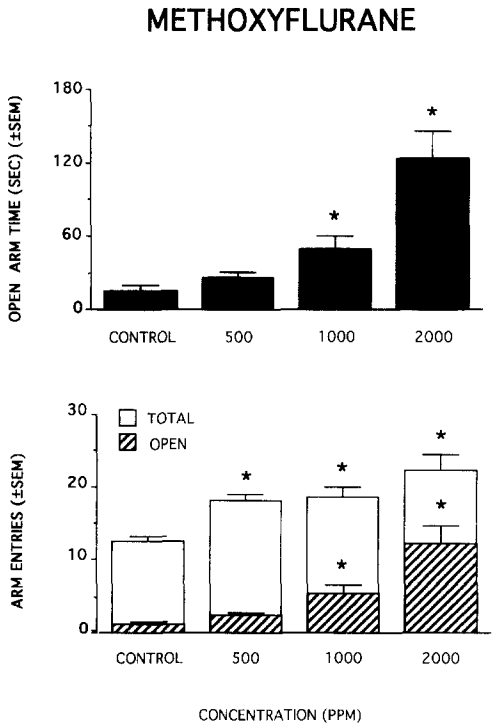

Fig. 4. Effects of methoxyflurane on mouse behavior in the elevated plus-maze. Time spent in the open arm of the maze (top panel) is shown as total number of seconds during the 300-s test. Error bars represent one standard error of the mean. All exposures were 30 min in duration and are shown as parts per million. * Significantly different from air control exposure (0 ppm).

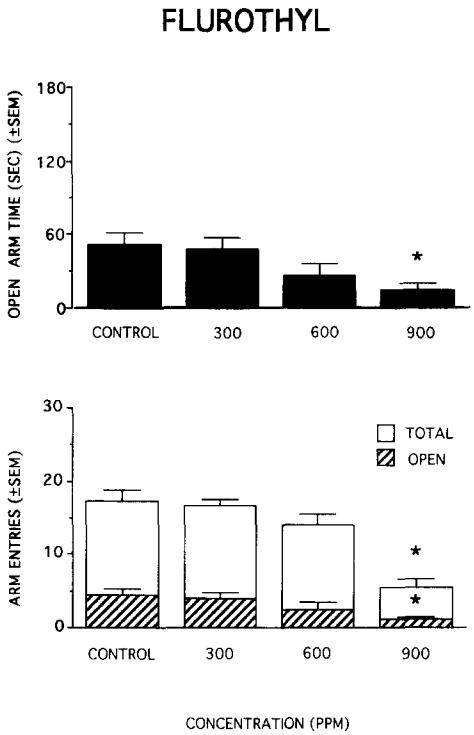

Fig. 5. Effects of flurothyl on mouse behavior in the elevated plus maze. Time spent in the open arm of the maze (top panel) is shown as total number of seconds during the 300-s test. Error bars represent one standard error of the mean. All exposures were 30 min in duration and are shown as parts per million. * Significantly different from air control exposure (0 ppm).

open arms (Fig. 5). Significant effects were only obtained at the highest flurothyl concentration for number of open arm entries and in time spent in the open arms. The 900 ppm concentration of flurothyl also significantly reduced the total number of arm entries.

4. Discussion

The purpose of the present investigation was to further investigate the purported anxiolytic properties of several abused inhalants and to compare them to a clinically active antianxiety drug in mice using the elevated plus-maze procedure. As in previous studies using the plus-maze (Brett and Pratt, 1990; Wiley et al., 1995), diazepam produced significant dose-dependent increases in time spent in the open arms and in number of open arm entries. Moreover, these increases were not accompanied by statistically significant changes in motor activity, as indicated by the number of total arm entries. Similar results are commonly obtained with benzodiazepines and other anxiolytic drugs at nonsedating doses in the plus-maze procedure (Pellow et al., 1985; Pellow and File, 1986) and a variety of other anxiolytic screening procedures (Barrett and Witkin, 1991). Although original validation of the elevated plus-maze procedure was performed in rats (Pel-

low et al., 1985), it has also been found to be selectively sensitive to the effects of anxiolytic and anxiogenic drugs in mice (Lister, 1987), as is suggested by the effects of diazepam in the present study.

Similar to what was obtained with diazepam, toluene was found to significantly increase open arm entries at concentrations that did not produce any gross ataxia or changes in total arm entries. Although the magnitude of effect was similar to that produced by diazepam, toluene's effects were not clearly concentration-related. The finding that toluene has anxiolytic-like effects in the elevated plus-maze supports previous research with rats that has shown toluene to have anxiolytic-like activity in other tests (Geller et al., 1983; Wood et al., 1984). In addition, the toluene concentrations that produced anxiolytic-like effects in the present study were similar to those of previous reports in which toluene inhalation has been shown to increase response rates suppressed by punishment (Wood et al., 1984) and increase approach behavior in avoidance paradigms (Shigeta et al., 1980). Furthermore, Geller and colleagues (Geller et al., 1983) reported that when rats were pretreated with diazepam and later exposed to 10 000 ppm of toluene, they received a significantly higher number of shocks in a punished responding procedure than when either compound was administered alone. This evidence for depressant drug-like effects of toluene in rodent tests of anxiety is consistent with results showing other depressant drug-like acute effects, including motor impairment (Bowen et al., 1996), biphasic effects on locomotor activity (Bowen and Balster, 1994), anticonvulsant activity (Wood et al., 1984), antipunishment effects (Wood et al., 1984) and cross-generalization of discriminative stimulus effects with barbiturates and ethanol (Knisely et al., 1990; Rees et al., 1985, 1987b,c).

1,1,1-Trichloroethane and methoxyflurane also produced increases in open arm entries and open arm time. Although the magnitude of 1,1,1-trichloroethane's and methoxyflurane's effects in the present study were similar to that of diazepam and toluene, the concentration range over which 1,1,1-trichloroethane and methoxyflurane produced their effects was much narrower than for toluene. While toluene concentrations between 2000 and 6000 ppm produced significant increases in open arm time and entries, only the 10 000 ppm concentration of 1,1,1-trichloroethane and the 1000 ppm and 2000 ppm of methoxyflurane produced significant increases in these measures. In addition, this increased open arm activity was accompanied by increases in number of total arm entries which suggests a possible nonspecific locomotor stimulation. Concentrations of 1,1,1-trichloroethane and methoxyflurane that produced anxiolytic effects were similar to those which produced increases in locomotor activity (Bowen and Balster, 1994, 1996) and decreases in operant rates of responding in rodents (Balster et al., 1982; Moser et al., 1985). In addition, the 1,1,1-trichloroethane concentrations used in the present investigation are within the concentration ranges reported to produce ethanol-like and pentobarbital-like discriminative stimulus effects in mice (Rees et al., 1987a,b). These depressant drug-like effects of 1,1,1-trichloroethane are also consistent with evidence for cross-dependence between 1,1,1-trichloroethane and ethanol, pentobarbital and midazolam (Evans and Balster, 1992). While methoxyflurane has not been tested in the aforementioned procedures, Evans and Balster (1992) have reported that methoxyflurane exposures between 1000–2000 ppm were effective in blocking the discriminative stimulus effects of pentylenetetrazole, a supraspinal convulsant. To our knowledge, these are the first empirical results suggesting that inhalation of 1,1,1-trichloroethane and/or methoxyflurane may produce anxiolytic-like effects. However, some degree of caution should be exercised in interpretation of these results since only the highest concentrations of 1,1,1-trichloroethane and methoxyflurane were able to produce effects in the two indices of anxiolytic activity. Further studies with these volatile compounds in other animal models of anxiety will be needed to determine the generalizability of these results.

A completely different profile of behavioral effects was produced by flurothyl. Flurothyl, a convulsant vapor chemically related to ether, was clearly not effective in producing anxiolytic-like activity in this model. Unlike with diazepam and the other vapors, flurothyl produced concentration-dependent decreases in open arm time and open arm entries. This reduction in open arm activity, which has been reported for other known anxiogenic compounds in the elevated plus-maze, may be indicative of an increased aversion to the open arms due to increased fear or anxiety (Lister, 1987; Pellow and File, 1986). Pentylenetetrazole, a drug with anxiogenic effects, has been shown to decrease punished drinking in a modified Vogel lick procedure (Vogel et al., 1971; Giusti et al., 1991) and to decrease open arm time and entries in an elevated plus-maze procedure (Cruz et al., 1994). These anxiogenic effects can be reversed by administration of a benzodiazepine. In mice trained to discriminate pentylenetetrazole from saline, flurothyl substituted for pentylenetetrazole (Evans and Balster, 1992). This lack of depressant drug-like effects with flurothyl is consistent with other evidence showing differences between it and abused vapors with a depressant drug-like profile of effects (Bowen et al., 1996).

In summary, 1,1,1-trichloroethane, toluene and methoxyflurane produced increases in open arm time and number of open arm entries, results which are similar to those of antianxiety drugs in the elevated plus-maze. While the anxiolytic-like effects of these volatile compounds were of similar magnitude to that of diazepam, the increases that were observed for TCE and methoxyflurane may have been produced a result of nonspecific changes in locomotor activity. In contrast, the convulsant vapor flurothyl was clearly ineffective in this model. The results of the present investigation provide additional support for the hypothesis that abused inhalants share pharmacological

properties with central nervous system depressants, but show that differences among the inhalants can be expected.

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