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Intravenous self-administration of abused solvents and anesthetics in mice

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Abstract

Volatile organic solvents, fuels and anesthetics are subject to abuse. The aim of the present study was to evaluate i.v. self-administration of several of these chemicals in drug- and experiment-naive mice using a commercially available vehicle, intralipid. Two strains of mice (DBA/2 and Swiss) were allowed to self-administer toluene (0.0017–0.17 μmol/infusion), 1,1,1-trichloroethane (0.006–0.19 μmol/infusion), ethanol (0.32–1.6 μmol/infusion), cyclohexane (0.0017–0.052 μmol/infusion), propofol (0.01–0.53 μmol/infusion) and flurothyl (0.00042–0.072 μmol/infusion) or their vehicles during 30-min tests. During the test, each nose-poke of the master mouse resulted in a 1.88-μl i.v. infusion to the master mouse and a yoked control mouse. When the delivery line was loaded with a reinforcing drug solution, the number of nose-pokes of the master mice significantly exceeded that for yoked control mice. In the present experiments, significant differences in rates of nose-poking were observed between mice receiving response-contingent and response-noncontingent deliveries of ethanol and toluene in both strains of mice and of 1,1,1-trichloroethane in Swiss mice. These data suggest that the reinforcing effects of abused inhalants can be studied using i.v. self-administration procedures.
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1. Introduction

Human exposure to volatile solvents is common due to their widespread industrial, commercial, and medical uses, as well as through voluntary self-administration to produce intoxication. Although inhalant abuse is a significant public health problem throughout the world (Kozel et al., 1995), much less is known about the properties of the chemicals that lead to their abuse than for most other classes of drugs of abuse. In particular, there have been very few studies of the reinforcing effects of abused solvents despite the well-established importance of animal drug self-administration studies with other classes of abused drugs (Schuster and Johanson, 1981; Brady, 1991). Such investigations can help establish the behavioral and neurobiological bases for drug-taking behavior. Also, because drugs abused by humans are typically self-administered by laboratory animals (Griffiths et al., 1980; Johanson, 1990; Balster, 1991), these methods can be used to assess the abuse potential of drugs (Johanson, 1990; Woolverton and Nader, 1990; Balster, 1991). Clearly, reliable animal methods for studying abused solvent self-administration are needed.

Solvents are usually abused by inhalation, and this is perhaps one of the reasons why animal models for assessing their reinforcing effects have been difficult to establish. There have been a few studies of self-administration via inhalation in animals. Yanagita et al. (1970) used rhesus monkeys implanted with nasal catheters. Lever-press responses resulted in 2- to 5-min deliveries of air or test vapors. In another study on self-administration of inhaled nitrous oxide (Wood et al., 1977), squirrel monkeys were seated in a chair with a helmet placed over

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their head. Lever presses resulted in 1-min exposures to various concentrations of nitrous oxide during 1-h daily sessions. Despite these earlier successes with monkeys, there have been no other reports of solvent vapor self-administration in these species and none that we are aware of using rodents, an important species for drug abuse research. In addition to the specific pharmacological effects these vapors may have, they also have very strong odors, which may deter voluntary exposure. Since inhaled vapors are carried to the brain by blood, where their abuse-related effects are presumably produced (Balster, 1998), it may be possible to circumvent the problems arising from inhalation studies by administering the test materials intravenously.

The present study sought to test whether several organic solvents and general anesthetics, toluene, 1,1,1-trichloroethane, cyclohexane, ethanol, propofol, and flurothyl are self-administered by mice. Self-administration behavior was assessed using a protocol that was specifically designed for studies in drug- and experiment-naive mice. Using this procedure, there were successful demonstrations of significant self-administration of all major abused drug classes such as cocaine, amphetamine, morphine, nicotine, ethanol, caffeine and others (e.g., Martellotta et al., 1995, 1998; Semenova et al., 1995; Zvartau et al., 1995; Kuzmin et al., 1997; Rasmussen and Swedberg, 1998). Our study was conducted with two strains of mice—DBA/2 and Swiss. The DBA/2 strain was selected because this strain readily acquires intravenous self-administration of various drugs such as morphine (Semenova et al., 1995; Kuzmin et al., 1997), cocaine (Kuzmin et al., 1997), ethanol (Zvartau et al., 1995) and nicotine (Paterson et al., 2003). Swiss mice (Charles River Swiss) have been extensively used for characterizing the behavioral effects of abused solvents (e.g., Bowen et al., 1996a,b; Balster et al., 1997). For the present studies, toluene and 1,1,1-trichloroethane were chosen because they are among the most commonly abused inhalants and their behavioral effects were previously shown to resemble those of major abused drugs such as barbiturates, benzodiazepines, phencyclidine and ethanol (Rees et al., 1987a,b; Knisely et al., 1990; Balster, 1998; Bowen et al., 1999). Cyclohexane is a solvent used for many industrial and household formulations (e.g., adhesives). Ethanol was selected to serve as a positive control since intravenous self-administration of ethanol is well documented both in humans and laboratory animals, including mice (e.g., Grahame and Cunningham, 1997). Propofol is an injectable anesthetic that acts at least in part through the GABA–benzodiazepine–barbiturate receptor complex and may therefore possess an abuse potential similar to that of other sedative-hypnotics with similar receptor interaction profiles (Concas et al., 1990; Sanna et al., 1995; Orser et al., 1998). For instance, a recent study in baboons revealed that propofol maintained high levels of self-injection behavior (Weerts et al., 1999). Finally, flurothyl, a proconvulsant agent (Adler, 1975), was added to the solvent test list as a potential negative control. Previous studies have suggested that flurothyl does not produce behavioral effects similar to those seen after exposure to toluene and 1,1,1-trichloroethane (Rees et al., 1987a; Bowen et al., 1996a). Fat emulsion, intralipid, was used as a vehicle in this study because of earlier reports demonstrating its utility for intravenous delivery of propofol and abused solvents (LeSage et al., 2000).

2. Materials and methods

2.1. Subjects

Adult male drug- and experiment-naive Swiss (Swiss bred at Rappolovo) and DBA/2 (20–33 g) were purchased from the State Breeding Farm Rappolovo (St. Petersburg, Russia). The animals were housed in groups of 10 with food and water available ad libitum. All experiments were conducted during the light period of a 12/12-h day–night cycle (08:00–20:00 h). The experiments were approved by the Institutional Ethics Committee of Pavlov Medical University and were performed in accordance with the recommendations and policies of the U.S. National Institutes of Health Guidelines for the Use of Animals.

2.2. Drugs

Ethanol ($d = 0.79$, m.w. = 46.1; University Pharmacy, St. Petersburg, Russia), toluene ($d = 0.867$, m.w. = 92.1; Kirishinefteorgsintez, St. Petersburg, Russia), cyclohexane ($d = 0.779$, m.w. = 84.2; ERA, St. Petersburg, Russia), 1,1,1-trichloroethane ($d = 1.338$, m.w. = 133.5; Aldrich, Milwaukee, WI), flurothyl ($d = 1.4$, m.w. = 182.1; Aldrich), and propofol ($d = 1.0$, m.w. = 178.27; Zeneca, Stockholm, Sweden) were dissolved in intralipid (20% fat emulsion, Baxter Healthcare, Deerfield, IL). All test solutions were prepared immediately before use.

2.3. Apparatus

Four identical $8 \times 8 \times 8$ cm test cages (RITEC, St. Petersburg, Russia) were used for the simultaneous testing of two pairs of mice (see below). Test cages were made from opaque plastic and were covered with an opaque lid during the test. Each cage had a frontal wall hole (diameter = 1.6 cm) for nose-poking and a semi-circle slot (diameter = 0.5 cm) in the back wall for immobilizing the mouse's tail. During the test, the mice were partially immobilized by fixing their tails with adhesive tape to a horizontal surface.

The nose-poke responses were recorded by means of infrared sensors interfaced to a microcomputer, which

controlled the activation of the two-syringe infusion pumps. The volume and duration of infusions were held constant at 1.88 μl and 1.0 s, respectively. During the infusion, the nose-poke responses were recorded but the infusion pump was not activated.

2.4. Procedure

A preliminary test was conducted for each mouse to record the operant level of nose-poking. Mice were placed into the test cages for 10 min, their tails were immobilized but needles were not inserted. Based on these pre-tests, the mice were grouped in pairs so that both animals in a pair exhibited approximately equal baseline levels of nose-poking. The animals were returned to their home cage following this pre-test.

Within 1 h after the pre-test, the selected pairs of mice were again placed into the experimental boxes and needles (OD = 0.4 mm) were inserted into the lateral tail veins of both animals of the pair. After 10 min of habituation to the test cages, intravenous deliveries of tested solvents or their vehicle were made contingent upon each nose-poke of one animal of the pair (the master mouse). Each nose-poke of the master mouse resulted in an infusion of 1.88 μl of the tested solution or intralipid to both the master mouse and the yoked control mouse. Nose-pokes of the yoked controls were counted but had no programmed consequences. Test sessions lasted 30 min. The mice were returned to their home cage after the experiment. Each mouse was tested only once.

The following concentrations (v/v) and unit doses of solvents were used to characterize the dose–effect relationships (μmol/infusion): toluene 0.01–0.3% (unit doses 0.0017–0.17), 1,1,1-trichlorethane 0.03–0.56% (unit doses 0.006–0.19), ethanol 1–4% (unit doses 0.32–1.6), cyclohexane 0.017–0.17% (unit doses 0.0017–0.052), propofol 0.1–3% (unit doses 0.01–0.53) and flurothyl 0.003–0.3% (unit doses 0.00042–0.072). Each treatment group consisted of 7–10 pairs of mice.

2.5. Data analysis

The data analysis was based on the assumption that the number of nose-pokes of the master mouse would exceed the corresponding value for the yoked control mouse when the delivery line was loaded with a reinforcing drug solution. Rates of nose-poking during the 30-min test sessions were also adjusted by the baseline rates of nose poking during the 10-min baseline pre-tests. A ratio (R) criterion was calculated for each pair of experimental animals according to the formula: $R = \log(A_T/P_T) - \log(A_{BL}/P_{BL})$, where A_T is the total number of nose-poke responses of the master mouse, P_T is the total number of nose-poke responses of the yoked control mouse during the 30-min test, A_{BL} is the total number of baseline nose-poke responses of the master mouse, and P_{BL} is the total number of nose-poke responses of the yoked control mouse during the 10-min pre-test (baseline). In addition, the cumulative doses of self-injected solvents were calculated.

The data were analyzed using SAS-STAT software (SAS Institute, Cary, NC). R-criterion and cumulative dose data were subjected to distribution-free one- and two-factorial analyses of variance (ANOVA). The General Linear Models (GLM) procedure was selected because of the unequal sample sizes. Dunnett's and Tukey's tests were used wherever the need for between-group pair wise comparisons was indicated by ANOVA results.

3. Results

There were no overall significant differences between treatment groups with regard to their performance during the 10-min pre-tests. The nose-poke activity of master and yoked control mice did not differ for any treatment group.

Fig. 1 presents dose–effect curves for each of the agents tested. Toluene concentration had overall significant effects on R-values for both Swiss ($F(6,63) = 3.4$, $P < 0.01$) and DBA/2 ($F(5,45) = 2.5$, $P < 0.05$) mice. Individual comparisons showed that R-values were significantly ($P < 0.05$) higher than the vehicle control in mice allowed to self-inject toluene at the concentration of 0.017% for Swiss mice and 0.056% for DBA/2 mice. Strain differences were confirmed as there was a significant strain-by-unit dose interaction ($F(5,109) = 4.9$, $P < 0.01$). Cumulative doses of self-injected toluene and other solvents are presented in Table 1.

The acquisition of toluene self-administration for Swiss mice is illustrated in Fig. 2. The nose-poke responses during the test sessions were recorded in six consecutive 5-min intervals. There were no differences between master and yoked control mice across all 5-min intervals when mice were exposed to intralipid. When vehicle was available, rates of nose-poking declined steadily over the session for both master and yoked-control mice. In contrast, at the toluene concentration of 0.017% nose-poke activity of master mice was significantly higher than that for yoked controls ($F(1,14) = 8.4$, $P < 0.05$), not showing the within-session decline in rates seen both in the yoked mouse receiving identical toluene injections and in the vehicle control group.

Experiments with 1,1,1-trichloroethane revealed significant self-administration in Swiss mice (Fig. 2). In this strain nose-poking activity depended significantly upon the concentration of 1,1,1-trichloroethane ($F(6,56) = 2.3$, $P < 0.05$), with the optimum concentration (concentration yielding highest R-criterion value) being 0.3%. For DBA/2 mice, there was no statistically significant effect of 1,1,1-trichloroethane concentration ($F(5,46) = 1.4$, $P = 0.23$). Nonetheless, the concentration of 0.1% 1,1,1-trichloroethane did produce a substantially higher R-value than

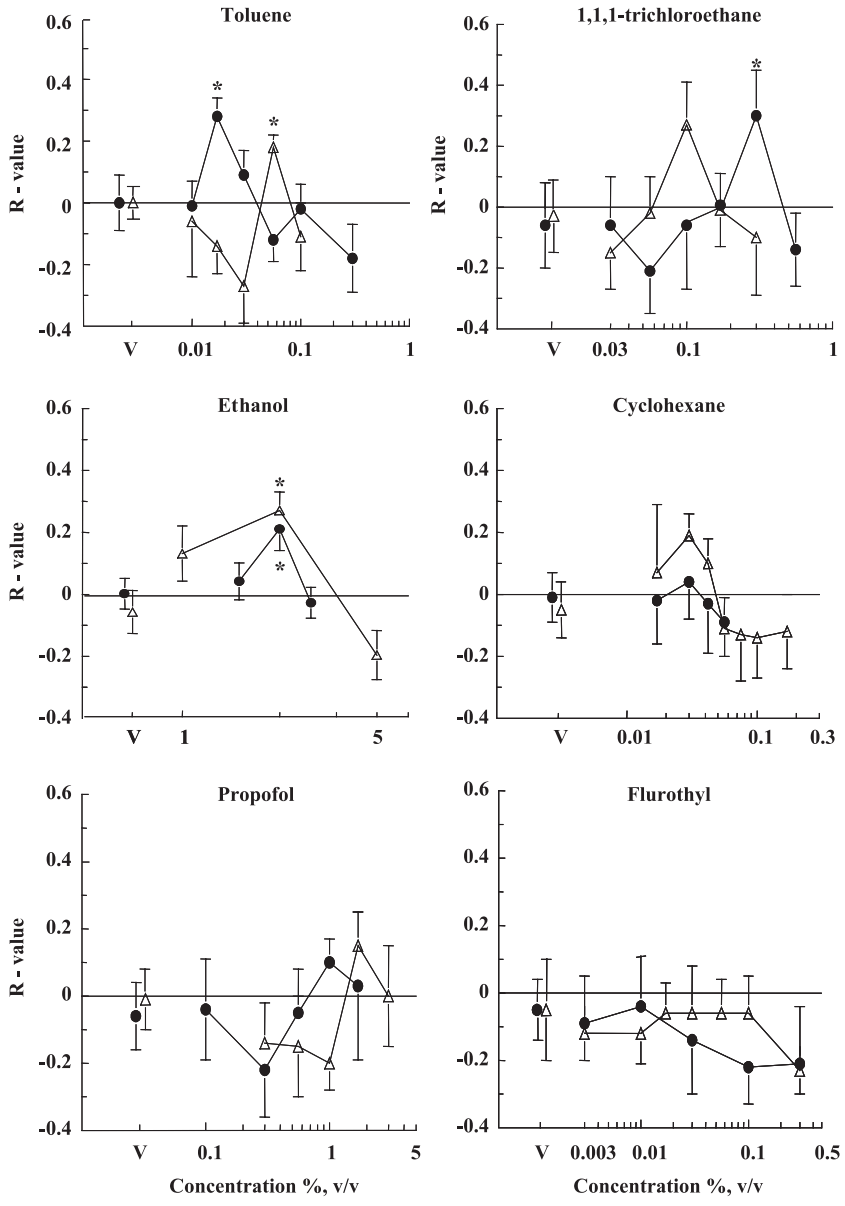

Fig. 1. Self-administration of toluene, 1,1,1-trichloroethane, ethanol, cyclohexane, propofol and flurothyl in drug-naive mice (filled circles—Swiss mice, open triangles—DBA/2 mice). Data (mean ± S.E.M.) are presented as *R*-criterion values for the 30-min test session. See text for details. For the sake of clarity, error bars are not shown for all data points. $N = 7–10$ for each data point. *$P < 0.05$ (Dunnett's test), compared to mice self-administering intralipid instead of solvents (data points above 'V').

did vehicle in this strain, but since the overall concentration factor was not significant, individual comparisons were not assessed.

As shown in Fig. 2, ethanol was confirmed to maintain significant self-administration behavior in both DBA/2 ($F(3,31) = 8.0$, $P < 0.01$) and Swiss ($F(3,31) = 3.2$,

Table 1
Cumulative self-injected doses of solvents at concentrations yielding maximal *R*-criterion values[a]

Solvent	Strain	Concentration (%, v/v)	Dose ± S.E.M. (mmol/kg)	Dose ± S.E.M. (mg/kg)
Toluene	DBA/2	0.056	0.0277 ± 0.0045	2.55 ± 0.41
	Swiss	0.017	0.0069 ± 0.0010	0.63 ± 0.09
1,1,1-Trichloroethane	DBA/2	0.1	0.0499 ± 0.0186	6.66 ± 2.48
	Swiss	0.3	0.1442 ± 0.0343	19.3 ± 4.6
Ethanol	DBA/2	2	1.93 ± 0.17	89.1 ± 7.7
	Swiss	2	2.03 ± 0.31	93.7 ± 14.1

[a] Data are presented only for those agents for which significant self-administration was observed in at least one of the two mouse strains tested.

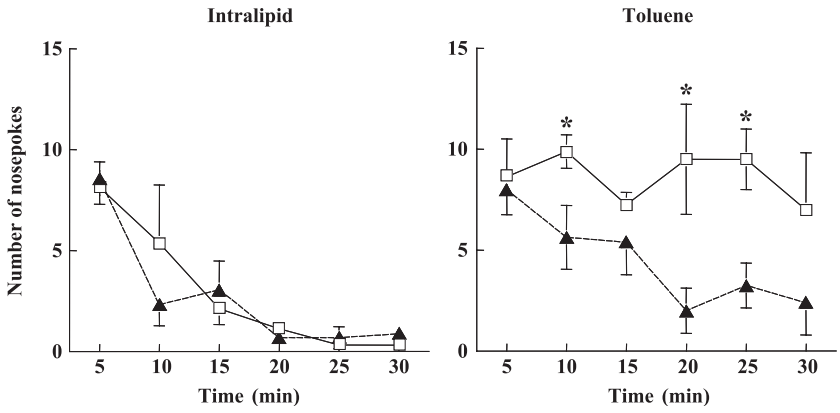

Fig. 2. Acquisition of toluene i.v. self-administration in drug-naive Swiss mice. Data (mean ± S.E.M.) are presented as numbers of nose-pokes of master (open squares) and yoked control mice (filled triangles) for each consecutive 5-min interval during the 30-min test session. For the sake of clarity, error bars are not shown for all data points. $N=8$ for each data point. *$P<0.05$ (Tukey's test), compared to yoked controls.

$P<0.05$) mice. For all other solvents tested, there was no evidence for significant effects of concentration in either mouse strain (Fig. 2; cyclohexane—DBA/2: $F(7,63)=1.3$, Swiss: $F(4,39)=0.3$; propofol—DBA/2: $F(5,47)=1.4$, Swiss: $F(5,47)=0.8$; flurothyl—DBA/2: $F(7,61)=0.4$, Swiss: $F(5,43)=0.2$).

4. Discussion

Evidence is presented that the reinforcing properties of abused inhalant can be studied using i.v. self-administration procedures in mice. Toluene and 1,1,1-trichloroethane are well established to be abused solvents (Balster, 1987; Gerasimov et al., 2003; Kozel et al., 1995) and both were self-administered. Two control procedures were used to establish that these chemicals were serving as reinforcers. One control was based on a yoked-control procedure. Ratios of nose-poking rates were obtained for pairs of mice. For one mouse in each pair, designated the master mouse, i.v. injections were contingent on nose-poking behavior; the other mouse in the pair, designated the yoked control mouse, received injections each time the master mouse did, but they were non-contingent on nose-poking behavior. Thus, differences in rates of nose-poking between the master and yoked-control mouse could not be due to any direct effects of the self-administered compounds since both mice received equal doses at identical times. The most likely explanation for differences between the mice is the contingent relationship between the response and solvent delivery. A ratio was established for each pair of mice that depended primarily on the ratio of rates of responding for master and control mice. When the ratio exceeded zero, rates of responding in the master mouse were higher than in the yoked-control mouse. Both toluene and 1,1,1-trichloroethane produced *R*-values greater than zero. The other control procedure involved comparing these *R*-values for mice receiving toluene or 1,1,1-trichloroethane to those for mice receiving only vehicle injections. As expected, vehicle injections resulted in *R*-values of about zero, indicating no difference between master and yoked-control mice. In Swiss mice, both toluene and 1,1,1-trichloroethane had a significant effect of concentration, with intermediate unit doses producing *R*-values significantly higher than those obtained with vehicle. Significant effects were also obtained with toluene in DBA/2 mice, replicating the results for Swiss mice. For 1,1,1-trichloroethane in DBA/2 mice, an *R*-value greater than zero was obtained at an intermediate concentration, although the overall effects of 1,1,1-trichloroethane were not significant.

Results with the positive and negative control test compounds were as predicted. Ethanol produced significant concentration-related effects in both strains of mice. Ethanol self-administration is widely observed in humans and can be readily established in various species of laboratory animals including monkeys, rats and mice (e.g., Macenski and Meisch, 1992; Grahame and Cunningham, 1997; Czachowski and Samson, 1999). Importantly, in animal subjects (including mice) ethanol is self-administered whether delivered orally (e.g., Elmer et al., 1988) or intravenously (e.g., Grahame and Cunningham, 1997). Flurothyl has been used as a negative control for the abuse-related effects of solvents in previous studies (e.g., Rees et al., 1987a; Bowen et al., 1996a). Although flurothyl shares physical–chemical properties with abused solvents (e.g., volatility and lipophilicity), its acute central nervous system (CNS) effects are in many ways the opposite, producing convulsions. It does not share abuse-related behavioral properties with compounds such as toluene, 1,1,1-trichloroethane and ether (Balster, 1998). In these studies, flurothyl did not produce concentrated-related effects, resulting in *R*-values less than zero. Thus, not every "solvent" is active in this procedure, providing support for the idea that we are studying selective abuse-related properties of this class of chemicals.

The injectable anesthetic, propofol, and the solvent, cyclohexane, were tested as unknowns in this procedure. Little information on either of these compounds was available to predict whether they would show reinforcing effects.

A previous study revealed that propofol had reinforcing effects in baboons with experience in cocaine self-administration (Weerts et al., 1999) and a similar study with rats showed propofol self-administration in animals experienced in methohexital self-administration (LeSage et al., 2000). In the present study, there was no evidence for propofol reinforcement, at least over the dose range studied. Higher doses of propofol could not be tested due to the profound sedative and hypnotic effects. In addition to the differences in species used in the two studies, another notable difference is that our study used drug-naive mice. Our negative mouse results provide further indication that not all "depressant" drugs are active in this procedure.

Cyclohexane is a solvent whose abuse potential is unknown. Abuse potential assessment of individual solvents can be important for predicting the propensity of products that contain them to be abused and for creating a database from which solvents with less abuse potential can be used in product formulation (Balster, 1987). Based on these negative results with cyclohexane, it could be predicted that it lacks the abuse potential of solvents such as toluene and 1,1,1-trichloroethane. These results are consistent with the inability of cyclohexane to facilitate brain stimulation reward (Bespalov et al., 2003). Our success in obtaining abused solvent self-administration suggests that this procedure may be useful as a component of a battery of preclinical tests for abuse potential assessment of solvent and anesthetics (Balster, 1987).

Self-administration of toluene, 1,1,1-trichloroethane and other abused inhalants has not been studied extensively. Among the possible reasons for this is that inhalation studies are technically difficult to do, requiring specialized vapor generation apparatus and analytical capability to measure vapor concentration. Although there have been some attempts to develop self-administration protocols for animals, using inhalation delivery routes (e.g., Yanagita et al., 1970), it is difficult to demonstrate reinforcing effects of solvent vapors in mice due, in part, to the aversive odorant qualities of these vapors, especially for rodent species where the olfactory system is important in their natural environment. These odorant properties are largely circumvented by use of the i.v. route, although it is possible that there are some olfactory or gustatory sequelae of solvent elimination that can still be detected by these animals. Since these solvents and anesthetics are not water soluble, a safe vehicle capable of producing stable and uniform solutions of solvent was needed. Intralipid is a medically useful fat emulsion that has been used by others for i.v. administration of abused solvents. It worked very well in this model, producing suspensions that could be easily delivered in standard infusion pumps. It remains to be determined if this vehicle system can be used with other species or other routes of administration. Nor do we know if this vehicle or the use of the i.v. route was essential for obtaining positive results since there are other aspects of the methodology that differed from those of previous unsuccessful attempts to obtain abused solvent self-administration.

The mouse self-administration procedure used in this study has several distinctive features. First, unlike conventional self-administration protocols, the animals are not prepared with chronic indwelling venous catheters. Instead, solvent deliveries are made via an acutely prepared tail vein port. Second, the entire test duration is limited to 30 min; this is a very short time compared to the protocols used elsewhere. Despite these differences, this mouse self-administration procedure was repeatedly shown to produce results consistent with the data obtained with other approaches. In previous studies, morphine, cocaine, amphetamine, nicotine, caffeine, cannabinoids, ethanol and various other drugs of abuse were reliably self-administered by drug- and experimentally naive mice (Martellotta et al., 1995, 1998; Semenova et al., 1995; Zvartau et al., 1995; Kuzmin et al., 1997; Rasmussen and Swedberg, 1998). The present study extends the list of drugs whose reinforcing properties can be examined with the use of this mouse procedure. Also, one should note that the results obtained in these studies are not confounded by any prior behavioral and/or pharmacological history.

It is also worth noting that this mouse procedure does not reveal the acquisition of self-administration behavior in the same way as is commonly seen with the conventional protocols. The mouse procedure relies on the differences between nose-poking rates for the animals that receive the drug in a response-contingent manner (i.e., master mice) and those that receive the drug irrespective of their behavioral activity (i.e., yoked controls). Because of the small working chamber size, the type of operant response (nose-poke), and the animals being compelled to face the nose-poke hole by tail restraint, this procedure is characterized by high operant levels (i.e., an average of 30–40 nose-poke responses per 10-min pre-test session). In the animals exposed to vehicle self-administration as well as in the yoked controls, the initially high response rates declined rapidly during the 30-min test sessions. In contrast, as illustrated in Fig. 2, in the master mice exposed to drug self-administration the operant responding persists for longer periods of time throughout the session, presumably as reinforcing effects override the natural habituation of the behavior. Thus, one may argue that the mouse self-administration procedure reveals dishabituating rather than reinforcing properties of the self-administered drugs. Dishabituation effects were described for several abused drugs such as amphetamine and can be seen in a form of failed habituation to the environment associated with the drug administration (Pickens and Dougherty, 1971; Damianopoulos and Carey, 1992; see, however, Tirelli and Terry, 1998). However, in our experiments, both master and yoked control mice were exposed to the same drug dose levels, suggesting that such direct drug effects are unlikely to account for the results. It should also be emphasized that many conventional drug self-administration protocols rely on procedures that serve to increase

the operant level. This is achieved with the use of pretraining with non-drug (food) reinforcement (e.g., Koob et al., 1987), schedule-induction contingencies (e.g., Singer et al., 1982), as well as several other procedures resulting in higher levels of spontaneous motor activity (food deprivation, reversed day–night cycle, etc.; e.g., DeVry et al., 1989). This may indicate that dishabituating effects of self-administered drugs may often be difficult to distinguish from the 'true' reinforcing effects. On the other hand, it is likely that the high initial rates of nose-poking in test sessions serve to put the animal in frequent early contact with the contingent relationship with injections, facilitating the very rapid acquisition of the behavior.

Genetic determinants of drug self-administration are known to exist, and the use of mice for these tests provides a powerful tool to exploit the ever increasing availability of genetically informative subjects for experimentation. We included two strains of mice in these experiments, primarily to provide a basis for assessing the reliability and generalizability of our results, but also to begin to examine strain differences in self-administration results. Strain influences were confirmed for mouse self-administration as well. In a previous study, DBA/2 mice appeared to be less sensitive to the reinforcing effects of oral ethanol than were C57BL/6 mice, although no such differences were reported when ethanol was delivered via intravenous route (Grahame and Cunningham, 1997). In our study, there were no notable differences in the results for ethanol for the DBA/2 and Swiss strains. For the abused solvents, strain was not a particularly important determinant of the results either. Toluene had reinforcing effects in both mouse strains, although the DBA/2 strain appeared to show maximal reinforcing effects at a higher unit dose than the Swiss strain. Consequently, these animals received a higher total toluene doses than did the Swiss strain. The reliability of this finding is unknown, but it appeared that the opposite strain sensitivity was observed for 1,1,1-trichloroethane (i.e., maximal *R*-values were obtained at lower unit doses in Swiss than DBA/2 mice). The results for 1,1,1-trichloroethane were also only significant in the Swiss mice, but because high *R*-values were seen in the DBA/2 strain as well, it is premature to claim that there are important strain differences for the reinforcing effects of 1,1,1-trichloroethane in mice. For the procedure used in this study, there is only one published report that identified DBA/2 mice as the strain most likely to develop self-administration of morphine and cocaine (Semenova et al., 1995). The results of the present study suggest that, despite some differences for various solvents, both DBA/2 and Swiss mice can be used for studying the self-administration of the solvents.

Progress in solvent abuse research is hampered by the diversity of cellular and subcellular targets that mediate the effects of these diverse compounds. For example, ethanol, toluene, 1,1,1-trichloroethane as well as several general anesthetics have been shown to interact with many ligand-gated ion channel receptors, including GABA and glutamate receptors (e.g., Beckstead et al., 2000; Cruz et al., 2000). Although the relative contributions and exact mechanisms of these interactions are not known (Balster, 1998), results of behavioral studies in laboratory animals have long suggested that various solvents produce a range of effects remarkably similar to those of abused depressant drugs such as barbiturates, benzodiazepines, ethanol, etc. (e.g., Evans and Balster, 1991; Balster, 1998). For example, it was shown that 1,1,1-trichloroethane, toluene and several other solvents substitute for ethanol, pentobarbital, and/or phencyclidine in the drug discrimination studies in rats and mice (Rees et al., 1987a,b; Bowen et al., 1999). Similarly, in animals trained to discriminate toluene, injections of either methohexital or oxazepam produced toluene-lever responding in a dose-dependent fashion (Knisely et al., 1990). These cross-generalization data indicate that toluene and other solvents have stimulus properties similar to those of CNS depressant drugs and that solvent abusers may be motivated to use these materials by a desire to produce alcohol-like intoxication. This forms part of the rationale for using ethanol as a positive control in this study. The finding that both ethanol and abused solvents and anesthetics have reinforcing effects in the same model invites the speculation that they may share some common substrates for these effects as well.

In conclusion, toluene and 1,1,1-trichloroethane are self-administered by drug- and experiment-naive mice, suggesting that the abuse potential of these volatile compounds can be studied using intravenous self-administration protocols.

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