Pharmacology Biochemistry and Behavior, Vol. 57, Nos. 1/2, pp. 191–198, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00308-5

Desflurane, Enflurane, Isoflurane and Ether Produce Ethanol-Like Discriminative Stimulus Effects in Mice[1]

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Received 23 February 1996; Revised 24 April 1996; Accepted 10 May 1996

BOWEN, S. E., AND R. L. BALSTER. *Desflurane, enflurane, isoflurane and ether produce ethanol-like discriminative stimulus effects in mice.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 191–198, 1997.—In the present studies, drug discrimination procedures were used to compare the discriminative stimulus effects of ethanol (ETOH) and several volatile anesthetics. Male albino mice were trained to discriminate between IP injections of ETOH (1.25 g/kg) and saline in a two-lever operant task in which responding was under the control of a fixed-ratio 20 (FR20) schedule of food presentation. Stimulus generalization was examined after 20-min inhalation exposures to desflurane (4,000–32,000 ppm), enflurane (3,000–12,000 ppm), isoflurane (1,000–8,000 ppm) and ether (4,000–32,000 ppm). Concentration-related increases in ETOH-lever responding were observed for all four volatile anesthetics. For enflurane and ether, maximal levels of > 85% ETOH-lever responding were obtained at one or more concentrations. For desflurane and isoflurane, the maximal mean percentages of ETOH-lever responding were somewhat lower, but 6 out of 7 mice showed full substitution with desflurane and 5 out of 7 for isoflurane. The shared discriminative properties of these compounds with ETOH suggest that these anesthetics may share some of ETOH's pharmacological properties. These results are similar to previous research results showing ETOH-like discriminative stimulus effects in mice with other anesthetics and abused volatile inhalants (i.e. halothane, toluene and 1,1,1-trichloroethane) and may reflect the CNS-depressant drug-like effects of inhaled anesthetics and abused solvents. © 1997 Elsevier Science Inc.

Solvents Inhalant abuse Drug discrimination Ether Desflurane Enflurane Isoflurane Ethanol Mice

WHILE inhalation anesthetics make up one of the oldest categories of centrally active drugs, surprisingly little is known about the nature of their behavioral effects at subanesthetic concentrations or the cellular mechanisms for these effects. A prominent hypothesis is that the acute intoxication produced by volatile inhalants may be similar to the intoxication produced by classic central nervous system depressants, such as barbiturates and ethanol (ETOH). Support for this theory has come from several recent investigations in which volatile compounds (e.g. toluene, 1,1,1-trichloroethane) have been shown to produce a profile of pharmacological and behavioral effects similar to that of pentobarbital and ETOH (5). These inhalants have also been shown to impair coordinated motor performance (11) and intensification of these effects have been described when inhalants are combined with ETOH (9,22).

If volatile anesthetics produce their behavioral and pharmacological effects via a depressant-like intoxication, then we would expect these anesthetics to produce discriminative stimulus properties similar to those of other classic CNS depressants like barbiturates or ETOH. While the discriminative stimulus properties of anesthetics have not been intensely investigated, several studies have shown that some volatile inhalants have discriminative stimulus effects similar to those of a number of CNS depressant drugs. For example, inhaled toluene, halothane, and 1,1,1-trichloroethane produce pentobarbital-like discriminative stimulus effects (13,14). In addition, Rees et al. (15) have shown that these same inhalants will produce ETOH-like discriminative stimulus effects in mice. However, not all volatile inhalants produce these effects. Neither flurothyl, a vapor with convulsant properties, nor isoamyl nitrate, a vapor with vasodilatory actions, produced pentobarbital-lever responding in animals trained to discriminate pentobarbital from saline (14).

The present study was designed to further characterize the discriminative stimulus effects of several volatile anesthetics. Stimulus generalization tests were conducted with vapor expo-

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[1]A preliminary report of the results of this study was presented at the annual meeting of the Society for Stimulus Properties of Drugs, San Diego, CA (November 1995).

sures to desflurane, enflurane, isoflurane and ether in mice trained to discriminate injections of ETOH from saline. The testing protocol employed for the ETOH discrimination in the present study was similar to conditions used in previous drug discrimination studies in ETOH-trained mice (15).

METHODS

Subjects

Seven experimentally naive male mice (CFW, Charles River Co., Wilmington, MA) were housed individually in standard mouse cages (18 × 29 × 13 cm) with wood chip bedding and steel-wire tops. Animals were kept in a room with controlled temperature (22–24°C) on a 12-h light/dark cycle. Mice were brought into the laboratory and tested during the light cycle. Water was available *ad lib* in the home cage and mice were maintained on a restricted diet by post session feeding of rodent chow (Rodent Laboratory Chow, Ralston-Purina C., St. Louis, MO) in sufficient amounts to maintain weights at 85% of free-feeding weights.

Apparatus

Behavioral training and testing were conducted in six computer-interfaced operant chambers which have been previously described (1). Briefly, all test chambers consisted of floors containing parallel stainless steel rods and walls constructed of aluminum with a single plexiglas wall containing a door. Each of the chambers was enclosed in a cubicle which attenuated external light and sound. Every chamber was equipped with two operant levers which extended 0.8 cm into the chamber. A recessed food trough was located midway between the levers into which a liquid dipper would deliver 0.02 ml of sweetened-condensed milk (1 part sugar, 1 part condensed milk, and 2 parts water by volume). Two houselights, located above each of the levers, signalled that the session was in progress.

Inhalation Exposure

Vapor exposures were conducted in 29-l cylindrical jars (47 cm H × 35 cm diameter; total floor space = 962 cm^2) which have been described previously (22). Briefly, vapor generation commenced when liquid anesthetic was injected through a port onto filter paper suspended below the sealed lid. A fan, mounted on the inside of the lid, was then turned on which volatilized and distributed the agent within the chamber. Nominal chamber concentrations did not vary by more than 10% from measured concentration as determined by single wavelength monitoring infrared spectrometry (Miran 1A, Foxboro Analytical, North Haven, CT). All vapor exposures were 20 min in duration.

Discrimination Training

Mice were initially trained under a fixed-ratio one (FR1) schedule to press either of two response levers for milk presentation during daily 15-min sessions. After several sessions of stable lever pressing, responding on only one lever was reinforced dependent upon whether the mouse had received an IP injection 20 min earlier of ETOH (1.25 g/kg) or saline. Subjects were returned to their home cages between injections and placement into the test chamber. The choice of drug and vehicle levers were randomly assigned for each subject. During this first phase of drug discrimination training, the mice were gradually shaped through progressive increases in the FR requirement to respond under a FR20 schedule on alternating levers. This required the subjects to produce 20 consecutive responses on the correct lever for milk presentation.

Acquisition Tests

Following reliable FR20 responding, each of the subjects was tested for stimulus control by ETOH and saline injections with test sessions conducted on each Tuesday and Friday. Completion of the response requirement on either lever during the 2-min test sessions produced a liquid reinforcer. These test sessions were followed immediately by a 13-min training session in which only correct responses were reinforced. Acquisition of the discrimination was defined as the successful completion of four consecutive test sessions (2 ETOH and 2 saline). Success was defined as both completing the first FR and responding at least 85% on the correct lever. After successful acquisition training, a short 2 week period of continued training occurred during which subjects were placed in the exposure chamber 20 min prior to the training session and subjected to "air-only" exposures in an effort to adapt subjects to the inhalation procedure.

Generalization Testing

Following the acquisition of discrimination between 1.25 g/kg ETOH and saline and the adaptation period, generalization testing was begun. Discrimination tests were performed on Tuesdays and Fridays contingent on the subject completing the first FR on the correct response lever and having over 85% correct-lever responding over the entire training session preceding the test day. Mice continued to be trained on the double alternation sequence of ETOH and saline training sessions between test days in order to preserve the discrimination. On test days, mice were placed into the operant chambers for a 2-min session in which responding on either lever was reinforced. Following the 2-min test, the subjects were returned to their home cages.

Initial discrimination tests were conducted with several doses of ETOH (0.5–2.5 mg/kg), its vehicle (water), and saline given 20 min pre-session. Cross-generalization tests to the vapors desflurane (4,000–32,000 ppm), enflurane (3,000–12,000 ppm), isoflurane (1,000–8,000 ppm) and ether (4,000–32,000 ppm) were then conducted. All anesthetics were administered for 20 min beginning 20 min prior to a test session with all animals receiving all of the drugs. Animals were rapidly removed from the exposure chambers and placed in the test chambers with test sessions beginning within 30 s of termination of the exposure. During ETOH generalization testing, animals were placed into the inhalation chambers and given "air-only" exposures. Control test sessions with the vehicle plus air exposure were conducted. In addition, test sessions with saline and the training dose of ETOH were performed before and after each concentration- or dose-effect curve.

Data Analysis

The ability of the tested anesthetic to substitute for the training dose of ETOH was measured as the percentage of responses emitted on the ETOH-appropriate lever during the 2-min test session. When an inhalant concentration resulted in the suppression of an individual subject's response rate to less than 0.05 responses/s, the corresponding percentage of ETOH-lever responding for that treatment was excluded from the group data analysis.

Response rates were expressed as the percentage of the

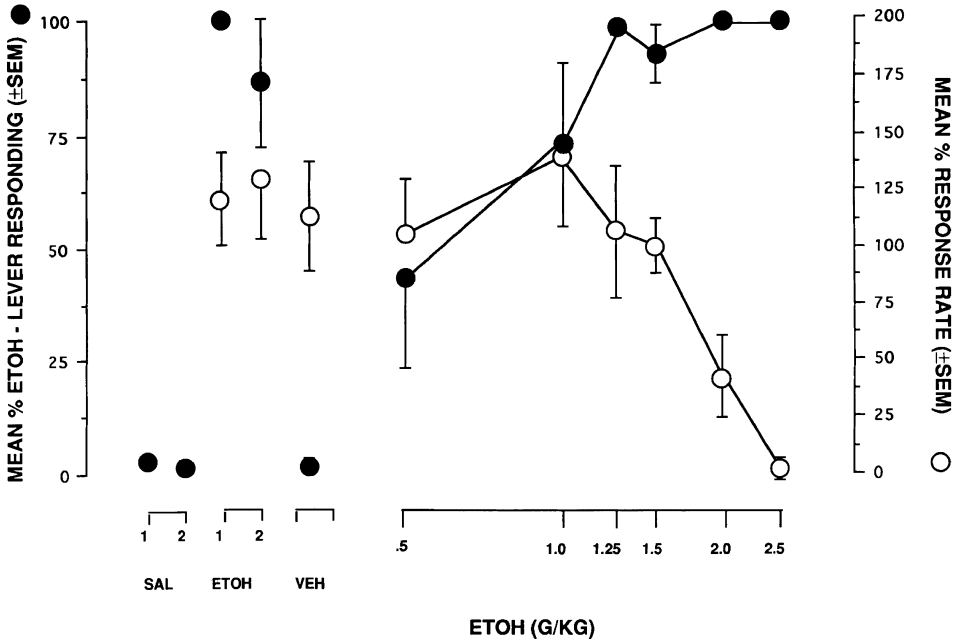

FIG. 1. Dose-effect curve for ethanol in mice trained to discriminate 1.25 g/kg ethanol from saline. Percentage of ethanol-lever responding (mean ± SEM) are shown as filled circles; response rates (mean ± SEM) are shown as empty circles. Values above SAL and ETOH represent the results of saline and 1.25 g/kg ethanol control test sessions which occurred immediately before (1) or after (2) ETOH testing. Values above VEH represent the results of a control test with air only exposure after a saline injection, $n = 7$.

control response rate which was determined by averaging the response rates on the saline test sessions for each animal conducted before and after the determination of the dose- or concentration-effect curve. When possible, group EC_{50} or ED_{50} values (estimated concentration or dose producing 50% ETOH-lever responding) and confidence limits (CL) were obtained using the least squares method of linear regression of the linear part of the dose or concentration-effect curve (20). Attrition due to illness resulted in the lost of three animals during ether testing. Incomplete concentration-response curves from these mice were withdrawn from data analysis.

Chemicals

The test agents were purchased commercially and were desflurane (Ohmeda Pharmaceutical Products, Liberty Corner, NJ), enflurane (Abbott Laboratories, North Chicago, IL), isoflurane (Ohmeda Pharmaceutical Products, Liberty Corner, NJ) and ether (Aldrich Chemical Company, Milwaukee, WI). Ethanol was diluted with sterile water and injections were given IP in a volume of 10 ml/kg.

RESULTS

Control

All seven mice were successful in acquiring the discrimination between 1.25 g/kg ETOH and saline. The results of the initial generalization tests over a range of ETOH doses are shown in Fig. 1. All seven mice displayed dose-dependent substitution for the training dose of ETOH. Greater than 85% ETOH lever selection was demonstrated at the training dose of ETOH and the three higher doses. The ED_{50} for ETOH substitution was 0.63 g/kg (C.L. 0.29–1.35 g/kg). While the training dose of ETOH produced no decrements in response rates, 2 g/kg depressed response rates to 48% of saline control levels. Response rates were depressed to less than 10% of saline control by the 2.5 g/kg dose of ETOH. Test sessions with saline or the vehicle, which were given in combination with air exposure, resulted in less than 5% ETOH-lever responding suggesting that subjects were under good stimulus control.

Desflurane

The results of substitution testing with desflurane are shown in Fig. 2. Desflurane demonstrated partial substitution with a maximum mean of 61% ETOH-lever responding observed at the concentrations of 24,000 and 32,000 ppm. However, these two higher concentrations also reduced response rates to approximately 50% of saline control levels. Forty-three and fifty percent ETOH-lever responding was observed in the absence of decreases in overall response rates at the lower concentrations of 8,000 and 16,000 ppm, respectively. Of the 7 mice test with desflurane, 6 showed greater than 85% ETOH-lever responding at one or more concentrations. The EC_{50} for increased ETOH-lever responding was about one-half the EC_{50} for suppression of overall response rates (see Table 1).

Enflurane

Exposure to enflurane also resulted in concentration-related increases in ETOH-lever responding (Fig. 3). Averages of greater than 90% ETOH-lever responding occurred

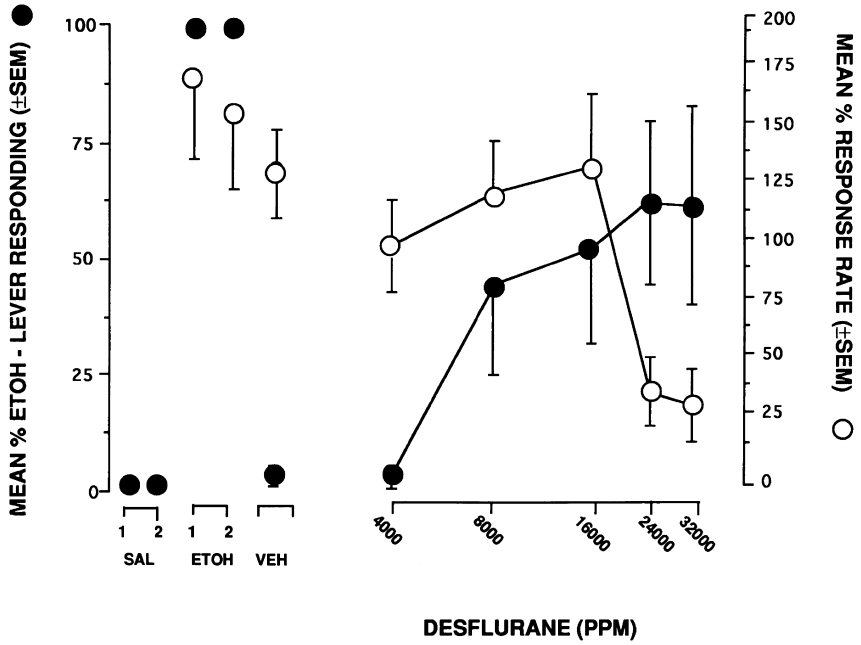

FIG. 2. Concentration-effect curve for desflurane in mice trained to discriminate 1.25 g/kg ethanol from saline. Percentage of ethanol-lever responding (mean ± SEM) are shown as filled circles; response rates (mean ± SEM) are shown as empty circles. Control data for both ETOH and saline represent the ETOH or saline test session which occurred immediately before (1) or after (2) desflurane testing. Values above VEH represent the results of a control test with air only exposure after a saline injection, $n = 7$.

following exposures to 9,000 ppm and 12,000 ppm with several animals showing full generalization at the two lowest concentrations as well. These increases in ETOH-lever responding were associated with decreases in response rates with the highest enflurane concentration of 12,000 ppm suppressing response rates to 38% of saline control levels. Generally, overall response rates were decreased by 50% at concentrations two times higher than those resulting in 50% ETOH-lever responding (see Table 1).

TABLE 1

POTENCIES (IN PPM) FOR ANESTHETICS IN MICE TRAINED TO DISCRIMINATE ETOH FROM SALINE

Test Agent	Generalization from ETOH	Response Rate Suppression
Desflurane	16,289 (7,313–36,281)	27,391 (20,937–35,836)
Enflurane	5,248 (3,734–7,375)	10,806 (out of range)
Isoflurane	2,928 (942–9,095)	5,222 (3,515–7,757)
Ether	11,358 (8,551–15,086)	20,930 (8,724–50,210)

Shown are the EC_{50}'s (with 95% confidence limits) for ETOH-lever responding and decreases in rates of responding.

Isoflurane

Mean ETOH-lever responding increased in a concentration-dependent fashion following exposure to isoflurane (Fig. 4). Isoflurane produced partial substitution for ethanol at concentrations of 4,000 and 6,000 ppm. A maximum mean of 70% ETOH-lever responding was observed at the 4,000 ppm concentration. Of the 7 mice tested with isoflurane, 5 showed greater than 85% ETOH-like responding at one or more concentrations. The highest concentration (8,000 ppm) reduced response rates to approximately 1% of saline control levels. Increases in the percentage of ETOH-lever responding were observed in several animals at concentrations as low as 1,000 ppm. As with the other anesthetics, the concentration that produced 50% ETOH-lever responding was half that needed to produced a 50% reduction in response rates (see Table 1). In general, isoflurane produced substitution for ETOH at concentrations lower than that observed for other volatile anesthetics.

Ether

Of the four animals tested with ether, three mice emitted over 85% of their responses on the ETOH lever at the 16,000 ppm concentration with the fourth animal producing responding above 70% ETOH responding, resulting in a maximum mean of 88% ETOH-like responding. At the two highest concentrations tested, ETOH-lever selection was slightly decreased. This was associated with large decreases in response rates (Fig. 5). Increases in the percentage of ETOH-lever responding were observed at concentrations as low as 8,000 ppm with one animal producing over 57% responding on the ETOH lever. In general, overall response rates were decreased

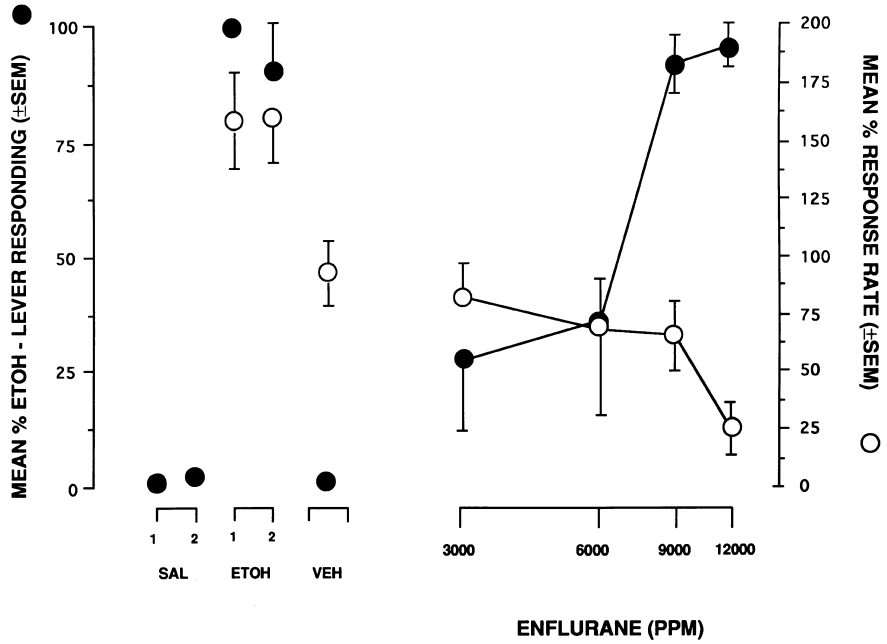

FIG. 3. Concentration-effect curve for enflurane in mice trained to discriminate 1.25 g/kg ethanol from saline. Percentage of ethanol-lever responding (mean ± SEM) are shown as filled circles; response rates (mean ± SEM) are shown as empty circles. Control data for both ETOH and saline represent the ETOH or saline test session which occurred immediately before (1) or after (2) enflurane testing. Values above VEH represent the results of a control test with air only exposure after a saline injection, $n = 7$.

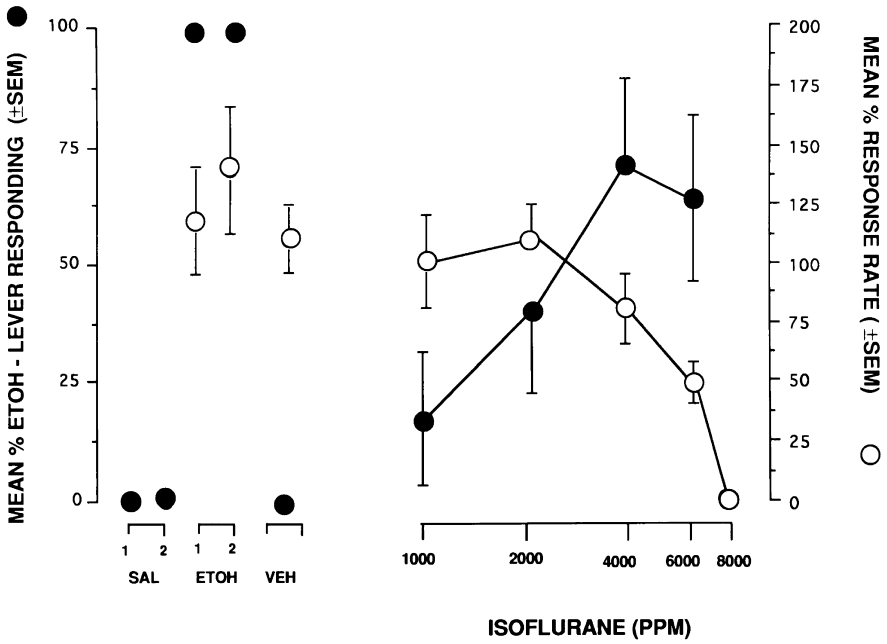

FIG. 4. Concentration-effect curve for isoflurane in mice trained to discriminate 1.25 g/kg ethanol from saline. Percentage of ethanol-lever responding (mean ± SEM) are shown as filled circles; response rates (mean ± SEM) are shown as empty circles. Control data for both ETOH and saline represent the ETOH or saline test session which occurred immediately before (1) or after (2) isoflurane testing. Values above VEH represent the results of a control test with air only exposure after a saline injection, $n = 7$.

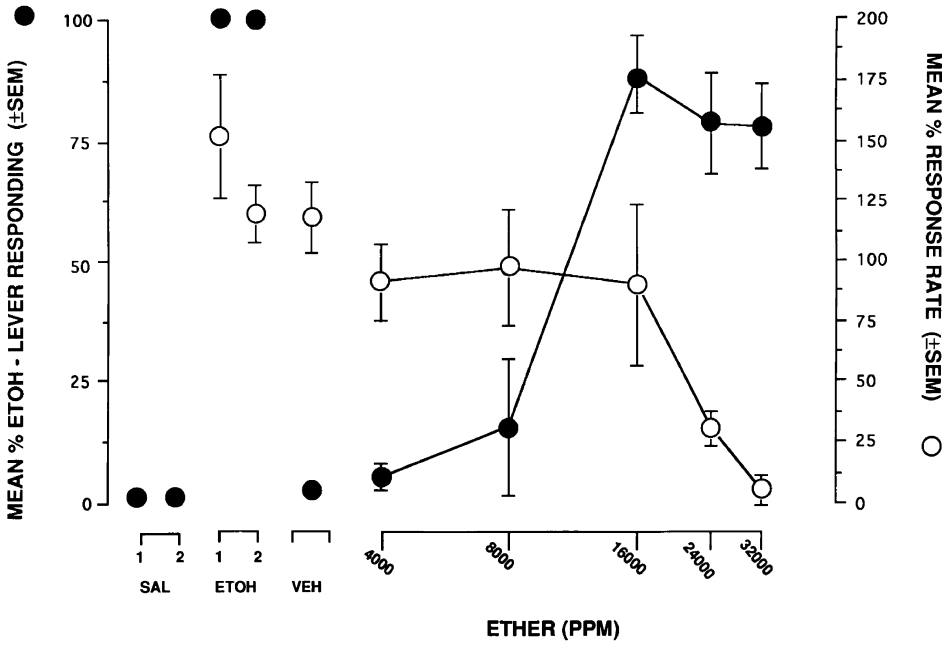

FIG. 5. Concentration-effect curve for ether in mice trained to discriminate 1.25 g/kg ethanol from saline. Data presented are the percentage of ethanol-lever responding for four mice (mean ± SEM) and are shown as filled circles with response rates (mean ± SEM) shown as empty circles. Control data for both ETOH and saline represent the ETOH or saline test session which occurred immediately before (1) or after (2) ether testing. Values above VEH represent the results of a control test with air only exposure after a saline injection, $n = 7$.

by 50% or more at concentrations about twice those which resulted in 50% ETOH-lever responding (see Table 1).

DISCUSSION

A growing number of studies have indicated that drug discrimination procedures can be used effectively in mice to examine the discriminative effects of drugs (1,16,17,18). It is only recently that these procedures been used to investigate the discriminative stimulus properties of various volatile chemicals (13,14,15). In the present investigation, the discriminative stimulus effects of several potent anesthetics were examined in an attempt to further clarify their ETOH-like activity. Evidence for concentration-dependent generalization from ETOH was obtained for inhaled enflurane and ether while desflurane and isoflurane produced partial substitution for the 1.25 g/kg training dose of ETOH. Enflurane and ether produced greater than 85% ETOH-lever responding at one or more concentrations in nearly all of the animals tested. While desflurane produced a maximum mean of only 61% ETOH-lever responding at any single concentration, 6 out of 7 mice showed full substitution for ETOH at one or more concentrations. For inhaled isoflurane, the largest ETOH-lever responding occurred at the 4,000 ppm concentration with five of the seven mice responding greater than 85%. These stimulus generalization test results are consistent with previous research showing ETOH-like discriminative stimulus effects in mice with other anesthetics and abused volatile inhalants. Halothane, toluene, and 1,1,1-trichloroethane have been reported to substitute in drug discrimination procedures for ETOH (15) and pentobarbital (13,14).

While all four of the volatile anesthetics at least partially substituted for ETOH, differences were obtained in the selectivity of these anesthetics for exhibiting ETOH-lever selection without producing reductions in response rates. In general, ether was the most selective of the anesthetics tested with the highest level of ETOH substitution produced at 16,000 ppm with only a moderate reduction in response rate. Enflurane and isoflurane both produced higher average levels of substitution for ETOH but at concentrations that produced greater than 50% decreases in response rates. In contrast, desflurane was unable to produce levels of substitution comparable to those of the other anesthetics tested without producing significant reductions in response rates. With the exception of the 16,000 ppm concentration of ether, none of the anesthetics tested was able to produce levels of substitution comparable with those of ETOH itself without noticeable decrements in response rates. It is not known with certainty what determines the response rate decreasing effects of volatile chemicals. Although it is possible that they result from CNS effects, it is also possible that they result from sensory effects such their strong odors or irritation. If these more local effects are important, than this would limit the upper range of concentrations that could be meaningfully tested in a drug discrimination procedure. It is therefore possible that for those inhalants, such as desflurane, which have a very poor separation of discriminative stimulus and response rate effects, only partial substitution might be obtained because concentrations that might produce full substitution cannot be tested. Until more is known about the determinants of the response rate effects of inhalants, failure to obtain full substitution in a drug discrimination procedure should not be taken as clear evidence that training drug-like effects could not be obtained under other testing conditions. Positive results in this procedure are much easier in interpret.

Although the number of published reports describing the behavioral effects of volatile anesthetics is limited, some comparisons can be made between previous and present investigations. In general, the concentrations at which these anesthetics produced an increase in total ETOH-lever responding were in the same range as those found in other behavioral studies. For example, the rate decreasing effects of enflurane reported in the present study were similar to those reported by Garfield and Vivaldi (7). They reported that 30-min exposures from 0 to 0.31% of halothane or 0% to 0.45% of enflurane disrupted FR30 responding in a concentration-dependent manner. Conversely, responding under a fixedinterval (FI) 5 min schedule remained unaffected except at the highest concentrations examined. Similar results have been reported for ether. Glowa (8) found that 30-min exposure to ether (3,000–10,000 ppm) produced substantial increases in rate of responding under FI 60 s schedules. Higher concentrations of ether produced response rate decrements with 30,000 ppm of ether abolishing all responses. In the present study, ether ED_{50} values for increased ETOH-lever responding and response rate reduction were 11,358 ppm and 20,930, respectively. The sedative potencies of the anesthetics tested in the present investigation from greatest to least potent as measured by EC_{50} values for response rate reductions were isoflurane > enflurane > ether > desflurane. These observed potencies correlated well with previously published minimum alveolar concentrations (MAC) and solvent/gas partition coefficients (4,19).

The present results support the hypothesis that similarities may exist between certain volatile chemicals and those of CNS depressants. The overlapping discriminative stimulus properties observed in the present investigation between the volatile anesthetics and the classic CNS depressant ETOH offers one example of the shared pharmacological properties beginning to emerge for these compounds. Additional support for these similarities extends from previous work that has demonstrated that other volatile compounds (i.e., toluene, 1,1,1-trichloroethane, halothane, etc.) produce a profile of pharmacological and behavioral effects similar to those of depressant drugs (see 5, for review). For example, these inhalants have been shown to disrupt coordinated motor performance (3,21), locomotor activity (2,11) and produce effects on schedulecontrolled activity that are similar to those of depressant drugs (10,11,12). 1,1,1Trichloroethane has also recently been shown to produce cross physical dependence with pentobarbital and ETOH (6). In addition, combinations of depressant drugs and exposure to volatile anesthetics with depressant-like effects have been shown to accentuate each others effects (9,11,22). Daniell (4) has also reported that subanesthetic doses of the noncompetitive *N*-methyl-d-Aspartate antagonists, MK-801, phencyclidine and ketamine increased the potency of general anesthetics as measured by changes in the loss of righting reflex and MAC values. While the cellular mechanisms for the behavioral effects of inhaled anesthetics are not understood, the similarities that exist between these compounds and those of ETOH and other classic CNS depressants may provide an essential link suggesting that studies on the cellular actions of ETOH may be very relevant to anesthetic and solvent effects as well.

In summary, subanesthetic concentrations of desflurane, enflurane, isoflurane and ether produced concentration-related increases in ETOH-lever responding with pronounced depressant effects on response rates. Although it is not yet clear which cellular mechanisms are responsible for the sedative effects produced by anesthetics, the present results demonstrate that these effects may be similar to the intoxication produced by classic CNS depressants. In addition, these results, along with other studies of the behavioral effects of vapors in animal models, are suggesting that general commonalities exist among abused solvents, subansethetic concentrations of anesthetics and other CNS depressants such as ETOH and pentobarbital. Finally, these results provide further evidence that the CNS depressant drug class should be expanded to include certain volatile anesthetics and other volatile chemicals.

ACKNOWLEDGEMENTS

The authors wish to thank Mary Tokarz for her technical assistance during the execution and analysis of this study. This research was supported by NIDA grant DA-03112, NIDA training grant DA-07027 and NIDA fellowship DA05670.

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