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Pharmacology, Biochemistry and Behavior 79 (2004) 261–267

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Direct relation between etonitazene dose and response rate: responding under a single FI per session

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Received 19 April 2004; received in revised form 10 July 2004; accepted 23 July 2004
Available online 12 September 2004

Abstract

Response-contingent injections of etonitazene (ETZ) have been shown to reinforce rats' lever pressing behavior. The objective of the present study was to determine the relation between response rate and ETZ dose when ETZ was administered subcutaneously once per session by the experimenter contingent upon completion of a 10-min fixed-interval (FI) schedule. When injections of the saline vehicle replaced drug injections, response rates dropped to low levels; rates subsequently increased above saline levels when drug injections were reintroduced, demonstrating that ETZ was serving as a reinforcer. A range of ETZ doses (0.01, 0.1, 1, 5.7, and 10 μg/kg) was administered subcutaneously to six rats, resulting in response rates that were directly related to drug dose. These findings are consistent with other studies that have found an increase in reinforcing effects with increases in drug dose. Thus, studies in which drug is administered once per session may be used to measure the reinforcing effects of drugs directly from rate measures, as the response rate in these studies is unaffected by satiation or direct drug effects.

Keywords: Drug dose; Drug self-administration; Etonitazene; Fixed-interval schedule; Opioid; Rat; Reinforcement magnitude; Response rate; Reward subcutaneous route

1. Introduction

Previous studies conducted in our laboratory have demonstrated the feasibility of reinforcing lever-press responding in rats by the response-contingent administration of investigator-delivered injections of the opioid etonitazene (ETZ; Ahlgren-Beckendorf et al., 1998; Gomez and Meisch, 2000). In such studies, rats are trained over several sessions to respond (lever press) on a single 8- or 10-min fixed-interval (FI) schedule of reinforcement, once per day, with an intraperitoneal or subcutaneous ETZ injection as the reinforcer. ETZ was demonstrated to be serving as a reinforcer under these conditions because response rates decreased and increased as a function of substituted saline vehicle or ETZ injections, respectively. Such studies are akin to previous studies in which responding was maintained by contingent investigator-administered injections of drug in both nonhuman primates (Goldberg, 1973; Goldberg and Morse, 1973; Goldberg et al., 1976; Katz, 1979, 1980; Nader and Barrett, 1990; Spragg, 1940; Valentine et al., 1983) and humans (Lamb et al., 1991).

These studies in rats have certain advantages and disadvantages. An obvious advantage is that drug can be administered parenterally without the need for surgical manipulation, apparatus, and extended catheter patency that is requisite in intravenous self-administration procedures. Conversely, training periods consisting of several steps are required to establish responding reinforced by subcutaneous injections on a 10-min FI schedule. However, the requirement for extended training should be assessed in relation to the durability of the preparation and the number of test conditions that can be studied per subject. Furthermore, in

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0091-3057/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2004.07.005

previous studies, rats were returned to the experimental chamber following each injection, a feature derived from and common to place-preference conditioning (see Bardo and Bevins, 2000; Carr et al., 1989) and runway studies (see Ettenberg, 1990). Because it was not known if this feature is necessary, a current objective was to determine the effect of not returning rats to the chamber on response rate during the maintenance phase of the experiment. Omission of this return would simplify and expedite the drug injection procedure in future studies.

Drug administered upon the completion of a single-interval schedule may be indicative of drug-seeking behavior and reflective of the magnitude of the drug dose's reinforcing effects (Corrigall and Coen, 1989; Everitt and Robbins, 2000). In our second study, in which ETZ was administered via the subcutaneous route, there was an indication that response rates increased monotonically with increases in ETZ dose (Gomez and Meisch, 2000, Fig. 3), suggesting that responding was varying as a function of the reinforcing effects of ETZ. The relation between drug dose and reinforcing effects has been demonstrated principally in studies of choice (e.g., Gomez et al., 2002), studies of relative persistence of behavior (Gomez and Meisch, 2003; Meisch, 2000), and runway studies (Wakonigg et al., 2003). However, the objective in this second study was not to examine dose–response effects, and the ETZ doses were not presented in a counterbalanced design or with criteria for determining stable behavior. Therefore, the objectives of this current study were to extend the findings of the first two studies by (a) establishing systematic dose–response functions of sc administered ETZ on a single FI schedule to determine the relation between ETZ dose and response rate, (b) replicating the establishment of response-contingent injections of ETZ as a reinforcer, and (c) determining the effects of the postinjection environment on established drug-maintained behavior.

2. Materials and methods

2.1. Subjects

Subjects were eight adult male Long-Evans rats (*Rattus norvegicus*; HsdBlu:LE, Harlan, Indianapolis, IN), experimentally naive and weighing 356–410 g at the start of the study. Rats were individually housed in wire-bottom cages with a 12-h light/dark cycle in effect (lights on at 7 a.m.); experiments were conducted during the light phase. During all parts of the study, rats were maintained at approximately 85% of their free-feeding weights measured at about 19 weeks of age (400–475 g) by being fed a restricted amount of their daily ration (Harlan Teklad Rodent Diet, Madison, WI) and ad libitum water. Body weights were measured daily. All experimental procedures were approved by the Institutional Animal Use and Care Committee of The UT Health Science Center at Houston and were in accordance with the guidelines of the NIH *Guide for the Care and Use of Laboratory Animals* (1996). Experiments were performed at an AAALAC International-approved facility.

2.2. Apparatus

Four identical sound-attenuated operant conditioning chambers (30×24×30 cm high; Lehigh Valley Electronics, Beltsville, MD) were each equipped with two levers located on one wall, three colored lights above each lever, a white house light centered above the lever lights, and a ventilating fan. Additionally, each chamber was equipped with a food-pellet dispenser, releasing 45-mg food pellets (Bioserve, Frenchtown, NJ) into a magazine located between the levers.

All programming and data recording were controlled by modulated solid-state logic boards (Coulbourn Instruments, Lehigh Valley, PA) located in an adjacent room. The number of lever presses and food-pellet deliveries was recorded by counters, and the temporal pattern of lever presses and deliveries was recorded by cumulative recorders (Gerbrands, Arlington, MA).

2.3. Drug

Etonitazene HCl was obtained in crystalline form from the National Institute on Drug Abuse, National Institutes of Health. Drug was dissolved in a sterile saline solution, filtered via 0.2-μm Nalgene syringe filters (Nalge, Rochester, NY), and stored in sterilized vials. Drug was administered via standard 26-G human tuberculin syringes and needles. The dose of ETZ is expressed in terms of the salt.

2.4. Procedure

2.4.1. Establishment of food-reinforced responding under a 10-min FI schedule

Rats were initially trained to respond (lever press) on the left chamber lever to produce food pellets on a continuous schedule of reinforcement (CRF). The start of each daily 60-min session was indicated by the illumination of the left lever lights. The presentation of each food pellet was signaled by a 3-s extinguishing of the lever lights and illumination of the house light, which blinked at a rate of 10 Hz. Responses during this 3-s period, as well as all responses on the right (inactive) lever, were recorded but did not have any programmed consequences. Once reliable responding was established, the schedule was switched to a 5-s fixed-interval schedule (FI 5 s); rats were maintained on this schedule until behavior was stable, i.e., until no increasing or decreasing trends in the number of responses were observed across six consecutive sessions. The interval length was subsequently doubled every other session until rats were responding on an FI 1.25-min schedule. At this point, the interval length and number of pellets available at the end of each interval were doubled

every other session until eight food pellets were available upon completion of each FI 10-min schedule. Under this condition, each of the eight pellets was available on a CRF schedule following the passage of each FI. The session length remained at 60 min, but the number of intervals was predetermined at the higher FIs, such that a maximum of 11 intervals could occur at FI 5 min and a maximum of 5 at FI 10 min. After two sessions consisting of two 10-min FIs each, sessions were limited to a single FI 10-min schedule, and a 30-min postreinforcement phase was introduced. This postreinforcement phase commenced following the collection of the last food pellet under the FI 10-min schedule and was signaled by stimulus conditions identical to those that accompanied reinforcement (extinguishing of the lever lights and blinking of the house light at 10 Hz). Responses during this phase were recorded but had no programmed consequences. To boost responding, the number of pellets available at the end of the 10-min interval was increased to 16, the number of FIs per session was increased to five, and the postreinforcement component was removed. After four sessions at this condition, the schedule length was again limited to a single FI 10 min, with the 30-min postreinforcement component in effect. Rats were maintained on this baseline condition until behavior was stable.

2.4.2. Establishment of ETZ-reinforced lever pressing

Following the acquisition of responding on the single FI 10-min schedule, rats were introduced to response-contingent injections of ETZ solution. Injections were administered by the investigator in the following manner. Subsequent to the delivery of the last food pellet, the rat was removed from the chamber, given a single subcutaneous injection of ETZ, and placed back into the chamber for exposure to the 30-min postreinforcement component. The dose of ETZ was increased every other session in the following increments: 0.1, 0.3, 1.0, and 3.2 μg/kg. All injections were given in a volume of 1 ml/kg. Once six sessions of stable behavior were obtained at the highest drug dose, the number of food pellets was decreased in the sequence 16, 11, 8, 6, 4, 3, 2, 1, 1, and 0 every other session until responding was maintained solely by an injection of 3.2 μg/kg ETZ, administered upon the completion of the FI 10-min schedule. At this point, a 2-min limited hold (LH 2 min) feature was introduced: If no response occurred on the appropriate lever within 2 min following the passage of the 10-min interval, the session was terminated and the rat was removed from the chamber without receiving an injection and without exposure to the postreinforcement phase. Rats were kept on this condition until responding was stable. The FI 10-min (LH 2 min) schedule remained in effect for the duration of the study. One rat demonstrated low responding during the "drug-alone" condition (mean±S.E.M.=17.7±9.1) and during a subsequent retest at the drug plus 16-pellet condition (mean=17±4.7). This rat was excluded from the remainder of the study.

2.4.3. Alternating blocks of ETZ and saline sessions

Once responding was maintained by 3.2-μg/kg ETZ injections, alternating blocks of saline vehicle and 3.2-μg/kg ETZ injections were repeated twice per subject. Rats were maintained on each condition until responding was stable for six sessions.

2.4.4. Postreinforcement environment

Following the completion of the last block of ETZ sessions from the previous phase, rats were maintained on the 3.2-μg/kg ETZ dose under the FI 10-min schedule, but with the 30-min postreinforcement component removed, so that following each drug injection, the rats were not returned to the experimental chamber following the session and thus did not receive exposure to the postreinforcement stimuli present in the chamber. Rats were maintained on this condition until behavioral stability was achieved. Because no difference in response rates for the group occurred as a function of this change, rats were not returned to the experimental chamber after injections during the subsequent dose–response analysis.

2.4.5. Dose–response analysis

A range of ETZ doses (0.01, 0.1, 1.0, and 5.7 μg/kg) was examined in each rat; each dose was examined twice per subject. In one group of rats (n=3), doses were examined in an ascending–descending sequence, and in the other group (n=4), doses were examined in a descending–ascending sequence. The initial dose selected for the descending–ascending group of animals was 10.0 μg/kg ETZ. However, because the first rat (004) tested at this dose exhibited occasional opioid-related signs of pronounced respiratory depression following injections, this rat was limited to a dose of 5.7 μg/kg. Subsequently, to avoid potential drug overdoses, 5.7 μg/kg was used as the high dose of ETZ in the dose series for both groups. Furthermore, one rat (001) in the ascending–descending group died for unrelated health reasons during the experiment and completed only the ascending series. Following the completion of the dose–response series, three rats in the descending–ascending series were tested at the 10.0-μg/kg ETZ dose. Rats were maintained on each condition for 13 to 25 sessions until behavior was stable for six consecutive sessions.

3. Results

3.1. Alternating blocks of ETZ and saline sessions

Fig. 1 shows that, with one exception, response rates during blocks of 3.2 μg/kg ETZ sessions were greater than those during blocks of saline sessions. Mean response rates for each block of drug sessions exceeded those for adjacent blocks of saline sessions, except for the second

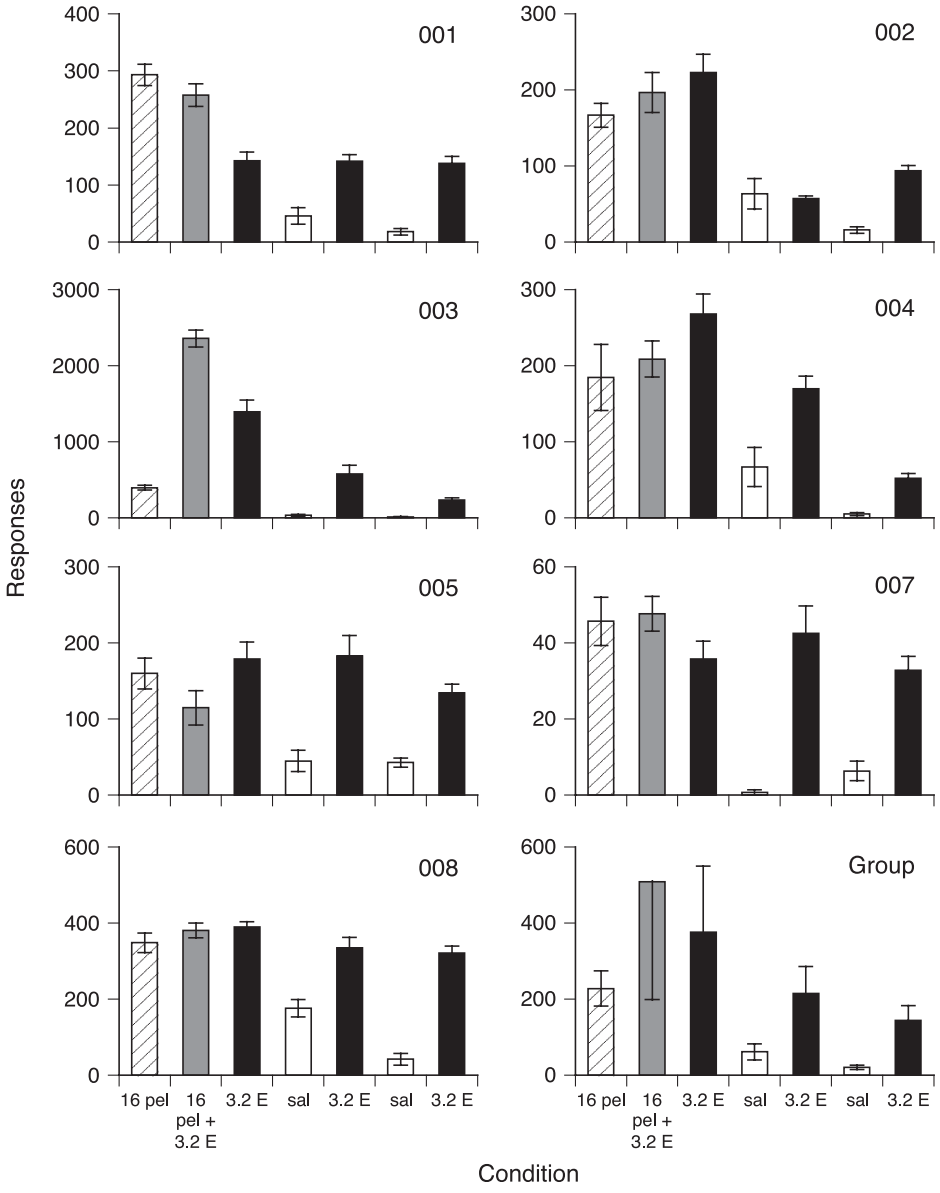

Fig. 1. Mean lever presses across successive conditions under an FI 10-min schedule. Striped bars represent the mean numbers of lever presses when the reinforcer was 16 food pellets; shaded bars represent the means when the reinforcer was 16 food pellets, plus a SC injection of ETZ (3.2 μg/kg); black bars represent the means when responding was maintained solely by drug; and empty bars represent the means for the saline-control conditions. Each mean is based on six consecutive sessions of stable behavior; error bars indicate the S.E.M. Note that the scales for the ordinates differ across subjects.

3.2 μg/kg ETZ test condition for Rat 002. Nevertheless, Rat 002's response rate for the third block of ETZ sessions was six times greater than that for the preceding block of saline sessions. Several rats (002, 003, and 004) showed decreases in mean response rates across sequential blocks of both drug and vehicle sessions, and this trend was also true for the mean group response rates. However, for these rats, as for the group, responding during ETZ sessions remained consistently higher than during saline sessions.

The mean rates for Rat 003 for the food+ETZ condition and the subsequent ETZ-alone condition were approximately three- to fivefold higher than rates obtained during the preceding food-alone condition and were 5 to 50 times higher than rates for any other rat (Fig. 1). Rates during subsequent conditions for Rat 003 returned to levels comparable with those of the other rats.

3.2. Postreinforcement environment

The mean number of responses per session (±S.E.M.) for the condition in which rats were returned to the operant chamber following drug injections (131.1±30.7) was almost identical to that for the condition in which rats were not returned to the chamber (128.7±27.4), when averaged across subjects (n=7). For four of the rats, the response rates

for the two conditions were similar, for two rats, the rates increased twofold when rats were not returned to the chamber, and for one rat, rates decreased fourfold when not returned (data not shown).

3.3. Dose–response analysis

Fig. 2 shows that response rate was directly related to dose, both for individual rats and for the group. The one exception occurred with Rat 003, for which the response rate at 1.0 μg/kg was approximately equal to the rate at 5.7 μg/kg. The direct relation between response rate and drug dose was obtained regardless of whether doses were given in an ascending or descending sequence, and results were well replicated on retest. Furthermore, mean response rates at each dose were similar for both test groups (ascending–descending vs. descending–ascending; data not shown).

To determine if response rates were increasing or decreasing as a function of time, test and retest values for the series were compared. For the six rats that were studied twice at each drug dose, the total number of lever presses was calculated separately for the test and retest conditions (24 means per condition; 6 rats×4 doses). The total values are similar: 1679.0 and 1615.6 for the test and retest series, respectively.

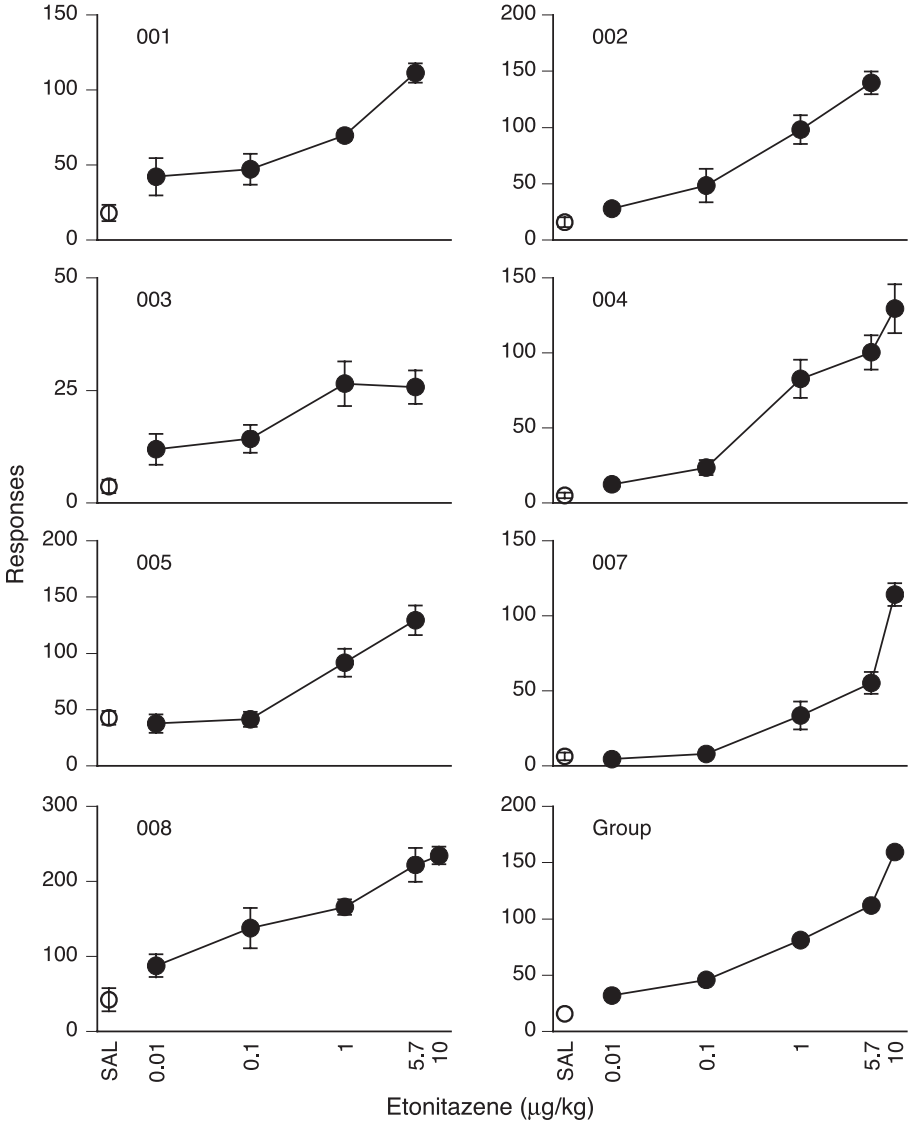

Fig. 2. Mean number of lever presses as a function of ETZ dose. Means are based on 12 sessions (two blocks of six sessions of stable behavior) at each dose except for (1) saline controls (SAL), which are based on means of one block of six sessions preceding the dose series, (2) the 10 μg/kg dose, which are means of one block of six sessions, and (3) Rat 001's data points, which are means of one block of six sessions. Means for group data are averaged across all subjects. Error bars represent the S.E.M.; the absence of vertical lines indicates that the S.E.M. fell within the space of the plotted point (S.E.M.s are not given for the group means). Means for saline sessions were always less than the means for ETZ sessions, and response rate increased directly with drug dose, except for rat 003 at 5.7 μg/kg. Note that the scales for the ordinates differ across subjects.

4. Discussion

Response rate reinforced by contingent injections of ETZ increased as a function of drug dose across a wide dose range. This relation between dose and response rate did not depend upon the sequence of dose presentation, as it was observed both when doses were presented either in an ascending or descending sequence. The finding of a direct relation between drug dose and response rate is contrary to that of many drug self-administration studies, in which an "inverted U-shaped" dose–response function is characteristically observed. This decrease in response rate at higher drug doses is generally attributed to direct drug effects on operant behavior (e.g., motor effects) or satiety effects; rate decreases may also be consistent with decreases in reinforcing effects (Meisch and Lemaire, 1993). In the current study, all behavior was measured prior to drug administration, which occurred only once per daily session. Because the dependent variable, response rate, was measured while rats were in a drug-free state, it was not influenced by direct drug effects or satiation.

This direct relation between dose and response rate is consistent with results from other studies that have administered drug only once per session (Corrigall and Coen, 1989; Goldberg and Tang, 1977). In two additional studies, rats received multiple intravenous injections per session; however, with these studies, response rate prior to the first injection was analyzed separately from rates over the entire session (Alderson et al., 2000; Arroyo et al., 1998). Response rate prior to the first injection increased directly with cocaine dose (Arroyo et al., 1998) but not with heroin dose (Alderson et al., 2000), perhaps due to the limited range of heroin doses used (Everitt and Robbins, 2000). Everitt and Robbins (2000) have noted that, under schedules where all drugs are delivered at the end of a session, a direct relation between drug dose and response rate usually exists. Our findings are consistent with this conclusion and support the notion that, with drugs from several classes, a direct relation exists between drug dose and the magnitude of reinforcing effects across a broad range of doses (Meisch, 2000).

Our findings of a direct relation between response rate and drug dose are consistent with results of choice studies in rodents. With both rats and mice, a direct relation between opioid dose and preference has been demonstrated (Cazala and David, 1995), and in a study with rats, drug choice increased directly with dose for both intravenous morphine (0.32, 1.0, 3.2, and 10 mg/kg) and heroin (0.032, 0.1, 0.32, and 1 mg/kg; Hutto and Crowder, 1997). Similarly, when morphine was injected into the lateral hypothalamus, mice preferred a morphine dose of 50 to 5, 15, or 30 ng (Cazala and David, 1995). Additionally, when an intravenous cocaine dose of 267 μg/kg was compared with higher doses, rats consistently preferred the higher doses (Manzardo et al., 2001). These studies provide further evidence that with rodents, as with monkeys, across a broad range of doses and drugs, reinforcing effects increase with increases in drug dose (Meisch and Lemaire, 1993).

In establishing investigator-administered ETZ as a reinforcer, a number of training steps are necessary. This extended training sequence was successful in obtaining ETZ-reinforced lever pressing and was conducted with the goal of making it highly probable that subcutaneous injections of ETZ would reinforce responding because all subsequent experimental manipulations were dependent on the establishment of reliable drug-reinforced behavior. However, it is likely that the number and duration of training steps can be reduced while still obtaining drug-reinforced behavior, and this will be a goal of future research. Furthermore, when conducting the dose–response series, an extended number of sessions (13 to 25) were obtained at each dose, a process that was done to ensure stable behavior because rats had only one opportunity to receive a drug injection per session. This conservative approach was adopted, in part, because no base of data to guide decision making existed. The use of multiple-interval schedules per session in future studies may reduce the number of sessions required per experimental condition, by permitting subjects to come into contact with the drug more than once per day.

Group means for responding during ETZ sessions decreased across the three blocks of drug sessions when these sessions alternated with blocks of saline vehicle sessions (Fig. 1). One possibility was that responding was slowly extinguishing across conditions; however, responding during blocks of drug sessions still remained higher than responding during adjacent blocks of saline sessions. Another possibility was that the decrease in responding was due to an increase in temporal discrimination of the FI 10-min schedule. Test and retest values for the dose–response function were compared by adding the means for the six rats that completed both dose series across the four doses studied. The two values were remarkably similar (1679.0 vs. 1615.6), supporting the position that responding was stable across the test and retest series and that responding was not extinguishing. Furthermore, in our earlier studies, extinction was not observed (Ahlgren-Beckendorf et al., 1998; Gomez and Meisch, 2000).

Results from the present study show that a return to the chamber is not required during the maintenance phase because response rates did not decrease when rats were no longer placed back in the operant chamber following drug injections. This finding is important, as it simplifies the experimental procedure and allows for flexibility in schedule design. However, it remains unknown whether a return to the chamber after drug injection is required during the establishment of drug-reinforced responding.

In the present study, lever-press responding was maintained in rats by daily response-contingent experimenter-administered subcutaneous injections of the opioid ETZ across a wide range of doses. These findings systematically replicate and extend our two earlier studies (Ahlgren-

Beckendorf et al., 1998; Gomez and Meisch, 2000). The present study and the two earlier ones demonstrate that experimenter-administered ETZ injections, either administered intraperitoneally or subcutaneously, can reliably maintain responding when given contingent upon schedule completion. The finding that response rates during blocks of drug injections were consistently higher than during blocks of saline vehicle injections provides strong evidence for ETZ reinforcement. The direct relation observed between drug dose and response rate provides additional evidence of reinforcing effects. Importantly, when each dose was tested a second time, the results of the second block of sessions replicated the initial results.

Acknowledgements

This research was supported by a supplement to grant DA08913 from the National Institute on Drug Abuse. The supplement was granted under a program for "Development of New Animal Models of Addiction." R.A. Meisch is the recipient of a Research Scientist Award (DA00159) from the National Institute on Drug Abuse. The authors wish to thank Lisa Brown, Bruce Clark, and David Hernandez for their technical assistance, and Oscar Brown for his professional care of the animals.

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