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# Diazepam Self-Administration and Resistance to Extinction

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GRANT, K. A. AND C. E. JOHANSON. *Diazepam self-administration and resistance to extinction.* PHARMACOL BIOCHEM BEHAV **28**(1) 81–86, 1987.—Self-administration behavior was maintained by a unit dose of 0.03 mg/kg diazepam in 4 of 5 monkeys trained to respond on a lever by successive approximation using diazepam or saline. A dose-response function was determined using diazepam doses ranging between 0.01 and 0.3 mg/kg/infusion. Peak rates of responding occurred at doses of 0.01 or 0.03 mg/kg/infusion and drug intake was directly related to dose. When saline was substituted for diazepam either before or again after the dose-response function was determined, levels of responding remained unexpectedly high, even after as many as 16 consecutive sessions. The rates of responding maintained under extinction conditions appeared to be directly related to the amount of diazepam previously self-administered. For instance, monkeys which did not initially have high rates of responding for saline showed increases in responding after additional exposure to diazepam. Furthermore, the one monkey with low diazepam self-administration rates also had low rates of responding for saline. However, following a period of cocaine self-administration, responding declined in all monkeys when saline was substituted for cocaine. The data suggest that diazepam self-administration affects responding under extinction conditions, an effect which makes the interpretation of diazepam's reinforcing properties difficult.

Diazepam Extinction Reinforcing efficacy Response perseveration Drug self-administration Monkeys Cocaine

IN a variety of experimental studies using humans, nonhuman primates, and rats, the reinforcing properties of benzodiazepines have been characterized as moderate compared to other classes of abused drugs [10]. The majority of studies investigating the reinforcing effects of benzodiazepines have used substitution procedures [2, 11, 12, 14]. In these procedures, contingent infusions of a known reinforcing drug (e.g., cocaine) are used to train a specific response, usually lever pressing. After responding is under the control of the schedule requirements, test drugs are substituted for the baseline drug. In addition, saline or the drug vehicle is also substituted in order to determine extinction levels of responding. If the substituted drug maintains responding above vehicle levels, the substituted drug is defined as a positive reinforcer [16]. One disadvantage of substitution procedures is that the baseline drug can influence the amount of test drug subsequently self-administered. For example, Young and Woods [28] found the dissociative anesthetics phencyclidine, dexoxadrol and dextorphan all maintained responding in rhesus monkeys when substituted for ketamine, but did not maintain responding when substituted for codeine.

Baseline drug effects have also been reported with benzodiazepines in substitution studies. For instance, Bergman and Johanson [2] found only 3 of 11 monkeys self-administered diazepam when cocaine was the baseline drug, whereas 5 of 5 monkeys maintained under a pentobarbital baseline self-administered diazepam. Similarly, Griffiths *et al.* [11] reported only low levels of diazepam self-administration in 3 baboons maintained under a cocaine baseline. Mixed results have been reported when a codeine baseline was used to assess diazepam self-administration, with one study reporting positive results [14] and another study reporting negative results [12]. In summary, previous studies using different baseline drugs have led to different assessments of diazepam's reinforcing properties.

The mechanisms underlying the differential baseline effects noted above are not well understood. These effects may be the result of differences between the reinforcing or discriminative stimulus properties of the baseline and substituted drugs [2]. For example, a difference in the reinforcing strength of two drugs could lead to a contrast effect [21], resulting in lower than predicted responding for drugs substituted for a highly reinforcing drug, such as cocaine, compared to a moderately reinforcing drug, such as pentobarbital. Alternatively, similarities in the discriminative stimulus properties of the baseline and the substituted drug may lead to increased self-administration of the substituted drug. This idea is supported by deWit and Stewart [8] who found that *d*-amphetamine, given non-contingently to animals with a history of cocaine self-administration resulted in the reinstatement of extinguished responding, while non-

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contingent heroin failed to reinstate responding previously maintained by cocaine. By extension, diazepam may have maintained responding in the pentobarbital baseline monkeys in the Bergman and Johanson [2] study because pentobarbital and diazepam have similar discriminative stimulus effects [1]. Finally, another possible explanation for different levels of substituted drug self-administration is the development of tolerance to the baseline drug. In the case of diazepam, cross-tolerance to certain properties of pentobarbital, for example rate-decreasing effects [18], may allow for increased rates of diazepam self-administration. Given the potential influence of experience with other drugs on measures of diazepam's reinforcing properties within a substitution procedure, the present experiments were designed to assess these properties in monkeys without a history of exposure to other drugs.

## EXPERIMENT 1

### METHOD

*Animals*

Five experimentally naive rhesus monkeys (*Macaca mulatta*), 4 females (4001, 4002, 4004, 2030) and 1 male (4005), ranging in weight from 5.2 to 7.1 kg, were used in this study. The monkeys had continuous access to water and were provided enough food (Purina Monkey Chow) following their experimental sessions to maintain stable free-feeding weights. Their diets were supplemented with vitamins and fresh fruit.

Each monkey had a single-lumen silicone venous catheter (i.d. 0.08 cm, o.d. 0.24 cm; Rodhelm Reiss, Belle Mead, NJ) surgically inserted into a major vein (internal jugular, external jugular or femoral) under pentobarbital anesthesia (up to 30 mg/kg IV, as needed). The catheter was passed into the vein for a distance calculated to place the bevelled tip inside the vena cava. The other end of the catheter was routed subcutaneously to the animal's back where it exited the body. If the catheter became dislodged during the course of the experiment, the animal was removed from the experiment until another catheter was placed in an available vein.

*Apparatus*

Each monkey was housed individually in a sound attenuating wooden cubicle (internal dimensions: 70×80×70 cm) equipped with a ventilation fan and a Plexiglas window on the cubicle door. Before each session, this window was covered. The cubicle served as the experimental chamber and had two lever boxes mounted on the inside of the door. Each lever box contained 4 Dialco stimulus lights, 2 with red lens caps and 2 with white lens caps located above a response lever (PRL-001, BRS/LVE, Beltsville, MD). On the ceiling of the cubicle was a Plexiglas encased light box containing a white house light (34 W) and a red infusion light (15 W).

Each monkey wore a stainless steel harness connected to a spring arm (approximately 46 cm) which was attached to the back wall of the cubicle. The catheter was threaded through the protective spring arm and connected to a peristaltic infusion pump (7540X, Cole-Parmer Instrument, Chicago, IL) located outside the chamber. Solid state circuitry recorded responses on the lever and controlled the operation of the stimulus lights and the infusion pump.

*Procedure*

The monkeys were trained to respond on the right lever by differentially reinforcing successive approximations toward the lever with infusions of diazepam (0.03 mg/kg) for monkeys 2030, 4001, and 4004 or infusions of saline for monkeys 4002 and 4005. Occasionally, the lever was baited with a raisin. During an infusion, the white session light and lever lights shut off and the red infusion light and red lever lights were illuminated. Responding on the left lever had no programmed consequences. The training sessions occurred once a day for 30–60 minutes. If responding did not increase after 21 sessions, the monkey was removed from the experiment. After responding on the lever became stable, the session length was increased to 2 hours and the response requirement per infusion was gradually increased to 10 (fixed ratio 10; FR 10). If responding declined to very low levels, the requirement was returned to a FR 1. Responding on the terminal schedule (FR 1 or FR 10) was considered stable when two consecutive sessions occurred in which total infusions did not differ by more than 10. Exposure to diazepam or saline continued until there was several consecutive sessions where the number of infusions received did not show an increasing or decreasing trend.

When responding maintained by diazepam under the terminal schedule was stable for monkeys 2030, 4001, and 4004, saline was substituted to determine extinction levels of responding. Next these monkeys were returned to diazepam availability and a dose-response function was determined by substituting doses ranging from 0.01 to 0.3 mg/kg/infusion, each available for several consecutive sessions. The doses were tested in a mixed order, beginning with 0.03 mg/kg. Each dose was available for a minimum of 5 and a maximum of 13 days. Following the dose-response determination, extinction conditions were reimposed by substituting saline for diazepam.

A similar dose-response function was also determined with monkey 4005 after an intervening period of additional manipulations including exposure to diazepam (0.03 mg/kg/infusion), described in experiment 2. Monkey 4002 was tested with only a single dose of diazepam (0.03 mg/kg/infusion), after a series of manipulations similar to those given monkey 4005 (see experiment 2). Both monkeys had saline available following the diazepam exposure.

*Data Analysis*

The average number of infusions received on the last two sessions of a given drug dose or saline was used to compare levels of self-administration across conditions.

*Drugs*

Diazepam was prepared in a suspension system composed of 95% ethanol and polyoxyethylated vegetable oil [Emulphor (El-620, GAF)] in a 1:1 ratio [6]. This suspension was diluted, as needed, with sterile saline to the desired concentration immediately before the session.

### RESULTS

All monkeys were successfully trained to respond on the lever for an infusion of diazepam or saline. The number of sessions required to shape a lever press response ranged from 4 to 14 for diazepam infusions and 3 to 12 for saline infusions. Responding was maintained as the FR was in-

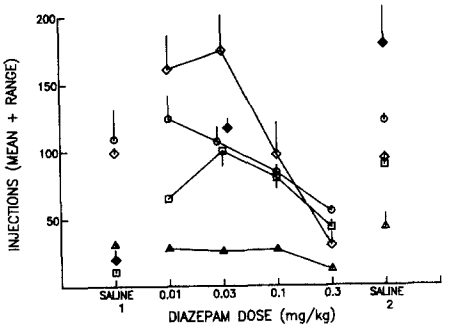


FIG. 1. Average number of diazepam injections received as a function of dose. Saline 1 and Saline 2 are the average number of saline injections self-administered directly before (1) and after (2) the various doses of diazepam were available. Open squares=monkey 2030; open triangles=monkey 4001; filled diamonds=monkey 4002; open circles=monkey 4004; open diamonds=monkey 4005.

creased to 10 in only one monkey (2030). The responding of the other 4 monkeys decreased when the FR was increased, so a FR 1 schedule was used throughout the remainder of the experiment with these animals. Directly after training, the average number of diazepam infusions (0.03 mg/kg/infusion) received under the terminal schedule was 47±5 (FR 10), 31±3 and 93±6 for monkeys 2030, 4001 and 4004, respectively. The average number of saline infusions received after training was 122±5 and 88±13 for monkeys 4002 and 4005, respectively.

The effects of testing different doses of diazepam on responding are presented in Fig. 1. For monkeys 2030, 4004 and 4005 responding was related to dose and the number of infusions received ranged from 35 to 175. Monkey 4002 also self-administered the only diazepam dose tested (0.03 mg/kg/infusion), and received over 100 infusions per 2 hour session. In the fifth animal (4001), the number of infusions self-administered was relatively low (ranging between 5 and 40) and generally did not change with dose. At the highest dose tested (0.3 mg/kg/infusion) the responding of all monkeys decreased relative to the levels maintained by the lower doses. Table 1 shows that as dose increased, the amount of diazepam taken increased. Intakes over 3.0 mg/kg/session consistently occurred when the dose of diazepam available to monkeys 2030, 4004, and 4005 was 0.03 mg/kg/infusion or greater. In contrast, the amount of diazepam self-administered by monkey 4001 was generally below 3.0 mg/kg/session.

The amount of saline self-administered before and after the diazepam dose-response determination is also shown in Fig. 1. The first saline determination shown in Fig. 1 (left side) followed a period of diazepam self-administration in all the monkeys (see experiment 2). Compared to diazepam levels, saline self-administration was initially low in monkeys 2030 (FR 10) and 4002, but increased after additional exposure to diazepam. The other 3 monkeys (4001, 4004, 4005) had comparatively high rates of responding for saline both prior to and following the dose-response determination. The findings regarding responding under extinction conditions following diazepam self-administration included monkeys trained to respond for either diazepam or saline. Thus, it does not appear that the failure to demonstrate extinction was an effect of diazepam upon learning during the training portion of the experiment.

TABLE 1

AMOUNT OF DIAZEPAM (MEAN ± SD) SELF-ADMINISTERED DURING THE LAST 2 SESSIONS EACH DOSE WAS AVAILABLE

| | Diazepam Dose (mg/kg) | | | |
|---|---|---|---|---|
| Monkey | 0.01 | 0.03 | 0.1 | 0.3 |
| 2030 | 0.65 | 3.00 ± 0.48 | 8.0 ± 0.1 | 12.3 ± 2.7 |
| 4001 | 0.28 ± 0.01 | 0.72 ± 0.03 | 2.7 ± 0.2 | 2.1 ± 2.1 |
| 4004 | 1.07 ± 0.01 | 3.21 ± 0.45 | 8.4 ± 0.6 | 16.5 ± 1.2 |
| 4005 | 1.61 ± 0.03 | 5.25 ± 1.11 | 9.7 ± 3.4 | 9.0 ± 3.6 |

## EXPERIMENT 2

The results of experiment 1 showed that monkeys with an immediate history of diazepam self-administration continued to respond under extinction conditions at rates equal to those maintained by diazepam presentation. Thus, the evaluation of diazepam's reinforcing properties remained difficult to interpret. To investigate whether continued responding under extinction conditions occurred following self-administration experience with another reinforcing drug, cocaine was made available and responding under extinction conditions was redetermined in the same monkeys and compared to saline responding following diazepam.

### METHOD

*Animals and Apparatus*

The subjects for this experiment were the 5 monkeys from experiment 1. They were housed and maintained under identical conditions.

*Procedure*

In the following study, either cocaine (0.03 mg/kg/infusion) or diazepam (0.03 mg/kg/infusion) was available for a number of successive sessions, with periods of saline availability interposed before and after each drug period. The schedule for each monkey remained the same as in the previous experiment. The order of presentation, described below, and the number of sessions per condition are shown in Table 2. In general, experiment 1 was completed first for monkeys 2030, 4001 and 4004, and experiment 2 was completed first for monkeys 4002 and 4005.

*Monkeys 2030, 4001, and 4004.* After the completion of experiment 1, cocaine was available to all three monkeys and this condition was followed by a redetermination of saline self-administration. Monkey 4001 was removed from the experiment following the cocaine-saline determination. However, for monkeys 2030 and 4004, diazepam was made available, again with saline substitution following the period of diazepam self-administration. This manipulation was repeated for monkey 2030.

*Monkeys 4002 and 4005.* After training, as described in

TABLE 2

ORDER OF PRESENTATION AND NUMBER OF SESSIONS IN EACH CONDITION[1,2] FOR THE DIAZEPAM- AND SALINE-TRAINED MONKEYS OF EXPERIMENT 1

| | Diazepam-Trained | | | Saline-Trained | |
|---|---|---|---|---|---|
| Drug Available | 2030 | 4001 | 4004 | 4002 | 4005 |
| Diazepam (0.03 mg/kg) | **8** | **14** | **20** | | 21 |
| Saline | **9** | **11** | **13** | | 11 |
| Diazepam (DR) | **46*** | **27** | **29** | | |
| Saline | **11** | **7** | **6** | | |
| Cocaine (0.03 mg/kg) | 4 | 6 | 4 | 7 | 11 |
| Saline | 8 | 11 | 8 | 13 | 11 |
| Diazepam (0.03 mg/kg) | 11 | | 8 | 21 | 34* |
| Saline | 11 | | 14 | 8 | 8 |
| Diazepam (0.03 mg/kg) | 17 | | | *22* | 27* |
| Saline | 7 | | | *16* | *5* |
| Diazepam (DR) | | | | | *36* |
| Saline | | | | | *13* |
| Cocaine (0.03 mg/kg) | | | | 8 | |
| Saline | | | | 16 | |

[1](DR) denotes the period when a diazepam dose-response function was determined.

[2]Bold type indicates data described in Experiment 1. When italicized, the data are described in both experiments for purpose of comparison.

*Indicates a catheter was lost and replaced during this determination.

experiment 1, but prior to completing the diazepam dose-response function (experiment 1), these monkeys were exposed to the following manipulations (see Table 2). Monkey 4005 was given access to diazepam (0.03 mg/kg), followed by saline availability. Next cocaine was made available again followed by a saline substitution. The cycle of diazepam-saline was then repeated twice before experiment 1 was begun. Similar manipulations were done with monkey 4002, but the order of the conditions was different (Table 2). This monkey was originally exposed to cocaine followed by a saline substitution. Next, two cycles of diazepam-saline were in effect, followed by an additional cocaine-saline determination.

*Data Analysis*

In Fig. 2, the average number of infusions received on the last two sessions of a given drug dose was used to compare levels of self-administration across conditions. All saline sessions were used to compare the patterns of extinction following the various drug conditions.

*Drugs*

Diazepam was prepared in the same manner as described in experiment 1. Cocaine hydrochloride was prepared in sterile saline and dose is expressed as the salt.

## RESULTS

Figure 2 shows the average number of infusions received during the last 2 sessions in each drug condition, as well as the amount of saline self-administered on every session. Four monkeys showed high levels of saline self-administration either following the first (monkeys 4004 and 4005) or the second (monkeys 2030 and 4002) period of diazepam availability. The fifth monkey (4001) had very low levels of diazepam self-administration, and although responding during saline substitution was not different compared to when diazepam was available, the overall levels remained low compared to the other monkeys.

Following a period of cocaine availability, 4 of the 5 monkeys showed decreases in saline self-administration compared to the amount of saline responding maintained after the most recent period of diazepam exposure (Fig. 2). Again, monkey 4001 initially had such low levels of saline responding that subsequent saline self-administration following cocaine was not different from levels preceeding cocaine exposure. However, relative to cocaine, these levels represent a decline in responding.

In 2 of the 3 monkeys exposed to diazepam after cocaine (4004 and 4005), saline rates again failed to decline, although monkey 4005 required 2 cycles of diazepam self-administration before saline rates remained comparable to rates of diazepam self-administration. In contrast, responding under extinction conditions was relatively low for monkey 2030, even after two cycles of diazepam-saline exposure. However diazepam intakes for this monkey had fallen compared to earlier levels. In summary, Fig. 2 illustrates responding under extinction conditions did not decline following exposure to large amounts of contingently available diazepam. In contrast, after exposure to cocaine, the self-administration of saline declined (i.e., extinction occurred). In most cases, perseverative responding for saline was again observed following additional diazepam experience, where drug intakes were maintained at fairly high levels.

## GENERAL DISCUSSION

The present results extend the finding that naive rhesus monkeys can be trained to initiate and maintain a lever-press response resulting in the delivery of intravenous diazepam [26]. Naive monkeys were also trained to initiate and maintain responding for saline infusions. In addition, 2 of the 3 monkeys trained to respond for diazepam and both monkeys trained to respond for saline reduced responding when the FR was increased to 10. A similar effect of increasing the FR requirement on diazepam self-administration has been reported in monkeys maintained under a codeine baseline [14].

The amount of responding maintained by diazepam was lawfully related to dose. The dose of diazepam maintaining the highest rates of responding ranged from 0.01 to 0.1 mg/kg/infusion. In several other studies that have determined diazepam dose-response functions under substitution conditions, doses of 0.01 to 0.05 mg/kg generally resulted in the highest levels of responding. Thus, the same range of doses maintain peak levels of responding in monkeys maintained either under a pentobarbital [2], codeine [14] or a cocaine baseline [2], as well as in the monkeys of the present study.

Despite the similar effect of diazepam dose on responding in the present and previous studies, an unexpected finding of the present study was the high level of saline responding maintained over an extended period of time. Other studies of diazepam self-administration [2, 11, 14] have found decreases in responding when saline or vehicle is substituted

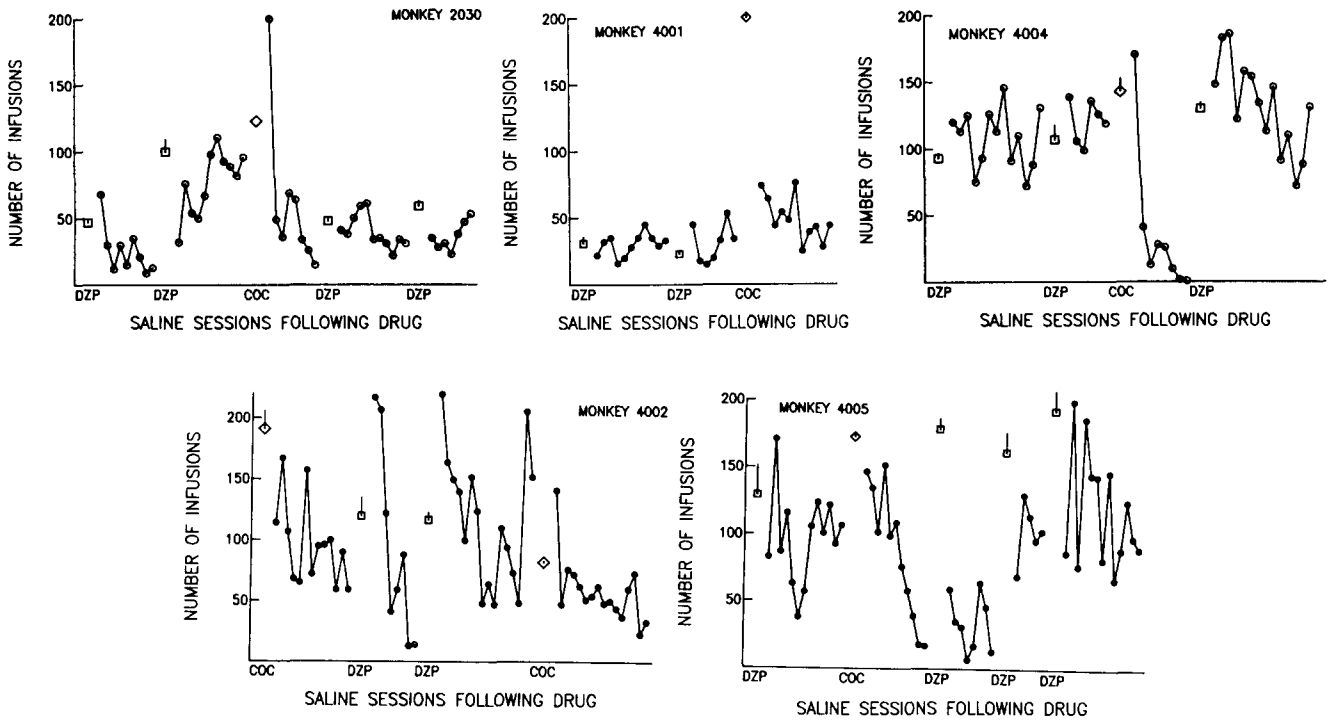


FIG. 2. Number of saline infusions received during each session, plotted by consecutive sessions, following a period of either diazepam (DZP) or cocaine (COC) self-administration. For each drug condition, the average number of drug infusions received on the last 2 sessions are plotted.

for the baseline drug. Such decreases in responding over time are similar to the pattern of extinction observed when reinforcement is withheld in paradigms using other types of reinforcers [9]. However, in drug substitution procedures, saline or vehicle are generally substituted immediately after sessions with the baseline drug available. In contrast, in the present study saline was substituted immediately after a period of diazepam availability. This procedural difference suggests that the failure to find decreased responding when extinction conditions were imposed is due to some properties of diazepam, distinct from those of other commonly used drugs in self-administration procedures. Indeed, when the monkeys were exposed to a short period of cocaine and then immediately exposed to extinction conditions, responding for saline decreased. With additional exposure to diazepam, the original effect of prolonged extinction was again observed in 3 of 4 monkeys tested. These data suggest that experience with diazepam self-administration is having a direct effect on the failure of responding to extinguish when saline is substituted.

It is possible that the continued responding for saline may be another example of benzodiazepines interfering with tasks involving response inhibition. In general, a robust effect of benzodiazepine administration is the inability of treated animals to withhold inhibited responding compared to nontreated controls in a number of experimental designs, including go-no go tasks [7, 13, 19], differential reinforcement of low rats of responding [4,22], reward delay procedures [24,25], reversal learning [15] and extinction of a learned task [23]. In the present experiment, this disinhibitory effect of diazepam may account for the continued responding for saline. However, in the studies cited above, release of inhibited responding was an acute effect of benzodiazepine administration (i.e., diazepam was present in the organism). Responding under extinction conditions in the present study continued for weeks after saline had been substituted for diazepam, long after the diazepam would have been excreted from the body. In addition, in order to produce prolonged resistance to extinction in the present self-administration experiment, relatively large amounts of diazepam administered over an extended period of time were required. For example, the one monkey (4001) that had consistently low levels of diazepam intake also had low levels of responding for saline, comparable to levels seen in other substitution studies. In addition, the two monkeys with initially low levels of responding for saline (2035 and 4002), both increased responding for saline following additional diazepam exposure. Finally, following cocaine availability, monkey 4005 required an additional period of diazepam self-administration before its responding for saline remained high. In contrast, the studies showing a release of inhibited responding due to diazepam administration used single infusions and doses usually under 10 mg/kg for rats and monkeys. Thus, the action of diazepam resulting in prolonged responding under extinction conditions differs in both total dose and time course compared to other studies. Whether these differences are dependent upon the type of task required and the extinction conditions imposed requires further investigation.

Another possible explanation for the prolonged responding under extinction conditions, other than direct pharmacological action, relates to diazepam's reinforcing properties. Studies using food as a reinforcer under continuous reinforcement schedules have found that the greater the magnitude of reinforcement during acquisition of a task, the

faster the rate of extinction [18]. By extension, the prolonged extinction observed following diazepam may have been due to its reportedly low reinforcing efficacy. Similarly, the rapid drop in responding seen when extinction conditions were imposed following cocaine availability may have been due to the high reinforcing efficacy of cocaine. The role of reinforcing efficacy, both within and between drug classes, on extinction from drug self-administration has not been systematically explored.

Regardless of the mechanism producing high levels of responding for saline, this action makes it difficult to assess the reinforcing properties of diazepam. If defined as the amount of responding for drug compared to responding for saline, diazepam would appear to have weak reinforcing properties. However, the amount of responding maintained by diazepam in 4 out of 5 monkeys was similar to the amount maintained in other studies in which diazepam was defined as a reinforcer [2, 11, 14]. On the other hand, it has been suggested that resistance to extinction can serve as a direct measure of reinforcer strength [20,27]. By this criterion, diazepam would appear to be an efficacious reinforcer in rhesus monkeys. Clearly, it is of both practical and theoretical importance to further explore which properties of diazepam interact with the extinction process.

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