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Effects of Diazepam on Responding Suppressed by Response-Dependent and Independent Electric-Shock Delivery

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HYMOWITZ, N. AND M. ABRAMSON. *Effects of diazepam on responding suppressed by response-dependent and independent electric-shock delivery.* PHARMACOL BIOCHEM BEHAV 18(5) 769–776, 1983.—While the effects of benzodiazepines on punished responding (response-dependent shock) are straightforward and unambiguous, their effects on behavior suppressed by response-independent shock are conflicting and inconsistent. Some investigators reported that benzodiazepines either have no effect on, or suppress further, responding during response-independent shock, while others reported that benzodiazepines enhance response rates during independent shock delivery in the same manner as during dependent shock. The present study compared the effects of diazepam on rates of lever pressing maintained by a variable-interval 35-sec schedule of food delivery in rats exposed alternately to fixed-interval 180 sec (response-dependent) and fixed-time 180 sec (response-independent) schedules of shock delivery. Diazepam increased punished responding in a dose-dependent manner for each animal. "Rate-dependency," degree of suppression and presence of external stimuli influenced rate-enhancement by the drug. Effects of diazepam on responding suppressed by response-independent shock were inconsistent, with two animals revealing rate enhancement comparable to punished responding, and two others revealing further increases in response suppression. Reasons for the differential effects of diazepam on response-rates suppressed by the two forms of shock delivery remain obscure, although the basic phenomenon seems to be real and not merely an artifact of "rate-dependency."

Diazepam Response-dependent shock Response-independent shock Response Suppression
Punishment Lever pressing Rats

BENZODIAZEPINES increase response rates suppressed by delivery of response-dependent shock (punishment) [5], with the relationship between dose of drug and rate of punished responding assuming the form of an inverted U. These effects have been found in the monkey [16], rat [14], pigeon [11] and pig [3], and under a variety of experimental conditions [4].

In view of the consistency and generality of the punishment data, it is surprising that studies of the effects of benzodiazepines on behavior suppressed by response-independent shock have yielded inconsistent and conflicting results. Stein and Berger [17] reported that benzodiazepines increase the suppression of responding caused by independent shock delivery, while McMillan and Leander [11] and Huppert and Iversen [7] showed that chlordiazepoxide increased punished response rates but had little or no effect on responding during response-independent shock.

Rawlins, Feldon, and Gray [13] studied the performance of individual rats under a multiple schedule in which one stimulus was associated with punishment and another with independent shock. Response rates were enhanced significantly more by chlordiazepoxide when shock delivery was dependent on behavior. However, behavior was suppressed to a greater degree during conditions associated with punishment than with independent shock, raising the possibility that the differential effect of the drug was an artifact of "rate-dependency," the tendency of drugs to increase low rates of responding more than high rates [14].

In a follow-up study, Rawlins *et al.* [12] varied shock intensity between groups of rats exposed either to response-dependent or independent shock, yielding similar degrees of suppression for each mode of shock presentation. Chlordiazepoxide increased response rates in both groups of rats to the same extent. In a second experiment, shock intensity was held constant so that behavior was suppressed more in groups of rats receiving punishment than free shocks. Response rates were enhanced significantly more by chlordiazepoxide in animals exposed to the punishment condition. Rawlins *et al.* [12] concluded that the differential effects of benzodiazepines on behavior suppressed by punishment and response-independent shock reported in the literature were artifacts of rate-dependency. When degree of response suppression is held constant, the drug increases responding to the same extent under each shock schedule.

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TABLE 1
ORDER OF SHOCK DELIVERY CONDITIONS

Rat 1		Rat 2		Rat 3		Rat 4	
No Signal		Signal (5 sec CS)		Signal (5 sec CS)		No Signal	
Independent	0.3 mA	Independent	0.3 mA	Dependent	0.25 mA	Dependent	0.4 mA
Dependent	0.25 mA	Independent	0.6 mA	Independent*	0.5 mA	Independent	0.25 mA
Independent*	1.3 mA	Dependent	0.3 mA	Dependent	0.2 mA	Independent	0.4 mA
Dependent	0.2 mA	Dependent	0.5 mA	Independent*	0.6 mA	Dependent	0.16 mA
Independent	0.4 mA	Independent	0.3 mA				
Dependent	0.5 mA	Dependent	0.2 mA				
Signal (15 sec CS)		Signal (15 sec CS)		Signal (15 sec CS)			
Independent	0.2 mA	Independent	0.25 mA	Dependent	0.2 mA		
Independent	0.5 mA	Independent	0.4 mA	Dependent	0.4 mA		

*Preliminary adjustment of shock intensity necessary to achieve desired level of response suppression.

Hymowitz [8] also reported that a benzodiazepine, diazepam, increased response rates suppressed by response-independent shock. While no direct comparison with punished responding was made, Hymowitz [8] reported that diazepam increased lever-press rates over a wide range of degrees of suppression, and, for each degree of suppression, the relationship between rate of responding and dose of diazepam was an inverted U.

In contrast to the earlier reports, the studies by Hymowitz [8] and Rawlins *et al.* [12] show that benzodiazepines increase response rates suppressed by shock which is independent of behavior. However, the issue of whether "rate-dependency" can account for the many conflicting findings in the literature merits further attention. McMillan and Leander [11] and Huppert and Iversen [7] reported differential rate-enhancing effects of benzodiazepines even though behavior was suppressed to similar degrees during response-independent and dependent shock. Hymowitz [8] reported that diazepam enhanced response rates during independent shock when behavior was only slightly suppressed, while others [12,17] failed to observe rate increases under conditions in which behavior was much more suppressed.

The present study seeks to clarify the relationship between the degree of response suppression during dependent and independent shock delivery and the rate-enhancing effects of diazepam. Specific objectives are to compare within the same animal the effects of diazepam during each mode of shock presentation and to assess the contribution of rate-dependency to the effects of diazepam.

METHOD

Subjects

Four experimentally naive male Sprague-Dawley rats, 300–350 g, were maintained at 80% of free-feeding weight and were housed in individual home cages with water freely available.

Apparatus

A Grason-Standler sound-attenuated operant rat chamber, Model 1101, contained a response lever, pellet dispenser, white masking noise, and fan. Counters and a cumulative recorder recorded responses, and programming was accomplished by electro-mechanical equipment. Two jewelled lights, located above and to the left and right of the response lever, served as the preshock stimulus. Electric shock to the grid floor was delivered by a Grason-Stadler shock generator, Model 700, and grid scrambler. Noyes food pellets (0.045 g) served as reinforcers.

Procedure

Following weight reduction to 80% of free-feeding weight and lever-press shaping, the animals were studied for 25–30 40-min daily sessions under a variable-interval 35 sec (VI 35-sec) schedule of food reinforcement. The distribution of inter-pellet intervals was symmetrical and ranged from 1 to 70 seconds. The initiation of the experimental sessions was specified by the onset of white masking noise.

Following acquisition of stable rates of lever pressing, a fixed-interval 180 sec (FI 180-sec) schedule of response-dependent electric-shock delivery or a fixed-time 180-sec (FT 180-sec) schedule of response-independent shock was superimposed upon the VI 35-sec food schedule. For two rats, a 5-sec conditioned stimulus (CS) (onset of two jewelled lights in an otherwise dark chamber) was presented every 180 sec (signaled shock). Offset of the two jewelled lights either was simultaneous with shock delivery (response-independent shock) or arranged that the next response would produce shock (response-dependent shock). Animals were never shocked during the CS. For two other rats, shock delivery was unsignaled (no CS during preshock period).

Table 1 shows the experimental conditions and order of shock intensities for each rat. For the initial block of food-and-shock sessions, two of the animals (Rats 3 and 4) were exposed to response-dependent shock and two (Rats 1 and 2) were exposed to response-independent shock. Thereafter, exposure to response-dependent and independent shock varied systematically for each animal. Two of the animals (Rats 2 and 3) were exposed to signaled shock throughout, while two others (Rats 1 and 4) were exposed to unsignaled shock delivery.

Blocks of successive food-and-shock sessions at a con-

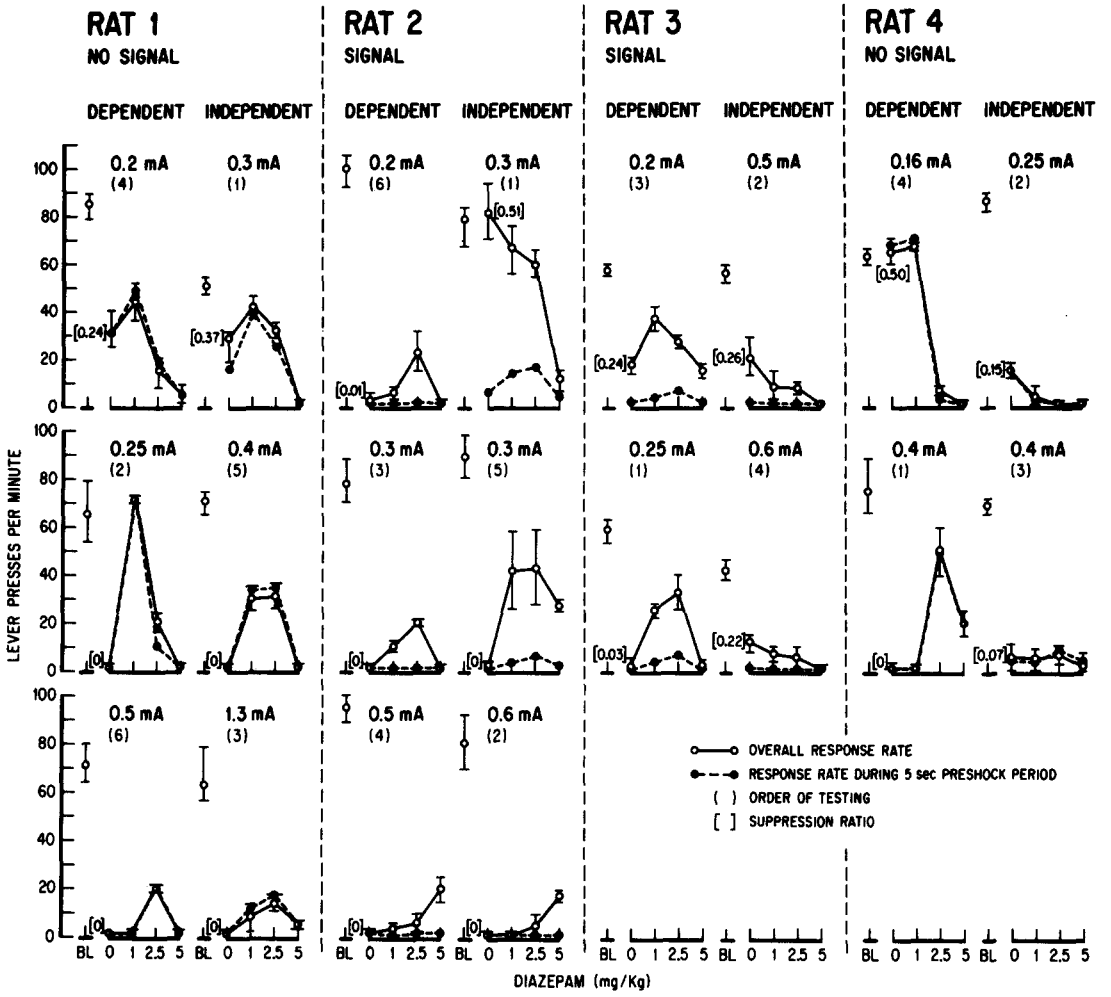

FIG. 1. Mean lever presses per minute and range for each animal during shock and drug conditions in which CS duration was 5 sec. Data points for the baseline conditions (BL) represent the mean of the final three food-alone sessions prior to the introduction of shock. Data points for the 0 mg/kg dose of diazepam represent the mean of the final three food-and-shock sessions prior to the introduction of diazepam. Data for administration of the placebo diluent for diazepam are not presented since no effects of the placebo were observed.

stant shock intensity alternated with blocks of food-alone sessions. Shock was not introduced until response rates returned to baseline levels during the food-alone sessions. Shock duration was 0.5 sec; shock intensity varied systematically over blocks of shock sessions. Diazepam was not introduced until there had been at least 10 sessions at a given shock intensity and until there was no systematic variation in the rate of lever pressing for a minimum of five successive sessions (cf. [8]). The diazepam and placebo solutions were supplied to the author by Hoffman-La Roche. The diazepam came dissolved in solvent (5 mg/ml) consisting of 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and 1.5% benzyl alcohol as preservative. The order of presenting the drug doses (1, 2.5, 5 mg/kg) followed a block randomization procedure. For each block of food-and-shock sessions, data for the first session in which diazepam was introduced was not included in the analysis. Typically, the performance of the animals was much more disrupted by the initial introduction of a given dose of drug than by subsequent administrations (cf. [16]). Each animal received a full range of doses in a mixed order before the same dose was repeated. A minimum of two drug-free sessions preceded each drug session. Each dose was administered 2–4 times. The animals also were studied under several volumes of the placebo diluent for diazepam (one time at each volume). All injections were administered (IP) 20 min prior to the start of the experimental session.

Following these analyses, Rats 1, 2, and 3 were studied further under conditions in which the CS duration was increased to 15 sec. This marked the first time Rat 1 was exposed to signaled shock. Rat 4 became ill and was not studied further. Rats 1 and 2 were studied under 0.2 and 0.5 mA signaled response-independent shock delivery; Rat 3, under 0.25 and 0.4 mA response-dependent shock delivery. As in the past, blocks of food-and-shock sessions at a constant shock intensity alternated with blocks of food-alone

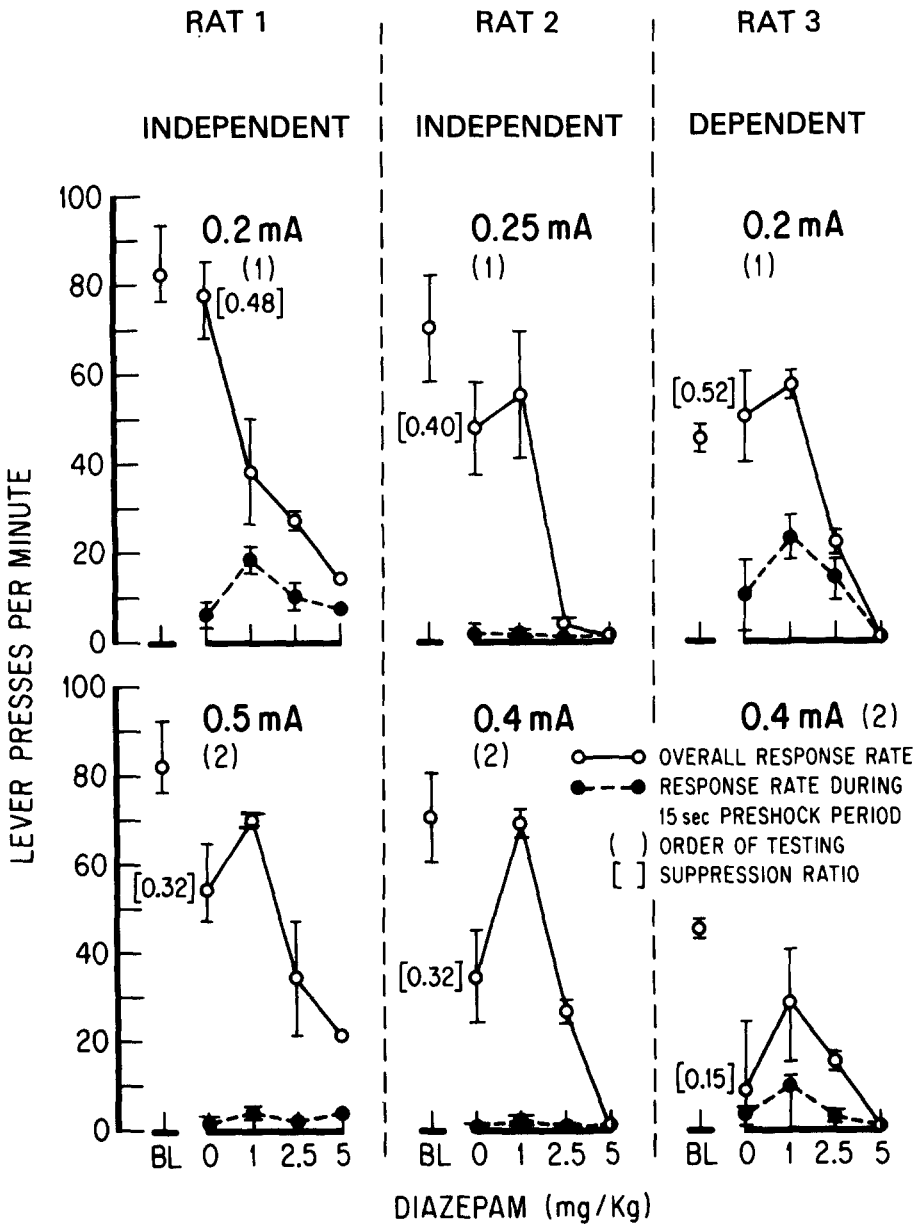

FIG. 2. Mean lever presses per minute and range for each animal during shock and drug conditions in which CS duration was 15 sec. See caption for Fig. 1 for further detail.

sessions. The manner of presenting the drug remained as described above. The main purposes of the additional analyses were to provide a wider range of response suppression for analysis of rate-dependency and to determine if CS duration influenced response suppression and the anti-suppressive effects of diazepam during CS presentations.

RESULTS

Baseline, No Shock

Figures 1 and 2 show for each animal mean rates of lever pressing during each experimental condition. With the exception of Rat 1, for whom baseline response rates increased after the first block of food-and-shock sessions, baseline response rates remained stable throughout the study.

Food-and-Shock, No Drug

For Rats 1 and 3, higher intensities of response-independent shock were needed to achieve the same level of suppression produced by response-dependent shock (Fig. 1). For Rat 3, 0.2 and 0.25 mA dependent shock suppressed response rates as much or more than 0.5 mA response-independent shock. For Rat 1, 0.3 mA response-independent shock had less suppressive effects than 0.25 mA response-

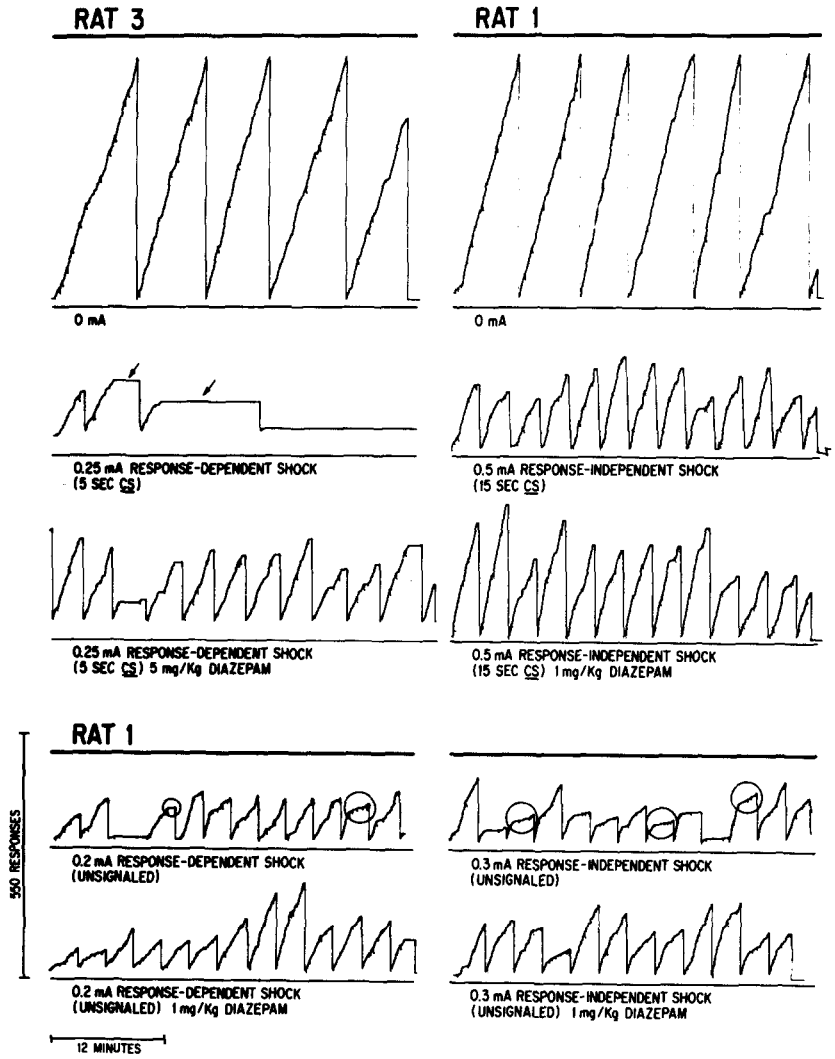

FIG. 3. Representative cummulative records of responding during selected experimental conditions. Vertical movement of the response pen represents lever presses; the downward pip of the response pen, pellets; and the resetting of the response pen, shock. The response pen also reset to the bottom of the scale after 550 presses. Arrows indicates pauses between offset of CS and initiation of next response. Circles indicate pattern of responding prior to unsignaled shock.

dependent shock which was introduced during the next block of food-and-shock sessions (Fig. 1). For Rats 2 and 4, comparisons between the suppressive effects of response-dependent and independent shock are precluded because of the marked degree of suppression during each shock condition (Fig. 1).

Figures 1 and 2 also show suppression ratios (a/a+b, where a is the mean rate of responding during shock, and b is the mean response rate for the last three days prior to the introduction of shock) [2]. A ratio of 0 indicates total response suppression; a ratio of 0.5, no suppression. Calculations of overall response rates do not include response rates emitted during preshock periods. In some instances, the suppressive properties of mild shock were increased following administration of more intense shock. For example, 0.3 mA signaled response-independent shock first failed to suppress Rat 2's behavior (Fig. 1, suppression ratio of 0.51). Following higher intensities of shock, reintroduction of 0.3 mA response-independent shock suppressed response rates for Rat 2 to a zero level (suppression ratio of 0) (Fig. 1).

Despite enhanced sensitivity to mild shock following exposure to more intense shock, the primary objectives of the study were achieved. Figures 1 and 2 show that systematic variation in shock intensities generated for each animal a wide range of degrees of response suppression so necessary for analyses of the influence of rate-dependency. The data also permit comparisons within the same animal of the effects of diazepam on response rates suppressed to comparable degrees by response-dependent and independent shock.

Figure 3 shows representative cumulative records of patterns of responding during shock and shock-free sessions. Prior to the introduction of shock, the animals maintained a

stable steady rate of food-maintained responding. The pattern of responding during shock differed, depending on whether or not shocks were signaled.

During signaled shock, the animals maintained a steady rate of responding in the absence of the CS, but ceased responding as soon as the CS was presented (see also Figs. 1 and 2). During mild-to-moderately intense response-dependent shock, the latency to press the lever and produce a shock when the CS terminated increased as the shock intensity increased (arrows). With signaled response-independent shock, the animals resumed responding soon after the shock was delivered. At more severe shock intensities, response rates were suppressed throughout the session.

During the unsignaled shock delivery, response-independent as well as response-dependent, the animals maintained a pattern of decelerated responding as the time for shock delivery approached (Fig. 3, circles). Following shock delivery, response rates increased but slowed markedly towards the final moments of the inter-shock intervals. During mild shock, response rates prior to unsignaled shock were much higher than response rates prior to signaled shock (i.e., in presence of CS) (Figs. 1, 2 and 3).

Food-and-Shock, Diazepam

Response-dependent shock. For all of the animals, diazepam increased the rate of pressing during response-dependent shock delivery (Figs. 1 and 2). The rate-enhancing effect of the drug depended upon the dose of diazepam, intensity of shock, and degree of response suppression. The relationship between rate of punished responding and dose of diazepam was an inverted U (Figs. 1 and 2). For Rats 1 and 2, response rates were most resistant to the rate-enhancing effects of diazepam at the highest shock intensities (Fig. 1). Response rates suppressed to the same zero level by less intense shock were much more readily enhanced by diazepam (Fig. 1).

Figure 4 pools data for each block of food-and-shock sessions to examine the issue of rate-dependency. Data are expressed as suppression ratios and drug enhancement ratios (see figure caption). This permits analyses of changes in the relative rates of responding which are not biased by the absolute rate. For example, a change from one response per min to 10 responses per minute is of a magnitude of 10. Yet, is the change actually greater than a change from, say, 10 responses/min to 50/min which yields a magnitude of 5? The suppression and enhancement ratios obviate this problem. For all of the animals, there was a direct relationship between the degree of response suppression and increases in response rates by diazepam. Low rates of punished responding were increased to a greater extent by a given dose of diazepam than high rates. These data are compatible with the concept of rate-dependency. The lone exception to rate-dependency are data points at the higher shock intensities for Rats 1 and 2 (Fig. 4). At these shock intensities, responding was resistant to rate-enhancing effects of diazepam despite the low rates of responding.

Figure 3 shows that the rate-enhancing effects of diazepam were due to a general increase in rates of food-maintained responding, a reduction in response deceleration prior to unsignaled shock, and a reduction in the latency to resume responding following termination of the CS (see arrows).

Responding during the CS was relatively unaffected by

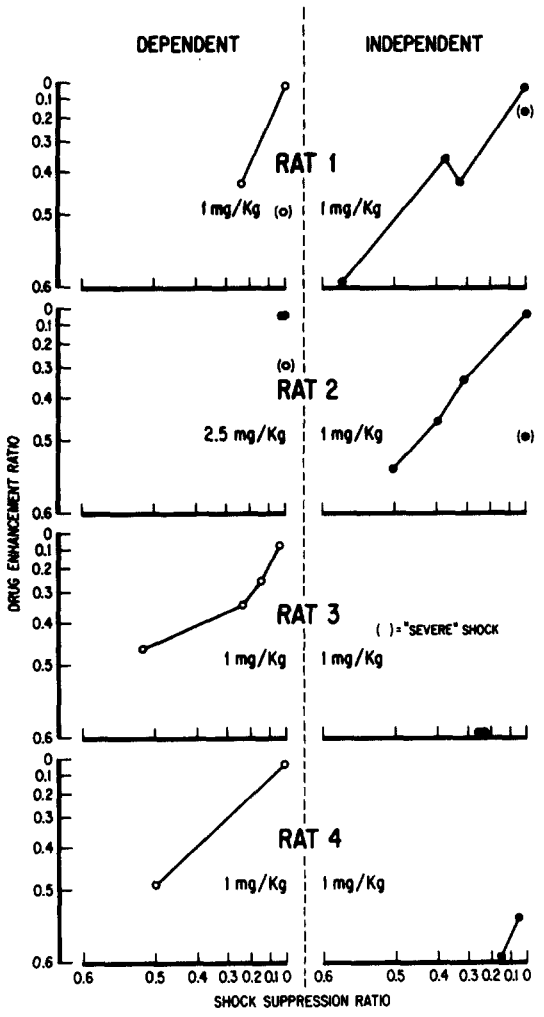

FIG. 4. Relationship between the enhancement of response rates during administration of diazepam (drug enhancement ratio c/c+d, where d equals the mean response rate during administration of a given dose of diazepam, and c equals the mean of the final three food-and-shock sessions which preceded the introduction of diazepam) and the degree of response suppression (shock suppression ratio a/a+b, where a indicates the mean rate of responding during a given intensity of shock, and b indicates the mean of the final three food-alone baseline sessions prior to the introduction of shock). For the drug enhancement ratio, a ratio of 0.5 means no rate enhancement, a ratio of greater than 0.5 means a decrease in response rates, and a ratio less than 0.5 indicates an increase in response rates; for the shock suppression ratio, a ratio of 0.5 indicates no suppression, ratio of 0 indicates complete response suppression, and a ratio greater than 0.5 indicates an increase in responding. The parentheses (Severe Shock) indicate conditions in which 1.3 mA(Rat 1) and 0.6 mA(Rat 2) produced approximately the same degree of response suppression as less intense shock (0.4 mA for Rat 1; 0.3 mA for Rat 2).

diazepam at each duration (Figs. 1, 2, 3). A slight increase in the rate of responding during the CS was found for Rat 3 (Fig. 2). When the CS duration was increased to 15 sec and 0.2 mA dependent-shock was introduced, the animal emitted about 10 responses per min during the CS. Diazepam in-

creased the response rate during the CS in a dose-dependent manner. On all other occasions, Rat 3 responded at a near-zero level during the CS, and diazepam failed to increase CS response rates.

Response-independent shock. For Rats 1 and 2, diazepam influenced response rates during response-independent shock in the same manner as dependent-shock (Figs. 1, 2, 3, 4). The relationship between rate of responding during independent shock delivery and dose of diazepam was an inverted U (Figs. 1, 2). As the degree of response suppression increased, the rate enhancing effects of diazepam increased (Fig. 4) (rate-dependency effect). On occasions in which independent shock had virtually no or little suppressive effects, diazepam decreased response rates in a dose-dependent manner (Figs. 1 and 2). This also is compatible with rate-dependency, although the decrease was not observed during response-dependent shock.

Response rates during the CS were also relatively insensitive to diazepam, and it seemed not to matter whether CS duration was 5 or 15 sec (Figs. 1 and 2). As was the case with dependent shock, response rates suppressed by severe shock intensities also were relatively insensitive to diazepam. Rate-enhancement was not observed until higher doses of the drug were introduced (Fig. 1).

The performance of Rats 3 and 4 during independent shock was very different from Rats 1 and 2. Whereas diazepam increased punished response rates in the same manner as Rats 1 and 2, response rates suppressed by response-independent shock either were unaffected or were decreased by diazepam (Fig. 1). These differential effects of diazepam were observed despite the fact that behavior was suppressed to the same degree by response-dependent and independent shock.

DISCUSSION

McMillan and Leander [11] and Huppert and Iversen [7] reported that benzodiazepines differentially increased punished response rates but had relatively little effect on rates suppressed by response-independent shock. Stein and Berger [17] reported that benzodiazepines actually increased response suppression during independent shock delivery. In contrast to these findings, Rawlins *et al.* [12] and Hymowitz [8] reported that benzodiazepines increased response rates during response-independent shock in an orderly manner. Rawlins and his colleagues concluded that the discrepancies in the literature were an artifact of rate-dependency. When behavior is suppressed to the same degree by each mode of shock delivery, benzodiazepines increase response rates to the same extent.

The present study employed a within-subject design in which the effects of diazepam on suppressed response rates for individual animals were assessed during each mode of shock delivery. In interpreting the data, it was important to be sure that the animals came into contact with the dependency, or lack of dependency, between shock delivery and behavior.

The behavior of the animals suggest that this fundamental objective was achieved. During signaled shock, animals ceased responding in the presence of the CS. This minimized the likelihood of an adventitious association between lever pressing and shock delivery. Moreover, the pattern of responding during signaled response-independent and signaled dependent shock differed. During signaled independent shock, responding ceased in the presence of the CS and resumed soon after the delivery of shock. During signaled response-dependent shock, responding ceased during the CS, but often did not resume until a considerable pause separated the termination of the CS and the next response which would produce shock.

Previous studies [1,2] showed that, for a given intensity of shock, response-dependent shock suppressed behavior more than response-independent shock. Rats 1 and 3 similarly revealed greater sensitivity to the suppressive effects of response-dependent over response-independent shock. Shock intensity data for Rats 2 and 4 are difficult to interpret because of the marked suppression of responding under each mode of shock delivery.

Finally, note that Rats 3 and 4 first received response-dependent shock and then received response-independent shock. Had they behaved as if response-independent shock actually depended upon behavior, one would predict that diazepam would have increased response rates during independent shock as it had during-dependent shock (Fig. 1). Response rates during response-independent shock delivery were not enhanced by the drug in Rats 3 and 4 (Figs. 1 and 2). These findings suggest that the animals came into contact with the experimental contingencies.

The findings on the effects of diazepam on punished behavior were unambiguous and straightforward. Diazepam increased punished response rates in each of the animals, and the relationship between rate of punished behavior and dose of drug formed an inverted U. Similar findings have been reported by Sepinwall *et al.* [16] and McMillan [10].

The increase in punished responding also was influenced by rate-dependency. Within limits, the greater the degree of suppression, the greater the relative increase in response rates. Two conditions in which rate-dependency did not apply were the use of severe shock and the presence of the CS. When shock intensity was increased to fairly high levels (0.5 mA for Rats 1 and 2) (Fig. 1), response rates were more resistant to the rate-enhancing effects of diazepam despite the marked degree of response suppression. McMillan [10] also reported that increases in shock intensity beyond certain limits reduced the sensitivity of punished behavior to drugs.

Response rates during the CS which preceded response-dependent shock also proved relatively insensitive to diazepam. This may reflect the relative insensitivity of behavior under "tight" stimulus control to disruption by drugs in general [9], and the marked degree of suppression generated by CSs associated with response-dependent shock. A modest rate-enhancing effect of diazepam on CS responding was observed for Rat 3 during 0.2 mA dependent shock (Fig. 2). The baseline rate of responding during the 15 sec CS was close to 10 responses per minute, whereas near zero rates of responding were found on most other occasions. It is likely that diazepam would increase rates of responding during stimuli which precede response-dependent shock provided that the behavior is not too suppressed.

Whereas diazepam increased rates of punished responding in each animal, only two of the animals revealed increased rates of responding during response-independent shock delivery. For two other animals, diazepam either had no effect or decreased further the rate of responding. As such, these data reflect the inconsistencies in the literature on the effects of benzodiazepines on behavior suppressed by response-independent shock [4].

The increases in response rates during independent shock delivery for Rats 1 and 2 are consistent with previous reports

[8,12]. For these animals, diazepam influenced suppressed behavior in the same manner whether or not shock delivery was dependent on, or independent of, behavior. Responding during the CS similarly was resistant to the effects of diazepam, with the exception being those few occasions (Rat 1, 0.2 mA signaled response-independent shock; Rat 2, signaled 0.3 mA independent shock) in which non-zero rates of responding were maintained during the CS.

The behavior of two other animals was more consistent with findings of McMillan and Leander [11] and Huppert and Iversen [7] who reported that benzodiazepines differentially affected behavior suppressed by response-dependent and independent shock. It is not clear why Rats 1 and 2 revealed rate-enhancement during dependent and independent shock while Rats 3 and 4 revealed enhanced response rates only during response-dependent shock. At present, two conclusions appear warranted. One, the rate-enhancing effects of benzodiazepines on suppressed behavior appear much more reliable and robust for punished response rates than for rates suppressed by response-independent shock. Second, it is unlikely that discrepant findings existent in the literature are mere artifacts of rate-dependency. While rate-dependency is an important concept for understanding effects of drugs on behavior, other variables, currently unspecified, most likely are responsible for the fact that some animals reveal orderly increases in response rates during independent shock when benzodiazepines are introduced and others do not.

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