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Effects of Diazepam on Behaviour Suppressed by Extinction in Pigs[1]

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DANTZER, R. *Effects of diazepam on behaviour suppressed by extinction in pigs.* PHARMAC. BIOCHEM. BEHAV. 6(2) 157–161, 1977. — Diazepam injected to pigs previously trained to perform an operant response for food according to a continuous reinforcement schedule significantly increased resistance to extinction compared to control pigs. In pigs submitted to a time-out procedure diazepam increased the number of nonreinforced responses at the beginning of the acquisition but was unable to disinhibit suppressed behaviour in the later stages of acquisition when the extinguished behaviour was well acquired. The results are discussed with respect to antiaversive or disinhibitory effects of benzodiazepines and an alternative interpretation, the strengthening of the prevailing behavioural tendency in the animal's repertoire at the time of test, is put forward.

Benzodiazepines Diazepam Pigs Extinction Nonreward Time-out Frustration theory Disinhibition theory Performance facilitation

SEVERAL interpretations have been put forward to account for the strong disinhibitory effects of benzodiazepines on punished responding ranging from motivational interference (anxiolytic activity [28] or increase in food motivation [26]) to a tendency to increase low levels of responding (rate dependency principle [23,27]) or a general disinhibitory action [19]). To decide between all these theories the effects of benzodiazepines on behaviour suppressed by other means than punishment are of interest. This is especially the case with nonreinforcement suppressed behaviour as it can be regarded either as a consequence of frustration [1] or as an example of non punished low rate behaviour. However a survey of the literature on the effects of benzodiazepines on nonreinforced behaviour reveals some inconsistencies: while oxazepam produced a large increase in the rate of non reinforced responding of rats trained to press a lever for sweetened milk [19] and chlordiazepoxide restored behaviour attenuated by nonreinforcement in a withdrawal procedure [16] or in a more conventional time-out procedure [25], in another series of experiments chlordiazepoxide was unable to affect suppressed bar pressing in a time-out procedure [20] or extinguished water intake [21].

The present experiments were designed to investigate further the effect of another benzodiazepine, diazepam, on operant behaviour of pigs submitted to an extinction or a time-out procedure.

EXPERIMENT 1

Extinction can be measured either acutely by no more rewarding a previously learned response, or repeatedly by the use of a time-out procedure in which operant behaviour is not rewarded during a fixed period of time eventually signalled by an appropriate exteroceptive stimulus. In the first experiment we examined the effects of a dose of diazepam known to release behaviour suppressed by punishment [7,9] on resistance to extinction of pigs previously trained to get a food reward by pressing a panel with their snout.

METHOD

Thirteen cross-bred pigs, castrated male or female, were used. They were 8 weeks old at the beginning of the experiment and weighed 16–20 kg.

The apparatus and the general experimental conditions have already been fully described [7,9]. Pigs were trained to press a panel with their snout to get a food reward (5 g of a commercial granular food) according to a continuous reinforcement schedule, i.e. one reinforcement for each response. Responding was considered to be stabilized when 80 reinforcements were obtained within less than 30 min in at least three successive daily sessions. On the subsequent day, a single session of extinction was given: the pigs were allowed to press the panel but no food was available; the session ended after 5 min without responding.

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TABLE 1

EFFECTS OF DIAZEPAM ON MEAN RESPONDING ($M \pm S_M$) DURING THE EXTINCTION SESSION

	diazepam-treated pigs (n=7)	saline-treated pigs (n=6)	comparison
Number of responses	265 ± 70.4	26 ± 10.4	$F^1_{11} = 9.6^*$
Duration of the session (sec)	1994 ± 392	408 ± 212	$F^1_{11} = 11.5^{**}$
Mean composition of each burst of responding	2.85 ± 0.15	1.88 ± 0.19	$F^1_{420} = 4.84^*$
Percent of IRT ⩽ 10s	79	66	$F^1_{11} = 5.38^*$
Percent of IRT ⩾ 100 s	18	31	$F^1_{11} = 5.38^*$

$^*p \leqslant 0.05$; $^{**}p \leqslant 0.01$.

One mg/kg diazepam in commercially available vials (Valium, Roche, 5 mg/ml) or an equivalent volume of isotonic saline was injected intramuscularly 30 min before the beginning of the extinction session; allocation of the treatment condition was random.

RESULTS

Diazepam increased the mean number of responses emitted during the extinction session as well as the duration of the session (Table 1). Moreover the pattern of re sponding differed according to the treatment: responses tended to be emitted by bursts with interresponse time (IRT) less than 1 sec; in diazepam-treated pigs each burst contained about 3 responses versus only 2 for the control pigs. A statistical analysis of the percent repartition of IRT's, after an arcsinus square root transformation revealed that there were also more smaller IRT's (less or equal to 10 sec) in diazepam-treated animals and more larger IRT's (superior or equal to 100 sec) in saline-treated pigs.

Figure 1 shows the extinction curve for the two experimental groups: while the control group displayed rapid decrement in responding as extinction progressed, the diazepam group was more resistant to extinction and exhibited a triphasic curve with an increase in responding between 1 and 7 min, an intermediary rate with some outbursts of responding from 8–24 min and a slow rate thereafter.

DISCUSSION

Several different theories have been proposed to account for the decline in responding under extinction [18] According to the generalization decrement theory, the sole effect of the omission of reinforcement is to change the stimulus situation affecting the animal: in this context diazepam should increase responding by interfering somewhat with the generalization decrement for instance by affecting discrimination abilities. However the available evidence does not support such an interpretation since it has been shown for instance that diazepam does not impair the performance of pigs presented with classically conditioned discriminative fear and safety signals but rather that the drug sharpens the discrimination [8].

In the frustration theory of nonreward [1] the omission of the anticipated reward is regarded as a punishment event [6,24] which elicits a variety of emotional reactions disrupting the execution of the previously learned response. From the evidence based mainly on the study of running speed of rats in a runway, frustrative nonreward has not only aversive but also invigorating effects: the strength of a nonrewarded response like for instance running down the alley in a runway situation [2] or pressing a lever in an operant situation [12], is increased when the subject has not been rewarded. If drug administered to the animal during extinction has antifrustration effects one would expect an increase in resistance to extinction, by reducing the aversive effects of nonreward: this is fully supported by the results of the present experiment and is in agreement with results of other studies using benzodiazepines [12] or barbiturates [14]; however the influence of drugs on the invigorating effects of non-reward is far less convincing: in the present study diazepam greatly increased the rate of

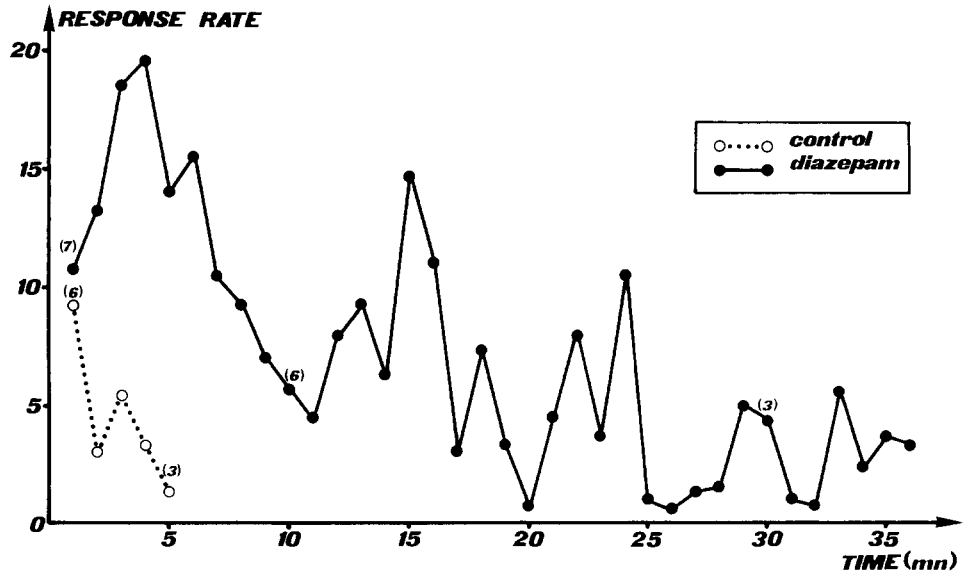

FIG. 1. Mean rate of response (responses per min) as a function of consecutive 1 min intervals in extinction. The numbers in brackets indicate the number of animals upon which each mean is based.

responding in the first minutes of the extinction session at a level above the initial level while the rate should be expected to be maximum at the very beginning of the session and decrease uniformly with time if the drug had only frustration reducing activity. In a study on the effects of chlordiazepoxide on response force in extinction [12] the drug treatment was shown to increase the force of responding instead of attenuating the force rise during extinction; similarly barbiturates were unable to reduce the increase of running speed after nonreward in the Amsel double runway [13, 14, 17].

EXPERIMENT 2

As frustration is only a temporary phenomenon produced by the initially unexpected omission of reinforcement, one would expect that repeated omission of reinforcement would eventually result in the disappearance of frustration reactions as the animal is learning that responding is no more rewarded. If diazepam releases extinguished suppressed behaviour by virtue of its anti-frustration properties, the resistance to extinction induced by the drug should decrease as the learning is progressing. Repeated omission of reinforcement can be scheduled by presenting the animal performing on an operant task with a stimulus signalling the cessation of reinforcement. Such a signal is called a negative discriminative stimulus, S_Δ, or time-out stimulus. The repetition of the signal will progressively elicit a suppression of behaviour. This time-out procedure was selected to examine the effects of diazepam on extinction at different stages of acquisition of the suppressed response in pigs.

METHOD

Eight cross-bred pigs, castrated male or female, were used. They were 8 weeks old at the beginning of the experiment and weighed 16–20 kg.

After having learnt to respond for food on a fixed ratio schedule in which they had to respond 10 times to get a reward (FR 10), they were submitted to a time-out procedure: 10 min after the beginning of the session, the sound of a buzzer signalled the transition from the FR 10 schedule to a nonreinforcement period which lasted 2 min and 30 sec. The cessation of the tone signalled the reinstatement of the FR 10 during the 10 following minutes. Each session lasted 22 min 30 sec and was run daily at the same time of the day for each pig, five days a week.

One mg/kg diazepam was injected intramuscularly 30 min before the 3rd, the 6th, the 9th, the 23rd, the 30th and the 35th session.

To evaluate the effect of the presentation of S_Δ within each session, a suppression ratio was computed by the following formula:

$$(A-B)/A$$

where A is the number of responses during the 2 min 30 sec just preceding the signal and B the number of responses during the S_Δ. This ratio equals 1 when the suppression is total, 0 when A = B and decreases when B > A.

RESULTS

Figure 2 shows the suppression ratio in the session just

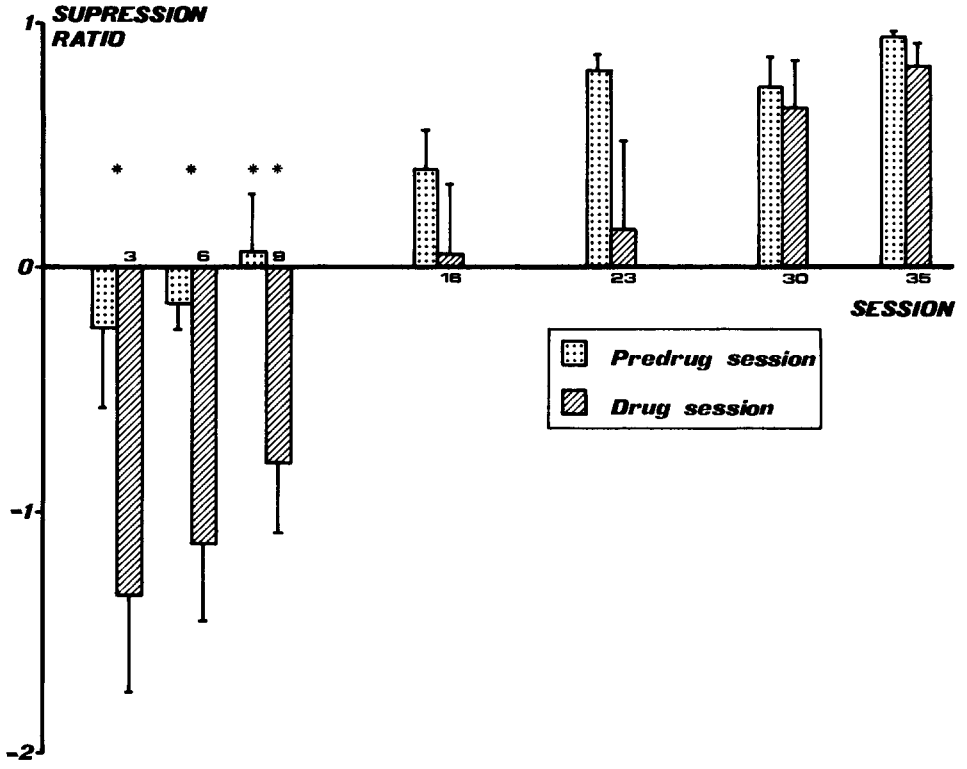

FIG. 2. Evolution of the suppression ratio during the course of extintion. The symbols above the columns indicate the significance level of the comparison between the predrug session and the drug session by a two-way analysis of variance (2 conditions × 8 replications)* = $p \leq 0.05$, ** = $p \leq 0.01$.

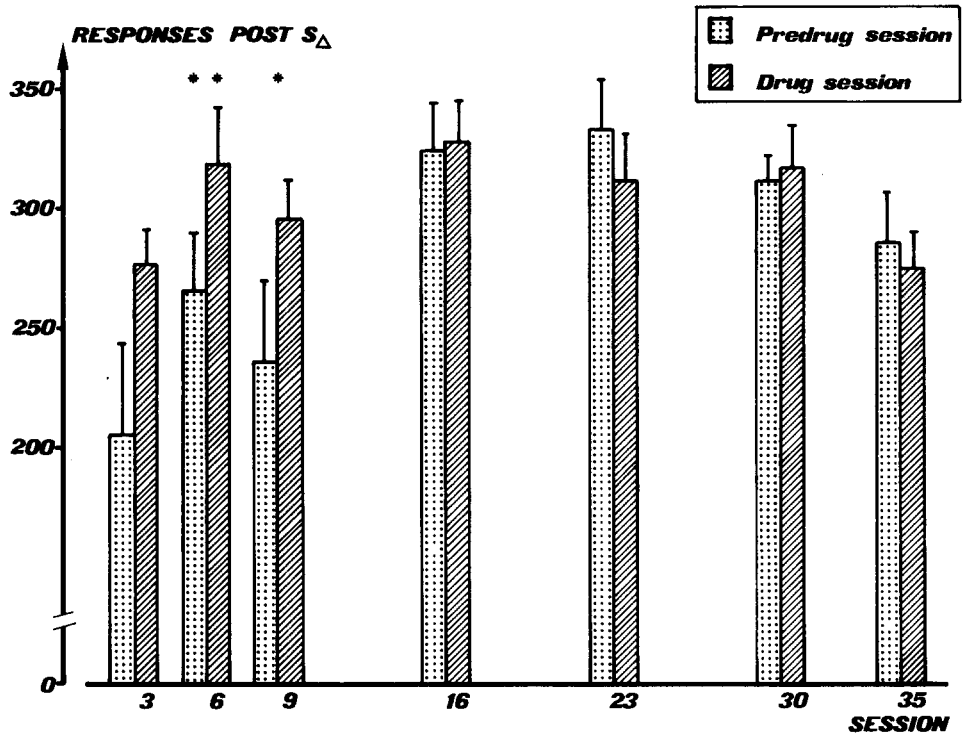

FIG. 3. Evolution of the mean number of responses after the presentation of the S_Δ, during the course of extinction. Same symbols as in Fig. 2.

preceding the drug session and the drug session, at different intervals during acquisition. It can be seen that extinction progressed slowly since a marked suppression was obtained only from the 20th session. The diazepam treatment produced a strong increment of responding during the first drug sessions and was unable to produce any significant change in the suppressed responding in the subsequent sessions.

Figure 3 shows the effects of the diazepam treatment on the FR 10 rate of responding which followed the time-out period: the drug increased significantly the response rate in the 6th and the 9th session, while the increase noted in the 3rd session failed to reach the significance level due to the high interindividual variability.

DISCUSSION

Diazepam appears to affect S_Δ performance differentially according to the stage of conditioning: when the drug is given early in conditioning it is able to increase substantially both the nonreinforced responding rate and the general response rate after the presentation of the S_Δ, while when the treatment is administered in the later stages of extinction it does not release any more the extinguished behaviour. It is of interest to note that oxazepam was observed to increase non reinforced responding while the rate of response during the time-out period was still dropping [19] and that chlordiazepoxide was unable to increase extinguished licking in rats stabilized in the conditioning procedure for several weeks [21]. Differences in time of testing could therefore well account for some of the contradictory results about the effects of minor tranquilizers on extinction-suppressed behaviour found in the literature.

It is tempting to explain the biphasic effect of diazepam on the extinction curve by the antifrustration properties of the drug: due to the high expectation of reinforcement during the initial stage of acquisition, frustration would be very intense, but as learning that responding is no more reinforced progresses frustration would decrease and finally disappear; if diazepam reduces frustration its effects would then be confined to the early portion of the extinction curve. Some supplementary evidence for this hypothesis comes from the striking parallel between the effects of diazepam on the suppression ratio and the effects of the drug on the response rate after the S_Δ presentation: pigs submitted for the first time to the nonreward procedure do not always resume responding after the presentation of the S_Δ and can be seen to attempt to escape the experimental situation.

GENERAL DISCUSSION

The present experiments show clearly that a rate dependent phenomenon or a general disinhibitory effect cannot account for the observed effects: a disinhibitory effect [19] should have released suppressed behaviour whatever the stage of extinction in the second experiment; according to the rate dependency principle [23,27] the increase of extinguished behaviour should have been greater when the suppression was maximum, which is just the opposite of the present results. The antiaversive properties of benzodiazepines appear to account well for the results of the second experiment but only partially for the results of the first experiment since the invigorating effects of frustration do not seem to be amenable to the activity of minor tranquilizers.

An alternative hypothesis would be that benzodiazepines strengthen the prevailing behavioural output: because of the animal's history and the environmental cues, the

operant response has a very high probability in the early stages of extinction; but as extinction progresses the subject learns that he is no more rewarded so that the prevailing behaviour during the S_Δ becomes the suppressed responding or the competing responses if any. Further support for this hypothesis comes from the effects of benzodiazepines on adjunctive behaviour, i.e. behaviour maintained at high probability by stimuli whose reinforcing properties in the situation are derived primarily as the result of schedule parameters governing the availability of another class of reinforcer [11]. Typically adjunctive behaviour like excess water drinking (schedule-induced polydypsia) occurs when water is freely available while rats are lever pressing for food on an interval schedule: administration of chlordiazepoxide does not prevent the development of adjunctive drinking but actually produces a significant facilitation of this behaviour [22]; similar effects have also been obtained in different experimental conditions, for instance schedule-induced drinking of rats maintained under a multiple fixed ratio 80, fixed interval 2 min schedule of food presentation [4], or in monkeys [3]. The main advantage of this hypothesis is that it gets rid of the disinhibition theory which is sometimes very tricky to refer to: each time there is an increase in responding, an inhibitory condition impeding the responding has to be identified . . . . By referring to the probability of responding rather than the strength of stimulus or drive level, this hypothesis is particularly suited to the conditioning experiments where the experimenter is familiar with the animal's previous history and has control over the set of factors which underlies the tendency to show one given type of behaviour [15].

However attracting this hypothesis may be, it must be reminded that all the known effects of benzodiazepines cannot be explained on the basis of a one-factor model of drug action, since they are also modulated by treatment, organismic and test factors [5]; moreover some state-dependent changes are also to be taken into account. For instance it has been shown recently that the effects of diazepam on acquisition and performance of conditioned fear needed at least a 3-factor model in which facilitation of performance but also state-dependency and acquisition deficit were of importance [10]. Further work is clearly needed in order to better understand the interactions between all these factors.

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