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Abolition of the Acquisition but not the Expression of Latent Inhibition by Chlordiazepoxide in Rats

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FELDON, J. AND I. WEINER. *Abolition of the acquisition but not the expression of latent inhibition by chlordiazepoxide in rats.* PHARMACOL BIOCHEM BEHAV 32(1) 123–127, 1989.—In the latent inhibition (LI) paradigm, prior nonreinforced exposure to a stimulus retards subsequent conditioning to that stimulus when it is paired with reinforcement. The development of LI reflects learning not to attend to, or ignore, stimuli which predict no significant consequences. The present experiment tested the effects of chlordiazepoxide (CDP) on LI using a conditioned emotional response (CER) procedure consisting of three stages given 24 hr apart: preexposure, in which the to-be-conditioned stimulus, tone, was presented without reinforcement; conditioning, in which the preexposed stimulus was paired with shock; and test, where LI was indexed by animals' suppression of licking during tone presentation. Preexposure and conditioning were given off-baseline. CDP (5 mg/kg) was administered only in preexposure, only in conditioning, in both stages or in neither. The administration of the drug during tone-shock conditioning conducted off-baseline markedly reduced animals' suppression to the tone in a subsequent licking test which was conducted without the drug. The administration of CDP during nonreinforced preexposure to the tone abolished the development of LI, i.e., drug-treated preexposed animals did not show reduced suppression as compared to drug-treated nonpreexposed animals. These results demonstrate that CDP: a) blocks the acquisition of classically conditioned fear and b) disrupts animals' ability to learn that stimuli predict no significant outcomes.

Chlordiazepoxide Off-baseline conditioned suppression Latent inhibition Rat

THE most widely studied and documented behavioral action of the benzodiazepines (BZD) is their "anticonflict" activity, i.e., an increase in operant responding that has been suppressed by punishment [e.g., (7, 16, 29, 41)]. The anticonflict activity of BZD is highly correlated with their clinical potency and is regarded as the animal analogue of their antianxiety action in humans [e.g., (17, 27, 29, 37)]. Gray (8–10) has emphasized a more general disinhibitory action of BZD, i.e., their capacity to disinhibit behaviors suppressed not only by punishment but also by other aversive events such as nonreinforcement and novel stimuli.

Several authors have suggested that BZD may exert disruptive effects on learning and information processing (2, 3, 11, 18, 40). Indeed, BZD impair performance in tasks using appetitive reinforcement, such as delayed stimulus matching in monkeys (28), or brightness or light discrimination in rats (5,13). However, it appears that performance impairments obtained in these tasks also stem mainly from a disinhibitory action of BZD, i.e., animals' failure to inhibit responding on trials which require such inhibition (2). Likewise, BZD-induced impairment in the *acquisition* of successive brightness discrimination is due to such a disinhibitory action of these drugs (2,10). The clarification of BZD-induced learning/information processing impairments is of particular importance in view of the wide use of these drugs and the growing awareness of their abuse liability (14). Yet, to date, there are very few reports of BZD-induced acquisition/performance impairments which cannot be easily interpreted in terms of their disinhibitory action [e.g., (12, 18, 21)].

The present experiment tested the effects of chlordiazepoxide (CDP) on the development of latent inhibition (LI). In the LI paradigm, nonreinforced preexposure to a stimulus retards subsequent conditioning to that stimulus when it is paired with a reinforcer (19). For example, if an animal is preexposed to a series of tones, these tones lose their capability to enter into associations with other stimuli, such as shock, or responses such as shuttle avoidance. LI was assessed in an off-baseline conditioned emotional response (CER) procedure (42), in which nonreinforced stimulus preexposure and conditioning are given while the animal cannot perform an instrumental response. LI was indexed subsequently by animals' suppression of licking during stimulus presentation.

The choice of the LI paradigm and the off-baseline CER procedure was prompted by two reasons. First, the LI paradigm is uniquely suited for elucidating drug action unconfounded with motivational/emotional effects (42). The preexposed stimuli are retarded in the subsequent develop-

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ment of both excitatory and inhibitory conditioning and show no evidence of conditioned inhibition in summation test procedures (31–33, 38). Such results have been taken to imply that nonreinforced preexposure reduces the attention value, or the associability, of the to-be-conditioned stimulus without altering its associative strength (24, 32, 35). This decremental process is considered to reflect a process of learning not to attend to, or ignore stimuli which predict no significant outcomes [e.g., (20, 22, 24, 25)]. The LI phenomenon is highly suitable for investigating the effects of BZD on learning. Learning to ignore, or not to attend to the preexposed stimulus not only lacks an aversive component, but is entirely devoid of motivational/emotional component, since it is learning in the absence of reinforcement. Consequently, the use of LI would enable one to determine the effects of BZD on learning which cannot be interpreted in terms of the disinhibitory action of these drugs.

Second, the off-baseline CER procedure enabled us to evaluate the effects of BZD on conditioned fear. While it is well established that BZD alleviate punishment-produced suppression and on-baseline conditioned suppression, i.e., when the conditioned and the unconditioned stimuli are presented while the animal performs an instrumental response, the effects of these drugs on conditioned suppression established by means of an off-baseline procedure, are debatable. Thus, Gray (9,10) argued that BZD are ineffective in such procedures, since they do no affect classical conditioning of fear, but this view is not unanimous [e.g., (15)]. The few studies which used an off-baseline CER procedure administered the drugs *after* suppression had been established [e.g., (1,39)]. These studies show that BZD disrupt the expression of fear, but do not clarify whether they impair conditioning of fear. Only one study (36) found a marked effect of chlordiazepoxide when it was given during CS-shock pairings. Since the control (nonpreexposed) group in the LI paradigm is given an off-baseline CER conditioning, it enables one to assess the effects of BZD on the acquisition of fear. In order to assess the effects of BZD on the acquisition of LI and on the acquisition of CER, CDP (5 mg/kg) was administered only in preexposure, only in conditioning, in both stages, or in neither.

METHOD

Subjects

Subjects were 64 male Wistar rats (Tel-Aviv University Medical School, Israel), approximately 4 months old, housed one to a cage under reversed cycle lighting. Upon delivery, subjects were maintained on ad lib food and water for one week. On the eighth day, all animals were weighed and placed on a 23-hr water deprivation schedule which continued throughout the experiment.

Apparatus

The conditioned emotional response (CER) apparatus consisted of two plastic test chambers set in a ventilated sound-insulated Grason-Stadler Research Chest (Model 1101). The internal dimensions of each chamber were 15× 20×17 cm, as measured from the raised grid floor. The chambers were flat grey, with small holes drilled in the side for ventilation. A drinking bottle could be inserted into the chamber through a 2-cm diameter hole which was 1.2 cm above the grid floor and 3 cm from the right side of the chamber. When the bottle was not present, the hole was covered by a plastic lid. Licks were detected by a drinkometer circuit. The preexposed to-be-conditioned stimulus was a 5 sec, 2.8 kHz tone produced by a Sonalert module (Model SC 628). The shock grid was made from stainless steel bars 0.25 cm in diameter set at 1.5 cm intervals. Shock was supplied by a Grason-Stadler scrambled shock source (Model E 1064 GS) set at 1 mA, 1 sec duration. A Rockwell AIM-65 microprocessor was used for equipment programming and data recording.

Procedure

The LI procedure consisted of the following stages:

Baseline. On each of seven days, rats were individually placed into the experimental chamber and allowed to make 600 licks. The subject was then returned to its home cage and allowed access to water for 30 min.

Preexposure (PE). On day 8, with the bottle removed, each animal was placed in the experimental chamber. The preexposed (PE) animals received 40 3-sec tone presentations with an ITI of 50 seconds. The nonpreexposed (NPE) animals were confined to the chamber for the identical period of time but did not receive the tone.

Conditioning. On day 9, with the bottle removed, each animal was given two tone-shock pairings. Tone parameters were identical to those used in preexposure. The 1-mA, 1-sec shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the conditioning session. Five minutes later the second pairing was administered. After the second pairing, animals were left in the experimental chamber for an additional five minutes.

Test. On day 10, each animal was placed in the chamber and allowed to drink from the bottle. When the subject completed 90 licks the tone was presented. The tone continued until 10 additional licks were completed. If the subject failed to complete the last 10 licks within 300 seconds, the session was terminated and a score of 300 was recorded. The times between licks 80–90 and 90–100 were recorded. The times between licks 90–100 were logarithmically transformed in order to allow analysis of variance.

Drug Injections

The appropriate drug, either 5 mg/kg chlordiazepoxide (CDP) dissolved in 1 ml of isotonic saline or an equivalent volume of saline, was administered IP 15 minutes prior to the start of preexposure and/or conditioning.

The animals were randomly assigned to one of 8 experimental groups in a 2×2×2 factorial design with main factors of stimulus preexposure (0, 40), drug in preexposure (placebo, CDP) and drug in conditioning (placebo, CDP).

RESULTS

A 2×2×2 ANOVA, with main factors of preexposure (0, 40), drug in preexposure (placebo, CDP) and drug in conditioning (placebo, CDP) carried out on the mean times to complete licks 80–90 in the absence of the CS, yielded no significant outcomes (all F's<1). The mean times in seconds to complete licks 80–90 in the eight groups were: Placebo-Placebo NPE—3.48; Placebo-Placebo PE—2.70; CDP-Placebo NPE—3.94; CDP-Placebo PE—3.61; Placebo-CDP NPE—4.30; Placebo-CDP PE—3.54; CDP-CDP NPE—4.08; CDP-CDP PE—2.55.

Figure 1 presents the mean log times to complete licks 90–100 in the presence of the CS for the preexposed and the

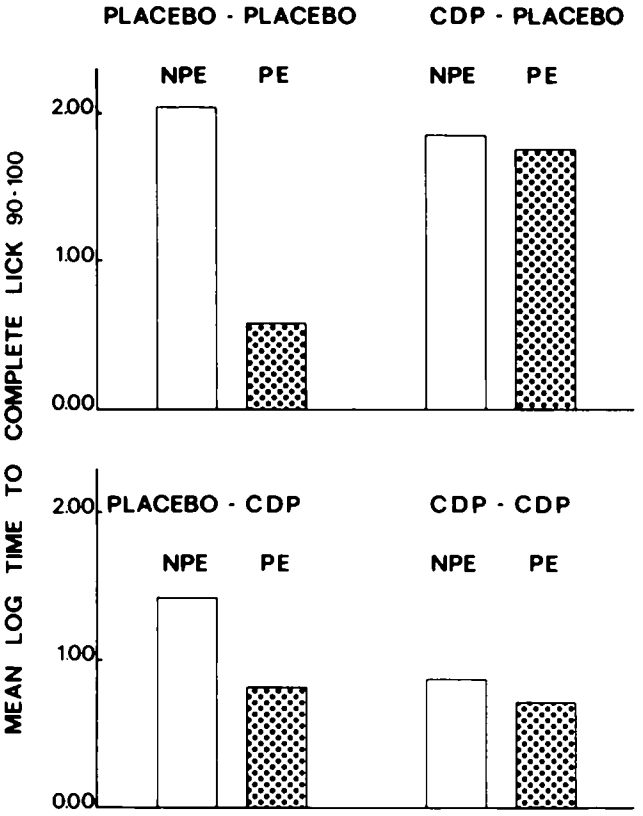

FIG. 1. Mean log times to complete licks 90–100 in the presence of the CS for the preexposed and nonpreexposed groups under four drug conditions in preexposure and conditioning: Placebo-Placebo; CDP-Placebo; Placebo-CDP; CDP-CDP.

nonpreexposed animals in the four drug conditions: placebo-placebo, CDP-placebo, placebo-CDP, and CDP-CDP. As can be seen, the administration of CDP during conditioning produced decreased suppression. This was supported by the significant main effect of Drug in Conditioning, $F(1,56)=13.17$, $p<0.001$. However, it can be seen that the drug-induced reduction in suppression was more pronounced in the groups which received CDP in preexposure (compare groups CDP-CDP with CDP-placebo) than in the groups which received placebo in preexposure (compare placebo-CDP with placebo-placebo). This was supported by the significant interaction of Drug in Preexposure × Drug in Conditioning, $F(1,56)=5.42$, $p<0.03$.

The presence of LI, i.e., lower suppression of the preexposed as compared to the nonpreexposed groups, was reflected in the significant main effect of Preexposure, $F(1,56)=17.55$, $p<0.001$. However, it can be seen in Fig. 1 that LI was present only in the groups which received placebo in preexposure. The two groups which received CDP in preexposure did not exhibit an LI effect. This was supported by the significant Drug in Preexposure × Preexposure interaction, $F(1,56)=6.88$, $p<0.02$. As can be seen in Fig. 1, the absence of LI in the CDP-placebo condition was exclusively due to increased suppression in the preexposed group. In other words, animals preexposed under CDP conditioned like their NPE counterparts. In the CDP-CDP condition, the absence of LI was accompanied by decreased suppression in both the NPE and the PE group, which was due to the presence of the drug in conditioning (see also suppression of placebo-CDP as compared to placebo-placebo). t-Tests, based on the error term of the ANOVA carried out to compare the mean log times of the nonpreexposed and the preexposed groups, revealed a significant LI effect in the placebo-placebo condition, $t(56)=4.86$, $p<0.01$, and in the placebo-CDP condition, $t(56)=2.03$, $p<0.05$, but not in the CDP-placebo condition, $t(56)=0.30$, $p>0.10$, or in the CDP-CDP condition, $t(56)=0.73$, $p>0.10$.

DISCUSSION

CDP administration during tone-shock conditioning, conducted off-baseline, markedly reduced animals' suppression to the tone in a subsequent licking test which was conducted without the drug. The administration of CDP during nonreinforced preexposure to the tone abolished the development of LI, i.e., drug-treated preexposed animals did not show reduced suppression as compared to drug-treated nonpreexposed animals. The above results cannot be attributed to state-dependent learning: LI was abolished both when animals were transferred from CDP in preexposure to no-drug in conditioning, and when both stages were carried out under CDP. In addition, LI was obtained in animals which were transferred from drug in conditioning to placebo in test.

Gray (9,10) argued that the disinhibition of response suppression by antianxiety drugs criticallly depends on the joint occurrence of an aversive UCS and an ongoing motor response, as in punishment-produced suppression or in on-baseline conditioned suppression. Conversely, antianxiety drugs do not affect classical conditioning of fear and consequently, are ineffective in reducing conditioned suppression established with an off-baseline procedure. Even when such a reduction occurs, it is due to a disruption of the expression, not the conditioning, of fear. Our results are inconsistent with this analysis: CDP disrupted the *acquisition* of conditioned fear in an *off-baseline* procedure. A similar, albeit lonely, result was reported by Scobie and Garske (36). The suppression of instrumental responding by a stimulus paired previously with shock is commonly attributed to the establishment of a central motivational state of fear or anxiety, which is independent of the direct skeletal CR's established during CS-US pairings (4, 23, 26, 34). Although BZD apparently do not affect direct responses conditioned to CS's paired with aversive US's (9,10), our results show that they do attenuate the conditioning of a central emotional reaction to a CS signalling shock. Indeed, this outcome is consistent with Gray's (10) general position that BZD block conditioned emotional states elicited by aversive stimuli but, contrary to Gray's position, indicates that such blockade encompasses classically conditioned emotional states established in the absence of instrumental contingencies.

The central outcome of this study is that CDP disrupts animals' ability to develop LI and that the locus of this disruption is the nonreinforced preexposure stage. Thus, CDP disrupts animals' ability to learn that a stimulus predicts no significant outcomes.

As for the mechanism underlying this impairment, two possibilities can be suggested. One derives from Gray's (10) argument that BZD attenuate the behavioral effects of stimuli associated with nonreinforcement. However, Gray limited his analysis to operant conditioning, and in this context, referred to nonreinforcement as an omission of expected reinforcement, emphasizing the emotional consequences (frus-

tration) of such an omission. Conversely, our results indicate that BZD-induced blockade of the behavioral impact of nonreinforcement is not dependent on a) its occurrence in the context of reinforcement and b) ongoing instrumental responding. Thus, BZD may in general disrupt the behavioral control/processing of stimuli signalling nonreinforcement. Another possibility, also raised by Gray (10), is that BZD impair attention to novel stimuli, thereby leading to poorer learning to such stimuli. All of the leading theoretical accounts of LI concur that repeated nonreinforced stimulus presentation results in a decrement in attention to this stimulus (6, 20, 24, 30, 35). Clearly, such decremental process is critically dependent on the initial attention to the stimulus. If, as Gray (10) argues, BZD block the initial attentional response, attentional decrement would not be expected to develop.

Whatever the mechanism whereby CDP impairs the acquisition of LI, it is clear that this impairment cannot be attributed to motivational/emotional/response effects of this drug, since learning in the preexposure stage takes place in the absence of reinforcement and in the absence of responding. Thus, BZD appear to produce a genuine interference with stimulus processing. This is consistent with Ljundberg *et al.*'s (18) recent conclusion that BZD impair animals' capacity to detect the significance of the information in the environment. Of major interest is the fact that exposure to nonreinforced stimuli under BZD leads to *increased* fear conditioning and response suppression in the subsequent encounters with such stimuli. This outcome has important clinical implications, since it suggests that BZD therapy may interfere with the behavioral mechanisms which allow to rob environmental events of their capacity to act as stressors as a result of previous, nonconsequential experience with such events.

Finally, it is important to emphasize the utility of the drug-no drug design as employed here for elucidating drug action. Amphetamine, similarly to BZD, abolishes LI but this abolition is *not* obtained when amphetamine is given in preexposure only. Thus, although both drugs exert a similar disruptive influence on LI, the locus of this influence differs: amphetamine disrupts the expression but not the acquisition of LI (43), whereas BZD disrupt the acquisition but not the expression of LI.

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