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BRIEF COMMUNICATION

Changes in the Amnesic and Aversive Properties of Avoidance Conditioning with Chlordiazepoxide[1]

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ESSMAN, W. B. *Changes in the amnesic and aversive properties of avoidance conditioning with chlordiazepoxide.* PHARMAC. BIOCHEM. BEHAV. 1(1) 125–127, 1973.–In two series of experiments the effects were investigated of chlordiazepoxide (CDP) upon acquisition of avoidance behavior in mice using footshock to establish an avoidance response and posttrial electroconvulsive shock (ECS) to retroactively disrupt the retention of that response. The relationship of either footshock and/or ECS during passive avoidance conditioning acquisition following prior drug treatment provided for reduced active avoidance response acquisition where such training was given following assessment of the retention of the passive avoidance behavior. The present experiments suggest that chlordiazepoxide interacts with acquired avoidance behavior such as to modify the amnesic properties of ECS. This may be due to a partial antagonism of the ECS induced retrograde amnesia, or to modification of active avoidance acquisition by drug treatment.

Chlordiazepoxide Avoidance behavior Retrograde amnesia

THE varied effects of chlordiazepoxide (CDP) upon appetetive and aversive behaviors in animals have been reviewed [6], and it was indicated that the differences observed, particularly in the mode of avoidance behavior, may be attributable to CDP action. Moreover, there has been the suggestion [5] that CDP provides for a state specificity upon which such behaviors may be dependent and for which they become state related. It would appear that both the observations and assumptions above are consistent with the view that the effects of CDP upon avoidance behavior, where performance factors may be excluded, relate to acquisition, fixation, or retrieval effects as probably dependent upon drug related changes in central synaptic activity. In the experiment reported here, it was our purpose to consider the effect of CDP upon passive avoidance conditioning in mice, the effect of postconditioning amnesic treatment upon such behavior, and measurements of the drug passive avoidance interaction as altered by an amnesic treatment upon active avoidance behavior.

The amnesic treatment utilized in this study was electroconvulsive shock (ECS), which has been shown to modify the status of several central putative transmitter systems [2], as well as producing a time dependent retrograde amnesia in experimental animals [1]. In previous experiments, we have indicated that the effects of drugs, amnesic agents, or environmental conditions upon passive avoidance behavior may not necessarily be reflected in differences in passive avoidance acquisition, as measured by one or more retention trials; it may, however, be more clearly indicated in the acquisition of active avoidance behavior in the same situation, where the animal actively avoids those stimuli which it has previously been trained to avoid passively [4]; the same basic technique was utilized in the present study, with CDP effects considered in interaction with the amnesic effects of postconditioning ECS.

METHOD

Eight groups of male CF-1S strain mice, matched for litter of origin, age (32 days), and weight (~28 g), were constituted with 20 animals each. Four groups were given IP injections of 4.0 mg/kg of CDP in 0.9% saline, while the remaining four groups were injected, IP, with an equivalent volume of the saline vehicle (Experiment 1). At 60 min following injection, all groups were given a single trial experience in an apparatus designed to provide for acquisition of a passive avoidance response [3]. The conditions used, each for one CDP treated group and one saline treated group were: (1) training footshock (FS), followed within 10 sec by electroconvulsive shock (ECS -- 10 mA, 200

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msec, 400 V, applied transcorneally); (2) no training footshock ($\overline{FS}$), followed within 10 sec by ECS; (3) FS with sham ECS ($\overline{ECS}$-application of the corneal electrodes without passage of current); (4) no FS ($\overline{FS}$), with sham ECS ($\overline{ECS}$). A testing trial was given 24 hr following training to assess both the incidence of passive avoidance acquisition and drug effect upon unconditioned behavior, It may be noted that the drug treatment did not alter the susceptibility of the mice to a full clonic-tonic convulsion induced by ECS which occurred in all mice given ECS, and it did not affect footshock threshold, as inferred from the onset of a motor response to shock onset in drug treated mice.

In a separate experimental series (Experiment 2) groups of mice (N = 20) were injected with CDP (4.0 mg/kg) or saline (0.9%) and provided with the passive avoidance training conditions, as previously described. These animals were treated with either CDP or saline, in a cross-matched design, 60 min prior to passive avoidance testing and active avoidance training; i.e., saline treated mice, on passive avoidance training, were given either saline or CDP prior to testing and active avoidance training, and CDP treated mice were then again given either CDP or saline.

RESULTS AND DISCUSSION

As may be expected among the saline treated mice, those trained with FS, and not given posttraining ECS, showed a high incidence (90%) of passive avoidance response retention. The percent incidence of active avoidance responses measured over the training series has been summarized in Fig. 1 for each of the prior conditions of drug treatment or passive avoidance training. It is apparent that decreased active avoidance acquisition was associated with those treatments in which either FS or ECS were given on passive avoidance training, or neither was used.

A high incidence of passive avoidance acquisition, as provided by FS with $\overline{ECS}$ was also consistent with a reasonable level of active avoidance responding; i.e., passive avoidance acquisition facilitated active avoidance. Under the control conditions of the experiment, the active avoidance data also served as an index of reliability for the stability of the amnesic effect of posttraining ECS, in that if there were residual retention of an avoidance response, this would likely be reflected in an improved rate of active avoidance acquisition; this was not observed for the FS-ECS group under saline treatment conditions.

The groups treated with CDP prior to passive avoidance training showed, for some of these conditions, active avoidance acquisition consistent with that observed for the FS-$\overline{ECS}$ group (a level of active avoidance responding, identical to that of saline controls, as would be expected from the conditions of the experiment); it would appear that either dual stimulation (FS-ECS) or no shock stimulation ($\overline{FS}$-$\overline{ECS}$), presented during the training experience after CDP treatment, provided for either sufficient preservation of the aversive properties of the situation or absence of any generalizable conflict cues so as to augment the active avoidance behavior shown under such conditions.

The results of drug crossover procedure (Experiment 2) were not essentially different from those previously observed, in that CDP treatment prior to passive avoidance testing and active avoidance training provided for an increased incidence of active avoidance responses ($\chi^2=6.66$; $p<0.01$) comparable to that which occurred

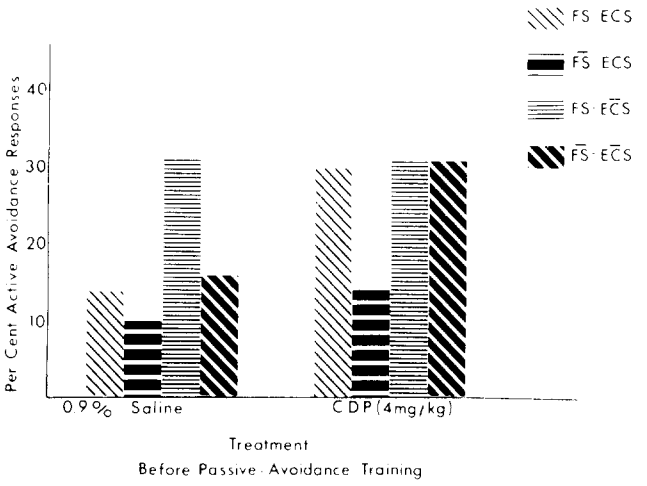

FIG. 1. Percent incidence of active avoidance responding as a function of prior conditions of drug treatment and conditions of passive avoidance training.
FS-ECS - Training trial footshock, with posttrial ECS.
$\overline{FS}$-ECS - No training trial footshock, with posttrial ECS.
FS-$\overline{ECS}$ - Training trial footshock, with no posttrial ECS.
$\overline{FS}$-$\overline{ECS}$ - No training trial footshock, with no posttrial ECS.

when no prior footshock or ECS were given. These findings indicate that the effects of CDP in the present experimental paradigm interact with the amnesic effects of ECS or modify situational aversive cues when the effects of the drug are manifest during passive avoidance training.

The same effect was not observed for active avoidance acquisition, nor was it appropriate to suggest drug state dependency or specificity. The contribution of the single passive avoidance training trial, with either its preceding drug treatment or its consequent ECS effect, to the acquisition of an active avoidance response seems further established from these results.

It would seem appropriate to note that the present results do not find a ready explanation in a state dependency hypothesis or in any simple response-specific effect of CDP. It appears likely that the effects of CDP, as reflected in the data from the present experiments, are two-fold: one action may be in the partial antagonism of the ECS induced retrograde amnesia of avoidance training, such that the active avoidance training serves as a reminder experience for a more rapid reinstatement of the aversive properties of the shock environment. The absence of FS or ECS, in the passive avoidance paradigm, obviously did not provide for any passive avoidance acquisition under saline or drug treatment conditions. The higher rate of active avoidance acquisition by mice previously given CDP with no FS or ECS may reflect a drug conferred generalized aversion to a darkened chamber in which no discrete positive or negative cues prevail. No actual support for this possibility can be derived from the present data. It does seem apparent that CDP active during passive avoidance conditioning interacts with the effects of ECS and relates to situational cues relevant for the expression of related active avoidance behavior.

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