Pharmacology Biochemistry and Behavior, Vol. 1, pp. 277–283. ANKHO International Inc., 1973. Printed in the U.S.A.

An Investigation on the Nature of Continuous Avoidance Deficits: Differential Response to Chlordiazepoxide Treatment

GIORGIO BIGNAMI AND LUIGI DE ACETIS

Department of Therapeutical Chemistry, Istituto Superiore di Sanità, Viale Regina Elena 299 00161 Roma, Italy

(Received 12 May 1972)

BIGNAMI, G. AND L.DE ACETIS. *An investigation on the nature of continuous avoidance deficits: differential response to chlordiazepoxide treatment.* PHARMAC. BIOCHEM. BEHAV. 1(3) 277–283, 1973.–Four groups of 18 rats each were given 12 30-min sessions of lever press avoidance training with long and equal response–shock (R-S) and shock–shock (S-S) intervals (30 sec) and a high shock intensity (2 mA for 2 sec), but with different stimulus conditions. A 2x2 design was used, with (A) light on versus light off as CS in the last 10 sec of R-S, and (B) different versus equal stimulus conditions in R-S and S-S (respectively CS on versus CS off in S-S). Each group was then subdivided into two subgroups receiving either placebo or chlordiazepoxide for 12 additional sessions, starting 23 days after the last pretraining session (20 mg/kg s.c. 30 min before testing for the first 6 sessions and 40 mg/kg for the remaining 6 sessions). Finally, all animals were given 3 additional series of 6 or 5 sessions each without treatment, starting respectively 2, 30 and 58 days after the last drug or placebo session. The data confirmed that continuous avoidance tasks with long and equal R-S and S-S intervals and strong punishment are difficult to learn. The use of light off as CS and the use of CS off in S-S led to a further retardation of avoidance learning. All untreated groups, except the one with light on as CS and CS on in S-S, still received an average of about 70% of the scheduled shocks after a total of 41 sessions (20.5 hr of training). A clear-cut drug facilitation was obtained in the schedule with light off as CS and CS on in S-S, while slight or even opposite effects were obtained in the other schedules. Furthermore, the very low asymptotic performance in the untreated group with light off as CS and CS on in S-S permitted the demonstration of a significant carry-over effect in this schedule, i.e., a much higher performance in previously treated, than in previously untreated animals during the posttreatment period. The above results were compared with those of limited tests carried out with amphetamine and scopolamine after the completion of the main experiment, showing a wider range of facilitating effects with the latter drugs, than with chlordiazepoxide. These results may be taken as evidence that chlordiazepoxide lacks general stimulant and/or response-disinhibiting properties. Therefore, the drug allows the emission of available responses suppressed by punishment, but not of responses not learned due to the lack of appropriate feedbacks in the early phases of training.

Rat Lever press avoidance Continuous discriminated avoidance CS type Response-CS relationships Response feedbacks Response suppression Instrumental learning deficit Chlordiazepoxide Amphetamine Scopolamine

---

SEVERAL studies have indicated that antianxiety agents of the barbiturate and benzodiazepine types can exert widely differing effects on active avoidance acquisition and performance, depending on several experimental conditions (see Discussion and References in [5]). In particular, recent work on rats pretrained in continuous avoidance tasks has shown an interaction between drug treatment and performance baseline, i.e., some avoidance impairment (increase in shock rate) in animals with low control shock rates, and a marked facilitation (decrease in shock rate) in animals with high control shock rate [5, 16, 23].

In a previous paper it was suggested that the facilitating action of the above drugs in low-avoidance animals could not be ascribed to a general response-enhancing or response-disinhibiting effect (amphetamine-like or scopolamine-like), since the marked reduction of shock rate was often obtained without any increase in overall response rate [5]. It was also hypothesized that barbiturates and benzodiazepines facilitated active avoidance by attenuating punishment effects, i.e., by the same mechanism proposed to account for the effects of these drugs on other behaviours suppressed by punishment [10, 18, 21], on fixated behaviours [14], and on frustration reactions [15, 19, 20]. In fact, it is well-known that in certain avoidance tasks, and particularly in some shuttle box and lever press situations, response suppression by punishment (via conditioned emotional responses; via passive avoidance responses due to bidirectionality and/or adventitious negative reinforcement) can prevail on active avoidance responding.

The study on chlordiazepoxide (CD) reported below was carried out with two main purposes. The first was to extend the investigation on rate-dependent effects from within-task

comparisons [5] to between-task comparisons. For this purpose the experiment used rats pretrained in continuous avoidance schedules yielding lower average rates of acquisition, lower asymptotes, and a higher proportion of nonlearners than those used previously. Without modifying the basic lever press task (i.e., using long and equal response-shock and shock-shock intervals---respectively R-S and S-S---, a visual warning signal, and shock of high intensity and fixed duration) the influence of two retarding contingencies and their interaction with drug treatment were investigated. These contingencies were (A) light off instead of light on as CS, presumably enhancing the response suppression mentioned above (see Experiment 1 in [6]), and (B) CS termination not only after an animal's response, as in previous studies in this laboratory [5, 6, 12, 16], but also at the time of shock termination in the absence of an animal's response. With shock of fixed duration and R-S = S-S the latter contingency virtually eliminates any difference in external stimulus conditions as between cycles in which the lever has been pressed during shock and cycles in which the response criterion has not been met. Since exteroceptive response feedbacks play an essential role in lever press tasks [8], the equalization of stimulus conditions in R-S and S-S may well superimpose a true deficit of instrumental learning to the suppression deficit which prevents the emission of available responses. Therefore, it was hypothesized that, if CD acts mainly on the latter phenomenon, it should be unable to compensate the deficit caused by equal stimulus conditions in R-S and S-S.

The second purpose of the study was to investigate possible carry-over effects, i.e., whether or not the drug facilitation observed in certain instances could be maintained in the posttreatment period. Facilitating carry-over effects after antianxiety treatment may have a similar meaning in the case of active avoidance as in the case of fixation prevention [14] and of conflict solution [21]. Basically, if a treatment attenuating a response bias produced by aversive experience is given for an extended period of time, allowing the repeated emission of adaptive responses, ample room should exist for the transformation of a transient performance effect into a more permanent adaptive change in the behaviour of the organism. As a general rule, previous experiments on avoidance with treatment sessions separated from each other by two or more control sessions showed a return to a high shock rate after the waning of drug effects [5, 16, 23]. On the other hand, a pilot experiment with more prolonged CD treatment showed in some animals a permanent change from a high to a low shock baseline, persisting after drug withdrawal [17]. The latter experiment, however, lacked appropriate controls for occasional shifts from low to high avoidance performance after long periods of training. Therefore, the last part of the present study attempted to measure long-term differences in avoidance levels between untreated rats and rats having had a two-week drug experience after an initial period of training.

METHOD

Animals

Adult male albino rats of an outbred strain maintained at Istituto Superiore di Sanità (Wistar-derived S. M. colony, [4]) were used.

Apparatus

Six one-lever avoidance boxes connected to conventional programming and recording equipment (Grason-Stadler Co., Inc., West Concord, Mass., U.S.A.) were used. Each chamber was enclosed in an insulating chest equipped with a fan for ventilation and background noise.

Procedure

Basic avoidance task. A continuous avoidance task with 30-min sessions was used (see diagram in Fig. 1). When an animal did not respond, scrambled a.c. footshocks of 2 mA (nominal) for 2 sec were administered at 30-sec intervals (S-S). Each lever press was followed by a shock-free period of 30 sec (R-S) with a warning signal (CS, see below) in the last 10 sec. The R-S interval was thus subdivided into a R-CS portion (response-CS onset, 20 sec) and a CS-S portion (CS onset-shock, 10 sec). Therefore, a lever press postponed both CS and shock if it took place within 20 sec after a previous response (R4 and R5 in Fig. 1), while it terminated the CS and postponed shock if it took place after CS onset (R3 in Fig. 1). Nonavoided shocks had a fixed duration, i.e., responses during shock administration (R2 in Fig. 1) started a new R-S, but did not reduce shock duration.

The four schedules. The experimental chamber was in total darkness except when the 10-W house light located at the upper right-hand corner of the chamber front (i.e., at about 15 cm from the lever) was turned on according to a particular schedule. The four schedules were obtained by means of a 2x2 design, with CS type and stimulus conditions in S-S as the criteria of classification. The CS consisted either of the turning on of the house light (CS light on, A1 in the figures) or of the turning off of the same light (CS light off, A2 in the figures). The stimulus conditions during S-S were varied as follows. In two out of the four schedules the CS remained on during S-S, i.e., it could be extinguished only by a response starting a new R-S (CS on in S-S, B1). In the other two schedules the CS terminated not only after a lever press, but also at the end of shock in the absence of an animal's response, and was turned on again 10 sec before the next shock (CS off in S-S, B2; used as an abbreviation of "CS off in the first part of S-S"). As shown by Fig. 1, the B1 and B2 conditions, given a certain CS type (A1 or A2), are different only as long as an animal does not respond. A1B1 and A2B1 become identical respectively to A1B2 and A2B2 when an animal gives at least one response during (or before) each scheduled shock (identical stimulus conditions in R-S). In summary, the four schedules were as follows: (A1B1), CS light on, CS on in S-S; (A1B2), CS light on, CS off in S-S; (A2B1), CS light off, CS on in S-S; (A2B2), CS light off, CS off in S-S.

Pretraining period. Seventy-two naive rats were subdivided at random between the four above schedules and trained for 12 sessions (one per day, except for a one-day rest after the sixth session). The design was balanced as concerns the assignment of animals belonging to different groups to boxes and times of day.

Treatment period. Twenty-three days after the end of the pretraining period (i.e., on Day 36 of the experiment) each group was subdivided into two equal subgroups of nine rats each and given 12 additional sessions in either the drug or the placebo state (one per day, except for a one-day

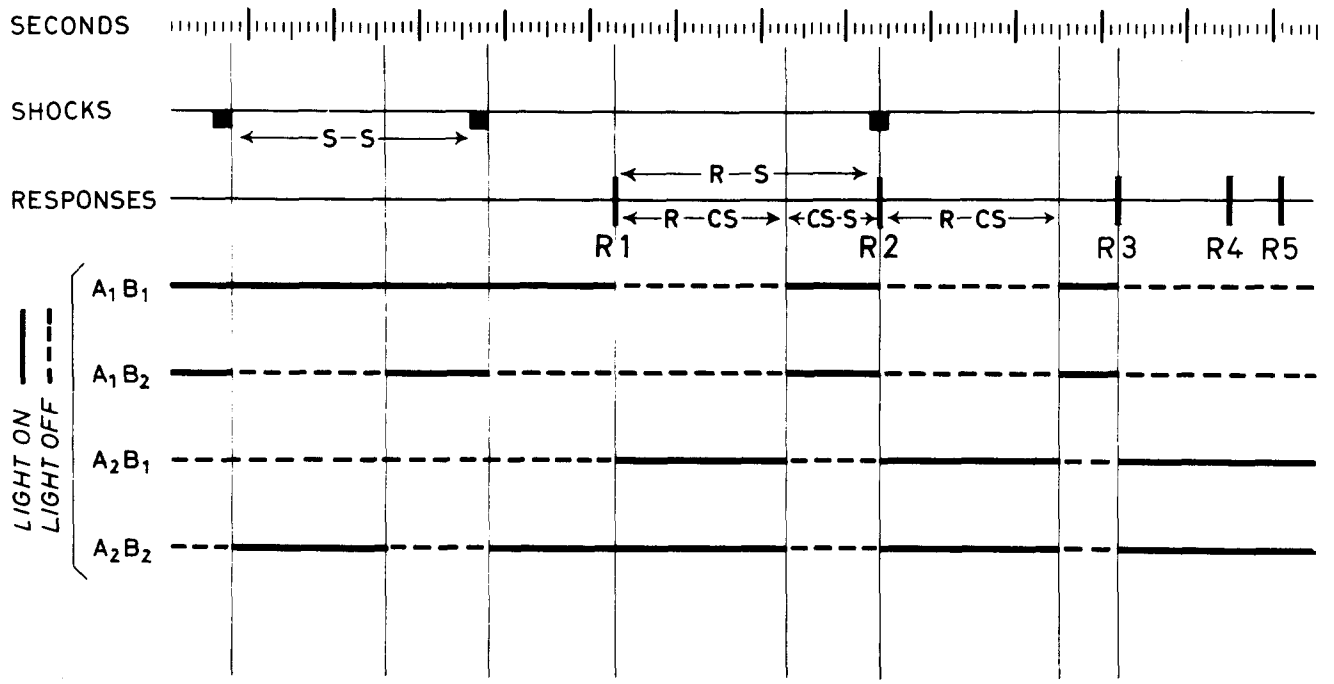

FIG. 1. Diagram illustrating the continuous discriminated avoidance schedules used in the experiment. Shock-Shock (S-S, 30 sec), response-CS (R-CS, 20 sec), CS-shock (CS-S, 10 sec), and response-shock intervals (R-S = R-CS + CS-S = 30 sec) were the same in all schedules. Stimulus conditions (light on, continuous line; light off, broken line) varied depending on the schedule and on the animal's responses. A1, light on as CS. A2, light off as CS. B1, CS on during the whole S-S (CS on in S-S). B2, CS turned off at the end of shock in the absence of a response, and turned on again 10 sec before the next shock (CS off in S-S). Remark that A1B1 differs from A1B2 and that A2B1 differs from A2B2 as long as an animal does not respond (see initial S-S to the left), or responds only after shock termination (R1). On the other hand, A1B1 = A1B2 and A2B1 = A2B2 when a response takes place either during shock (R2), or during the CS-S interval (R3), or during the R-CS interval (R4, R5).

rest after the sixth session). Drug treatment consisted of CD dissolved in distilled water and given sc 30 min before each session, the dose being 20 mg/kg per day for the first six sessions and 40 mg/kg for the remaining sessions.

Measurement of asymptotic performance. All animals were given three additional testing series consisting respectively of six, six and five sessions, and starting respectively 2, 30 and 58 days after the last drug or placebo session (i.e., on Days 50, 78 and 106 of the experiment). No treatments were given during this period.

Analysis of data. Schedule effects were measured by 2x2 analyses of variance (first 12 sessions) and by 2x2x2 analyses (following sessions), both on individual sessions and on blocks of sessions. Depending on the results of Bartlett tests, either raw or transformed scores were used (mainly arcsin transformed data in the case of shock rates and logarithm transformed data in the case of response rates). Treatment and carry-over effects were measured by two series of 2x2x2 analyses on shock and response difference scores [11], i.e., on data corrected to account for differences in the baselines before the beginning of drug or placebo treatments. The various scores for each animal were obtained by using as constant subtrahend the shock rate (or, respectively, the response rate) in the last pretraining session, and as minuends shock and response rates in Sessions 36, 41 and 48 from the treatment period, and in Sessions 56, 83 and 110 from the posttreatment period (Figs. 2 and 3). These scores were corrected to eliminate negative numbers whenever transformations were needed to eliminate a variance heterogeneity. It was assumed that a main effect of previous treatment or an interaction between previous treatment and (a) schedule factor(s) in the analyses concerning the posttreatment period would constitute statistical evidence for the existence of carry-over effects [6].

RESULTS

Schedule effects. The data on the pretraining sessions and the data from the untreated groups in all following sessions (Figs. 2 and 3, solid lines) indicate that only the rats with CS light on and CS on in S-S (A1B1), although learning slowly, reached relatively high levels of avoidance performance in the absence of CD treatment. All other untreated groups showed much lower levels of shock avoidance and lower response rates.

None of the analyses on shock scores in the first two weeks of the experiment showed significant effects. All subsequent analyses pointed out a significant effect of the stimulus conditions in S-S (factor B; e.g., in block 106-110 of Fig. 2 $F=10.60$, df 1/64, $p<0.005$). On the other hand, no evidence for a significant effect of the other schedule factor (CS light on versus CS light off, factor A) was obtained.

The analyses on response scores showed a significant effect of CS type (CS light on versus CS light off, factor A) in the first two of the post-treatment session blocks (e.g., in block 78–83 of Fig. 3 $F=4.18$, df 1/64, $p<0.05$). A significant effect of stimulus conditions in S-S (factor B), similar to that observed in the analyses on shock scores,

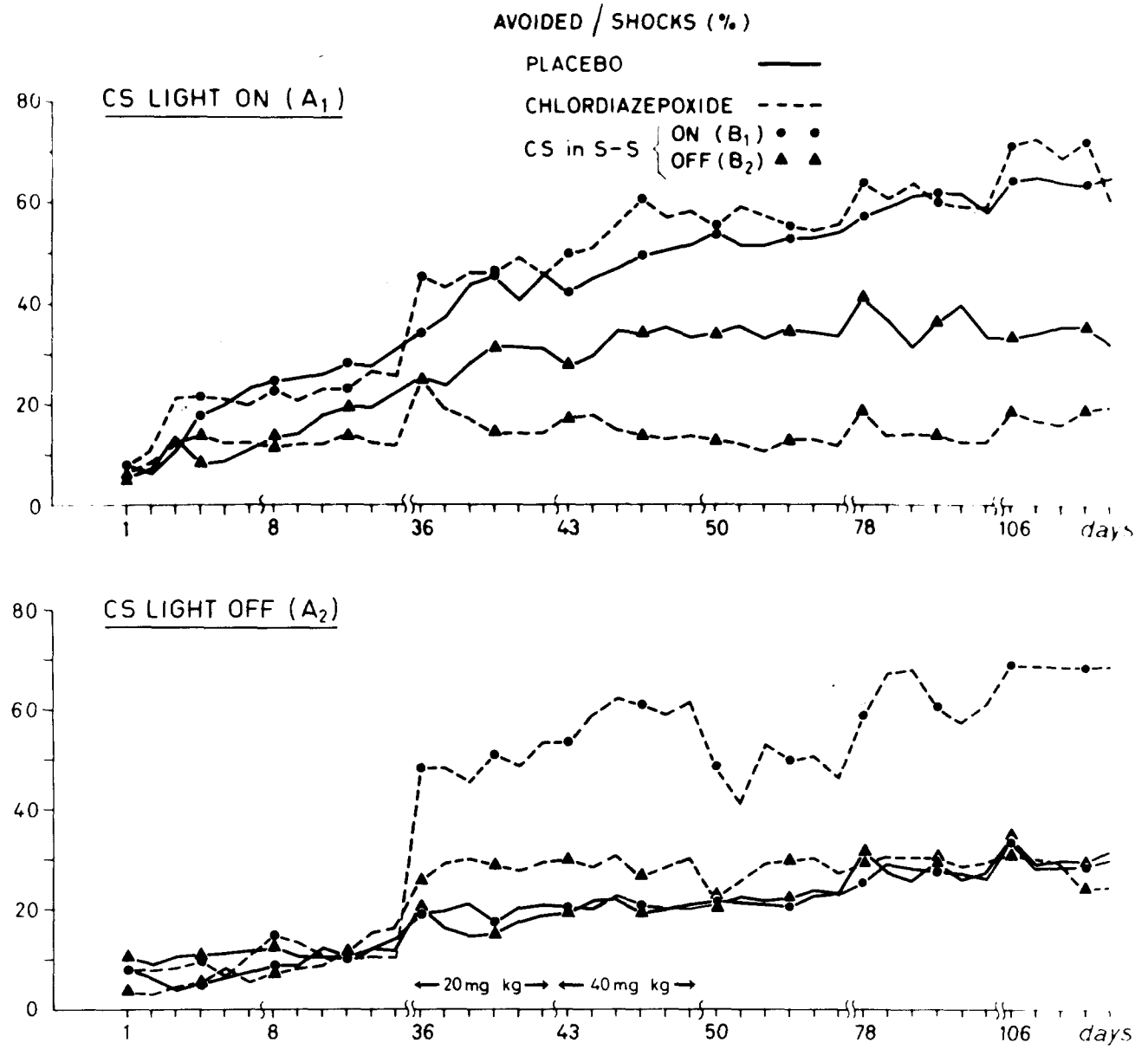

FIG. 2. Effects of CS type (light on, A1; light off, A2), of stimulus conditions in shock-shock intervals (CS on in S-S, B1; CS off in S-S, B2), and of chlordiazepoxide treatment on the acquisition of continuous lever press avoidance. Each point indicates a 30-min session. The figures at the bottom of the graphs, corresponding to the days from the beginning of the experiment, allow to calculate the intervals between the various phases (e.g., 23 days between the last pretraining session and the first treatment session). Chlordiazepoxide (20 mg/kg for six days and 40 mg/kg for six other days) or placebo were administered 30 min before sessions.

prevailed in most of the session blocks after the initial two weeks of pretraining (e.g., in the last block 106–110 $F=6.44$, df 1/64, $p<0.025$).

Treatment and carry-over effects. Fig. 2 shows that CD caused a marked increase in the frequency of avoided shocks in the schedule with CS light off and CS on in S-S (A2B1). Except for a temporary performance drop after drug discontinuation such facilitation was carried over to the post-treatment period. The effects of CD in the other schedules were slight or even in the opposite direction. In fact, the analyses on shock difference scores (see Method) showed a significant interaction between treatment and stimulus conditions in S-S (factor B) both in the treatment period (e.g., for the difference scores of Day 48 $F=9.48$, df 1/64, $p<0.005$) and in the posttreatment period (e.g., for the difference score of Day 110 $F=7.20$, df 1/64, $p<0.01$).

Median response rates were initially enhanced by CD in the schedules with CS on in S-S (A1B1 and A2B1), but not in the others (Fig. 3). However, the first of the analyses on difference measures (those of Day 36) revealed a significant effect of the drug treatment ($F=5.87$, df 1/64, $p<0.025$) rather than a significant interaction between treatment and stimulus conditions in S-S. Later on, the variability in response rate became very large in the five groups which

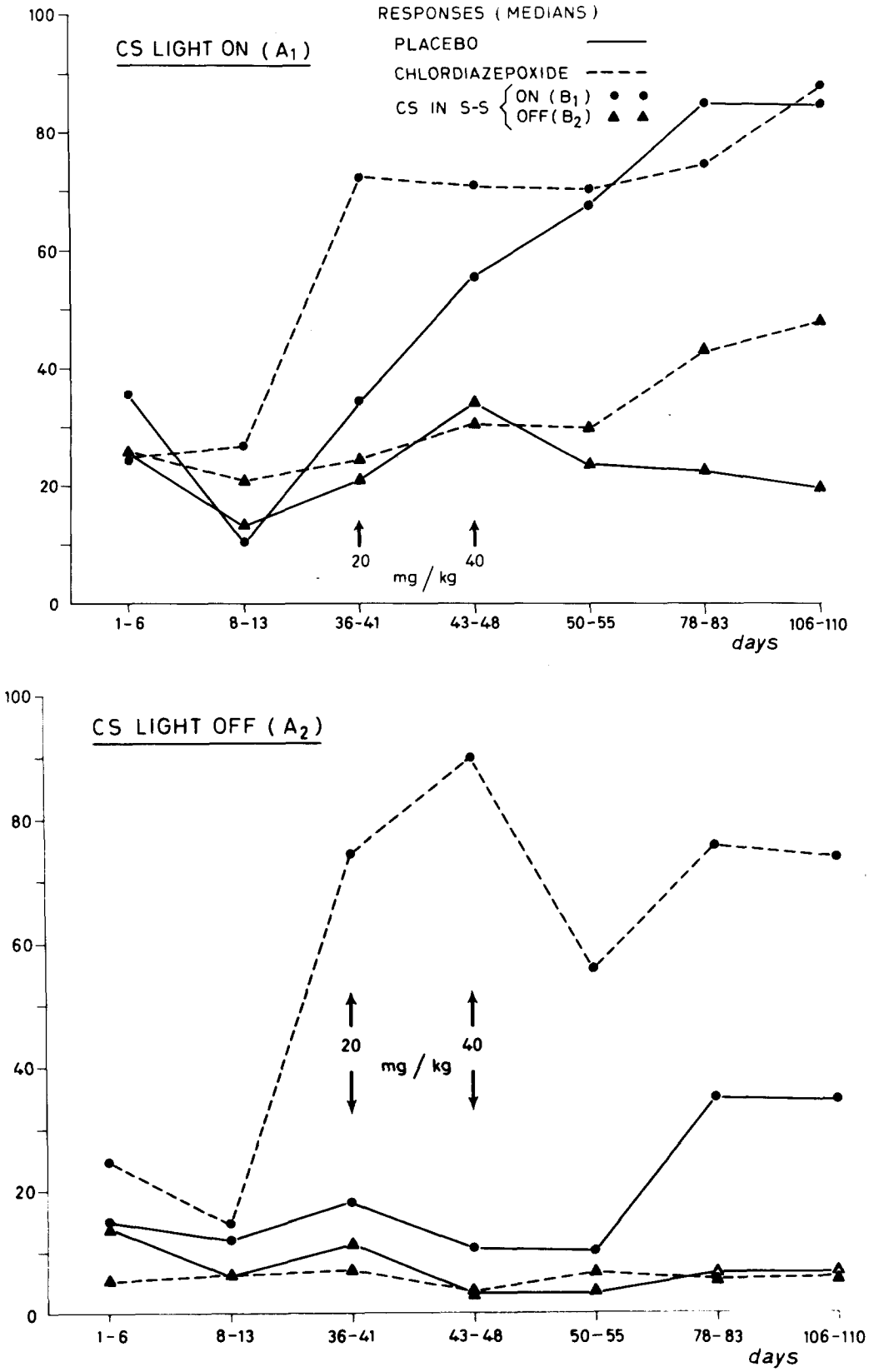

FIG. 3. Median daily response rates in successive session blocks (for abbreviations and other explanations see Figs. 1 and 2).

went on receiving most of the scheduled shocks. The analyses on response difference measures either gave non significant results, or could not be carried out due to a highly significant heterogeneity of variance not attenuated by several transformations.

DISCUSSION

Schedule effects. The data from the untreated groups of animals further confirm that continuous lever press avoidance with long and equal R-S and S-S and strong punishment is learned only with difficulty or not at all [22]. Untreated rats exposed to the schedule with light on as CS and CS on in S-S learned even more slowly than the corresponding control animals in previous acquisition experiments [6, 12]. This postponed, but did not prevent the appearance of one of the expected schedule effects, namely, a further impairment due to CS termination at the end of shock in the absence of an animals's response (CS off instead of CS on in S-S; see further discussion in the following section). The impairing effect of a light off CS was shown to be significant in the analyses on response rates, but not in those on shock rates. This may be ascribed at least in part to the fact that the present experiment used four schedules with smaller groups of untreated and treated animals in each, while the previous experiment used larger groups for a direct comparison of light on and light off as CS, with CS on in S-S in either case (Experiment 1 in [6]).

Interactions between treatment and schedules. A discussion of the pharmacological results is in order here, since a unitary explanation should be found accounting both for the nature of avoidance deficits in different conditions, and for the interactions between treatment and schedules. The results show that rate-dependent drug effects, although accounting for a significant portion of the variability in response to CD within a given avoidance schedule [5, 16, 23], cannot account for the variation observed across schedules. Rats with similar low performances showed a large facilitation in one of the stimulus conditions (light off as CS and CS on in S-S), but were unaffected or even slightly retarded in both tasks with CS off in S-S. The effect of other facilitating agents on avoidance has also been shown to be rate-dependent. However, several experiments with scopolamine and shuttle-box tasks have pointed out that animals with similar base lines in different schedules can show different, or even opposite types of drug effects [6,9]. These data suggest that, even when similar rate-dependent effects are found in different schedules (e.g., with CD [24]), rate-dependence per se does not constitute an explanation. One should rather attempt to understand the mechanisms underlying a given high or low rate and drug effects thereon.

As concerns the CD facilitation in the schedule with CS on in S-S and light on as CS, the effect was less marked than that previously observed in a larger group of animals having stabilized at a high shock rate [5]. The latter had been given a much longer series of sessions prior to the beginning of benzodiazepine or barbiturate treatments, which suggests that the size of the drug effect may depend to some extent on the phase in which an antianxiety agent is administered. In fact, work just completed has shown that the effect of CD in the schedules which allow a facilitating action (i.e., those with CS on in S-S) are minimal or absent for several weeks when the treatment is started at the beginning of training.

The absence of any marked change in drug effect when the CD dose was doubled confirms previous results, i.e., that 20 and 40 mg/kg of the drug have approximately similar effects on continuous avoidance [5]. (In the present experiment, the dose was increased after several days of treatment simply to make sure that facilitating effects were not missed in the animals unaffected by the lower dose). Furthermore, state dependence can be ruled out in the present experiment, carried out with tasks not learned or incompletely learned at the time of drug treatment. The large CD facilitation observed in one schedule already during the first treatment session, and the temporary performance drop after treatment withdrawal are clearly in favour of a performance effect and against state-dependence.

Mechanisms of drug action and nature of avoidance deficits. The interactions discussed above appear to confirm the main hypotheses put forward in the Introduction, namely, (1) that different mechanisms underly apparently similar deficits in continuous avoidance with the same R-S, S-S and shock parameters, but with different stimulus conditions; and (2) that the facilitation previously observed with antianxiety agents cannot be ascribed to a general response enhancement or disinhibition. In particular, different mechanisms appear to underly the retarding effects of a light off CS (with the more favourable CS on in S-S contingency) and those of a lack of an appropriate exteroceptive feedback for a response with a low status in the defensive repertoire [8]. If the analysis of the two deficits outlined in the Introduction is correct, one should conclude that CD can attenuate the suppression of an already available repertoire, but not compensate for a genuine absence of instrumental learning.

The above conclusions are supported by some additional data on amphetamine and scopolamine. These need not be reported in detail, since it is well known that these agents can reverse a wide variety of active avoidance deficits caused by response factors and/or other schedule factors (for discussion and references see [3, 4, 7, 13]). Several tests were carried out with amphetamine and scopolamine after the completion of the CD experiment described above, using untreated animals and animals which had failed to show a CD facilitation. Both drugs were able to enhance response rate and reduce shock rate in several low-avoidance animals, independently of schedule. This difference between amphetamine and scopolamine, on one side, and CD, on the other, suggests that enhancement of response probability through hyperactivity and/or response disinhibition can reverse a wider variety of avoidance deficits than a selective attenuation of the suppressant effects of punishment. Once a minimal response rate is established, schedules with different or similar conditions in R-S and S-S (CS on versus CS off in S-S) become indistinguishable (see Fig. 1), since the stimulus conditions in R-S are the same within any given CS type. Therefore, a performance effect due to response enhancement and/or disinhibition, different from that obtained with CD, can create conditions which allow to overcome a schedule-induced deficit in instrumental learning.

The data on scopolamine reported in [6] and those on CD reported above and in [5] point out another important difference between these agents. When certain continuous lever-press tasks sensitive to both drugs are considered (i.e., those with R-S = S-S, a high shock intensity, and CS on in S-S), one finds that scopolamine, but not CD is active in the

early acquisition phases. On the other hand, the acquisition of other tasks such as shuttle box avoidance can be accelerated both by antimuscarinics and by benzodiazepines and barbiturates (references in [4, 5, 6, 7]). It appears therefore that the time at which a CD attenuation of response suppression can reflect itself in an avoidance facilitation depends on the relative ease with which a given item of the behavioural repertoire is selected as the appropriate avoidance response in a given species [8].

The carry-over effects observed in the schedule showing a marked CD performance enhancement indicate that a prolonged pharmacological attenuation of the consequences of aversive experience can lead to a permanent change towards more adaptive behaviour. A carry-over of avoidance facilitation has also been found after the administration of amphetamine and scopolamine [2,6]. Furthermore, exposure to shock in the amphetamine state has been shown to facilitate active avoidance acquisition at a later time (in the absence of treatment) [1]. Therefore, one may tentatively conclude that the mechanism by which a drug facilitates avoidance or modifies the organism's response to punishment is not the critical factor for the obtention of carry-over effects.

REFERENCES

1. Anisman, H. and T. G. Waller. Effects of methamphetamine and shock duration during inescapable shock exposure on subsequent active and passive avoidance. *J. comp. physiol. Psychol.* **77**: 143–151, 1971.
2. Barrett, R. J., N. J. Leith and O. S. Ray. Permanent facilitation of avoidance behavior by *d*-amphetamine and scopolamine. *Psychopharmacologia* **25**: 321–331, 1972.
3. Bignami, G. Anticholinergic agents as tools in the investigation of behavioral phenomena. *In: Proceedings of the Vth International Congress of the Collegium Internationale Neuropsychopharmacologicum, Washington, D. C., 1966,* edited by H. Brill. Amsterdam: Excerpta Medica, I. C. S. 129, 1967, pp. 819–830.
4. Bignami, G., L. Amorico, M. Frontali and N. Rosić. Central cholinergic blockade and two-way avoidance acquisition: the role of response disinhibition. *Physiol. Behav.* **7**: 461–470, 1971.
5. Bignami, G., L. DeAcetis and G. L. Gatti. Facilitation and impairment of avoidance responding by phenobarbital sodium, chlordiazepoxide and diazepam - The role of performance base lines. *J. Pharmac. exp. Ther.* **176**: 725–732, 1971.
6. Bignami, G. and N. Rosić. Acquisition and performance effects of scopolamine and of treatment withdrawal in avoidance situations. *Physiol. Behav.* **8**: 1127–1134, 1972.
7. Bignami, G. and N. Rosić. The nature of disinhibitory phenomena caused by central cholinergic (muscarinic) blockade. In: *Advances in Neuropsychopharmacology. Proceedings of the Symposia held at the VIIth Congress of the Collegium Internationale Neuropsychopharmacologicum, Prague, 1970,* edited by O. Vinař, Z. Votava and P. B. Bradley. Amsterdam: North Holland, 1972, pp. 481–495.
8. Bolles, R. C. Species-specific defense reactions. In: *Aversive Conditioning and Learning,* edited by F. R. Brush. New York: Academic Press, 1971, pp. 183–233.
9. Carro-Ciampi, G. and G. Bignami. Effects of scopolamine on shuttle-box avoidance and go-no go discrimination: response - stimulus relationships, pretreatment baselines, and repeated exposure to drug. *Psychopharmacologia* **13**: 89–105, 1968.
10. Cook, L. and R. T. Kelleher. Effects of drugs on behavior. *A. Rev. Pharmac.* **3**: 205–222, 2963.
11. Edwards, A. L. *Experimental Design in Psychological Research.* New York: Holt, Rinehart and Winston, Revised Ed., 1960.
12. Escaleras, R. and G. Bignami. Azione facilitante della scopolamina sull'acquisizione di un condizionamento continuo di salvaguardia nel ratto: effetti reversibili ed effetti permanenti. *Ann. Ist. Super. Sanità* **3**: 515–527, 1967.
13. Essman, W. B. Drug effects on learning and memory processes. *Adv. Pharmac. Chemother.* **9**: 241–330, 1971.
14. Feldman, R. S. The mechanism of fixation prevention and "dissociation" learning with chlordiazepoxide. *Psychopharmacologia* **12**: 384–399, 1968.
15. Freedman, P. E. and A. J. Rosen. The effects of psychotropic drugs on the double alley frustration effect. *Psychopharmacologia* **15**: 39–47, 1969.
16. Gatti, G. L. and G. Bignami. Effects of chlordiazepoxide, diazepam, phenobarbital, meprobamate and phenytoin on continuous lever-pressing avoidance with or without warning stimulus. In: *The Present Status of Psychotropic Drugs. Proceedings of the VIth International Congress of the Collegium Internationale Neuropsychopharmacologicum, Tarragona, 1968,* edited by A. Cerletti and F. J. Bové. Amsterdam: Excerpta Medica, I. C. S. 180, 1969, pp. 255–256.
17. Gatti, G. L., G. Bignami and W. Pinto-Scognamiglio. Analogie e differenze fra gli effetti delle benzodiazepine e dei barbiturici nel ratto. Interazioni fra fattori organismici e trattamento. In: *Atti della Tavola Rotonda sulle Associazioni Psicofarmacologiche, Il Ciocco, 1970,* edited by F. Di Carlo and G. Germano. Pisa: Pacini Mariotti, 1971, pp. 49–61.
18. Geller, I. Use of approach-avoidance behavior (conflict) for evaluating depressant drugs. In: *Psychosomatic Medicine,* edited by J. H. Nodine and J. H. Moyer. Philadelphia: Lea & Febiger, 1962, pp. 267–274.
19. Gray, J. A. Sodium amobarbital and effects of frustrative nonreward. *J. comp. physiol. Psychol.* **69**: 55–64, 1969.
20. Rosen, A. J. and R. E. Tessel. Chlorpromazine, chlordiazepoxide, and incentive shift performance in the rat. *J. comp. physiol. Psychol.* **72**: 257–262, 1970.
21. Sherman, A. R. Therapy of maladaptive fear-motivated behavior in the rat by the systematic gradual withdrawal of a fear-reducing drug. *Behav. Res. Therapy* **5**: 121–129, 1967.
22. Sidman, M. Avoidance behavior. In: *Operant Behavior. Areas of Research and Application,* edited by W. K. Honig. New York, Appleton-Century-Crofts, 1966, pp. 448–498.
23. Takaori, S., N. Yada and G. Mori. Effects of psychotropic agents on Sidman avoidance response in good- and poor-performed rats. *Jap. J. Pharmac.* **19**: 587–596, 1969.
24. Wuttke, W. and R. T. Kelleher. Effects of some benzodiazepines on punished and unpunished behavior in the pigeon. *J. Pharmac. exp. Ther.* **172**: 397–405, 1970.