Pharmacology Biochemistry and Behavior, Vol. 62, No. 4, pp. 719–725, 1999

0091-3057/99/$–see front matter

PII S0091-3057(98)00211-1

Effects of Diazepam or Chronic Alcohol Treatment on Spatial Reversal Learning in Mice

NATHALIE BORDE AND DANIEL J. BERACOCHEA

Laboratoire de Neurosciences Comportementales et Cognitives, Université de Bordeaux I, 33405 Talence-cedex, France

Received 10 February 1998; Revised 12 October 1998; Accepted 12 October 1998

BORDE, N. AND D. J. BERACOCHEA. *Effects of diazepam or chronic alcohol treatment on spatial reversal learning in mice.* PHARMACOL BIOCHEM BEHAV **62**(4) 719–725, 1999.—Mice submitted to chronic alcohol consumption (CAC; 11 months) or to systemic diazepam administration were trained in a spatial reversal learning task. Although CAC-treated mice were able to learn the initial acquisition at normal rates, they were impaired during the first reversal of the discrimination and subsequent reversal sessions. In contrast, diazepam administration induced no deficits for any behavioral measure. In conclusion, CAC, but not diazepam administration, induces an exaggerated sensitivity to proactive interference. The two treatments spared, however, the development of the learning set curve. These results are congruent with clinical data showing that nondeclarative or implicit forms of memory processes are spared in diazepam-treated subjects or in chronic alcoholics. © 1999 Elsevier Science Inc.

Alcohol Benzodiazepines Memory Reversal learning Nondeclarative memory

AS pointed out by several authors, a consensus of the literature supports the view that benzodiazepine drugs induce memory deficits that parallel the patten of cognitive dysfunction seen in the Korsakoff syndrome. In both cases, amnesia is characterized by an anteroretrograde deficit (6,7,23,24), particularly affecting episodic memory (12,34) and which is tightly linked to the spatiotemporal context in which the information was acquired. In contrast, implicit memory and semantic or procedural memory (12,13,31) are spared by these treatments. The memory deficits of Korsakoff subjects have been attributed to permanent neuroanatomical damage located mainly in diencephalic areas (mamillary bodies, thalamic nucleus) (2,23,38), but many other studies have also emphasized the importance of frontal cortex dysfunctions in the cognitive disturbances observed in diencephalic amnesia (7). Thus, Korsakoff subjects and chronic alcoholics exhibit difficulties in organizing information into spatiotemporal sequences (25,29–32) that could be the cause of their exaggerated sensitivity to proactive interference. On the other hand, limbic structures and the frontal cortex are known to exhibit high densities of GABA–benzodiazepine receptors (14), whose functions are permanently altered following chronic alcohol consumption because the deficits continued after a withdrawal period (16,28); these brain areas are also particularly damaged in chronic alcoholics and more particularly diencephalic structures (38). Such finding suggest that the cognitive disorders observed in Korsakoff subjects could be mediated, at least in part, through changes in the GABA–BDZ receptors, and more particularly within the brain structures damaged by chronic alcoholism.

The aim of our study was, therefore, to determine whether, after chronic alcohol consumption (CAC) followed by a 1-month withdrawal period or benzodiazepine (diazepam) administration, mice would present differential memory deficits on a task that has already been found to be differentially impaired by diencephalic and frontal cortical lesions. The behavioral paradigm used in the present study was designed to determine how readily mice can learn to reverse, across successive sessions, a spatial discrimination response in a T-maze. It has been shown that normal mice exhibited in such a spatial reversal learning (SRL) task a progressive improvement of learning over successive sessions, as reflected by a decrease in

Requests for reprints should be addressed to D. J. Beracochea, Laboratoire de Neurosciences Comportementales et Cognitives, Université de Bordeaux I, 33405 Talence-Cedex, France.

the number of trials required to master each successive discrimination. Previous studies have shown that the evolution of the learning set curve over sessions is differentially impaired by distinct cortical and subcortical lesions, and varied greatly as a function of the species and of the nature (spatial, nonspatial) of the to-be-remembered information as well as the specific neuroanatomical connections linking cortical and subcortical structures (19,35). However, in the mouse strain used in the present study, it has been reported that lesions of the cingulate cortex impaired the ability to develop a learning set curve (27,28). In contrast, neither lesions of the mediodorsal thalamic nucleus or the mamillary bodies, which are differentially connected to the cingulate cortex, impaired the learning set curve; these subcortical lesions rather produced a day-to-day increase of sensitivity to interference that spared the ability to develop the learning set rule (22). Thus, the SRL task enables distinguishing between frontal and diencephalic dysfunction in rodents.

METHODS

Animals

The study was conducted using male mice of the Balb/c strain obtained at 6 weeks of age from Iffa-Credo, Lyon (France). On arrival, mice were housed collectively in colony cages (40 cm long × 25 cm high and 20 cm wide), matched for weight and housed under standard conditions (room temperature: 22°C; 12 L: 12 D cycle), with free access to food and water. They remained in collective cages for at least 16 weeks. In all cases, at least 2 weeks before behavioral testing began, mice were housed in individual cages, with free access to food and water.

Apparatus

Behavioral testing was carried out in T-maze constructed of grey Plexiglas. The stem and arms were 35 cm long, 10 cm wide, and 25 cm high. The start box (10 × 12 cm) was separated from the stem by a horizontal sliding door. Horizontal sliding doors were also placed at the entrance of each arm. A low-intensity diffuse illumination (10 lx) was provided above the apparatus.

Procedure

Before testing began, mice were handled for 10 min per day over 3 consecutive days. They were then submitted to a food-deprivation schedule initiated over 4 consecutive days so that, at the time of training, the mice weighed 88% of their initial free-feeding weights. Food ration was adjusted individually to maintain the same level of deprivation throughout the ensuing experimental period.

Habituation

Habituation was carried out on the fourth day of deprivation. All animals were allowed 10 min of free exploration of the apparatus to familiarize them with the experimental conditions. Food reward was available during this free-exploration session (BIOSERV pellets, 20 mg) to ensure that each animal learned to reach the end of the maze arms to collect the food reward.

Formal Testing

As described in Fig. 1 (upper part), the formal testing was composed of different phases including an acquisition phase (day 1) followed by a "reversal phase" constituted of a series of five reversal sessions (day 2 to day 6).

The acquisition session (day 1) consisted of a succession of trials. On each trial, the muse was placed in the start box, and 20 s later, the door of this box was opened. When the animal entered one of the two arms, the door of that arm was closed. After a 20-s confinement in the chosen arm, the mouse was removed and placed again in the start box for the next trial. For each trial, the chosen arm and the time that elapsed between the opening of the door of the start box and the closing of the door of the chosen arm (running time) were recorded. For each mouse, the baited arm selected on day 1 was its "nonpreferred" arm during the habituation (i.e., the opposite arm to the one that the animal had chosen first). The acquisition session was continued until the subject reached the criterion of five correct responses in five consecutive trials.

Following acquisition, daily reversal sessions (learning phase) took place over 5 consecutive days (day 2 to day 6), during which the baited arm was reversed from day to day. Each reversal session was pursued until the animal achieved the same criterion of five consecutive errorless trials.

After the criterion was met at the end of each session, mice were returned to their home cage for 5 min before being replaced in the maze for an additional trial (see Fig. 1, lower part) to verify short-term retention of the localization of the baited arm. The following session being carried out 24 h after, the first trial was considered as a long-term retention trial. In this case, the reward was placed into the goal arm opposite to the one baited the day before; previous studies showed that the animal did not anticipate the reversal of the baited arm, so that it continued to respond at the first trial according to the last discrimination acquired (22,26,27).

Whatever the session, the maze was always cleaned between each trial with water to eliminate any odor trials.

This behavioral paradigm enabled us to measure: (a) the rate of acquisition of the initial spatial discrimination (day 1); (b) the performance on the first reversal session (day 2), (c)

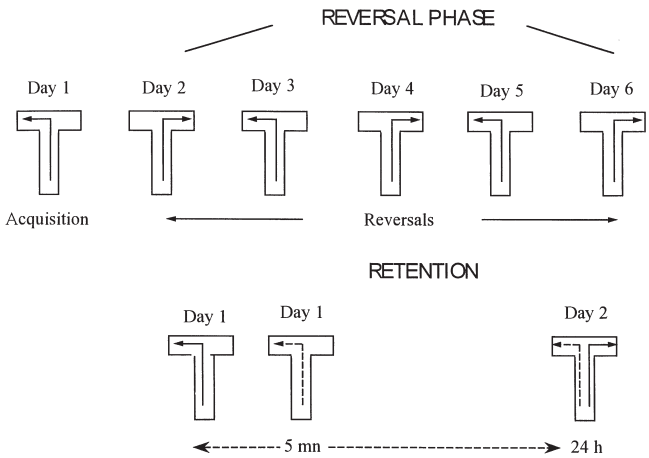

Fig. 1. Behavioral procedure. Upper part: learning sessions consisted of an initial acquisition session (day 1) followed by five reversal sessions (days 2–6). The five reversal sessions were given at 24-h intervals. Solid arrows indicate the correct response for each session. Lower part: two single retention-test trials were given at 5 min and 24 h after the end of each learning session (day 1 in the example). In this way, the 24-h test trial (day 2 in the example) constituted the first trial of the following learning session. Broken arrows depict the correct response for each retention-test trial.

the performance savings over successive daily reversal sessions (day 2 to day 6), and (d) the rate of forgetting of each daily discrimination over a 5-min and 24-h period.

Alcohol Administration

Mice of the alcohol group were given as their sole source of liquid increasingly concentrated solutions of ethanol (PROCHILAB) as follows: 4% (v/v) the first week, 8% (v/v) the second week, and 12% (v/v) the remaining time. The solutions were mixed from 95% ethanol and supplemented with saccharose (PROLABO; 30 g/l) and were freely available to subjects in two 250-ml bottles. Twice weekly, the subjects were weighed, and the quantities of food and ethanol solution consumed were measured. At the same time, the animals were replaced in clean cages with fresh ethanol solution. Mice of the alcohol group remained under the alcohol regime for 11 consecutive months. The control group is constituted of either pair-fed animals with an isocaloric solution of dextri-maltose or with water. Dry food was freely available by all the animals throughout this period (Extra-Labo, Pietrement, France). Before starting the experiments, mice of the alcohol group and the pair-fed animals of the control group were withdrawn, (i.e., progressively replaced on access to water only) at least 4 weeks before behavioral testing began. At the time of testing, mice were 18 months old.

Because statistical analysis showed no significant difference within the subjects of the control group, they were pooled together (alcohol control group: $n = 6$) for further statistical comparisons with alcohol-treated mice ($n = 8$).

Diazepam Administration

Independent groups of mice were used. Subjects were 17–20-week-old mice at the time of testing. The animals were divided into four subgroups: a "no treatment group" ($n = 6$), a vehicle group that received a saline solution at 0.9% ($n = 6$) and two diazepam groups (1.5 mg/kg ($n = 8$) and 2.0 mg/kg ($n = 7$)). Diazepam (Roche) was diluted in 0.9% saline and administered intraperitoneally (0.1 ml/10 g of mouse). The choice of these two doses was based on previous studies showing that both of these doses of diazepam induced delay-dependent working memory deficits in nonmatching-to-place tasks (4,5); in the present study, a higher dose of diazepam (2.5 mg/kg) was found to induce large sensorimotor impairments in this mouse strain (unpublished results).

Behavioral testing started 30 min after diazepam or saline injections. Because no significant statistical differences were observed between saline-treated and nontreated mice ($p > 0.05$ for all comparisons), these two groups were pooled (diazepam control group: $n = 12$) for further statistical comparisons with diazepam-treated groups.

Ethical Statement

All pharmacological and experimental procedures were in accordance with official French Regulations for the Care and Use of Laboratory Animals.

Data Analysis

In order to use normal distribution statistics, the number of trials necessary to reach criterion was converted into square root and the data expressed in percentage (perseverative response over the first trials of each reversal sessions or retention responses) in Arc sin values. Homogeneity of the variance of the transformed data were verified with Bartlett's and Lenvene's statistical tests. Two-way analysis of variance with one repeated measure (either days of testing or retention intervals) were performed to assess the effects of treatments on performance. Differences between groups were analyzed using post hoc factorial ANOVA.

RESULTS

Experiment 1: Effects of Alcohol Consumption on Spatial Reversal Learning

The homogeneity of the data was verified before employing statistical analysis of variance ($p > 0.1$ for all comparisons).

Results are summarized in Fig. 2A.

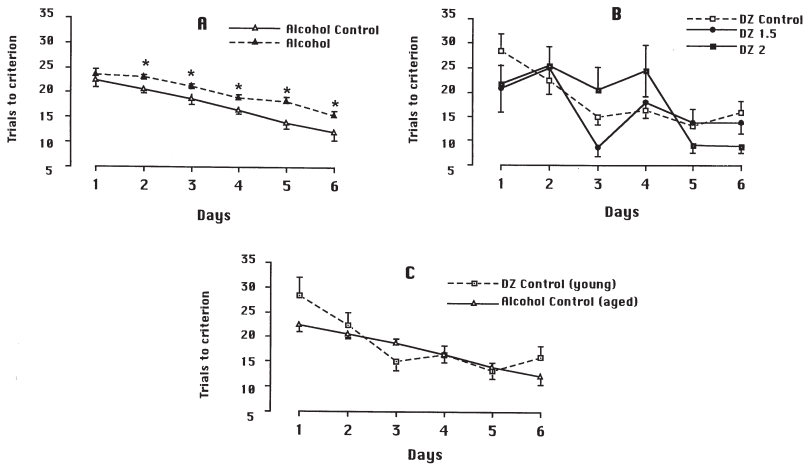

Fig. 2. Mean number of trials required to master the criterion (five successive errorless trials) over the 6 days of testing in (A) alcohol-treated mice and controls, (B) diazepam-treated mice and controls, and (C) diazepam controls (young mice) and alcohol controls (aged mice). *p , 0.04.

Acquisition (day 1). During day 1 of testing (first discrimination), the number of trials required to reach the criterion was not significantly different among the groups [group effect: $F(1, 12) = 0.37, p = 0.55$].

First reversal (day 2). Overall analysis showed that alcohol-treated mice required more trials to master the discrimination on day 2 of testing [first reversal; group effect: $F(1,12) = 10.9, p = 0.006$], but no significant interaction was found between groups and days (days 1 and 2) of testing [interaction groups × days: $F(1, 12) = 0.76, p = 0.40$].

Successive reversals (day 1 to day 6). The rate of learning across a succession of daily discrimination reversal was evaluated by repeated analysis of variance of the animal's performance from day 1 to day 6. The global analysis showed that the number of trials necessary to reach the criterion decreased significantly over days of testing [days: $F(5, 60) = 30.57, p = 0.0001$] but similarly in all groups [interaction groups × days: $F(5, 60) = 1.09, p = 0.37$]; however, a between-groups difference was observed [group effect: $F(1, 12) = 10.84, p = 0.0064$) on day 2, $F(1, 12) = 10.93, p = 0.0063$, day 3, $F(1, 12) = 5.74$, $p = 0.0033$, day 4, $F(1, 12) = 5.56, p = 0.036$, and day 5, $F(1, 12) = 9.03, p = 0.01$. This between-groups difference was no longer significant on day 6, $F(1, 12) = 3.53, p = 0.08$.

To further characterize the effects of alcohol, we analyzed the number of errors (perseverative response to the previous discrimination) over the five reacquisition trials (from the second to the sixth trials of the reversal sessions). No difference was observed between groups [group effect: $F(1, 12) = 2.16$, $p > 0.05$], indicating that the impairment exhibited by the alcohol-treated mice was not due to an inability to suppress or inhibit prior responses in the early stage of reversal learning but rather to a difficulty to form and maintain new responses over each discrimination.

Rate of forgetting. Results are summarized in Table 1. Analysis of performance was carried out for the two trials given 5 min and 24 h after the criterion was met over the six successive sessions. A two-way analysis of variance showed no significant between groups differences at either delay [group effect: $F(1, 12) = 2.29, p = 0.15$]. In contrast, there was a significant delay effect because performance accuracy declined from the 5-min retention trials to the 24-h retention trials, $F(1, 12) = 18.5, p = 0.001$, but no significant differences between the two groups [interaction group × delays: $F(1, 12) = 3.07, p = 0.10$] were observed.

Latencies. Running latencies were similar in both alcohol-treated and control groups, $F(1, 12) = 2.2, p = 0.16$, and decreased progressively over the sessions, $F(5, 60) = 14.43, p = 0.0001$ (means ± SEM for control and alcohol groups, respectively: 9.04 ± 0.5 and 10.07 ± 0.4 s).

Experiment 2: Effects of Diazepam Administration on Spatial Reversal Learning

Bartlett's and Levene's tests revealed that the degrees of variance were homogeneous ($p > 0.1$ for all comparisons). The results are represented in Fig. 2B.

Acquisition (day 1). During day 1 of testing (first discrimination), the number of trials required to reach the criterion was similar in all groups, $F(2, 24) = 0.66, p = 0.52$.

First reversal (day 2). Overall analysis showed no significant between groups differences on day 2 of testing, $F(2, 24) = 0.34, p = 0.71$, and no significant interaction was observed between groups and days (days 1 and 2) of testing [interaction groups × days: $F(2, 24) = 2.89, p = 0.074$].

Successive reversals (day 1 to day 6). A global analysis showed that the number of trials necessary to reach the criterion decreased significantly over days of testing, $F(5, 120) = 9.52, p = 0.0001$. No between-groups difference was observed, $F(2, 24) = 0.66, p = 0.52$. The number of trials to reach the criterion decreased significantly over days of testing, $F(5, 120) = 9.52, p = 0.0001$, but differently int he three groups [interaction groups × days: $F(10, 120) = 1.92, p = 0.048$]. Thus, one can see that the number of trials to criterion diminished particularly in the DZ 2 mg/kg from the fifth session (respectively: 13.16 ± 1.5 and 9.14 ± 1.6 trials for control and DZ 2 groups, $p > 0.05$ to the sixth session, $F(1, 1) = 4.82, p = 0.042$, respectively; 15.91 ± 2.3 and 9 ± 1.4 trials for control and DZ 2 groups).

To establish comparisons with Experiment 1, the number of errors due to the intrusion of responses corresponding to the last discrimination over the second to the sixth first trials were analyzed. Diazepam-treated subjects significantly differed from controls [interaction groups × days: $F(8, 96) = 2.08, p = 0.044$], particularly with the dose of 2 mg/kg, $F(4, 68) = 2.58, p = 0.044$. These results reveal a tendency for the diazepam group to more rapidly abandon on each session the previously learned responses compared to controls but the large standard deviations in the performance of diazepam-treated mice preclude the obtainment of statistical significance (60 ± 9.2% and 34.28 ± 11.3% of errors in control and DZ 2-mg/kg groups, respectively).

Rate of forgetting. Results are summarized in Table 1. A global ANOVA revealed that overall performance did not differ significantly among the groups at both delay intervals [group effect: $F(2, 24) = 0.47, p = 0.62$]. Performance accuracy declines significantly with the increase of the retention interval [delay effect: $F(1, 24) = 14.07, p = 0.001$] similarly in all groups interaction groups × delay: $F(2, 24) = 0.23, p = 0.79$].

Latencies. Running latencies were significantly reduced over sessions, $F(5, 120) = 6.19, p = 0.0001$, in all groups [interaction groups × days: $F(10, 120) = 0.89, p = 0.53$], this effect being particularly observed following diazepam administration [group effect: $F(2\ 24) = 4.47, p = 0.022$] (mean for controls, DZ 1.5 mg/kg and DZ 2 mg/kg, respectively; 7.83 ± 1.2, 3.5 ± 0.2, and 4.88 ± 1.1 s).

Effects of Aging on Spatial Reversal Learning

According to the different ages of the control subjects in Experiment 1 (18 months old) and 2 (4/5 months old), comparisons were applied to specify the role of aging in CCA-induced deficits.

Results are shown in Fig. 2C.

TABLE 1

RATES OF FORGETTING OF SPATIAL DISCRIMINATIONS OVER A 5 min OR A 24-h RETENTION INTERVAL IN ALL GROUPS

	Performance en % ± esm	
	5 min	24 h
Alcohol control (aged)	94.4 ± 3.5	76.7 ± 10.9
Alcohol	95.8 ± 2.7	57.5 ± 7
DZ control (young)	86.8 ± 4.1	63.9 ± 6.8
DZ 1,5	85.7 ± 5.4	68.8 ± 6.6
DZ 2	89.8 ± 4.1	73.8 ± 8

No significant statistical differences between groups were observed.

Acquisition (day 1). Statistical analysis showed that the number of trials required to reach the criterion was similar in the young control group (Experiment 2) and the aged control group (Experiment 1) during the first day of testing [aging effect: $F(1, 16) = 0.68$, $p = 0.42$].

First reversal (day 2). No significant between-group differences were observed on day 2 of testing, $F(1, 16) = 0.05$, $p = 0.81$, nor significant interaction between groups and days (days 1 and 2) of testing [interaction aging × days: $F(1, 16) = 1.15$, $p = 0.29$].

Successive reversals (day 1 to day 6). The global analysis showed that the number of trials to the criterion was similar in aged control mice (Experiment 1) and young control mice (Experiment 2) [aging effect: $F(1, 16) = 0.09$, $p = 0.75$] and decreased significantly over days of testing [days: $F(5, 80) = 7.47$, $p = 0.0001$] similarly in the two groups [interaction aging × days: $F(5, 80) = 0.75$, $p = 0.58$].

Rate of forgetting. Results are summarized in Table 1. Statistical analysis showed no significant differences between groups on both delay intervals [group effect: $F(1, 16) = 2.27$, $p = 0.15$]. The performance accuracy declines from the 5 min to the 24 h retention trials, $F(1, 16) = 6.29$, $p = 0.023$, similarly in the two groups [interaction groups × delays: $F(1, 16) = 0.08$, $p = 0.76$].

Latencies. Running latencies were similar in both young and aged control mice, $F(1, 16) = 0.43$, $p = 0.51$, and progressively decreased over sessions, $F(5, 80) = 5.02$, $p = 0.0005$ (means ± SEM for young and aged mice, respectively; 7.83 ± 1.2 and 9.04 ± 0.5 s).

DISCUSSION

The results of our study show that the effects of chronic alcohol consumption on the SRL task differ from those of diazepam administration. The major findings of the present experiments are: (a) neither CAC or diazepam affected the initial acquisition of a spatial discrimination; (b) the acquisition of the second discrimination (the first reversal) was retarded by CAC but not by diazepam; (c) performance over successive reversals was impaired by CAC but not by diazepam administration; the speed of learning was not impaired in both groups; and (d) aging does not account for the CAC-induced deficit.

Effects of Alcohol Consumption on Spatial Reversal Learning

Results showed that CAC did not produce a performance deficit for the acquisition of a spatial discrimination (day 1 of testing) suggesting that it is unlikely that mice suffer from an incapacity to encode spatial information. In contrast, although alcohol-treated mice exhibited a daily increment in performance, they required significantly more trials to master the day to day criterion compared to controls. Because alcohol-treated mice exhibited normal rates of forgetting, we assume that the general impairment exhibited by alcohol-treated mice was not linked to a loss of memory, but could rather reflect a performance deficit possibly due to an intrusion of previously acquired information (exaggerated sensitivity to proactive interference). This hypothesis is supported by the fact that the performance deficit was observed on the second discrimination session (day 2) but not on the first acquisition session, which is free from any previous interfering information (day 1). Previous studies had already shown that alcohol-treated animals suffer from a reduced ability to block out competing responses resulting from repetitive testing in the same context (3). Taken together, these findings and the presently reported ones suggest that the memory processes underlying the incremental development of the learning set rule, which is not impaired by alcohol consumption, are relatively independent of the memory processes involved in the day-to-day discrimination that is impaired by alcohol consumption. However, the improvement of performance observed at day 6 as reported above may indicate that the impairments are time limited, and that the processes involved in the selection of strategies are not completely impaired.

Because previous studies have shown that frontal dysfunction impaired the establishment of the learning set rule (26,27), it seems unlikely that CAC-treated mice suffer from a frontal dysfunction in this task. In contrast, the pattern of deficits observed in CAC-treated mice resembles that resulting from diencephalic lesions that increase day-to-day sensitivity to proactive interference without impairing the learning set curve (22). This analysis is in agreement with anatomical studies showing that the CAC treatment used in this mouse strain produced diencephalic but not cortical damage (3).

Effect of Diazepam Administration in Normal Mice on Spatial Reversal Learning

Surprisingly, diazepam-administration induced no deficits at any stage of the SRL task. Indeed, our experiment shows that diazepam does not induce any encoding deficit on the initial discrimination (day 1). This findings are in contrast to those reported by several studies showing that benzodiazepines impair the encoding stage of memory processes (8,37). A possible explanation of the spared learning abilities in diazepam-treated animals would be that diazepam would enhance motivation for food compared to the alcohol and control groups, and thus would improve learning processes. Several arguments weigh against such an hypothesis. Indeed, the hyperphagic effects of benzodiazepines are not completely elucidated, because several studies have shown that these drugs would rather impair satiety mechanisms with no significant effect on food appetite (10,11). In addition, food deprivation in rodents (that enhances food appetite) increases win-shift behavior in tasks involving a spatial component (20), rather than win-stay strategy, which is required in the present study to solve each daily discrimination. Thus, a putative enhancement of appetite in diazepam-treated subjects should also increase the number of errors in experimental subjects compared to controls, at least in the first days of testing, which is not the case.

Pardoxically, several side effects of diazepam known to produce impairments in some tasks, could favor the SRL performance in BDZ-treated subjects. Thus, the lack of deficits presently reported could be due to the "disinhibitory" effect of the drug. Indeed, benzodiazepines are known to increase impulsivity, as shown by the reduction of waiting capacity that leads animals to present an impairment in a go no-go successive discrimination by increasing responding during the no-go (waiting) periods of the task (9) or by increasing choices of small but immediate reward as opposed to a large but delayed one in a DRL task (36). The spatial discriminations in our study do not require waiting periods but favor the repetition of a similar behavioral response pattern to master the criterion (five consecutive identical responses). So, the dishinibitory effect of diazepam that can be deleterious in some tasks involving waiting periods or inhibitory processes (such as spatial alternation) may actually be an advantage in our behavioral paradigm because every repetition of similar response is reinforced during a given daily session.

Second, one could suggest that diazepam-treated subjects process the task in a different manner compared to controls or CAC-treated subjects. Indeed, the perseveration of the previously acquired responses over the six first trials of each session decreases at a significantly faster rate after diazepam administration compared to controls. Thus, diazepam-treated mice have learned to apply a day-to-day win-stay rule involving an egocentric strategy that consists of reentering the arm being rewarded on a given *N* session, regardless of the information received at the previous $N - 1$ session. This behavioral rule protects from any proactive interference effect, as observed following CAC. Interestingly, we have shown that the same doses of diazepam produce large and long-lasting spatial working memory impairments in delayed nonmatching-to-place tasks that cannot be solved by the use of alternative egocentric strategies (4,5). Thus, the use of an egocentric strategy in the SRL task could compensate for a spatial memory dysfunction. This interpretation is congruent with several findings, suggesting that both allocentric visuospatial and egocentric or associative mechanisms normally interact during place learning, and that the emergence of search strategies could maintain or support the acquisition of spatial tasks in drug-treated or lesioned animals (1,16,18,33). Thus, according to the deficits induced by a given treatment, experimental animals are able to shift during the learning phase of a task from a given strategy (e.g., spatial strategy) to another one (e.g., egocentric strategy) to solve the task, as a function of the memory mechanisms that remain spared by the treatment (21). Findings sustaining this view have already been reported in chlordiazepoxide-treated rats (17). Pharmacological investigations should more critically analyze the behavioral and cognitive processes that are left intact following a given drug treatment, because the determination of spared functions are as important as the determination of cognitive dysfunction induced by a given drug (15,18).

CONCLUSION

The aim of our study was to compare the effects of chronic alcohol consumption or the administration of diazepam in normal mice in the successive reversal of spatial discriminations in a T-maze. The main result of our study is to show that CAC does not produce a frontal-like dysfunction (26,27), as shown by the sparing of the speed of learning, but rather a diencephalic-like impairment as reflected by increased day-to-day proactive interference (22); diazepam administration does not impair either the speed of learning or day-to-day rates of performance.

The differential effects of the two treatments in the SRL task contrast with previous findings showing similar deficits in spatial delayed working memory tasks in this strain of mice (4,5). According to our analysis, the discrepancy between the two treatments could be due to a different processing of information, diazepam-treated mice using more rapidly than the other groups an egocentric strategy (procedural rule) that prevents the occurrence of interference effects. However, it is important to observe that both treatments (CAC and diazepam administration) spared the development of the learning set curve, which rely on the progressive implementation of implicit knowledge over successive days of training. Thus, the present results together with previous ones (4,5) are in agreement with clinical data showing that explicit (or declarative) but not implicit (or non declarative) memory processes are impaired by benzodiazepines administration and in Korsakoff subjects (12,13,31).

REFERENCES

1. Aggleton, J. P.; Mishkin, M.: Mammillary-body lesions and visual recognition in monkeys. Exp. Brain Res. 58:190–197; 1985.
2. Belzunegui, T.; Insausti, R.; Ibanez, J.; Gonzalo, L. M.: Effect of chronic alcoholism on neuronal nuclear size and neuronal population in the mammillary body and the anterior thalamic complex of man. Histol. Histopathol. 10:633–638; 1995.
3. Béracochéa, D.; Lescaudron, L.; Tako, A.; Verna, A.; Jaffard, R.: Build-up and release from proactive interference during chronic ethanol consumption in mice: A behavioral and neuroanatomical study. Behav. Brain Res. 25:63–74; 1987.
4. Borde, N.; Krazem, A.; Jaffard, R.; Béracochéa, D.: Memory deficits following diazepam administration in mice: Evidence for a time-dependent retrieval impairment. Psychobiology 25:202–209; 1997.
5. Borde, N.; Jaffard, R.; Béracochéa, D.: Effects of chronic alcohol consumption or diazepam administration on item recognition and temporal ordering in a spatial working memory task in mice. Eur. J. Neurosci. 10:2380–2387; 1998.
6. Brown, J.; Lewis, V.; Brown, M.; Horn, G.; Bowes, J. B.: A comparison between transient amnesias induced by two drugs (diazepam or lorazepam) and amnesia of organic origin. Neuropsychologia 20:55–70; 1982.
7. Butters, N.: Alcoholic Korsakoff syndrome. An update. Semin. Neurol. 4:226–244; 1984.
8. Chapoutier, G.; Raffali-Sebille, M. J.; Venault, P.; Simiand, J.; Dodd, R. H.: Comparison between the effects of the benzodiazepine receptor ligands methyl beta-carboline-3-carboxylate and diazepam in two learning situations in mice. Psychobiology 19: 58–63; 1991.
9. Cole, S. O.: Reversal of chlordiazepoxide-induced impairment in successive discrimination performance by RO 15-1788. Drug Dev. Res. 18:229–236; 1989.
10. Cooper, S. J.; Estall, L. B.: Behavioural pharmacology of food, water, and salt intake in relation to drug actions at benzodiazepines receptors. Neurosci. Biobehav. Rev. 9:5–20; 1985.
11. Cooper, S. J.: Bidirectional changes in the consumption of food produced by β-carbolines. Brain Res. Bull. 19:347–358; 1987.
12. Danion, J. M.; Zimmermann, M. A.; Willard-Schroeder, D.; Grangé, D.; Singer, L.: Diazepam induces a dissociation between explicit and implicit memory. Psychopharmacology (Berlin) 99:238–243; 1989.
13. Danion, J. M.; Weingartner, H.; File, S. E.; Jaffard, R.; Sunderland, T.; Tulving, E.; Warburton, D. M.: Pharmacology of human memory and cognition: Illustrations from the effects of benzodiazepines and cholinergic drugs. J. Pharmacol. 7:371–377; 1993.
14. Eymin, C.; Koll, N.; Laurent, B.: Central benzodiazepines-binding sites in human cerebral structures associated with memory processes. Dementia 3:232–238; 1992.
15. File, S.; Sharma, R.; Schaffer, J.: Is lorazepam-induced amnesia specific to the type of memory or to the task used to assess it? J. Psychopharmacol. 6:76–82; 1992.
16. Freund, G.: Benzodiazepine receptor loss in brains of mice after chronic alcohol consumption. Life Sci. 27:987–992; 1980.
17. Hodges, H.; Green, S.: Effects of chlordiazepoxide on cued radial maze performance in rats. Psychopharmacology (Berlin) 88:460–466; 1986.
18. Hodges, H.: Maze procedures: The radial-arm and water maze compared. Cogn. Brain Res. 3:167–181; 1996.
19. Holmes, E. J.; Butters, N.; Jacobson, S.; Stein, B. M.: An examination of the effects of mamillary-body lesions on reversal learning set in monkeys. Physiol. Psychol. 11:159–165; 1983.
20. Jaffard, R.; Dubois, M.; Galey, D.: Memory of a choice direction in a T-maze as measured by spontaneous alternation in mice: Effects of intertrial interval and reward. Behav. Processes 6:11–21; 1981.

21. Kesner, R. P.; Farnworth, G.; Di Mattia, B. V.: Double dissociation of egocentric and allocentric space following medial prefrontal and parietal cortex lesions in rat. Behav. Neurosci. 5:956–961; 1989.
22. Krazem, A.; Béracochea, D. J.; Jaffard, R.: Effects of mammillary bodies and mediodorsal thalamic lesions on the acquisition and retention of a learning set in mice: Paradoxical effect of the intersession interval. Behav. Brain Res. 67:51–58; 1995.
23. Lhermitte, F.; Signoret, J. L.: Analyse neuropsychologique et différenciation des syndromes amnésiques. Rev. Neurol. 126:161–178; 1972.
24. Lister, R. G.: The amnesic action of benzodiazepines in man. Neurosci. Biobehav. Rev. 9:87–94; 1985.
25. Meudell, P. R.; Mayes, A. R.; Ostergaard, A.; Pickering, A.: Recency and frequency judgements in alcoholic amnesics and normal people with poor memory. Cortex 21:487–511; 1985.
26. Meunier, M.; Jaffard, R.; Destrade, C.: Differential involvement of anterior and posterior cingulate cortices in spatial discriminative learning in a T-maze in mice. Behav. Brain Res. 44:133–143; 1991.
27. Meunier, M.; Destrade, C.: Effects of radiofrequency versus neurotoxic cingulate lesions on spatial reversal learning in mice. Hippocampus 7:355–360; 1997.
28. Mhatre, M. C.; Ticku, M. K.: Chronic ethanol administration alters gamma-aminobutyric acid A receptor gene expression. Mol. Pharmacol. 42:415–422; 1992.
29. Oscar-Berman, M.; Zola-Morgan, S. M.: Comparative neuropsychology and Korsakoff's syndrome. I. Spatial and visual reversal learning. Neuropsychologia 18:499–512; 1980.
30. Salmon, D. P.; Butters, N.; Schuckit, M.: Memory for temporal order and frequency of occurence in detoxified alcoholics. Alcohol 3:323–329; 1986.
31. Schacter, D. L.: Memory, amnesia and frontal lobe dysfunction. Psychobiology 15:21–36; 1987.
32. Shaw, C.; Aggleton, J. P.: Evidence for the independence of recognition and recency memory in amnesic subjects. Cortex 31:57–71; 1995.
33. Slotnick, B. M.; Kaneto, N.: Role of the dorsomedial thalamic nucleus in olfactory discrimination learning in rats. Science 214: 91–92; 1981.
34. Squire, L. R.: Comparisons between forms of amnesia; Some deficits are unique to Korsakoff's syndrome. J. Exp. Psychol. (Learn. Mem. Cogn.) 8:560–571; 1982.
35. Staubli, U.; Schottler, F.; Nejat-Bina, D.: Role of the dorsomedial thalamic nucleus and piriform cortex in processing olfactory information. Behav. Brain Res. 25:117–129; 1987.
36. Thiébot, M. H.; Bizot, J.; Soubrié, P.: Waiting capacity in animals: A behavioral component crossing nosologic boundaries of anxiety and depression? In Soubrié, P., ed. Anxiety, depression and mania, animals models of psychiatry disorders, vol. 3. Basel: Karger; 1991: 48–67.
37. Venault, P.; Chapouter, G.; Prado de Carvalho, L.; Simiand, J.; Morre, M.; Dodd, R. H.; Rossier, J.: Benzodiazepine impairs and beta-carboline enhances performance in learning and memory tasks. Nature 321:864–866; 1986.
38. Victor, M.; Adams, R. D.; Collins, G. H.: The Wernick-Korsakoff syndrome. Philadelphia: Davis; 1971.