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ORIGINAL INVESTIGATION

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Effects of chlordiazepoxide and FG 7142 on a rat model of diencephalic amnesia as measured by delayed-matching-to-sample performance

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Abstract The intralaminar thalamic nuclei (ILn) have been implicated as a critical site of pathology in amnesia. Lesions of the ILn have been found to produce behavioral effects comparable to benzodiazepine (BDZ) receptor agonists. We compared the effects of chlordiazepoxide (CDP), a BDZ agonist, and FG 7142, a partial inverse agonist at the BDZ receptor, in rats with thalamic lesions and in unlesioned controls. Delayed matching-to sample (DMS) performances were studied during treatment with ascending doses of CDP, counterbalanced trials with 2.5 mg/kg CDP and saline, ascending doses of FG 7142, and (for unlesioned controls only) counterbalanced trials with saline and higher doses of CDP. CDP had effects similar to the ILn lesion, decreasing response speed and percent correct responding in a delay-independent fashion. These effects were additive with the impairments associated with the ILn lesion. The effects of FG 7142 were more complex. At lower doses, it increased response speed without affecting response accuracy. At higher doses, it diminished both the speed and the accuracy of DMS responding. These results support the hypothesis that ILn lesions and BDZ agonists have similar effects on DMS performance. The biphasic effects observed for FG 7142 are consistent with other evidence that low doses of this drug enhance while higher doses impair memory performance. Although DMS accuracy was not improved, the enhancement observed for response speed provides evidence that partial inverse BDZ agonists have potential utility as treatments for cognitive impairments associated with amnesia.

Key words Chlordiazepoxide · FG 7142 · Rat · Diencephalic amnesia

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Introduction

There is no satisfactory treatment for amnesia. The Wernicke-Korsakoff syndrome (WKS), a relatively pure form of amnesia, has been associated with lesions in periventricular areas of the diencephalon (Mayes et al. 1988; Victor et al. 1989) and with signs of monoaminergic dysfunction (Mair and McEntee 1983; McEntee and Mair 1990). While some of the cognitive impairments associated with WKS have been found to respond positively to treatment with catecholaminergic or serotonergic drugs, none of these treatments has resulted in clinically significant improvements in mnemonic function (Mair and McEntee 1986; McEntee and Mair 1990; McEntee and Crook 1991). Recent studies of animal models of WKS have identified the intralaminar thalamic nuclei (ILn) as a critical site of pathology, that is: (i) sensitive to the effects of thiamin deficiency, the main etiologic factor in WKS; (ii) consistent with the location of lesions observed in WKS; and (iii) a location where lesions in animal models disrupt performance of delayed conditional discrimination tasks used to measure remembering in multiple sensory modalities (Burk and Mair 1998; Mair et al. 1998; Zhang et al. 1998; see Mair 1994 for review).

The effects of ILn lesions resemble those of benzodiazepine (BDZ) receptor agonists on tasks used to measure working memory. Lesions affecting the ILn have been found to increase the latency and to decrease the accuracy of responding in a delay-independent fashion for delayed non-matching (DNMS) and matching (DMS) to sample tasks, whether these lesions are produced by thiamin deficiency (Knoth and Mair 1991; Robinson and Mair 1992), electrolytic heating (Mair and Lacourse 1992; Koger and Mair 1994; Young et al. 1996), or excitotoxic treatment (Burk and Mair 1998; Mair et al. 1998; Zhang et al. 1998). BDZ agonists also have been reported to impair both the speed and the accuracy of responding on delayed conditional discrimination tasks used to measure working memory, although these tasks differ from the procedures that have been used to mea-

sure the effects of ILn lesions on remembering (McNaughton and Morris 1987; Tan et al. 1990; Ohno et al. 1992; Cole and Hillman 1994). In contrast to the detrimental effects of BDZ agonists, BDZ receptor inverse agonists have been found to have beneficial effects, increasing measures of behavioral activity and enhancing measures of remembering (Venault et al. 1986, 1987; Cole and Hillman 1994; Smith et al. 1994). At high doses, however, at least some BDZ inverse agonists are reported to disrupt remembering, an effect that has been related to increased release of dopamine in frontal cortex associated with anxiogenic doses of these drugs (Murphy et al. 1996, 1997; Zahrt et al. 1997).

The beneficial effects of low doses of BDZ inverse agonists suggest that these drugs may have utility as treatments for the impairments of response speed and accuracy associated with ILn lesions. Forster et al. (1995) reported that treatment with the inverse BDZ agonist RO15-3505 was effective in improving the performance of aged mice on an adversively conditioned T-maze task involving a 2-h memory delay. Unfortunately, Forster et al. (1995) did not compare the effects of this treatment on younger animals, and thus could not determine if the response to this treatment was affected by the age of the animals.

It is not known whether drugs having agonist or inverse agonist effects at the BDZ receptor will have the same effects on the behavior of animals with ILn lesions as they do in intact animals. The current study addressed this issue by comparing the effects of a BDZ agonist, chlordiazepoxide (CDP), and a BDZ partial inverse agonist, FG 7142, on DMS impairments in intact control rats and in rats with surgical lesions of the ILn, the adjacent mediodorsal nucleus (MDn), and the lateral internal medullary lamina (L-IML), a site affecting both the ILn and the MDn. By assessing the response to CDP treatment with the same task used to measure behavioral impairments in ILn-lesioned rats, the current study also provides a direct test of the hypothesis that BDZ agonists and ILn lesions have comparable effects on working memory.

Experiment 1

The first experiment compared the effects of different doses of CDP on the performances of lesioned and unlesioned rats. The doses were tested in ascending order because of concern that thalamic lesions might increase the sensitivity of rats to high doses of BDZ agonists. Based on the available evidence, we expected that CDP treatment would slow responding and impair DMS accuracy and that these effects would increase at higher doses (McNaughton and Morris 1987; Tan et al. 1990; Ohno et al. 1992; Cole and Hillman 1994).

Materials and methods

Subjects

Subjects were 26 male Long-Evans rats (Charles River Breeding Labs), including seven control, seven ILn, six MDn, and six L-IML animals. These numbers represent the survivors of an initial group of 28 that were first trained to perform the DMS task, randomly assigned to a surgical treatment (n=7/group), and then trained for 4 months after recovery from surgery to assess the effects of the experimental lesions (Burk and Mair 1998). One of the MDn and one of the L-IML animals died during this phase of training, and thus only 26 of the original 28 animals were included in the present studies. Rats were 10 months old at the start of the pharmacological experiments and had received a minimum of 4000 trials of DMS training. The experiments were conducted according to the "Principles of laboratory animal care" (NIH publication No. 85-23) and were approved by the Institutional Animal Care and Use Committee.

Surgical procedures

Rats were anesthetized (85 mg/kg ketamine and 8.5 mg/kg xylazine IM) and placed in a Kopf (Tujunga, Calif., USA) stereotaxic instrument (with the incisor bar set 3.3 mm below the interaural line), the skull was opened with sterile procedures, and lesions were made by injecting *N*-methyl-D-aspartate (NMDA; 100 mM in phosphate buffer, pH=7.4) through a 26-gauge cannula using a 10 µl Hamilton syringe in a Kopf 5000 microinjection unit. The stereotaxic coordinates for injections were defined in mm relative to the interaural line for the anterior-posterior (AP) and dorsal-ventral (DV) dimensions, and relative to the midline for medial-lateral (ML). ILn lesions were made by infusing 0.4 µl of the NMDA solution at: AP=7.2, DV=4.0, ML=±1.4; AP=6.2, DV=3.6, ML=±1.4, and AP=5.2, DV=3.6, ML=±1.6; and 0.2 µl of the NMDA solution at: AP=7.2, DV=4.0, ML=±0.6; AP=6.2, DV=3.0, ML=±0.6; and AP=5.2, DV=3.0, ML=±0.6. L-IML lesions were made by infusing 0.6 µl of the NMDA solution at DV=3.6 and 4.6; ML=±1.0; AP=7.2, 6.2, and 5.2. The MDn lesions were made by infusing 0.6 µl of the NMDA solution at AP=7.2, DV=4.8, ML=±0.6; AP=6.2, DV=4.6, ML=±0.6; and AP=5.2, DV=3.6, ML=±0.6.

Apparatus

Rats were trained in operant chambers (ENV-007; Med Associates, Georgia, Vt., USA) enclosed within ventilated wooden sound insulating boxes, and programmed by an interface (MED Associates) connected to a 486 computer. Each operant chamber had three retractable levers (ENV-112AM), one centered on the back wall and two on the front wall on either side of a water dipper (ENV 202AM) that was used to allow access to 0.1 ml tap water for 3.0 s as a positive reinforcement. A photocell (ENV-254) was positioned to record head entries into the dipper and a house light (ENV-215 M) was positioned above the back lever.

Behavioral training

After completing the initial series of postsurgical behavioral tasks (Burk and Mair 1998), rats were trained for approximately 30 sessions with the DMS procedures used for the drug trials. These DMS trials began with the back lever extending. Pressing this lever caused it to retract and one of the two front levers (randomly selected as the sample for that trial) to extend. After this lever was pressed twice, it was retracted and the back lever extended for the duration of the retention interval (randomly selected as 1.0, 5.0, or 15.0 s on a trial by trial basis). The first press on the back lever, after the retention interval ended, caused the back lever to retract and both front levers to extend for the choice response. When the

sample lever (extended previously during the sequence) was pressed first, the dipper was raised to deliver reinforcement and the trial was scored as correct. When the other lever was pressed first (an incorrect non-matching response), the trial ended without reinforcement and a correction trial was run. Correction trials were a repeat of the trial on which the error was made. There was a maximum of two correction trials for each error and these trials were not considered in analyses of behavioral performance. Performance was measured as percent correct responding and by the average time taken for each response completed. Sessions were ended after 45 trials were completed or 75 min had elapsed.

Drug treatments

Experiment 1 compared the effects of ascending doses of CDP (chlordiazepoxide HCl; Research Biochemicals International, Natick, Mass., USA). Rats were trained for three sessions following vehicle (normal saline) injection and then two sessions with CDP at doses of 0.5, 2.5, 5.0, and 10.0 mg/kg body weight. Doses were presented in an ascending fashion to identify potentially disruptive effects of drugs on lesioned animals and to equate animals for their history of drug treatments in comparing results across lesion groups. All treatments were given IP, 20 min before the start of behavioral training, with the concentration of CDP adjusted to produce a constant injection volume of 0.5 ml/kg body weight.

Results and discussion

CDP affected both the accuracy and the speed of DMS responding in a dose-related fashion. Accuracy, measured by percent correct, tended to decrease as the dose of CDP increased. Figure 1 shows the percent correct for each of the treatment groups at all of the doses tested. A two-factor (lesion group×CDP dose) ANOVA showed significant effects of lesion group [$F(3,22)=3.272$, $P=0.0403$] and CDP dose [$F(4,88)=6.633$, Geisser-Greenhouse $P=0.0018$], but not for the interaction of these factors ($F<1$). The effects of the different doses of CDP were analyzed by planned comparisons with saline using an α-level of 0.05, adjusted by the Bonferroni procedure to compensate for the effects of multiple comparisons (Meyers and Well 1991). By this analysis, percent correct was affected significantly when CDP was administered at doses of 2.5 and 10.0 mg/kg.

The rate of responding was also decreased at higher doses of CDP. Figure 1 shows the responses/min for each of the treatment groups at all of the doses tested. A two factor (lesion group×CDP dose) ANOVA showed significant effects on response rate for lesion group [$F(3,22)=3.995$, $P=0.0206$] and CDP dose [$F(4,88)=20.870$, Geisser-Greenhouse $P<0.0001$], but not for the interaction of these factors ($F<1$). Planned comparisons of specific doses to saline, using an α-level of 0.05 adjusted by the Bonferroni procedure, showed significant effects for doses of 5.0 and 10.0 mg/kg.

These results are consistent with the results of other studies that have examined the effects of BDZ agonists (McNaughton and Morris 1987; Tan et al. 1990; Ohno et al. 1992; Cole and Hillman 1994) and of thalamic lesions affecting the ILn (Knoth and Mair 1991; Mair and Lacourse 1992; Burk and Mair 1998) on the accuracy and rate of responding on delayed conditional discrimination tasks. The similarity between the effects of CDP in the current study to the effects of BDZ agonists in previous studies of DMS responding (Tan et al. 1990; Cole and Hillman 1994) suggests that our decision to test doses in an ascending order did not distort the results observed. It should be noted that the low rate of responding of the ILn group during treatment with the highest (10 mg/kg) dose of CDP tested (Fig. 1) would have raised serious questions about carry-over effects had the order of doses been randomized. Previous studies have not analyzed the effects of BDZ agonists in rats with thalamic lesions. The lack of a significant interaction suggests that lesions of the ILn do not alter the response to CDP treatment.

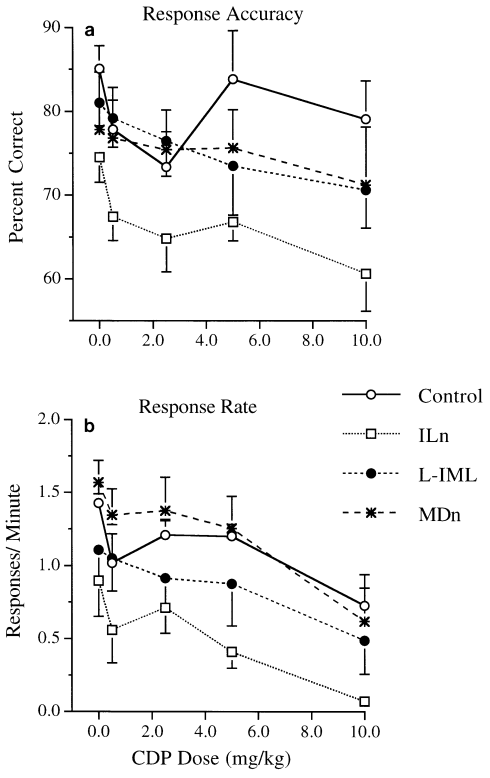

Fig. 1a, b Mean percent correct **a** and mean response rate (measured as responses/min) **b** for the DMS task for the doses of CDP tested during the first experiment. *Error bars* show the SEM. ○ Control, □ ILn, ● L-IML, ✶ MDn

Experiment 2

The results of the first experiment suggested that DMS accuracy is diminished when CDP is administered at doses as low as 2.5 mg/kg. Experiment 2 was designed to test this result with a more extensive series of training trials, in which saline and CDP treatments were counterbalanced and a sufficient number of trials run for performances to be compared at different retention intervals.

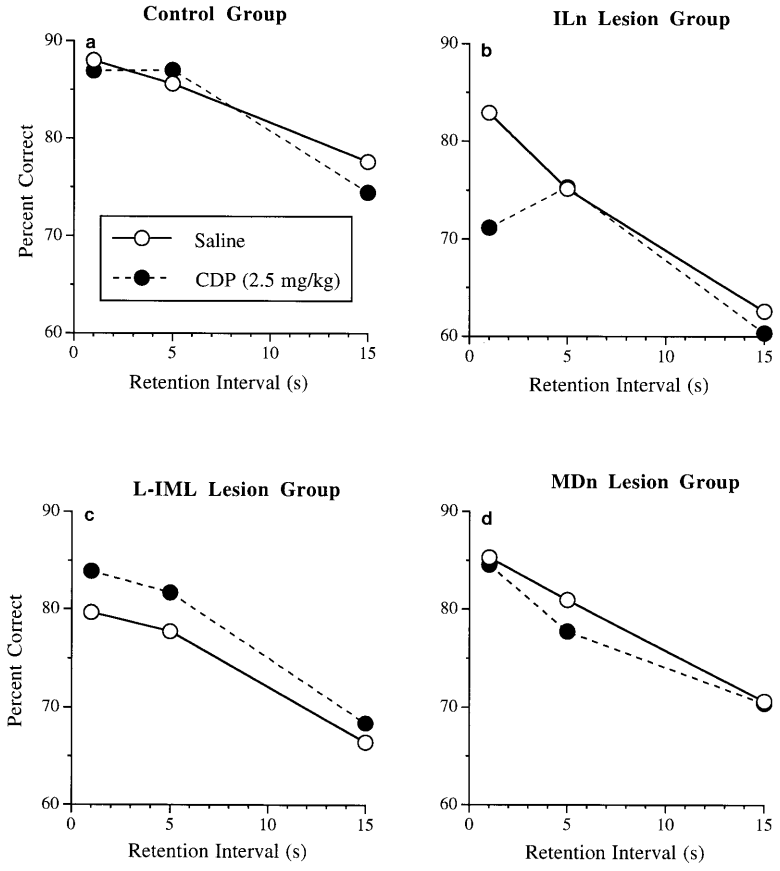

Fig. 2a–d Mean percent correct responding during treatment with CDP and saline during experiment 2. Results are shown for each of the retention intervals tested. ○ Saline, ● CDP (2.5 mg/kg)

Materials and methods

The subjects were the same as in experiment 1, except for the loss of one animal in the MDn group that died during the course of experiment 2 and thus was not included in any of the analyses. The apparatus and training procedures were the same as in experiment 1. A washout period of 2 weeks was interposed after the end of experiment 1 during which DMS training was continued to maintain performance on this task. Experiment 2 consisted of 12 training sessions for each animal. In the first three, they were treated with saline. During the next six sessions, they were treated with 2.5 mg/kg of CDP. During the last three sessions, rats were again treated with saline.

Results and discussion

When administered across a series of sessions, the 2.5 mg/kg dose of CDP had very little effect on DMS performance. A three-factor (lesion×drug treatment×retention interval) ANOVA showed a marginally significant effect of lesion [$F(3,21)=3.051$, $P=0.0510$] and a significant effect of retention interval [$F(2,42)=42.789$, Geisser-Greenhouse $P<0.0001$], but not for drug treatment ($F<1$). The interactions of drug treatment with lesion [$F(3,21)=1.284$, $P=0.3056$], delay [$F(2,42)=1.030$, $P=0.3659$], and lesion and delay [$F(6,42)=1.761$, $P=0.1306$] were not significant. Thus the effect of the 2.5 mg/kg dose on percent correct observed in experiment 1 was not verified in experiment 2 (Fig. 2). Treatment with the 2.5 mg/kg dose of CDP also had little effect on response rate. A two factor (lesion group×drug treatment) ANOVA showed that there was no significant effect of lesion [$F(3,21)=1.997$, $P=0.1453$], drug treatment ($F<1$), or for the interaction of these factors [$F(2,21)=1.939$, $P=0.1542$].

Experiment 3

Experiment 3 compared the effects of different doses of FG 7142 on the performances of lesioned and unlesioned rats. As in experiment 1, doses were tested in ascending order because of concern that thalamic lesions might increase the sensitivity of rats to high doses of BDZ inverse agonists. We expected that the effects of FG 7142 would be biphasic, enhancing DMS performance at lower doses and impairing performance at higher anxiogenic doses associated with increased release of cortical dopamine (Venault et al. 1986, 1987; Cole and Hillman 1994; Smith et al. 1994; Murphy et al. 1996, 1997; Zahrt et al. 1997).

Materials and methods

The subjects, apparatus, and procedures for training DMS were the same as in experiment 2. FG 7142 (*n*-methyl-β-carboline-3-carboxamide; Research Biochemicals) was administered as a suspension in a mixture of distilled water and Tween 80 (1 drop per ml). The drug concentration was adjusted to maintain a constant

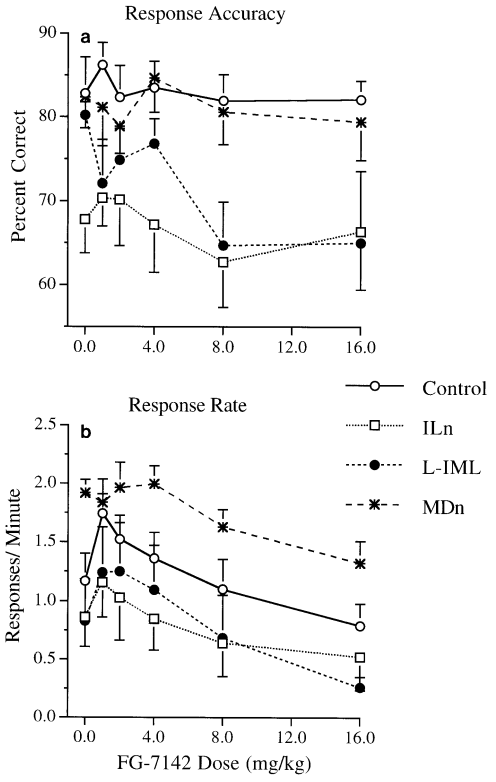

Fig. 3a, b Mean percent correct **a** and mean response rate (measured as responses/min) **b** for the DMS task for the doses of FG 7142 tested during the third experiment. *Error bars* show the SEM. ○ Control, □ ILn, ● L-IML, ✶ MDn

volume of 0.5 ml/kg body weight that was injected IP 20 min before the start of behavioral training.

A washout period of 1 week was interposed after the end of experiment 2 during which DMS training was continued. Experiment 3 consisted of 13 sessions. Animals were first trained for three sessions during which they were injected with the Tween/water vehicle and then ten sessions when they were injected with ascending doses of FG 7142 (two sessions each at doses of 1.0, 2.0, 4.0, 8.0, and then 16.0 mg/kg body weight). As in experiment 1, doses were presented in an ascending fashion to identify potentially disruptive effects of drugs on lesioned animals and to equate animals for their history of drug treatments in comparing results across lesion groups.

Results and discussion

Treatment with FG 7142 had little effect on DMS accuracy except at higher doses (8.0 and 16.0 mg/kg), where it tended to impair performance (Fig. 3). These trends were verified by a two-factor (lesion group×FG 7142 dose) ANOVA showing a significant effect of lesion group [$F(3,21)=5.043$, $P=0.0087$], a marginal effect of FG 7142 dose [$F(5,105)=2.495$, Geisser-Greenhouse $P=0.0607$], with no significant interaction ($F<1$). Although the effect of drug treatment was not significant when probability was adjusted by the conservative Geisser-Greenhouse criteria, it was when probability was adjusted by the less conservative Huynh-Feldt criteria ($P=0.0401$) or when no adjustment was applied ($P=0.0355$). Examination of Fig. 3 suggests that much of the overall decrease associated with the higher doses of FG 7142 can be ascribed to the L-IML group. However, given the lack of a significant interaction effect (between dose and lesion) and the marginal significance of the dose effect it seems premature to make much of this trend. Planned comparisons of specific doses to saline, using an α-level of 0.05 adjusted by the Bonferroni procedure, did not show significant effects for the any of the doses tested on percent correct.

Treatment with low doses of FG 7142 tended to increase response rate, whereas treatment at higher doses tended to decrease response rate (Fig. 3). These trends were verified by a two factor (lesion group×FG 7142 dose) ANOVA showing significant effects for lesion group [$F(3,21)=4.373$, $P=0.0153$] and FG 7142 dose [$F(5,105)=10.612$ Geisser-Greenhouse $P<0.0001$]. The interaction between lesion group and FG 7142 dose was not significant ($F<1$). Planned comparisons of specific doses to saline, using an α-level of 0.05 adjusted by the Bonferroni procedure, verified the significance of the increase in response rate at the 1.0 mg/kg dose and the decrease in response rate at the 16.0 mg/kg dose.

Experiment 4

Experiment 4 was conducted to determine whether DMS performance would be disrupted by higher doses of CDP than were tested in experiment 2. To avoid the very low rates of responding observed in experiment 1 for rats with thalamic lesions treated with high doses of CDP, these trials were conducted with unlesioned controls only. Because this would create a confound for any subsequent analysis of lesion effects, the long-term effects of lesions were assessed first, without drug treatments, from 8 to 10 months after surgery (see Burk and Mair 1998). Experiment 4 was then conducted to determine the effects of high doses of CDP for the unlesioned control animals.

Materials and methods

Subjects were the seven control animals used in the first three experiments. One of the controls failed to complete a sufficient number of trials during treatment with high doses of CDP and was eliminated from the experiment, thus leaving a total of six animals. The apparatus and procedures for training DMS were unchanged.

Animals were first run for two sessions following injections of saline. They were then trained for four sessions at 10.0 mg/kg CDP, eight sessions at 15.0 mg/kg of CDP, four sessions at 10.0 mg/kg of CDP, and then two sessions with saline injections. Rats were given at least a 1-day washout between each of the days on which these high dose CDP treatments were given. DMS was trained on the washout days to maintain performance and to control for any prolonged effects of the treatments. Session to session washouts were continued until animals achieved at least 80% accuracy while completing a minimum of 20 trials. Thus all CDP treatments were given on the day after this criterion was reached during a washout.

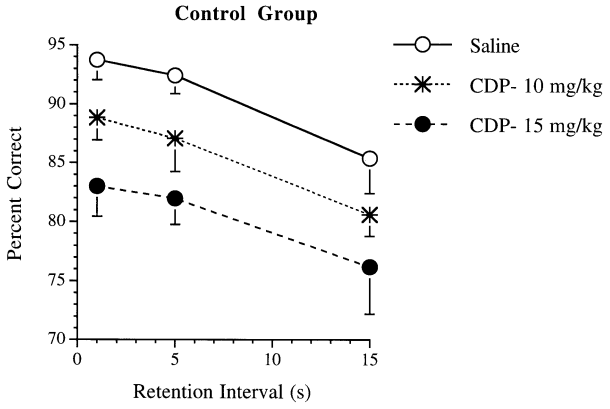

Fig. 4 Mean percent correct responding during treatment with the two doses of CDP and saline during experiment 4. Results are shown for each of the retention intervals tested. *Error bars* show the SEM. ○ Saline, ✶ CDP 10 mg/kg, ● CDP 15 mg/kg

Results and discussion

The 10.0 and 15.0 mg/kg doses of CDP had consistent and substantial effects on DMS performance. Rats averaged 90.5% correct during saline trials, compared with 86.1% during the 10.0 mg/kg and 80.4% during the 15.0 mg/kg CDP treatment. They averaged 1.54 trials/min during saline, 0.68 trials/min during the 10.0 mg/kg and 0.43 trials/min during the 15.0 mg/kg CDP treatment. The effects of CDP on DMS accuracy were delay-independent when performances were compared at different retention intervals (Fig. 4).

Percent correct responding was analyzed by a two factor (drug treatment×retention interval) ANOVA that showed a significant effect of drug treatment [$F(2,10)=9.658$, Geisser-Greenhouse $P=0.0201$] and retention interval [$F(2,10)=5.952$, Geisser-Greenhouse $P=0.0336$] but not for the interaction between these factors ($F<1$). A one-factor ANOVA showed a significant effect of drug treatment on response rate [$F(2,10)=21.935$, Geisser-Greenhouse $P=0.0002$].

Histological analyses

After completion of behavioral training measuring the long-term effects of thalamic lesions on DMS (Burk and Mair 1998), rats were killed under deep anesthesia (100 mg/kg ketamine, 10 mg/kg xylazine IM) by transcardiac perfusion of physiological saline followed by 5% (vol/vol) neutral buffered formalin. Tissue was sectioned frozen in the coronal plane and stained with cresyl violet for histological verification of the extent of the lesions.

Each of the lesions affected their intended targets. Figure 5 shows photomicrographs of typical ILn, MDn, and L-IML lesions (see also Figures 10, 11, and 12 in Burk and Mair 1998). ILn lesions involved the full extent of the paracentral and central lateral nuclei and resulted in damage of variable extent of the central medial, MDn, lateral dorsal, lateral posterior, and the ventromedial nuclei. MDn lesions affected the full extent of this nucleus in five of seven cases, and produced partial damage in the other two. Only one of the MDn lesions in-

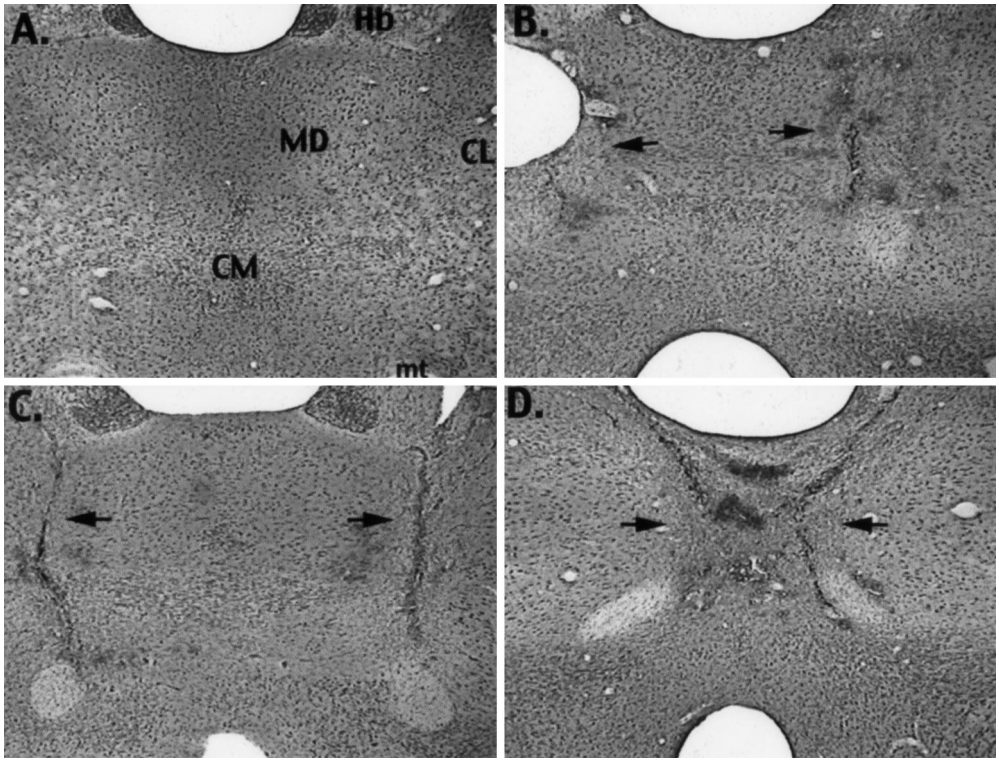

Fig. 5A–D Photomicrographs showing typical examples of the thalamic lesions in coronal section approximately 6 mm anterior to the interaural line. Histological analyses were conducted after approximately 1 year of recovery from the time that the lesions were made. **A** Control to show the appearance of unlesioned tissue and the location key landmarks. **B** An intralaminar (*ILn*) lesion. **C** An example of a lateral internal medullary lamina (*L-IML*) lesion. **D** An example of a mediodorsal nucleus (*MDn*) lesion. The *arrows* show the medial (for **B** and **C**) or the lateral (for **D**) limits of the lesions. Lesions were characterized by loss of nerve cell bodies, gliosis forming a dark band at the center of the lesion, calcifications, and signs of tissue shrinkage in the area of the lesion. Abbreviations are: *MD* mediodorsal nucleus, *CM* central medial nucleus, *CL* centrolateral nucleus, *Hb* habenular nuclei, *mt* mammillothalamic tract

volved substantial portions of the surrounding ILn. The L-IML lesions extended to involve tissue more ventral than did the ILn lesion, while sparing more medial areas of thalamus. The paracentral and central lateral nuclei were involved in all of the L-IML lesions, along with adjacent portions of the MDn, lateral dorsal, and ventromedial nuclei.

General discussion

Effects of chlordiazepoxide (CDP)

Treatment with high doses of CDP had similar effects for each of the lesion groups on the accuracy and rate of DMS responding. In experiment 1, treatment with CDP doses ranging from 0.5 to 10.0 mg/kg resulted in decreases in percent correct and responses/ minute that were exacerbated at higher doses (Fig. 1). The apparent effects of the 2.5 mg/kg dose were not verified in experiment 2. The effects of higher doses in experiment 4 were more consistent with the impairments observed in experiment 1. Treatment with 10 mg/kg CDP resulted in a substantial decrease from saline trials for response rate (1.54 versus 0.68 responses/min for controls in experiment 1 compared to 1.43 versus 0.73 responses/min for experiment 4) and a decrease in accuracy on the order of 5% (Figs. 1 and 4). Increasing the dosage of CDP to 15 mg/kg exacerbated both these effects.

The observation of a delay-independent impairment in DMS accuracy is consistent with the findings of Tan et al. (1990) for rats treated with CDP. The increase in latency is consistent with the effects observed by Cole and Hillmann (1994) for a similar DMS task during treatment with lorazepam. Ohno et al. (1992) also reported sharp increases in working memory errors corresponding with increased response latency in rats performing a three panel runway task during treatment with CDP at 10 mg/kg IP. Ohno et al. (1992) observed similar impairments following intrahippocampal injection of CDP or of muscimol and thus argued that these effects were related to the activation of the $GABA_A$/BDZ receptor complex in hippocampus. Other evidence, however, has shown that the DMS task used in the present study is unaffected by complete hippocampal lesions (Mair et al. 1998). Thus it seems unlikely that the effects of CDP on this task were mediated by hippocampus.

The DMS impairment observed at higher doses of CDP resemble the effects of ILn lesions. Both treatments decreased response rate and diminished accuracy in a delay-independent fashion. The effects of the lesion can be illustrated by comparing the performances of the control and ILn groups during treatment with saline or the Tween 80/water vehicle during the first three experiments. Controls averaged 1.43, 1.39, and 1.17 responses/min, compared to 0.90, 0.90, and 0.86 responses/min for the ILn group in experiments 1, 2, and 3, respectively. Controls averaged 85.1, 83.7, and 82.8% correct, compared to 74.5, 74.5, and 67.8% correct for the ILn group in the same three experiments. The extent of these impairments and the delay-independence of the lesion effect (Fig. 2), are consistent with the results of the more complete behavioral analyses conducted both before and after completion of these drug trials (see Burk and Mair 1998).

Effects of FG 7142

Treatment with FG 7142 had significant effects on response rate and, except for the very conservative Geisser-Greenhouse criteria, on response accuracy. These effects were consistent with an inverted U-shaped dose-response curve. At higher doses, both response rate and accuracy were diminished. At lower doses, response rate was increased but there was little change in accuracy. Planned comparisons with saline indicated that only the increase in response rate at the 1.0 mg/kg dose and the decrease in rate at the 16.0 mg/kg dose were statistically significant. Other reports have indicated that low doses of BDZ receptor inverse agonists can increase response speed and improve mnemonic function in other tasks (Venault et al. 1986, 1987; Smith et al. 1994; Forster et al. 1995). Cole and Hillman (1994) measured the effects of FG 7142 on a DMS task similar to the present study and found significant improvement in accuracy but not for response latency for a 1.0 mg/kg dose and significant decreases in speed and accuracy for a 10.0 mg/kg dose. While the present findings differ from Cole and Hillman (1994) in showing beneficial effects of the 1.0 mg/kg dose on speed rather than accuracy, the results of both studies are consistent with inverted U-shaped dose response curves in which accuracy or speed is enhanced at low doses and both are impaired at higher doses.

In the current study, FG 7142 was not associated with significant improvements in the accuracy of DMS responding. Nevertheless, the findings of this study provide evidence that encourage further study of the utility of partial inverse agonists as treatments for the cognitive impairments associated with ILn lesions. First, the greatest improvement in response rate was observed at the lowest dose administered in the present study. This suggests that we may have tested a range of doses that was too high to accurately assess the potential benefits of FG 7142 on mnemonic function. Second, there was no interaction between the effects of the lesions and the drug treatments administered in the present study. This provides evidence that ILn lesions do not interfere with the behavioral effects of drugs acting on BDZ receptors and thus that the beneficial effects of BDZ receptor inverse agonists observed for intact animals (Venault et al. 1986, 1987; Cole and Hillman 1994; Smith et al. 1994) may extend to ILn-lesioned animals.

Third, treatment with 1.0 mg/kg FG 7142 was associated with a significant increase in response rate without a concomitant decrease in accuracy. There is a well-known tradeoff in cognitive psychology between the speed and accuracy of responding (Ratcliff 1978; Posner 1986).

Specifically, error rates tend to increase when response rates increase beyond an optimal level. In rats, thalamic lesions involving the ILn have been found to affect both aspects of responding, decreasing the speed and accuracy of responding on DNMS and DMS tasks (Knoth and Mair 1991; Mair and Lacourse 1992; Burk and Mair 1998). Similar impairments in speed and accuracy have been observed in human Korsakoff syndrome patients performing comparable tasks (Oscar-Berman and Bonner 1985; Oscar-Berman et al. 1992). Thus the increase in response rate in the current study can be taken as evidence of enhanced cognitive function and of a positive response to at least one aspect of behavioral impairment associated with ILn lesions in rats and Korsakoff's syndrome in humans. It remains an empirical question whether the enhancement observed for response speed will be found to extend to other measures of mnemonic function (cf. Cole and Hillman 1994; Smith et al. 1994).

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