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Subchronic cocaine produces training paradigm-dependent learning deficits in laboratory rats

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Abstract

The effect of cocaine on spatial learning was investigated by exposing male Sprague–Dawley rats to 0, 20, or 40 mg/kg cocaine prior to and during training on a water maze task. Half the animals were pretrained on cued trials prior to hidden platform trials, while the remaining animals completed hidden platform trials immediately. Escape latencies for all animals improved with training, but pretrained animals located the hidden platform faster than untrained animals ($P < .001$). Pretraining also decreased the effect of cocaine. In pretrained animals, only the high dose of cocaine caused significant increases in escape latency ($P < .001$), while in the untrained group the lower dose of cocaine also caused a significant increase ($P < .001$). On working memory measures, cocaine affected both the pretrained ($P < .01$) and untrained ($P < .001$) groups. Dwell ratio measurements indicated unaffected reference memory in both pretrained ($P < .001$) and untrained ($P < .001$) animals, and no significant differences were detected among the treatment conditions in either group ($P > .05$). Thus, while cocaine did not abolish learning, the efficiency with which the task was learned was compromised. However, this effect was reduced by pretraining.

Keywords: Cocaine; Hippocampus; Learning; Memory; Rat; Spatial navigation; Water maze; Long-term potentiation

1. Introduction

Within the brain, cocaine acts as an indirect dopamine agonist. Its primary mechanism of action is to inhibit reuptake of monoaminergic neurotransmitters (dopamine, in particular) through competitive antagonism of presynaptic reuptake transporters (Earles and Schenk, 1999; Giros et al., 1991; Hitri et al., 1994). The subjective effects of cocaine intoxication are thought to be largely the result of this action taking place in the nucleus accumbens (NA), an area in the ventral striatum that receives rich dopaminergic innervation from the ventral tegmental area (VTA) and plays an important role in modulating reward mechanisms (Koob and Nestler, 1997; Koob et al., 1994).

Researchers have shown that cocaine causes learning deficits in animals. In animal models of short-term memory, it was shown that cocaine decreases accuracy on delayed and titrating matching-to-sample (Branch and Dearing, 1982; Hudzik and Wenger, 1993; Wenger and Wright, 1990), and on delayed spatial alternation and matching to position (Baron et al., 1998) tasks. Further, rats given postsession injections of cocaine were deficient in their ability to gain an autoshaped lever-touch response (Janak et al., 1997), suggesting that cocaine interferes with the ability to consolidate information learned during training; an indication that cocaine affects reference memory. As evidence that cocaine also affects higher levels of cognitive functioning, it has been reported that cocaine inhibits the ability of monkeys to acquire chains of behavior (Evans and Wenger, 1992; Moerschbaecher and Thompson, 1980; Moerschbaecher et al., 1979). In addition, cocaine results in persistent deficits in the ability of the rat's brain to inhibit incoming irrelevant sensory stimuli (Boutros et al., 1997), which indicates that cocaine may also disrupt attentional processes.

On the other hand, there are also reports indicating that cocaine facilitates learning. Moderate doses of cocaine have been reported to enhance avoidance learning (Intro-

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ini-Collison and McGaugh, 1989; Janak et al., 1992; Weinberger et al., 1992; White et al., 1995a), and conditioned avoidance (White et al., 1995b). Cocaine also increases accuracy on some discriminative learning tasks (Grilly and Grogan, 1990; Grilly and Nocjar, 1990). It may be significant that enhanced learning, as the result of cocaine, is typically observed only at low to moderate doses (0.1–10 mg/kg) on relatively simple tasks. When performance on more complex tasks, such as conditional discriminations, is measured, cocaine is usually associated with performance deficits. Further, the doses of cocaine used in studies that show cocaine facilitates learning are far below those necessary to reach the plasma levels of cocaine reached in human cocaine users (Siegel, 1982; Spear et al., 1989).

The fact that cocaine has been shown to both inhibit and facilitate learning indicates that it may interact with multiple neurobiological substrates that affect behavior. Indeed, the list of structures and processes affected by cocaine is extensive (Koob and Nestler, 1997; Pert, 1998). In terms of its effects on learning processes, however, the effects of cocaine on the hippocampus are of particular interest. The hippocampus has been implicated as a central mediator of memory consolidation, and has been shown to be crucial for learning on spatial memory tasks (Fremouw et al., 1997; Moser and Moser, 1998; Moser et al., 1995). While many effects of cocaine on the hippocampus have been reported (Onaivi et al., 1996), the effects of cocaine on spatial memory processes have not been fully investigated.

It has been shown that D-2-amino-5-phosphonopentanoate (D-AP5), a potent *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, interferes with in vivo long-term potentiation (LTP) in anesthetized rats at concentrations that produce dose-dependent impairments in spatial memory (Butcher et al., 1990; Davis et al., 1992). Our laboratory has previously reported similar effects on spatial memory performance upon delivery of dextromethorphan (Bane et al., 1996), also an NMDA glutamate receptor antagonist that inhibits in vivo LTP (Krug et al., 1993).

It is widely accepted that LTP is a substrate of spatial memory (Butelman, 1989; Eichenbaum, 1995; Morris, 1996), though it may not be a necessary substrate (Saucier and Cain, 1995; Silva et al., 1998). Thus, substances that inhibit LTP would be expected to affect the ability of rats to perform well on spatial memory tasks. Smith et al. (1993) have demonstrated that cocaine inhibits LTP in vitro, and Heyser et al. (1995) have shown that prenatal exposure to cocaine disrupts performance of male rats on a spatial navigation task. To date, however, there has been no report of the direct effects of cocaine on spatial memory processes in freely moving animals. The purpose of the present study is to examine the effects of subchronic doses of cocaine on spatial memory in rats and to determine whether such effects can be ameliorated with pretraining (Saucier et al., 1996). Measures of performance were included to specifically characterize the effects of cocaine administration on working and reference memory.

2. Materials and methods

2.1. Subjects

Forty-eight 2-month-old male Sprague–Dawley rats (Charles River, MA) weighing between 290 and 450 g were used as subjects in these experiments. All animals had free access to water throughout the study. During the initial phase of the study, all animals had free access to food (Purina rat chow). Each was then randomly assigned to either a saline control group (SAL), the 20-mg/kg cocaine (C20) treatment group, or the 40-mg/kg cocaine (C40) treatment group. Thus, a total of eight animals were assigned to each treatment group.

Cocaine hydrochloride (generously supplied by NIDA) was dissolved in 0.9% saline to the appropriate concentrations. Injections were given subcutaneously with 27-gauge needles. Once drug injections commenced, animals in the SAL control group were matched by weight to an animal in the C40 group, and pair-fed the amount of food that the C40 animal consumed on the previous day. This procedure was continued for the remainder of the study, and was designed to control for the transient weight loss associated with cocaine exposure.

Each animal was housed individually in a hanging plastic cage, and a 12-h light/dark cycle remained in effect throughout the study. All animals were treated in accordance with applicable guidelines regarding the care and use of laboratory animals, and the research was conducted according to a protocol approved by the institutional Animal Care and Use Committee.

2.2. Apparatus

The Morris water maze (MWM) was used to assess spatial memory. The maze consisted of a circular, galvanized steel trough, 183 cm in diameter and 61 cm deep. It was filled to a depth of 30 cm with 18°C water rendered opaque by the addition of nontoxic, black Drytemp paint. Two circular escape platforms (8.8 cm in diameter) were used. The first platform, used for standard trials, was painted black, and was submerged 1 cm below the surface of the water making it invisible to a swimming animal. The second, used for cued trials, was left white and allowed to protrude 1 cm above the surface of the water, thus, remaining visible to animals inside the maze. Escape platforms were centered in one of the quadrants of the maze 41 cm from the edge of the maze.

A video tracking system (San Diego Instruments, San Diego, CA), coupled to a computer and a video cassette recorder, was used to track and record the

movements of the animals inside the maze. Data collected included escape latency, swim speed, path distance, and dwell time.

2.3. Procedure

2.3.1. Injection protocol

The injection protocol employed was based on protocols used in previous studies employing subcutaneous cocaine injections (Heyser et al., 1995; King et al., 1993; Spear et al., 1989). During the 5 days prior to maze training, each animal was given daily injections of 2 ml/kg 0.9% saline to habituate responses to handling and receiving injections. For the next 8 days, animals were given daily injections of 2-ml/kg 0.9% saline, 20-mg/2-ml/kg cocaine hydrochloride, or 40-mg/2-ml/kg cocaine hydrochloride depending upon the group to which they had been assigned. Injections were given at the same time each day at the end of the dark cycle (06:00 am) and training in the MWM was initiated at least 1-h postinjection.

Due to the potent vasoconstrictive properties of cocaine, tissue necrosis can occur at injection sites with subcutaneous delivery. To avoid necrotic lesions, injection sites were systematically varied on a daily basis. All injections were given below the skin on the dorsal surface near the level of the scapulae. Four sites representing the four corners of a square laid across the back of each animal were used. On each day, injections were given into corresponding sites on each animal. The site of injection was rotated daily in a clockwise fashion throughout the study. By rotating the injection site and using a dilute cocaine concentration visible tissue necrosis was negligible. In addition, no visible signs of leakage from injection sites were observed.

The dose range of cocaine used in this study was selected for its ability to produce plasma cocaine levels at or above those measured in human cocaine users. Siegel (1982) reported that plasma cocaine concentrations in humans approach 900 ng/ml for smoked cocaine. Spear et al. (1989) showed that similar concentrations are reached in rats given subcutaneous injections of 20 mg/3 cc/kg and 40 mg/3cc/kg resulted in higher sustained plasma cocaine concentrations. Since rats metabolize cocaine more rapidly than humans, it was decided to include the higher dose to maintain high levels of plasma cocaine for an extended period.

2.3.2. Maze procedure

Two types of trials occurred during the experiment, standard trials and cued trials. On standard trials, the hidden platform was placed in the maze, and rats were required to swim until the platform was located or 60 s elapsed, whichever came first. In this situation, no intramaze cues were available to the animals that would indicate the location of the hidden platform. During cued trials, the taller, white platform replaced the hidden platform so that a distinct visual intramaze stimulus was available for the rats to use as a cue to facilitate escape.

For half the animals, the Cued First (CF) group, 4 days of cued trials preceded 4 days of standard trials. The remaining animals, the Standard First (SF) group, completed 4 days of standard trials prior to 4 days of cued trials. This procedure allowed an analysis of the effects of prior training on water maze performance (Saucier et al., 1996).

For each rat, training consisted of three trials each day with two runs in each trial for a total of six runs each day. For each run, a rat was placed in the water at one of three randomly assigned start locations along the wall of the apparatus at the center of one of the nonplatform quadrants. The subject was released and allowed to swim for 60 s or until the platform was found. Subjects that failed to locate the platform within 60 s were placed on the platform for a 30-s platform interval. Rats that successfully located the platform were allowed to remain on the platform for 30 s. The second run of each trial started immediately upon completion of the 30-s platform interval. For both runs within a trial, the start point was unchanged. Between trials, rats were placed under a heat lamp for a 2-min intertrial interval, during which feces were removed from the maze and the water was stirred to eliminate the possibility of olfactory cues which might bias the swim path of the animals.

The second and third trials were run in the same manner as the first. However, start locations were changed according to a random sequence that allowed each animal to start from each of the three possible start locations (quadrants not containing the platform) on each of the 4 days of testing.

On each day, the platform remained in the same location on all trials for each rat, but the platform location was varied randomly across rats. Each day, the platform was moved to a different location for each rat such that the platform was located in each of the four quadrants for 1 day of the experiment for each rat. This procedure resulted in each rat starting from, and swimming to, each of the four quadrants an equal number of times. The same procedure was used for standard and cued trials. Training continued until all rats completed six runs with the platform in each of the four quadrants under both standard and cued conditions; thus, each rat swam 48 trials.

2.3.3. Data analysis

Kolmogorv–Smirnov analyses were performed to compare performance between CF and SF groups. Within each group, standard parametric statistical analyses were performed. Escape latency and path distance data were subjected to repeated measures analyses of variance (Treatment condition × Day × Trial × Run). It is possible that treatment conditions could affect escape latency by affecting physiological substrates of behavior that are not involved with spatial learning per se, but rather with coordination or motivational factors. To control for such possibilities, swim speed on all trials and escape latency on cued trials were

coded as covariates in analyses of standard trials performance. This strategy allows detection of treatment condition effects while accounting for variance due to differences in swim speed and cued trails performance among treatments groups. Post-hoc comparisons were performed using Tukey's HSD.

Dwell ratios were analyzed for each group separately. An initial one-sample *t*-test was performed to determine if the group mean proportion of time spent in the quadrant that contained the escape platform on the previous day was significantly greater than 0.25, indicating a preference for that quadrant. This test was followed by one-way ANOVA to determine if dwell ratios differed among treatment conditions within groups.

3. Results

As illustrated in Fig. 1, animals exposed to 4 days of cued trial training prior to standard trial training (CF) were able to locate the hidden platform in significantly less time than their SF counterparts, $Z(1152) = 3.95$, $P < .001$. For this reason, all subsequent analyses were performed separately for each group.

Cocaine treatment resulted in increased escape latency in the SF group. Analysis of mean escape latency revealed significant main effects for Treatment condition, $F(2,479) = 6.14$, $P < .002$; Day, $F(3,479) = 58.23$, $P < .001$; Trial, $F(2,479) = 62.00$, $P < .001$; and Run, $F(1,479) = 32.59$, $P < .001$. A significant Trial × Run interaction, $F(2,479) = 19.50$, $P < .001$, was also found. Animals in both cocaine treatment groups took significantly longer to locate the hidden platform than animals in the SAL control group; however, there was not a significant difference in escape latency between the two cocaine treatment groups (Fig. 2, top).

As shown in the bottom of Fig. 2, cocaine treatment resulted in increased swim path distances in the SF group that paralleled the observed differences in escape latency. Main effects were detected for Treatment

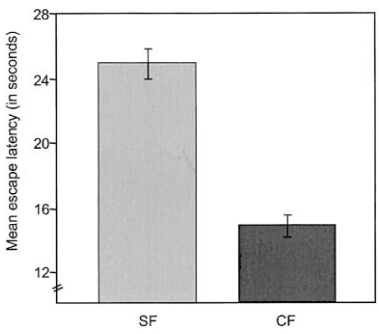

Fig. 1. Pretraining affected hidden platform escape latency on standard trials. Mean escape latency was pooled for all trials and plotted for SF and CF animals. SF animals took significantly longer to escape the water than CF animals. Error bars represent S.E.M. ($Z < 0.01$).

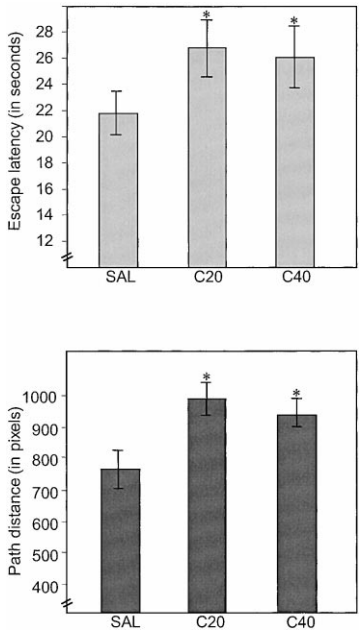

Fig. 2. Cocaine treatment increased mean escape latency (top) and swim path distance (bottom) for SF animals on standard trials ($P < .01$). Error bars indicate ±S.E.M. Asterisks indicate values that are significantly different than the SAL control value.

condition, $F(2,482) = 7.28$, $P < .001$; Day, $F(3,482) = 54.24$, $P < .001$; Trial, $F(2,482) = 73.56$, $P < .001$; and Run $F(1,482) = 43.33$, $P < .001$. A significant Trial × Run interaction, $F(2,482) = 20.62$, $P < .001$, was also detected. These data suggest that the length of time taken to locate the hidden platform is a function of the distance animals swam before locating the platform and escaping the water.

Statistical analysis of escape latency data for the CF group revealed significant main effects for Treatment condition, $F(2,479) = 8.56$, $P < .001$; Day, $F(3,479) = 6.20$, $P < .001$, Trial; $F(2,479) = 50.76$, $P < .001$; and Run, $F(1,479) = 20.53$, $P < .001$. Significant Treatment condition × Day, $F(6,479) = 2.97$, $P < .01$, and Trial × Run, $F(2,479) = 7.11$, $P < .001$, interactions were also found, as was a significant three-way interaction among Treatment condition, Day, and Trial, $F(12,483) = 1.92$, $P < .03$. Inspection of the top panel in Fig. 3 illustrates the significant increase in escape latency for the C40 group compared to the SAL and C20 groups. No significant difference in escape latency between SAL and C20 groups was detected.

As was the case for the SF animals, swim path data from the CF animals paralleled the escape latency data (Fig. 3, bottom). Significant main effects were found for Treatment condition, $F(21,482) = 1.97$, $P < .01$; Day, $F(3,482) = 8.03$, $P < .001$; Trial, $F(2,482) = 58.76$; and Run, $F(1,482) = 22.38$, $P < .001$. Significant two-way Day - × Treatment condition, $F(6,482) = 3.25$, $P < .01$, and Trial × Run, $F(2,482) = 8.28$, $P < .001$, interactions were also found, along with a significant three-way Day × Treat-Treatment condition × Trial interaction, $F(12,482)$ $P < .01$. As was the case for the SF animals, these data indicate that

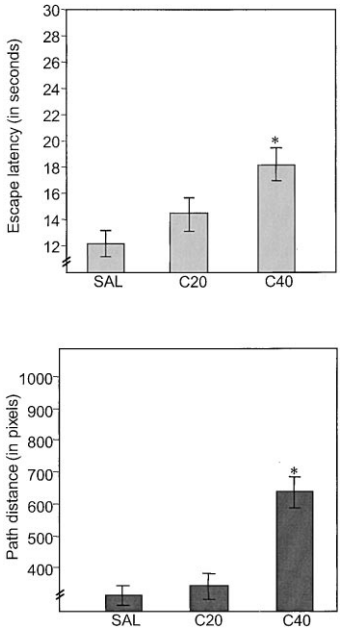

Fig. 3. Only the 40-mg/kg cocaine treatment increased mean escape latency (top) and swim path distance (bottom) for CF animals on standard trials ($P<.001$). Error bars indicate ±S.E.M. Asterisk indicates a value significantly different from the SAL control value.

increases in swim path distance account for increases in escape latency.

As evidenced by decreases in escape latency over days (Fig. 4), the performance of animals in all treatment conditions improved over the course of training. However, escape latencies of SAL animals were typically shorter than those of the C20 and C40 groups on each of the 4 days of standard trial training. Similar trends were seen for escape latency as a function of trial within days and runs within trials for the SF (Fig. 5) and CF (Fig. 6) groups. In all cases, CF animals, those that had experience in the maze prior to swimming on standard trials, located the hidden platform faster than their SF counterparts.

It should be noted that, in all the analyses of variance performed on escape latency and swim path distance data, significant interactions were detected. By observing the data presented in Figs. 4–6, it is apparent that these interactions reflect, in most cases, that the initial performance of animals in the SAL group was superior to that of the cocaine-treated animals. In addition, performance often improved more rapidly in SAL animals than in animals in the C20 and C40 groups. In other cases, the initial improvement was comparable among groups, but animals in the SAL group reduced escape latencies to levels lower than those seen in the other groups by the end of training. Thus, the significant interactions suggest that cocaine treatment affects the rate of learning, perhaps more than the ability to learn the task.

Dwell ratios for both SF, $t(71)=4.06$, $P<.000$, and CF, $t(71)=2.59$, $P<.001$, groups were significantly greater than 0.25 indicating that animals in both groups were able to effectively consolidate information into reference memory. However, there was no significant difference among treatment conditions within groups for the SF, $F(2,21)=0.391$,

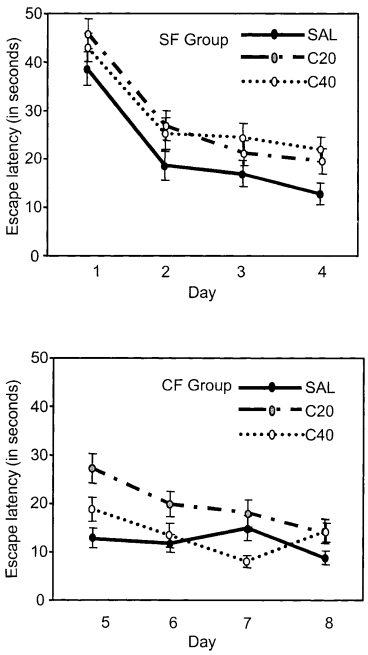

Fig. 4. Escape latency decreased over days of training on standard trials in both SF and CF groups. Escape latency is plotted as a function of days of training for SF and CF groups. SF animals completed standard trials on days 1–4, while CF animals completed standard trials on days 5–8 of training. Error bars indicate ±S.E.M.

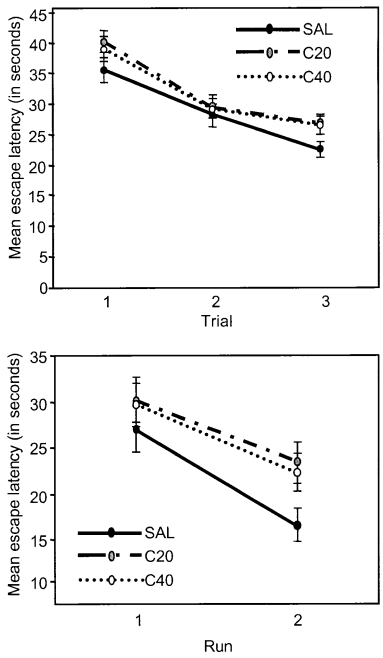

Fig. 5. Working memory was functional regardless of treatment condition, but SAL control animals tended to performed better than cocaine-treated animals. Escape latencies decreased as a function of trials within days (top) and runs within trials (bottom) for SF animals. Error bars indicate ±S.E.M.

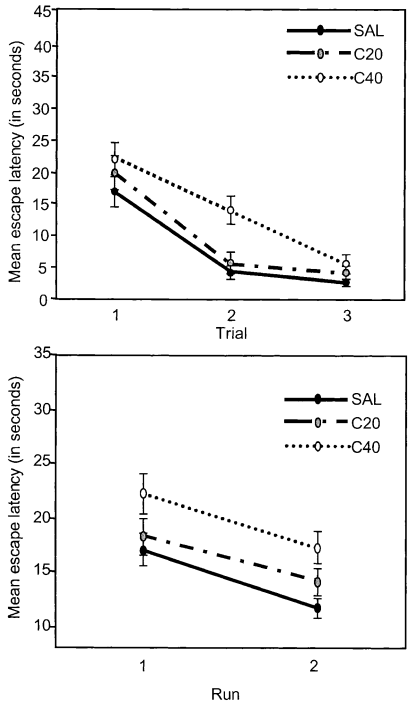

Fig. 6. Working memory was functional regardless of treatment condition, but SAL control animals tended to performed better than cocaine-treated animals. Escape latencies decreased as a function of trials within days (top) and runs within trials (bottom) for CF animals. Error bars indicate ±S.E.M.

$P>.05$, or CF, $F(2,21)=0.212$, $P>.05$, which suggests that cocaine, given according to this dose schedule, does not affect this measure of reference memory to a significant extent. These results indicate that subjects remembered something about the platform location from the previous day, which suggests they are capable of consolidating information into long-term memory regardless of cocaine treatment.

On cued trials, all animals rapidly located the elevated platform and escaped the water. However, as illustrated in Fig. 7, the mean escape latency on cued trials was shorter in the SF group than in the CF group, $Z(1152)=2.42$, $P<.001$, which suggests that swimming and escape experience gained on standard trials carried over into the cued trials, thus, facilitating escape. In both CF and SF groups, animals exposed to 40-mg/kg cocaine took longer to escape the water than their SAL and C20 counterparts (Fig. 8). However, by the fourth day of cued trial training, the escape latencies were comparable among all groups with the exception of the C40 SF animals. Even for those animals, however, considerable decreases in escape latency over training were observed. As was the case in standard trials, the increased escape latency for C40 animals in cued trials was mirrored by an increase in swim path distance (data not shown). The fact that C40 animals had increased escape latencies may reflect a difference in attention or motivational processes that are affected by high doses of cocaine. Further research will be necessary to investigate these possibilities.

Regardless of training condition, dwell ratios on cued trials did not significantly differ from chance levels, $t(71)=1.33$, $P>.05$, and there was no significant difference among treatment conditions, $F(2,21)=1.27$, $P>.05$. This suggests that animals in both groups and all treatment conditions were capable of seeing the elevated platform, and were sufficiently motivated to swim to it rather than persevering in quadrants that previously contained the escape platform.

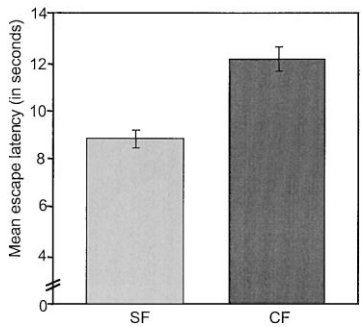

Fig. 7. Pretraining affected escape latency on cued trials. Mean escape latency was pooled for all cued trials and plotted for SF and CF animals. SF animals took significantly longer to escape the water than CF animals. Error bars represent S.E.M. ($Z<0.01$).

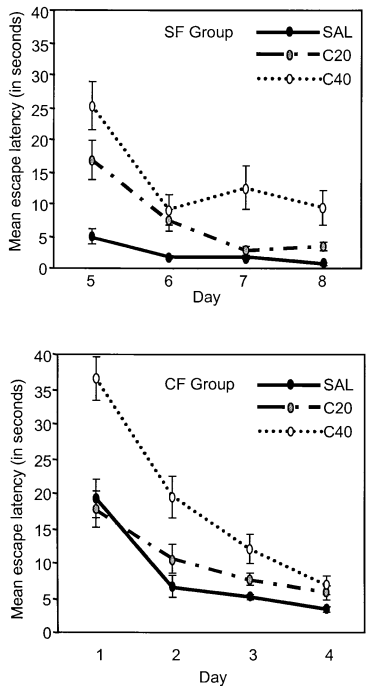

Fig. 8. Escape latency on cued trials decreased over the course of training for animals in both SF and CF groups. Escape latency is plotted as a function of days of training for SF and CF groups. SF animals completed standard trials on days 5–8, while CF animals completed standard trials on days 1–4 of training. Error bars indicate ±S.E.M. In some cases, error bars are obscured by the data points.

4. Discussion

To analyze the effects of chronic exposure to cocaine on spatial memory, rats were given daily injections of cocaine prior to and during training on a water maze task. Half the animals were trained on cued trials prior to standard trials, while the other half was required to locate the hidden platform without prior training. It was shown that pretraining allowed rats to escape the water in less time than if they had no previous experience in the maze regardless of treatment condition. However, animals exposed to high doses of cocaine took longer to escape the water than their control counterparts regardless of training history, suggesting that cocaine does affect the ability of rats to learn this spatial memory task.

Further, animals that did not receive pretraining on the task were more sensitive to the effects of cocaine. This was evidenced by the fact that there was no significant difference in escape latency between SAL and C20 animals in the CF group, but in the SF group C20 animals took longer to find the hidden platform than their SAL counterparts. Analysis of swim path distance data showed that increases in escape latency were due to increases in swim path distance.

Dwell ratios were analyzed to specifically identify effects of cocaine on reference memory. On standard trials, all animals spent more time than would be expected by chance in the quadrant of the maze in which the escape platform was located on the previous day. This suggests that any effects of cocaine on reference memory are not sufficient to disrupt memory over a 24-h period. This finding is supported by the fact that dwell ratios for all animals in cued trials were not indicative of perseverative responding, showing that all animals were physically able and sufficiently motivated to escape the water by swimming to the elevated platform.

Additional support for the lack of reference memory effects is derived from the fact that escape latency on standard trials decreased over days in all groups, indicating that animals were able to learn the behaviors required to efficiently escape the water and to use that information on subsequent days. Thus, reference memory was not abolished by cocaine exposure. However, it is important to note that animals in the C40 consistently took longer to find the hidden platform than their SAL and C20 counterparts.

The measures taken to analyze the effect of cocaine on working memory revealed similar effects. In all cases, performance improved from one run to the next, where identical responses were required within a very short period of time. This indicates that all the animals were capable of retaining some information about the run that had just been completed, and were able to use that information to improve performance on the upcoming run. However, animals exposed to high doses of cocaine typically had longer escape latencies than their C20 and SAL counterparts on standard trial runs. As was the case for the day-to-day measure of reference memory, this indicates that cocaine affects, but does not abolish, working memory.

The effect of cocaine on working memory was also assessed by trial-to-trial measurements. This was more complex than the run-to-run situation because animals were required to retain information regarding extramaze visual cues rather than, or in addition to, proprioceptive cues, which could be used exclusively to improve run-to-run performance. This raises the point that it is not possible to know the nature of the information being retained and used by the animals. It is possible that the information is visual in nature, as it has been shown that rats are hindered in this type of experiment if visual cues are removed from the environment (Zeldin and Olton, 1986). However, between runs within trials, it is possible that the information is purely proprioceptive in nature since the series of responses (i.e., right vs. left turns) required to locate the platform is identical between the first and second runs. This raises a question regarding the nature of what type of information is retained in working memory, and suggests that different types of information may be retained, but only a subset of the retained information used to perform a task. These are testable hypotheses and further research will be required to address these issues.

It is clear that subchronic cocaine administration affects performance on this water maze task, particularly at high doses. However, pretraining attenuates the effects, as significant cocaine effects were only detected in the CF group on standard trials at high doses of cocaine. This may be explained by the fact that pretrained animals are placed in a less stressful situation than their naive counterparts. Since animals in the CF group had prior experience with swimming and seeking refuge on a platform, their task on the standard trials required learning fewer novel skills than was required of the SF group.

For the CF animals, the only difference between the cued trials and the standard trials was that the platform was hidden. CF animals were already proficient swimmers, and it was not necessary for them to habituate to the new environment. Thus, standard trials were less complex, and hence less stressful for the CF animals than for the SF animals. It may be the case that as problems become more complex or stressful, the effects of cocaine become more salient (Holscher, 1999), which has been shown to occur in rats exposed to cocaine prenatally (Spear et al., 1998).

While the present research has illustrated the behavioral effects of cocaine on memory processes involved with water maze performance, future studies will be necessary to identify the neural substrates that may underlie the learning deficit produced by cocaine. Cocaine impinges upon several aspects of cognitive function that could hinder the performance of rats on a spatial learning task. For example, cocaine has been shown to affect attentional processes in human subjects (Ardila et al., 1991). However, in this study, no data were generated that directly indicate attentional or motivational factors were responsible for the differences in

escape latency (although they cannot be ruled out). Therefore, cocaine treatment likely affected some neurobiological change that compromised the spatial learning ability of these subjects. There are a number of neural mechanisms that are affected by cocaine. Researchers have shown that cocaine differentially regulates proteins important for learning and memory, such as CREB, cFos, cJun, and Zif268 (Bhat et al., 1992; Hope et al., 1992; Moratalla et al., 1993; Nestler et al., 1993). In addition, cocaine can inhibit LTP in the hippocampus (Smith et al., 1993), a widely accepted neurophysiological substrate of spatial memory.

In previous studies, it has been shown that lesions of the hippocampus or injections of substances capable of inhibiting LTP cause deficits in spatial navigation abilities in rats (Bane et al., 1996; Bannerman et al., 1997; Butcher et al., 1990). Cocaine has the capacity to inhibit LTP in vitro, and may therefore interfere with the spatial learning abilities of rats through its capacity to block LTP in the hippocampus. However, unlike dextromethorphan or AP-5, well characterized inhibitors of LTP, cocaine does not block LTP by directly interacting with NMDA glutamate receptors in the hippocampus (Smith et al., 1993). Therefore, if the effects of cocaine on spatial memory are due to inhibition of LTP in the hippocampus, a mechanism other than direct interaction with NMDA receptors must be posited.

Regardless of the mechanism by which cocaine exerts its effects, it clearly has the capacity to compromise performance of rats on the spatial navigation task, particularly under stressful conditions. Further research will be required to determine the neurobiological mechanisms by which cocaine exerts its effects, and to elucidate the more subtle aspects of the effects of cocaine on memory, such as what types of memory (e.g., visual or proprioceptive) are affected, and to what extent motivational factors are responsible for impaired learning in cocaine-treated animals.

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