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Effects of Electroconvulsive Shock on the Retention of Cocaine-Induced Conditioning

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ROTHMAN, R. B. AND A. PERT. *Effects of electroconvulsive shock on the retention of cocaine-induced conditioning.* PHARMACOL BIOCHEM BEHAV 49(2) 399–404, 1994.—The purpose of these studies was to determine if ECS is capable of preventing the retention of cocaine-induced conditioned increases in locomotor behavior. One group of rats (paired) was injected with 40 mg/kg of cocaine immediately before a 30 min exposure to a locomotor monitoring chamber while the other group (unpaired) was injected with saline prior to a similar exposure. One hour following return to their home cages, the paired rats were injected with saline while the unpaired animals were injected with 40 mg/kg of cocaine. On day 2, both groups were injected with 10 mg/kg of cocaine and returned to the test apparatus. The presence of conditioned cocaine effects are indicated by enhanced locomotor output in the paired group relative to the unpaired group on day 2. ECS delivered immediately following training on day 1 was effective in preventing the retention of conditioning. ECS delivered 1 h prior to training, 1 h after or 1 h before on day 2 were ineffective. Cocaine-induced conditioning appears to involve associative learning that can be disrupted by ECS delivered immediately following training.

Cocaine Conditioning Locomotor activity Electroconvulsive shock

STIMULI associated with the pharmacological actions of psychomotor stimulants appear to acquire the ability (through classical conditioning) to elicit responses similar to those produced by the drugs themselves or to potentiate their actions during subsequent injections. Tatum and Seevers (28) and Downs and Eddy (5) were among the first investigators to report that situational cues associated with cocaine injections acquired the ability to elicit increased activity, excitement, and eagerness in anticipation of the drug. More contemporary studies in rodents have focused on characterizing the conditioning of either locomotor activity, stereotypy, or motor asymmetries induced by psychomotor stimulants. Cocaine and amphetamine, as well as apomorphine, for example, have been found to serve as effective unconditional stimuli in a variety of studies that have examined the conditioning of general locomotor activity elicited by these drugs (2,8,15–17,22,26). The implicit assumption underlying most of these studies is that the increases in motoric behaviors by stimuli associated with psychomotor stimulants is the result of associative processes. Indeed, conditioning of locomotor activity evoked by such drugs does appear to follow many of the principles of classical conditioning. For example, the magnitude of the conditioned effect appears to be related to the intensity of the unconditioned stimulus (dose of drug) as well as the interval between the conditioned and unconditioned stimulus (16,29). The conditioned response decays with time (1) and is subject to extinction (1,8,9) and the conditioned stimulus follows principles of stimulus generalization (30).

Although all of the studies cited above suggest the involvement of associative learning processes in the apparent acquisition of such conditioned locomotor behaviors, it is possible that nonassociative mechanisms may also be involved. Rushton et al. (21) as well as Gold et al. (7), for example, have proposed that a drug during the training phase could simply interfere with habituation of animals to the apparatus cues. Thus, when tested subsequently with saline, their locomotor responses are greater in magnitude than those trained under saline, because they failed to habituate during the training phase. This is a serious concern that only seldom has been addressed (16).

The purpose of the present series of studies was to evaluate the contribution of associative learning in the acquisition of cocaine-induced conditioned increases in locomotor behavior. Electroconvulsive shock (ECS) is a procedure that is well

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known to disrupt the mechanisms of memory consolidation or retrieval involved in associative learning (10,11,13). In these studies, ECS and sham ECS were administered at various intervals either before or after the conditioning session to evaluate the ability of this manipulation to prevent the expression of conditioned behaviors.

METHOD

Subjects

Male Sprague-Dawley rats (Taconic Farms, PA), weighing 225-250 g at the start of experimentation, were group housed (10/cage) and maintained on a 12 L : 12 D cycle (lights on 0700-1900 h), with food and water available ad lib in the home cage. All animals were adapted to the vivarium conditions for at least 1 week before experimentation was begun. Behavioral testing was always performed between 0900 and 1700 h.

Apparatus

Locomotor activity was assessed in Digiscan photocell activity monitors (Omnitech Electronics, Columbus, OH) which were constructed from clear Plexiglas (30.5 cm H × 42 cm W × 42 cm L). The activity monitors were enclosed in sound-attenuating compartments equipped with a 15 W fluorescent light, a ventilating fan that also provided masking noise, and a one-way mirror (21 × 21 cm) mounted on the door to allow visual observation of the animals during testing. A series of 16 equally spaced infrared photocell detectors were located along two adjacent walls of the chamber 4 cm from the floor surface. Interruptions of the infrared light sources by the animal were recorded and stored by an IBM AT computer. The chambers were scented with peppermint extract to enhance saliency of the environmental cues.

Procedure

We utilized a relatively efficient design to establish and assess the conditioned effects of cocaine. Two groups of rats are employed in this paradigm. On day 1, the first group (paired) is injected with cocaine HCl (40 mg/kg IP) and placed in the locomotor activity chambers for 30 min. One hour following return to their home cages, these rats are injected with saline. The second group (unpaired) is treated in a similar fashion but receives saline prior to placement in the locomotor activity chamber and cocaine (40 mg/kg) in the home cage. On day 2, all animals are challenged with 10 mg/kg of cocaine immediately prior to placement in the locomotor activity chamber. We have previously shown significant conditioned effects of cocaine using this design, which is reflected by significant increases in locomotor output in the paired group on the test day relative to the unpaired group (30). This design has several advantages over those of other studies that have assessed the conditioned effects of psychomotor stimulants with saline or vehicle challenges (see the Discussion section).

In the first experiment, half of the paired (n = 19) and half of the unpaired (n = 21) rats were administered ECS (80 mA of AC current for 0.5 s) through alligator clips attached to the ears immediately following removal from the locomotor chambers on day 1. A full tonic/clonic convulsion was observed in each rat receiving ECS. The other half of the paired (n = 19) and unpaired (n = 20) rats had alligator clips attached to their ears but were not administered ECS following removal from the activity chambers (sham ECS). In the next three studies, a similar design was employed with the exception that ECS was administered 1 h prior to conditioning in Experiment 2, 1 h following conditioning in Experiment 3, and 1 h prior to testing on day 2 in Experiment 4. In Experiment 3, saline and cocaine injections were made 90 min following removal from the activity chambers.

Results

Findings from Experiment 1 are illustrated in Fig. 1. A two-way ANOVA of locomotor activity in the four groups on day 1 (top, Fig. 1) revealed a significant conditioning (paired vs. unpaired) effect, $F(1, 75) = 219$, $p < 0.001$. The treatment effect (ECS vs. sham ECS) and treatment vs. conditioning interaction did not prove to be statistically significant ($F < 1$). Individual post hoc comparisons indicated that the paired groups were significantly different from the unpaired groups under both treatment conditions ($p < 0.01$).

A two-way ANOVA of locomotor activity on day 2 re-

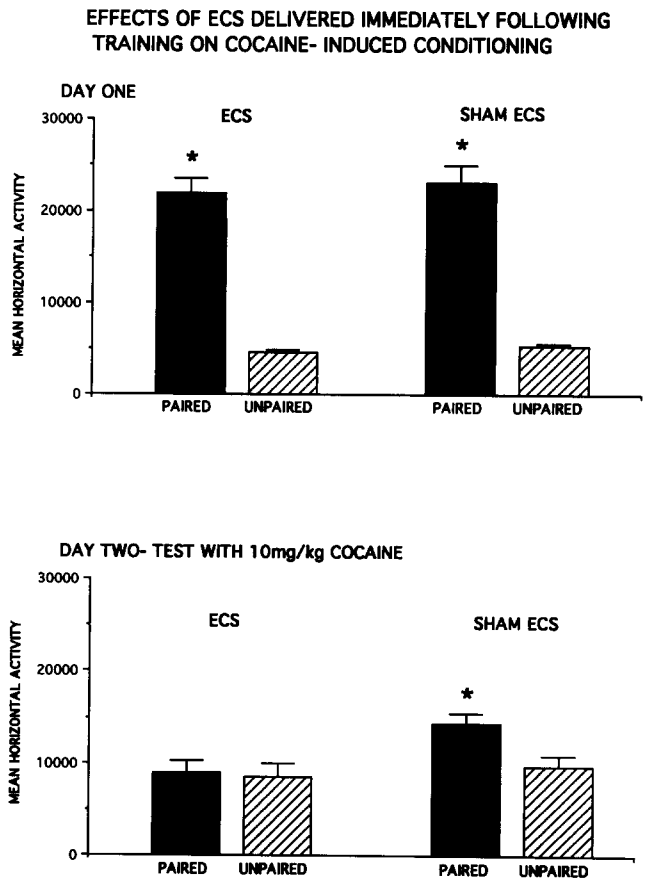

FIG. 1. Effects of ECS delivered immediately following training on the retention of cocaine-induced conditioned increases in locomotor activity. Top portion of figure illustrates horizontal locomotor activity of the paired (40 mg/kg cocaine) and unpaired (saline) rats on day 1. The bottom portion of the figure illustrates the effects of ECS and sham ECS treatments following day 1 training on the expression of cocaine-conditioned increases in locomotor activity when all rats were challenged with a low dose of cocaine (10 mg/kg). n = 19 and 21 for the paired and unpaired ECS groups, respectively, and 19 and 20 for the paired and unpaired sham ECS groups, respectively. *$p < 0.05$ for comparison of the paired groups with their unpaired controls. Vertical lines indicate the SEM.

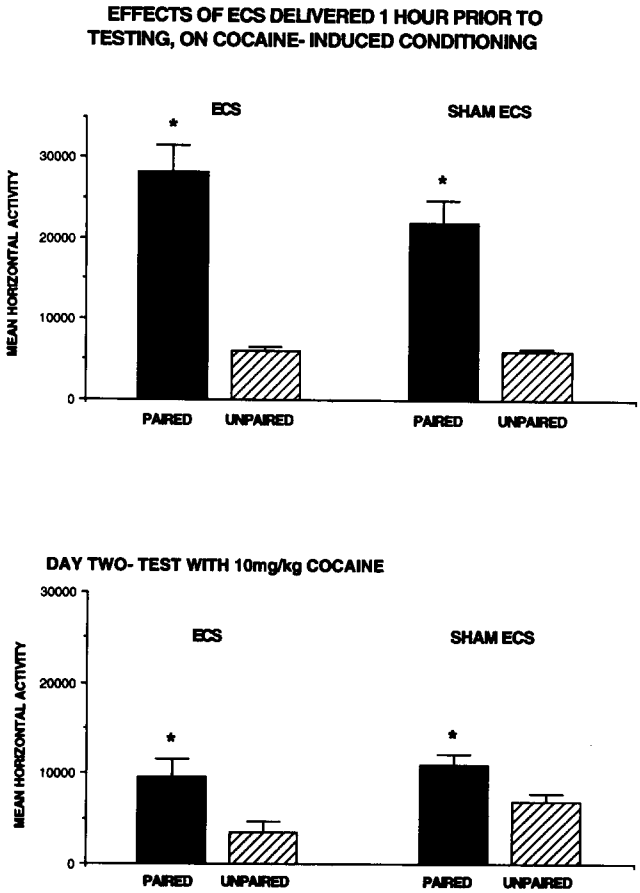

FIG. 2. Effects of ECS delivered 1 h prior to the conditioning session on the retention of cocaine-induced conditioning. n = 12 and 11 for the paired and unpaired ECS groups, respectively, and 12 and 12 for the paired and unpaired sham ECS groups, respectively. *$p < 0.05$ for comparisons of the paired groups with their respective unpaired controls. Vertical lines indicate the SEM.

vealed a significant conditioning effect, $F(1, 75) = 7.26, p < 0.01$, and a significant treatment effect, $F(1, 75) = 4.32, p < 0.05$. Individual post hoc comparisons indicated that only the paired and unpaired sham ECS groups were significantly different from each other ($p < 0.05$). These findings indicate that ECS delivered immediately following the conditioning on day 1 eliminated the behavioral difference between the paired and unpaired groups on day 2.

Findings from Experiment 2 in which ECS was delivered 1 h prior to conditioning are illustrated in Fig. 2. A two-way ANOVA of locomotor activity in the four groups on day 1 revealed a significant treatment (ECS vs. sham ECS) effect, $F(1, 43) = 12.94$, $p < 0.001$, a significant conditioning (paired vs. unpaired) effect, $F(1, 43) = 113.18$, $p < 0.001$, and a significant treatment × conditioning interaction, $F(1, 43) = 4.92$, $p < 0.05$. Post hoc comparisons indicated that ECS had decreased locomotor activity in both conditioning groups (paired vs. unpaired), and that cocaine had increased locomotor activity significantly under both treatment conditions ($p < 005$). A two-way ANOVA of the day 2 data revealed a significant conditioning effect, $F(1, 43) = 15.56$, $p < 0.0005$. Neither the treatment effect nor the treatment × conditioning interaction proved to be statistically significant ($F < 1$).

Findings from Experiment 3 in which ECS was delivered 1 h following conditioning are illustrated in Fig. 3. A two-way ANOVA revealed a significant conditioning effect on day 1, $F(1, 43) = 5.06$, $p < 0.0002$. The treatment effect of treatment × conditioning interaction was not significant ($F < 1$). Individual post hoc comparisons indicated that cocaine had induced statistically significant increases in locomotor activity under both treatment conditions ($p < 0.05$). On day two, a two-way ANOVA revealed a significant conditioning effect, $F(1, 41) = 4.54, p < 0.05$. The treatment effect and the treatment × conditioning interaction failed to reach statistical significance ($F < 1$). Post hoc comparisons indicated that the paired groups were significantly different from the unpaired groups under either treatment condition ($p < 0.05$). Thus, ECS administered 1 h following training failed to alter cocaine-induced conditioned increases in locomotor activity on day 2.

Figure 4 illustrates findings from Experiment 4 in which ECS was delivered 1 h prior to testing. A two-way ANOVA revealed a significant conditioning effect on day 1, $F(1, 42) = 79.26$, $p < 0.0002$. Post hoc comparisons indicated that

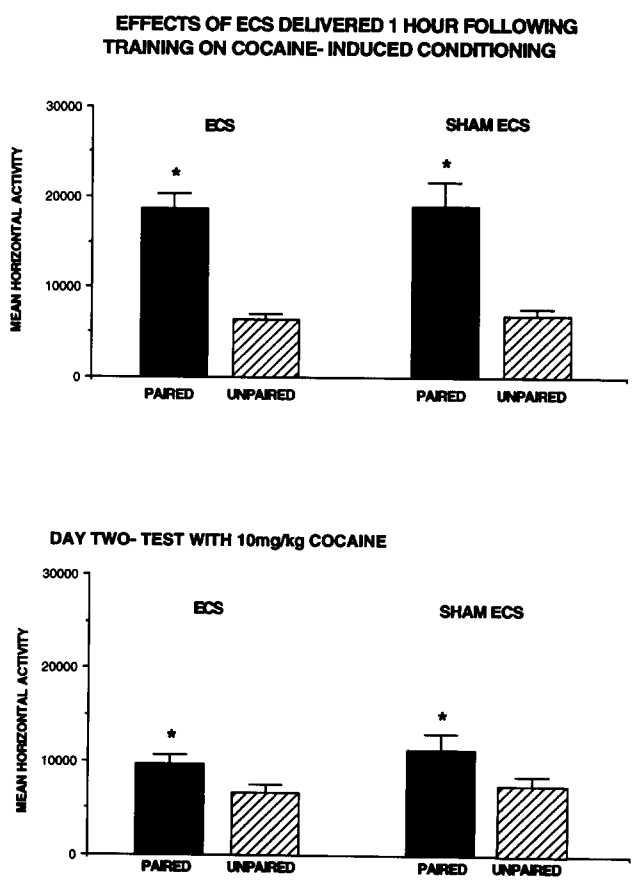

FIG. 3. Effects of ECS delivered 1 h after training on the retention of cocaine-induced conditioning. n = 15 and 8 for the paired and unpaired ECS groups, respectively, and 10 and 14 for the paired and unpaired sham ECS groups, respectively. *$p < 0.05$ for comparisons of the paired groups with their respective unpaired controls. Vertical lines indicate the SEM.

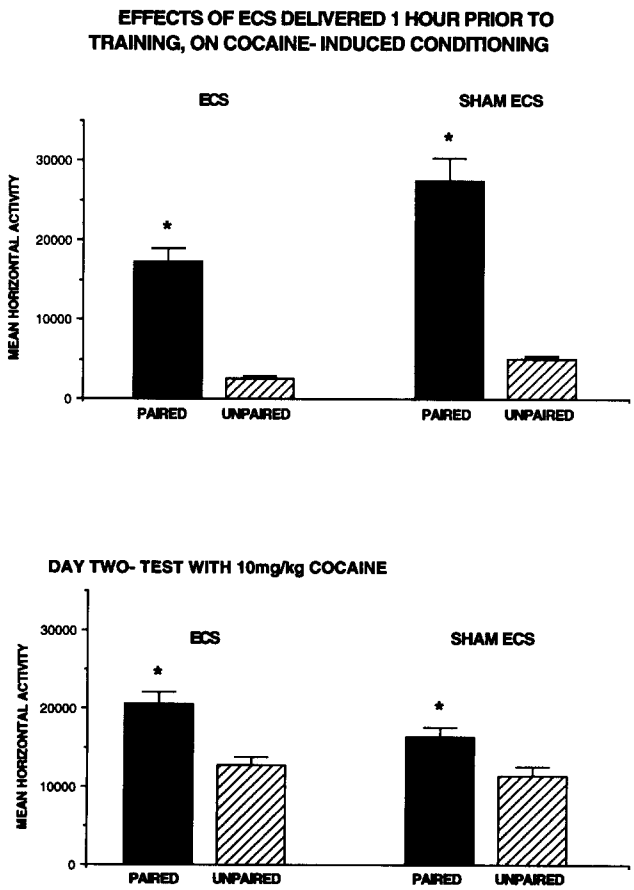

FIG. 4. Effects of ECS delivered 1 h prior to the test session on day 2 on the retention of cocaine-induced conditioning. $n = 11$ and 12 for the paired and unpaired ECS groups, respectively, and 11 and 12 for the paired and unpaired sham ECS groups, respectively. $^*p < 0.05$ for comparisons of the paired groups with their respective unpaired controls. Vertical lines indicate the SEM.

cocaine had increased locomotor output significantly under both treatment conditions ($p < 0.05$). A two-way ANOVA also revealed a significant conditioning effect on day 2, $F(1, 42) = 8.56$, $p < 0.006$. Post hoc comparisons indicated that the paired groups were significantly different from the unpaired groups under either treatment condition. Thus, ECS delivered 1 h prior to testing also failed to prevent the expression of cocaine conditioned behavior.

DISCUSSION

In the first experiment, rats injected with high doses of cocaine (40 mg/kg) on day 1 prior to placement in the locomotor activity chambers (paired) exhibited significant increases in horizontal locomotor activity relative to those injected with saline (unpaired). On day 2, when the sham ECS-paired and -unpaired rats were tested with a low dose of cocaine (10 mg/kg), the paired animals had activity levels that were significantly higher than the unpaired. Because both groups of rats received the same exposure to cocaine on day 1, the difference in locomotor behavior must be related to the context in which the drug was experienced. One presumption is that the apparatus (and other) cues in the paired group on day 1 had acquired (through classical conditioning) the ability to elicit increases in locomotor activity on day 2.

It should be noted that the conditioning paradigm in these studies is somewhat unconventional in that the unconditioned stimulus (cocaine) is present during the test for conditioning, although at a lower dose (intensity). Conditioned drug effects in other studies have generally been assessed in the conditioning chamber following injections of saline or the drug vehicle. This may not always be appropriate or adequate to reveal conditioned drug effects in all circumstances, especially when rather subtle conditioned responses are expected—as in the present paradigm utilizing a single 30-min conditioning session. The pharmacological actions of cocaine on the training day produce two critical effects that enter into the conditioning process. First, cocaine has motivationally significant consequences that probably serve as the basis for its ability to act as an unconditioned stimulus (14). Second, cocaine also produces a variety of interoceptive cues (e.g., alterations in the heart rate, blood pressure, etc.) through peripheral sympathetic activation, that have the potential of contributing to the total stimulus complex which comes to serve as the conditioned stimulus. It has been shown, for example, that leg flexion reactions in dogs can be conditioned to interoceptive cues produced by peripherally administered epinephrine, norepinephrine, and acetylcholine (3). It is likely that the locomotor stimulatory effects of cocaine (determined through the CNS) are conditioned to a stimulus complex consisting of both environmental as well as drug-produced interoceptive cues. If this is the case, the most robust conditioned responses would be expected to be elicited in the presence of cues that are most similar to those present during the conditioning process (i.e., both interoceptive as well as environmental).

An additional reason to test in the presence of a low dose of cocaine is to amplify the rather subtle conditioned effects that are likely following a 30-min conditioning session. There is considerable evidence, for example, to indicate that psychomotor stimulants enhance conditioned responses in other learning paradigms (12,20). Using a conditioning paradigm similar to the one described, we have found recently that the rather modest conditioned effects seen following a saline pretreatment on day 2 are accentuated considerably by 10 mg/kg of cocaine (unpublished observations). The ability to rapidly establish and measure conditioned drug effects is critical for the success of the present studies.

ECS delivered immediately following removal of the animals from the locomotor chambers on day 1 prevented the appearance of a difference in locomotor output between the paired and unpaired groups on day 2. It seems likely that ECS delivered at this temporal interval relative to the training session interfered with the ability of the conditioned animals to recall the association between the pharmacological actions of cocaine and the environmental, situational, and interoceptive cues present during the training session.

ECS has classically been found to produce retrograde amnesia in humans (24,25) as well as animals in appetitively (11) and also aversively motivated learning tasks (4,10,11). The initial assumption was that ECS disrupted neural activity necessary for memory consolidation to occur (4). This assumption has been challenged by a number of investigators (11), and other mechanisms have been proposed to account for performance deficits seen following ECS. Lewis (13), for example, has postulated that ECS blocks retrieval mechanisms underlying memory rather than its storage. Whatever the mechanism, it is well established that ECS has the ability to disrupt subsequent performance of learned behaviors when

administered at certain critical intervals following the initial learning. The posttraining interval over which ECS is effective in disrupting learning varies from seconds to hours depending on the task, length of ECS, and intensity of current as well as other factors (4). In the present study this interval appears to lie between a few minutes and 1 h after training. ECS delivered 1 h following the conditioning session was no longer effective in preventing the expression of conditioned behavior on day 2. ECS delivered 1 h prior to training or 1 h prior to the test session on day 2 were equally ineffective, suggesting that whatever memory process is disrupted occurs within 1 h following conditioning.

Although the assumption here is that ECS has disrupted the recall of conditioned drug effects, two other alternative mechanisms merit consideration. It could be argued, for example, that ECS has interfered with the recall of habituation to the apparatus cues on day 1. Thus, when the paired and unpaired ECS rats are reexposed to the apparatus on day 2, their performance should be equivalent because both groups fail to recall the habituation on day 1 (as well as the drug conditioning in the paired group). This explanation, however, is not supported by the findings. If ECS prevents habituation, the ECS-unpaired as well as the ECS-paired rats should have activity levels on day 2 that are significantly higher than the sham-ECS unpaired rats. This was not the case, because no difference in locomotor output was detectable among the three groups in question. ECS apparently did not disrupt the memory of habituation on day 2. Interestingly, the disruptive effects of ECS appeared to be selective for the association between the conditioned stimuli and the drug. Another possibility is that ECS is an aversive event that results in the establishment of a conditioned emotional response to stimuli (locomotor chamber) preceding it. Such a mechanism could be expected to decrease locomotor behavior in the activity chambers on day 2 by eliciting competing freezing behavior that would eliminate the difference between the paired and unpaired ECS groups. This mechanism, however, also cannot account for the lack of a behavioral difference between the paired and unpaired rats on day 2, because no difference in locomotor output on day 2 was observed between the unpaired rats treated with ECS and those treated with sham ECS. There is no evidence that ECS per se is able to decrease subsequent locomotor behavior on day 2 (for whatever reason).

Performance deficits indicative of memory disruptions can also be produced by pharmacological manipulations. A variety of protein synthesis inhibitors, for example, have been shown to prevent the formation or maintenance of memory when administered immediately following learning (4). The assumption behind such studies has been that memory storage is in some way associated with the synthesis of protein molecules. In a recent study, Silverman et al. (23) evaluated the effects of cycloheximide (a protein synthesis inhibitor) on conditioned drug effects in rats. These investigators conditioned apomorphine-induced rotational behavior in rats with unilateral lesions of the dopaminergic nigrostriatal pathways to apparatus cues. Injections of cycloheximide immediately following removal of the animals from the apparatus were found to inhibit conditioned rotational behavior assessed 2 weeks later. In summary, it appears that conditioned responding to cues associated with drugs involves similar memory processes to those seen in other learning paradigms, and that such conditioning requires the operation of associative learning processes.

Although ECS did not prevent the retention of conditioning when administered 1 h prior to the training session, it did decrease significantly basal locomotor activity as well as cocaine-induced increases in locomotor activity on day 1. Interestingly, using microdialysis procedures, we have previously found that a single ECS produces significant decreases in extracellular dopamine of the nucleus accumbens in rats, which can be detected 1 h following seizures (6). This area of the brain is assumed to mediate the locomotor stimulatory actions of cocaine (19) as well as motoric behavior (27) in general. A compromise in dopaminergic function in the n. accumbens by ECS might underlie the decrease in motor output seen in Experiment 2 as well as in Experiment 4 following seizure induction.

ECS delivered 1 h after training had little impact on the subsequent expression of cocaine-induced conditioned increases in locomotor activity on day 2. Administration of ECS 1 h prior to testing seemed to decrease locomotor output in the unpaired rats without having a significant impact on the paired animals. The consequences of this was to enhance the differential between the two groups relative to that seen in the sham ECS-treated animals.

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