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Selective Facilitation of Memory Attributes by Strychnine[1]

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BRENNAN, M. J. AND W. C. GORDON. *Selective facilitation of memory attributes by strychnine.* PHARMAC. BIOCHEM. BEHAV. 7(5) 451–457, 1977. — In two experiments, the effects of strychnine on the specific memory attributes of prior discrimination training were assessed in terms of subjects' performance under various discrimination reversal conditions. Mice were trained in a discrimination task with two redundant relevant cues. Immediately after their last training trial, subjects were administered an intraperitoneal injection of either strychnine (1.0 mg/kg) or saline. When both training cues were reversed (Experiment 1), strychnine treated subjects were observed to exhibit greater performance decrements than saline-treated subjects upon initial exposure to reversal conditions, suggesting that strychnine had enhanced the memory of a relatively specific stimulus-response association. When subjects were tested under partial cue-reversal conditions (Experiment 2) strychnine treated animals exhibited greater utilization of one of the redundant relevant stimuli than the other, while saline-treated animals exhibited no preference.

Discrimination learning Memory attributes Memory facilitation Strychnine

NUMEROUS published reports suggest that when subconvulsive doses of CNS stimulants are administered to rodents shortly after a learning trial, subsequent retention test performance is improved (cf. [3]). Such facilitated retention test performance has been noted within a variety of learning paradigms and with drugs having a variety of specific mechanisms of action (cf. [3]). Aside from a few notable exceptions (e.g., [1,5]; but also see [8]), most experiments have been consistent in reporting that this enhanced performance decreases as the interval between training and drug administration is increased (e.g. [13]). For this reason, the facilitation effect has been interpreted primarily within the framework of a memory consolidation model (cf. [12]). According to this interpretation, the improved retention test performance results from the drug-induced enhancement of the neurobiological processes which underlie memory storage.

As a result of the proposed relationship between CNS stimulants and memory storage, most of the studies dealing with the effects of these drugs on retention performance have been conducted to delineate the characteristics of memory storage processes. Such studies have not been concerned with the specific characteristics or components of the memory being stored, nor have they dealt with the possibility that the effects of the drugs might differ depending on the specific characteristics of the memorial representation of a learning experience. Because of this absence of attention to the multiple components of a memory, much of the research concerning memory enhancement seems to imply that a memory is a unitary element, processed and stored as a single bit of information. Such an idea, however, is not consistent with much of the recent evidence concerning learning and memory retrieval in animals. It is clear that within any learning situation an animal is confronted with a variety of stimuli which could, in effect, serve as CS's or discriminative stimuli for instrumental responding. It is equally clear that when redundant relevant stimuli are available (i.e., compound stimuli each component of which is equally predictive of reinforcement), certain stimuli tend to gain control over responding whereas others gain only minimal control (e.g. [6]). Furthermore, it has been demonstrated that while a variety of stimuli from a learning situation may serve as retrieval cues on a subsequent retention test, certain cues are more effective than others in aiding retrieval (e.g. [15]).

These kinds of data suggest that memories may consist of a variety of attributes, each representing some part of a previously learned event (cf. [14,16]) and that these different attributes may be differentially stored or processed so that some attributes are more accessible than others. Such a theoretical framework raises a number of questions concerning the specific manner in which CNS stimulants enhance retention test performance. It is possible, for example, that the enhancement results almost totally from the strengthening of the memory attributes

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representing the critical aspects of learning (i.e., stimulus-response or response-reinforcer associations), and that attributes representing contextual stimuli are too weak to benefit from the drug treatment. On the other hand, it is feasible that in many cases the critical memory attributes are at maximal strength following learning and that drug-induced enhancement results primarily from strengthening attributes representing contextual stimuli. Finally, drug-induced facilitation could result from the strengthening of general memory attributes which have little specific relevance to a particular learning situation. Such attributes might represent experiences such as being handled or the use of attentional strategies which could transfer positively to almost any retention test situation.

Since such alternatives have received little or no attention in the drug-enhancement literature the present studies represent an initial effort to explore the question of how CNS stimulants affect the specific attributes of a memory. In these studies, mice were injected with strychnine sulphate following acquisition of a complex discrimination task. The particular task employed was able to be solved on the basis of either a brightness or spatial pattern discrimination. Specifically, these studies attempted to determine (1) the degree to which strychnine enhances the memory of the specific stimulus-response association in this task, and (2) whether strychnine differentially affects the retention of important, relevant stimuli in the learning situation.

EXPERIMENT 1

The purpose of Experiment 1 was to determine if the posttraining administration of strychnine enhances an animal's memory of the specific association formed in training between the discriminative stimuli and the correct response. To make this determination, animals underwent discrimination training followed by drug administration and were tested under a reversal of the previously correct stimulus conditions. It was reasoned that if strychnine acts to enhance the memory of a specific S^+ – response association, strychnine-treated animals should perform more poorly under reversal conditions than saline-injected controls, especially upon initial exposure to the new contingency. However, if strychnine acts only to enhance the memory of a nonspecific features of learning (e.g., handling or apparatus exposure), the drug injected animals would be expected to show better performance under reversal conditions than controls since this more general information should transfer positively to the retention test situation.

METHOD

Animals

Forty-two male, Heterogenous (Binghamton HET) mice, 60–80 days old, were used. The Binghamton HET stock was derived from an 8 way cross (LP/J, Balb/cJ, MA/J, LG/J, SM/J, 129/J, DBA/2J and C57BL/6J). Animals were housed 4–5 to a cage in a temperature-controlled vivarium, with a 12 hr/12 hr light-dark cycle in effect.

Apparatus

The apparatus represented in Fig. 1, was a Plexiglas maze consisting of a start compartment, 6 separate discrimination units, and a goal compartment. The start compartment was 10 cm long, 3.5 cm wide and 5 cm high and was painted flat gray. Each of the 6 discrimination units consisted of an 8 × 3.5 × 5 cm flat gray entryway which led to a chamber divided into 2 alleyways – one painted flat white and the other flat black. A 5 cm high barrier, beginning 3 cm past the end of the entryway, separated the two alleyways. Each alleyway was 25 cm long, 3.5 cm wide and 5 cm high. A piece of clear vinyl was used to block the exist of the incorrect alleyway of each maze unit. The vinyl barrier was positioned so that it could not be seen from the choice point of each unit.

The discrimination units were positioned linearly such that the entryway of each unit followed either the start compartment (in the case of Unit 1) or the exits from the preceding discrimination unit. Sliding doors, painted flat gray, could be inserted between any compartment of the maze and the entry-way to the next compartment.

Following the last discrimination unit was a goal compartment, which consisted of an entryway (7 × 3.5 × 5 cm) painted flat gray and a white goal area (15 × 3.5 × 5 cm). A plastic drinking cup, 1.5 cm in dia, was mounted on the floor of the goal area, 1 cm from the end of the goal compartment. The entire maze was covered with a sheet of clear Plexiglas, with separate removable sheets of clear Plexiglas covering the start and goal compartments.

Procedure

Prior to the start of training, all animals were placed on water deprivation for 48 hr. Subjects in each of the four experimental groups (N = 8 in each group) were given either one or two acquisition trials in the maze (1 trial per day), since previous studies in our laboratory had suggested that the effects of strychnine on retention of the present learning task often varied as a function of degree of learning (e.g. [2]). During training, the white alleyway allowed the animal entry into either subsequent discrimination units or the goal compartment. The discrimination units were arranged such that the white alleyways appeared in a L, R, R, L, L, R sequence (L = Left, R = Right) during training. The decision to make the white alleyways correct for all animals during acquisi-

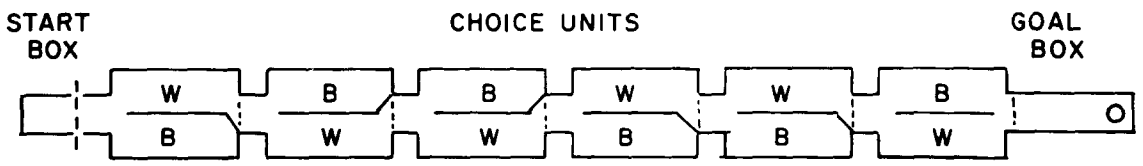

FIG. 1. Schematic representation of discrimination training apparatus (W = White, B = Black).

tion was based on the fact that pilot animals had shown a marked initial preference for the black alleyways in this maze. Thus, all animals were originally trained to go away from the preferred alleys.

At the start of a training trial, the door between the start compartment and the first discrimination unit was closed; the doors between the maze compartments were open. The subject was placed into the start compartment and the door between the start compartment and the first discrimination unit was opened. A correctional procedure was in effect during training and testing, i.e., within a discrimination unit, animals could repeatedly enter the incorrect alleyway. However, only the initial entry of the incorrect alleyway was scored as a choice error.

Following entry into the goal compartment, animals were given a 10 sec access to a 0.3% saccharin solution. Immediately after removal from the goal compartment on Day 1, animals, in two of the experimental conditions (ST1 and SA1) received an intraperitoneal injection of either strychnine sulphate (1.0 mg/kg dissolved in 0.9% saline) or 0.9% saline, respectively, adjusted for an injection volume of 1 cc/0.1 kg body weight. In prior work in this laboratory with HET mice, the 1.0 mg/kg dose appeared to be the most effective of the various dose levels of strychnine tested.

Animals in the remaining two experimental conditions (ST2 and SA2) received no injections on the first day of training. After removal from the goal compartment, these animals were returned to their home cages. On Day 2, animals in the ST2 and SA2 treatment conditions were given an additional acquisition trial in the maze. Immediately after removal from the goal compartment, animals were administered an intraperitoneal injection of either strychnine (1.0 mg/kg) or physiological saline, respectively.

To determine any possible proactive effects of strychnine on maze performance, two groups of mice ($N = 5$ in each group) were included in this study. These animals received no prior training in the maze, instead they were placed in the goal compartment, given a 10 sec access to the saccharin solution, and immediately after removal from the goal compartment were administered an intraperitoneal injection of either strychnine (1.0 mg/kg) or saline.

Twenty-four hr after drug treatment, testing was initiated for all animals. During testing both the brightness cue and the spatial sequence of correct choices were reversed such that the black alleyway of each discrimination unit was correct during testing and the black alleyways appeared in a R, L, L, R, R, L sequence. Animals were tested for four days (1 trial per day). No further drug treatment was administered during testing. During both training and testing, all animals were given a 10 min access to water in their home cages, 30 min following each experimental session.

RESULTS AND DISCUSSION

Prior to drug treatment, no significant differences in choice errors were noted between the various experimental groups. Separate repeated measures analyses of variance (cf [10]), performed on the choice errors by subjects within each of the two degree of training conditions revealed that, in neither case were there significant acquisition differences between animals in the two drug treatment conditions. Further, the absence of a significant treatment groups by maze unit interaction suggested that patterns of error responding were comparable for the various experimental groups during training. Animals receiving two acquisitions trials did, however, exhibit a significant reduction in choice errors on the second training trial, $F(1,14) = 5.14$, $p<0.05$.

The choice errors exhibited by subjects in the various experimental groups during the 4 test trials were analyzed by a repeated measures analysis of variance with degree of training and drug treatment as between group factors and test days and maze units as the repeated factors. While no significant main effect of drug treatment or degree of training was observed, a significant maze unit by drug treatment interaction was noted, $F(5,140) = 3.80$, $p<0.01$. In order to further examine this finding, separate analyses of variance were performed on the choice errors in each of the various discrimination units during testing. The results of these comparisons revealed that strychnine treated animals made significantly more choice errors in the first discrimination unit than saline-treated animals, $F(1,28) = 8.39$, $p<0.01$. No significant differences in errors as a function of drug treatment were noted in the remaining discrimination units.

While strychnine-treated subjects tended to make more choice errors in maze Unit 1 than saline treated animals across all 4 test days, the disruption of performance by strychnine was evidenced primarily in terms of animals performance on the first test day. As illustrated in Fig. 2, subjects administered strychnine after training, made significantly more choice errors in the first discrimination unit than saline-treated animals on the first test trial, $F(1,28) = 4.85$, $p<0.05$. However, on the remaining test trials, between groups differences in error responding in the first discrimination unit failed to reach statistical significance.

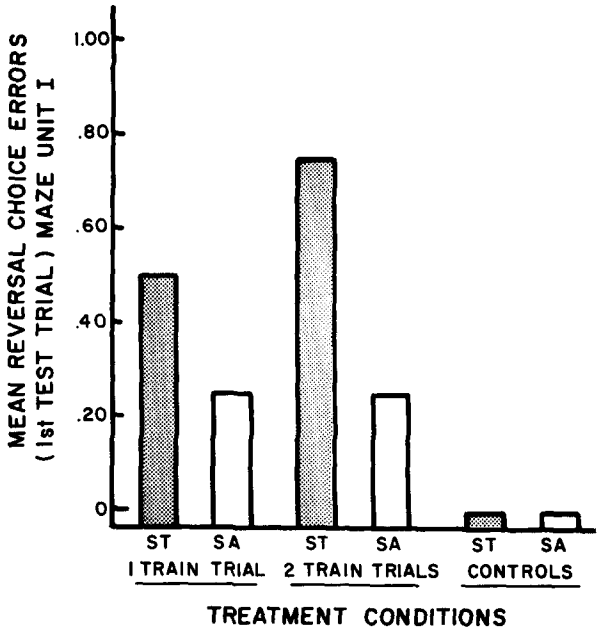

FIG. 2. Mean choice errors in the first discrimination unit on test trial 1 as a function of degree of training and drug treatment.

A comparison of the test performances of the control group animals suggested that the observed differences in errors made by experimental animals was not due to some proactive influence of strychnine such as a change in motivational state or a change in brightness preference. A repeated measures analysis of variance on choice error responding by control subjects revealed that there was neither a significant main effect of drug treatment nor a significant interaction of maze unit by drug treatment, suggesting that the response patterns of control subjects were comparable during testing. It should be noted that control animals made a few errors during testing which is consistent with the previous finding that untrained animals prefer the dark alleyways in the present maze (e.g [4]). Importantly, strychnine administration did not appear to alter this preference in untrained control animals.

Finally, there was no significant main effect of degree of training on choice errors in the present experiment. Animals given two acquisition trials prior to drug treatment, did, however, exhibit a tendency towards a greater number of choice errors during initial reversal testing. This tendency was reflected in a significant interaction of degree of training by test trial by maze unit, $F(15,420) = 2.12$, $p<0.05$. Further the performance of subjects given only a single acquisition trial tended to be more variable during testing. On this account, animals in the subsequent study were given two acquisition trials prior to drug treatment.

Taken together, the results of Experiment 1 suggest that when strychnine is administered following low levels of discrimination training, subsequent performance under reversal conditions is impaired relative to saline-treated mice. These findings are consistent with the notion that strychnine enhanced the memory of the specific association between the discriminative stimuli and the correct response. Such an interpretation is supported by the finding that the performance decrement occurred only early in retention testing prior to the animals' introduction to the new contingencies (i.e., errors in the initial maze unit). This result suggests that strychnine did not simply inhibit the learning of the new contingencies present on the retention test. These results do not rule out the possibility that strychnine also may have enhanced memory attributes associated with more general aspects of prior training (i.e., handling, etc.). However, had such enhancement occurred, one might have expected that strychnine treated mice should perform at least as well if not better than saline treated animals under reversal conditions, since such general features of training would have remained the same during testing.

EXPERIMENT 2

The results of Experiment 1 suggest that strychnine facilitated the retention of specific associations between discriminative stimuli and responses. However, since in Experiment 1 both brightness and spatial cues were available redundantly as discriminative stimuli, it is impossible to determine whether the facilitation occurred for only one of the possible associations or both. The purpose of Experiment 2 was to determine whether or not strychnine differentially affects the retention of the redundant relevant stimuli in this learning situation. This was accompanied by training animals as in Experiment 1 and then reversing either the brightness or the spatial cues while leaving the other cue the same as in training. This procedure does not allow for any clear assessment of positive or negative transfer to the retention test situation. However, it does permit an evaluation of whether strychnine-injected and control mice differ in the tendency to utilize one of the stimulus dimensions as opposed to the other.

METHOD

Animals and Apparatus

Twenty-two male (60–80 day old) HET mice were used for the present experiment. Animals were trained and tested in a six-unit maze, identical to that described in Experiment 1.

Procedure

Prior to training, all mice were placed on water deprivation. Training conditions were similar to those employed in Experiment 1. Mice were given two training trials (1 per day) in the maze with two redundant relevant stimulus cues. During training, the white alleyway of each discrimination unit was correct and the discrimination unit was arranged such that the white alleyways appeared in a L, R, R, L, L, R sequence. No injections were administered following the first training trial. After removal from the goal compartment, animals were returned to their home cages and after 30 min were given a 10 min access to water. On the basis of initial choice errors on the first training trial, animals were matched and randomly assigned to one of two drug treatment conditions-strychnine (ST) or saline (SA). The animals within a given drug treatment condition were subsequently randomly assigned to one of two partial reversal test conditions (BR = Brightness reversed/Sequence same; or SR = Brightness same/Sequence reversed), resulting in four experimental conditions: ST/BR (N = 6), SA/BR (N = 6), ST/SR (N = 5) and SA/SR (N = 5).

On Day 2, all mice were administered an intraperitoneal injection of either strychnine (1.0 mg/kg) or 0.9% saline, immediately after removal from the goal compartment were returned to the home cage, and after 30 min received a 10 min access to water. Twenty-four hr after drug treatment, reversal testing was initiated for all animals. For animals in the Brightness reversed condition (BR), the black alleyway of each discrimination unit was correct; the discrimination units were arranged so that the black alleyways appeared in the same sequence of correct choices as was in effect during training (e.g., L, R, R, L, L, R). For animals in the sequence reversed condition (SR) only the sequence of correct choices was reversed; during testing the white alleyway of each maze unit was correct and the maze units were arranged so that the white alleyways appeared in a R, L, L, R, R, L sequence. Animals were tested for 4 days (1 trial per day).

RESULTS AND DISCUSSION

Prior to drug treatment, there were no significant differences in the choice errors made by the various experimental groups. As was the case in Experiment 1, however, subjects in the present experiment exhibited a significant reduction in number of choice errors on the second training trial, $F(1,18) = 11.916$, $p<0.01$.

The mean number of choice errors for all test conditions over all test days is represented in Fig. 3. A repeated measures analysis of variance was conducted on these data with drug treatment and test condition as between group factors and test trials and maze units as repeated factors. The analysis revealed a significant effect of drug treatment, $F(1,18) = 10.92$, $p<0.01$, as well as a significant three way interaction of drug treatment, test condition and test trials, $F(3,54) = 3.06$, $p<0.05$.

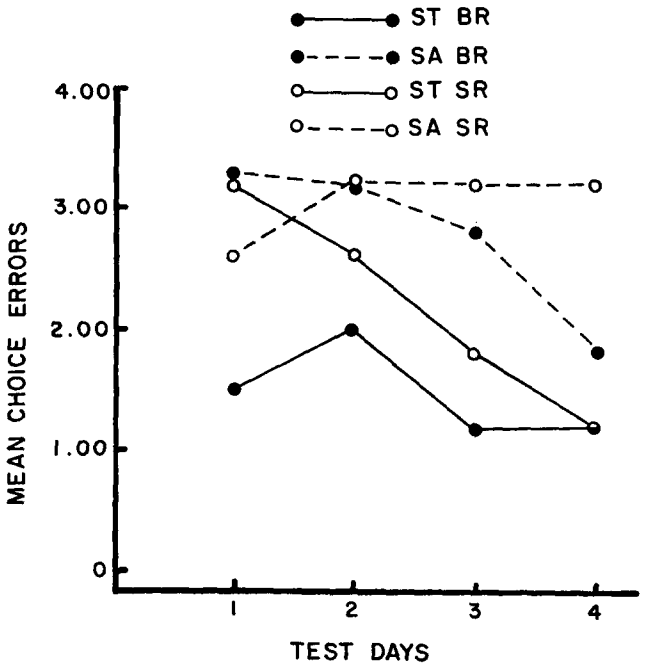

FIG. 3. Mean choice errors during testing as a function of drug treatment and test condition.

To determine the basis of the interaction effects in these data, a separate repeated measures analysis was performed on the data for each individual test trial. As in Experiment 1, the most pronounced effects of drug treatment appeared to be in evidence on the first test trial. The analysis of choice errors on the first test trial revealed a significant interaction of drug treatment by test condition, $F(1,18) = 5.79$, $p<0.05$, as well as a significant test condition by maze unit interaction, $F(5,90) = 2.53$, $p<0.05$. Critical difference tests [11], used to compare the individual treatment means, revealed that the test condition by drug treatment interaction resulted from the fact that the ST/BR animals made significantly fewer errors than the ST/SR animalss ($p<0.05$), while the SA/BR and SA/SR animals did not differ from each other ($p>0.05$). This interaction between drug treatment and test condition was even more pronounced in the initial units of the maze. Figure 4 represents the mean choice errors for all groups in the first 2 maze units on Day 1. An analysis of these data revealed a significant effect of test condition, $F(1,18) = 14.55$, $p<0.01$, as well as a significant interaction between test condition and drug treatment, $F(1,18) = 5.77$, $p<0.05$. A comparison of the individual group means again, showed that the ST/BR animals made significantly fewer errors than the ST/SR animals ($p<0.05$), and that the SA/BR and SA/SR animals did not differ significantly ($p>0.05$). However, these comparisons also showed that the ST/SR animals made significantly more errors than the SA/SR animals.

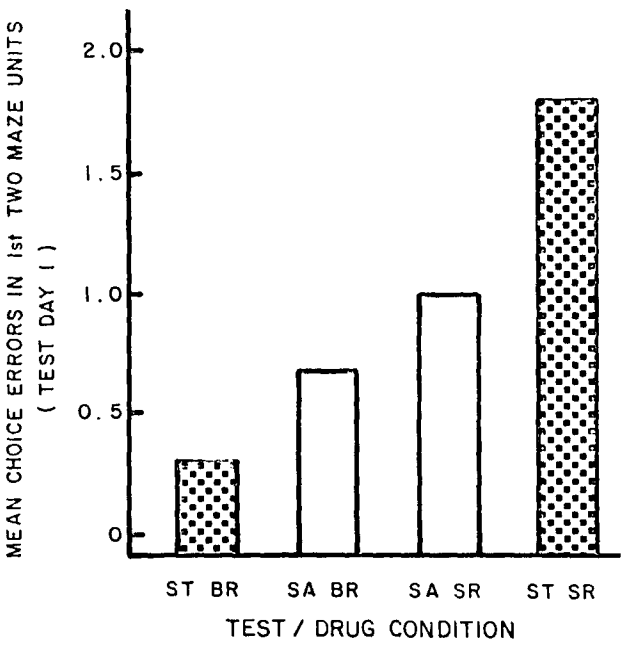

FIG. 4. Mean choice errors in the first two discrimination units on test trial 1 as a function of drug treatment and test condition.

The fact that the two saline injected groups did not differ significantly in number of errors suggests that these animals were able to utilize brightness and sequence information equally well during testing. There is little in these results to suggest that the saline-treated animals processed brightness and sequential information differentially. On the other hand it is clear that the strychnine-treated animals performed better when the previously acquired sequence information was available (i.e., ST/BR group) than when only the originally correct brightness information was present (i.e., ST/SR group). These results suggest that strychnine enhanced the processing of sequence information much more than information concerning brightness. Furthermore, the finding that the ST/SR animals performed more poorly than the SA/SR animals suggests that strychnine may have enhanced the processing of sequence information at the expense of processing brightness cue information.

Analyses of the error data on the remaining test days revealed no significant differences on Day 2, but significant effects of the drug treatment on Day 3, $F(1,18) = 11.07$, $p<0.01$ and Day 4, $F(1,18) = 6.91$, $p<0.05$. In both cases the significant effects resulted because the strychnine-injected animals made significantly fewer errors than the saline-treated controls. As Fig. 3 would suggest, this main effect of drug treatment resulted primarily from the gradual decline in errors by the ST/SR animals, relative to the saline controls. A variety of explanations for this decrease in errors might be advanced. It is possible, for example that the strychnine-injected animals not only showed better retention of the specific sequence of turns during tests, but also attended more to the sequence dimension during testing (a view supported by the data from Day 1) and that this enhanced attention

resulted in faster learning of the new sequence cue contingencies. On the other hand, it also would be possible to explain this finding by suggesting that the administration of strychnine enhances the subsequent ability of an animal to learn any new contingency. While this explanation is impossible to rule out in the present study, data from numerous other studies suggest that strychnine has little proactive effect on learning 24 hr after drug administration (e.g. [8]). A third, related possibility is that strychnine enhances the processing of general task related information, and thus, may facilitate the learning of a new contingency that occurs in the same situation as original training. This interpretation is always difficult to rule out because it is virtually impossible to equate trained and nontrained animals in terms of all aspects of training other than the learning contingencies.

GENERAL DISCUSSION

While the present studies represent only a preliminary attempt to look at the effects of CNS stimulants on specific attributes of memory, the results of these studies provide an important base for future work in this area. First, it is clear from the results of Experiment 1 that strychnine does not facilitate retention test performance simply by enhancing an animal's memory of general aspects of training such as handling or apparatus exposure. The relatively poor performance of the strychnine-treated animals under reversal conditions suggests that the drug acts in some way to enhance an animal's memory of a specific association between discriminative stimuli and the correct response. Otherwise, reversal of these specific associations should have had no greater effect on the strychnine-injected animals than on the saline-treated controls. This finding is similar to that reported by Gordon and Spear ([9]; see also [7]) using passive avoidance as the training task and active avoidance learning as the retention test. In these studies animals which were injected with strychnine following original learning acquired active avoidance more slowly than the control animals, suggesting that strychnine had enhanced the memory of the specific response tendency acquired during training.

Second, the results of Experiment 2 provide initial evidence that the facilitative effects of strychnine may be restricted, at least functionally, to selected memory attributes. This evidence stems from the fact that mice injected with saline performed comparably when brightness and sequence cues were reversed on the retention test. This suggests that there was little differential retention of brightness and sequence information by the control animals. In contrast, the strychnine treated animals performed significantly better when the original sequence cues were available on the retention test than when the original brightness cues were present. This suggests that the strychnine-treated animals retained the sequence information to a greater extent than the brightness cue information. Such a result may indicate that strychnine acts to induce some type of stimulus selection while the postlearning processing of information is ongoing. In this sense the posttraining administration of strychnine appears to have effects similar to those of additional training trials in the present paradigm. In pilot studies conducted in our laboratory we have found that when mice receive only 1 or 2 training trials prior to retention testing there is little evidence of preference for one training cue over the other, a finding replicated by the saline-treated mice in the second study. However, when 4 or more trials are given prior to retention testing, mice do tend to evidence stimulus selection.

Finally, it was observed that with extended testing strychnine-injected mice tend to perform better than the saline-injected animals regardless of the testing conditions. This finding suggests that strychnine also may act to enhance the memory of general aspects of prior training or of attentional strategies used in prior training. Concerning this point it would be of interest to determine whether or not strychnine would enhance the solution of problems in a learning set paradigm, since improved performance in such a situation should be based almost entirely on the transfer of general information or strategies from one problem to the next.

Certainly, the present experiments represent a departure from the work done thus far on the enhancement of retention by CNS stimulants. Instead of attempting to determine under what circumstances certain agents facilitate retention, these studies attempt to determine the nature of facilitation by looking at the behavioral effects responsible for enhanced performance. We believe that such an approach can be helpful in understanding the characteristics of a memory as well as the relationship between a drug's biological mechanism of action and its behavioral effect.

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