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# Facilitation of the Long Term Memory Store with Strychnine: A Reexamination[1]

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GORDON, W. C., M. J. BRENNAN AND R. C. ROSE. *Facilitation of the long term memory store with strychnine: a reexamination.* PHARMAC. BIOCHEM. BEHAV. 3(6) 967–972, 1975. – Contrary to previous findings, some recent studies have reported that several daily injections of strychnine, beginning 24 hr after learning, facilitates subsequent retention. The present paper reports 3 studies using mice which suggest that strychnine has no effect on retention when the learning-injection interval is 24 hr. This absence of an effect was found using a range of strychnine doses. Furthermore, the absence of the facilitation effect was found not to be due to any failure of animals to learn prior to injection or to the fact that all animals performed asymptotically on the retention test.

Strychnine Memory enhancement Consolidation Long-term memory Brightness discrimination

ALPERN and Crabbe [1] recently reported that daily injections of strychnine sulphate appear to facilitate retention in mice, even when the interval between learning and the first drug injection is extended to 24 hr. These same authors have since reported a replication of this effect in which metrazol, as well as strychnine, were used to facilitate retention [3]. The conclusion drawn from these studies was that the long-term memory store in mice is susceptible to facilitation with neural excitants if several daily injections are administered between training and a retention test.

These results are notable since most previous studies had reported that strychnine and other analeptic agents acted to facilitate retention only when administered within minutes after learning (cf. [2]). Such results had provided strong evidence for the notion of a gradual memory consolidation in which a labile, short-term memory trace was replaced by a relatively intractable long-term memory trace (e.g., [8]). However, the Alpern-Crabbe results appear to directly challenge the notion of two memory traces which differ in susceptibility to analeptic compounds.

Aside from the Alpern-Crabbe findings, at least two other studies have reported facilitation of retention with strychnine when the learning-drug injection interval was extended to several hr (72 hr) [4,5]. In both studies, however, facilitation resulted only when the drug injection followed a memory reactivation treatment intended to remind the subjects of prior learning. These treatments consisted of confronting animals with a portion of those stimuli which were present during learning, without exposing the animals to a complete relearning trial. In these studies, the authors suggested that facilitation may have occurred because reactivation treatments may reinitiate those memory processes which are normally thought to occur only during the interval shortly after learning. This same interpretation is applicable to other recent studies which indicate that long-term memories are susceptible to disruption with ECS, if ECS is administered shortly after a reactivation treatment (e.g., [9]).

Given the theoretical importance of the Alpern-Crabbe results and the similarity of their results to those found with reactivation treatments, the present studies were originally intended as a replication and extension of the Alpern-Crabbe experiments. It was the intent of these studies to determine whether or not the Alpern-Crabbe findings were dependent on some form of subtle reactivation treatment inadvertantly administered by the experimenters prior to drug injection. Such an analysis was unable to be completed however, since the present studies, while replicating many of the essential findings by Alpern and Crabbe, provided no evidence that strychnine, injected long after learning, facilitates subsequent retention.

## EXPERIMENT 1

The purpose of Experiment 1 was to repeat the Alpern-Crabbe paradigm as closely as possible in an effort to replicate the reported strychnine effect.

### METHOD

*Animals and Apparatus*

The animals were 109 female mice of the C57BL/6J

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strain purchased from Jackson Laboratories (Bar Harbor ME). All mice were approximately 70 days old at the beginning of the experiment and were housed 6–8 per cage throughout the experiment.

The apparatus was a 6 unit brightness discrimination maze built to conform to the description of the apparatus used in the Alpern-Crabbe experiments [1,3]. The maze was constructed of Plexiglas and consisted of a start compartment, 6 separate brightness discrimination units and a goal compartment.

The start compartment, painted flat gray, was 10 cm long, 3.5 cm wide and 5 cm high. 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 flat white and the other flat black. A 5 cm high barrier, beginning 3 cm past the end of the entryway and ending 3 cm from the end of the compartment separated the black and white alleys. Each of the alleys was 25 cm long, 3.5 cm wide and 5 cm high. The end of each black alley was blocked by a clear vinyl barrier positioned so that it could not be seen from the choice point of each unit.

The 6 units were positioned linearly so that the entryway to each unit followed either the start box (in the case of Unit 1) or the exit from the preceding unit. The units were arranged so that the white alley was on the left side of Units 1, 4 and 5. In Units 2, 3 and 6, the white alley was on the right. Sliding doors, painted flat gray, could be inserted between any compartment of the maze and the entryway to the next compartment.

Following the last discrimination unit was a goal box which consisted of a flat gray entryway, 7 × 3.5 × 5 cm and a flat white goal area, 17 × 3.5 × 5 cm. At the terminal end of the goal area, a plastic drinking cup, 1.5 cm in dia. was mounted on the floor. The entire maze was covered by a sheet of clear Plexiglas, with separate removable sheets covering the start and goal compartments.

*Procedure*

Two days prior to the start of the experiment, all animals were placed on a 23 hr water deprivation schedule. Each animal received 2 initial training trials, 1 trial per day during which a 0.3 percent saccharin solution was present in the goal box drinking cup. At the start of each trial, the door between the start box and the first unit was closed; the doors between each of the other units of the maze and the door between the last unit and the goal box were open. Each animal was placed into the start box and the door between the start box and the first unit was opened. The number of initial errors (first entry into the black alley of any unit), total errors (first entries and all re-entries into the black alleys of the 6 units), and latency to reach the goal box were recorded. Once an animal had entered any unit of the maze, re-entries to prior units of the maze were blocked by the doors which separated the units.

On the first day of training, each experimental animal was retained in the goal box until it had completed 20 sec of drinking of the 0.3 percent saccharin solution, before being returned to its home cage. On the second day of training, animals were removed from the goal box 20 sec after entry. On both training days, Control animals were not given experience with the maze. Control animals were simply placed in the goal box for a 20 sec opportunity to drink before being returned to their home cages. After the second training day, animals were given water ad lib for the duration of the injection period.

Experimental animals were matched on the basis of the total number of initial errors made over the 2 training days and were divided into 5 approximately equal groups. Twenty-four hr following the second training day, each animal received the first of a series of 10 daily interperitoneal injections. Animals were injected with equal volumes (1 cc/0.1 kg body weight) of either a 0.9 percent saline solution or 0.2 mg/kg strychnine sulphate dissolved in a 0.9 percent saline solution. Of primary interest were the SA group which received saline on all ten days (N = 18) and the St group which received strychnine on all 10 days (N = 18). To determine whether the reported facilitory effect of strychnine was due to an effect of repeated strychnine injections and whether there is a specific temporal locus of this facilitory effort, animals in 3 other groups were given a single strychnine injection either 1 day after original training (St-1, N = 19), 5 days after original training (St-5, N = 18) or 10 days after training (St-10, N = 18). Animals in each of these 3 groups received saline injections on each of the remaining 10 injection days. Control animals received a series of 10 daily injections of 0.2 mg/kg strychnine beginning 24 hr after the second training day. All injections were given at approximately the same time each day.

On the tenth day of injections, all mice were placed back on a 23 hr water deprivation schedule. Twenty-four hr following the last daily injection, all animals were re-trained in the maze, one trial a day for 4 days, according to the procedures in effect on the second day of original training.

## RESULTS AND DISCUSSION

Analyses of variance revealed that there were no significant differences between the experimental groups on Day 2 of training in terms of either initial errors, total errors or latencies. These results suggest that the groups were essentially equated for degree of learning prior to the injection treatments.

Analyses of variance were also used to compare the initial errors, total errors and latencies of the 5 experimental groups on test day 1. No significant differences between any of the groups were found either in terms of initial errors, $F(4,86) = 0.80$, $p>0.05$, total errors, $F(4,86) = 0.78$, $p>0.05$, or latencies, $F(4,86) = 0.55$, $p>0.05$.

A second set of analyses were used to compare the same measures across all 4 test days. The analysis of initial errors indicated that the groups did not differ significantly across the 4 test days, $F(4,86) = 0.63$, $p>0.05$; however, there was a significant effect of days, $F(3,258) = 11.41$, $p<0.01$, reflecting a general decrease in initial errors as the test days progressed. The interaction of treatments and days failed to approach signifiance, $F(12,258) = 1.34$, $p>0.05$.

The mean number of total errors for the 5 treatment groups (and the control group) during the 4 test days is represented in Fig. 1. An analysis of these data, excluding the control data, revealed the same pattern of results found with the initial errors analysis. Neither the effect of treatments, nor the interaction of treatments and days approached significance ($p>0.05$ in both cases). However, a general decrease in total errors across test days was reflected in a significant effect of the days variable, $F(3,258) = 8.53$, $p<0.01$. In terms of latencies across the test days, an analysis of variance revealed no significant

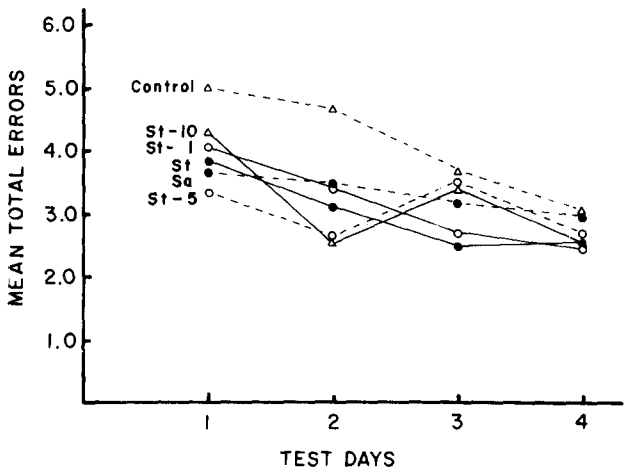


FIG. 1. Mean total errors across test days for all treatment groups.

effects of either treatments, days or the interaction of these variables ($p>0.05$ in all cases).

A Dunnet's T test [10] was used to compare the initial errors, total errors and latencies of the control group to each of the 5 experimental groups on each of the 4 test days. Regarding initial errors, the control group had significantly more errors than each of the 5 treatment groups on Day 2 of testing ($p<0.05$ in all cases). These differences were not significant, however, on Days 1, 3, and 4.

A comparison of the total errors revealed that the control group had significantly more errors than both the SA ($p<0.05$) and the St-5 ($p<0.05$) groups on test day 1. On test day 2, the controls had significantly more errors than the St group ($p<0.05$), the St-5 group ($p<0.01$) and the St-10 group ($p<0.01$). No other differences on these or other days achieved statistical significance.

Finally, regarding latencies, the controls were found to have significantly longer latencies than groups St, SA, St-5, and St-10 on Day 1 of testing ($p<0.05$ in all cases). On test day 2, the control latencies were significantly longer than those in the St-1 and the St-10 groups ($p<0.05$). No other differences achieved significance.

These results appear to demonstrate at least 3 points. First, it is clear that some learning did occur in the 5 treatment groups on training Days 1 and 2. This is reflected by the significantly greater number of errors (both initial and total) made by the control animals than by various of the experimental animals on Day 1 and 2 of testing. It is further evidenced by the finding that the control animals had significantly longer latencies than all other animals (except for animals in Group St-1) on test Day 1.

Secondly, the significant reduction of total errors and latencies among the 5 treatment groups over the 4 test days indicates that learning continued to occur between test days 1 and 4. This finding indicates that while some learning did occur on training days 1 and 2, there was still an opportunity for facilitated performance to occur on test days 1–4 as the result of the injection treatments.

The third point, however, is equally clear. The present study reveals no evidence to support the notion that strychnine sulphate facilitates retention of prior learning when injected 24 hr after learning. Instead, the present results appear to be consistent with previous studies which suggest that drugs such as strychnine are ineffective in producing facilitation if the learning-drug treatment interval exceeds an hour (cf. [8]).

## EXPERIMENT 2

The first experiment demonstrated that all animals continued to decrease errors and latencies on the 4 retention test trials. This finding suggests that the failure to find strychnine-induced facilitation was not caused by asymptotic retention performance on the part of all animals on the first retention test trial. It is notable, however, that forgetting over the 10 day retention interval was minimal in all experimental groups. A comparison of the training day 2 and test day 1 performance by all groups revealed that while animals in the St-1 group showed a slight increase in errors and latencies over the retention interval, all other animals either maintained the same error rate and latencies present on training day 2 or showed slight decreases in errors and latencies. It is conceivable, therefore, that the relatively good retention test performance by all animals tended to mask any drug related facilitation of retention in Experiment 1.

It was hypothesized that this minimal forgetting in Experiment 1 might have resulted from the handling of the animals during the retention interval. Previous studies have shown that such handling may have memory reactivation effects (e.g., [7]). Since it was necessary to continue the handling of animals during the retention interval (for purposes of drug injections), an attempt was made simply to decrease the reactivation effects of handling by habituating animals to the handling prior to the experiment (cf. [7]). Experiment 2 used the prior handling procedure in an effort to decrease the probability that any drug-related facilitation would be masked by handling-induced memory reactivation.

### METHOD

*Animals and Apparatus*

The animals were 59 mice, identical in description to those used in the prior experiment. The apparatus was the same as was used in Experiment 1.

*Procedure*

The injection groups and the procedure for this experiment was identical to that of Experiment 1, with one exception. Prior to the start of initial training, each animal was handled (picked up and held in injection position) for about 1 min each day for 10 days. There were 10 animals in each of the experimental groups and 9 animals in the control group.

### RESULTS AND DISCUSSION

As in the previous experiment, there were no significant differences between the treatment groups on Day 2 of training in terms of any of the recorded measures. To determine whether or not the handling procedure retarded the excellent retention evidenced in Experiment 1, analyses of variance were used to compare the test day 1 performance by all animals to the training day 2 performance levels. In terms of initial errors these analsyes revealed a significant effect of days, $F(1,45) = 4.33$, $p<0.05$, and a

significant interaction of the days and treatment groups variables, $F(4,45) = 3.25$, $p<0.05$. Individual group comparisons showed that the SA group significantly decreased initial errors from training to testing, while the St-10 group significantly increased initial errors ($p<0.05$, in both cases). No other groups differed in performance on the 2 days. In terms of total errors and latencies there were no significant differences between training day 2 and test day 1 performance for any of the groups. As in Experiment 1, these results suggest that forgetting over the 10 day retention interval was minimal, even with the prior handling treatment. As a result, Experiment 2 serves primarily as a replication of Experiment 1. Again, analyses of variance were used to compare the experimental groups both on day 1 of testing and across all 4 test days. On Day 1, in terms of initial errors, an analysis revealed a significant effect of treatment conditions, $F(4,45) = 5.78$, $p<0.01$. A comparison of the individual treatment means was completed using a Duncan Multiple Range Test [6]. This comparison showed that the significant effect of treatment conditions resulted from the fact that the St-10 group made significantly more initial errors than each of the other 4 groups ($p<0.05$, in all cases).

The same pattern of results was evident in the analysis of total errors on Day 1. Again a significant treatment condition effect was found, $F(4,45) = 5.22$, $p<0.01$, and this difference was shown to result from more errors in the St-10 group than in each of the other groups ($p<0.05$, in all cases). This pattern of results did not hold, however, for the Day 1 latency data, since an analysis on these data revealed no significant effect of treatment condition, $F(4,45) = 1.90$, $p>0.05$. It should be noted however, that the mean latencies on Day 1 ranged between 49.8 and 88.1 seconds, and the longest mean latency was obtained by animals in the St-10 condition.

Regarding initial errors across all 4 test days, an analysis of variance revealed significant effects of treatment conditions, $F(4,45) = 2.88$, $p<0.05$, and test days, $F(3,135) = 5.04$, $p<0.01$. The interaction of these variables did not approach statistical significance. Again, the effect of test days reflected a general decrease in errors across days. However, comparisons of individual treatment means revealed no significant differences between groups. Apparently, the significant effect of treatment conditions (which achieved only marginal significance) resulted from the fact that the St-10 group approached having significantly more errors than the St-5 group animals ($0.10 > p > 0.05$.).

The mean total errors across the 4 test days for both the experimental and control group animals is represented in Fig. 2. An analysis of these data excluding the control group data revealed no significant effect of treatment condition, $F(4,45) = 1.22$, $p>0.05$. However, this same analysis showed significant effects of both test days, $F(3,135) = 3.40$, $p<0.05$ and the interaction between treatment conditions and test days, $F(12,135) = 1.99$, $p<0.05$. Comparisons of individual treatment means revealed that the interaction resulted from significantly more errors by the St-10 group than by any other group on Day 1, while there were no significant differences on subsequent days. Finally, an analysis of the latency data across the 4 test days revealed no significant sources of variance due to either of the main variables or their interaction.

An analysis of differences between the control group and each of the other groups revealed significant differences only on Day 1 of testing. The control group made

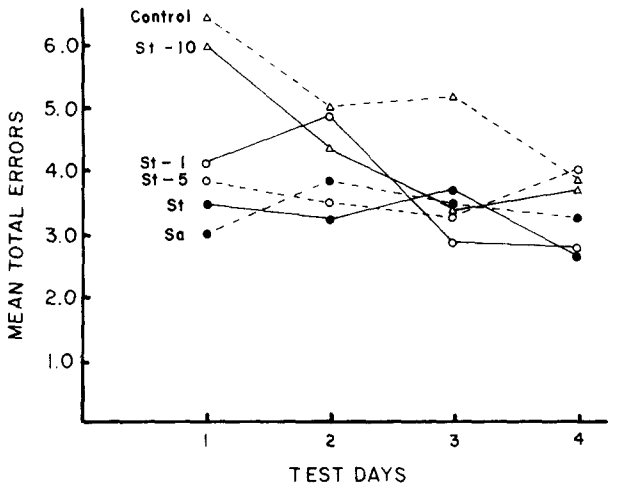


FIG. 2. Mean total errors across test days for all treatment groups.

significantly more initial errors than the SA group on Day 1, but did not differ significantly from any other groups. In terms of total errors, the control group made significantly more errors than the St-1 and St-5 groups ($p<0.05$) and the SA and St groups ($p<0.01$) on this first test day. Latencies for the control animals were also significantly longer than those of the St-1 and St-10 groups ($p<0.05$), as well as those of the St, SA and St-5 groups ($p<0.01$) on test day 1.

The results of the present experiment are remarkably similar to those of Experiment 1. Again, it is clear from the relative performance of the control group on test Day 1, that learning had occurred in the treatment groups during the 2 training days. This finding is important, since it indicates that any failure to obtain facilitated retention with strychnine was not due to a failure to provide a viable learning situation during training. Secondly, as in the previous experiment, the present results suggest that there was an opportunity for animals to show facilitated retention during the 4 test days despite the fact that retention loss over the 10 day interval was minimal. This suggestion comes from the general decrease in errors across the 4 test days which indicates that the animals had not achieved asymptotic performance on Day 1 of testing. This finding is also important since it indicates that any failure to find strychnine-induced facilitation in the present study is not due to any artificial ceiling on retention test performance.

Thirdly, the present results again failed to support the notion that daily injections of strychnine, begun 24 hr after learning, facilitate subsequent retention. If anything, the present findings would indicate that strychnine had a slightly disruptive effect on retention, since on test day 1 the SA group animals had the lowest number of initial and total errors, as well as the lowest mean latency among the treatment groups. Furthermore, strychnine injected on the tenth day of the retention interval (i.e., St-10 group) had a clearly disruptive effect on retention test performance. Why such an effect should have occurred is unclear at the present time.

## EXPERIMENT 3

The strychnine dosage employed in the first 2 experiments had been chosen because of its effectiveness in the Alpern-Crabbe studies [1,3]. However, since neither of

these 2 experiments produced a strychnine-induced facilitation effect, it remained possible that the dosage used was not the most effective in the present situation. The purpose of Experiment 3 was to employ a range of strychnine doses to determine if any of these doses would effectively facilitate retention test performance.

## METHOD

### *Animals and Apparatus*

The animals were 46 mice with the same characteristics as those used in the previous experiments. The apparatus was the same as that employed in Experiments 1 and 2.

### *Procedure*

The training procedure was identical to that of Experiment 1. Animals were matched on the same basis and divided into 5 groups. Twenty-four hr after the second training day, all animals received the first of a series of 10 daily interperitoneal injections. Animals were injected with either 0.9 percent saline (N = 9) or with strychnine sulphate dissolved in a 0.9 percent saline solution at one of the following 4 dose levels: (St-.2) 0.2 mg/kg (N = 9); (St-4.) 0.4 mg/kg (N = 8); (St-.8) 0.8 mg/kg (N = 9); (St-1.0) 1.0 mg/kg (N = 11). All injections were of equal volume (1 cc/0.1 mg/kg body weight).

On the tenth day of injections, animals were placed back on a 23 hr water deprivation schedule. Twenty-four hr after the last injection, animals were re-trained, one trial per day for 4 days.

## RESULTS AND DISCUSSION

On training day 2 there were no significant differences between any of the experimental groups in terms of either initial errors, total errors or latencies, suggesting that the groups were equated for degree of learning prior to injection. On test Day 1, analyses of variance revealed no significant differences between any of the treatment groups either in terms of initial errors, $F(4,41) = 0.16$, $p>0.05$, total errors $F(4,41) = 0.85$, $p>0.05$, or latencies, $F(4,41) = 1.23$, $p>0.05$. It is notable, however, that the SA group animals had the lowest mean latency, the lowest number of total errors and the second lowest number of initial errors of all the groups on test day 1.

Across the 4 test days, an analysis of initial errors revealed no significant effect of either treatment condition or the interaction of treatment condition and test days. However, the effect of test days was significant, $F(3,123) = 5.25$, $p<0.01$, indicating a decrease in initial errors as the test phase progressed.

The same pattern of results was evident in the analysis of total errors during the 4 test days. The mean total errors for each of the treatment groups on each of the 4 test days is represented in Fig. 3. The analysis of these data showed only 1 significant source of variance which was due to the test days variable, $F(3,123) = 6.05$, $p<0.01$. No other effect approached significance. In terms of latencies, an analysis of variance revealed no significant effects of either treatment condition, test days or the interaction of these variables.

Certainly, the present findings support those of the previous experiments. While errors do tend to decrease during the course of the test trials, no dose of strychnine had the effect of facilitating this decrease. Furthermore,

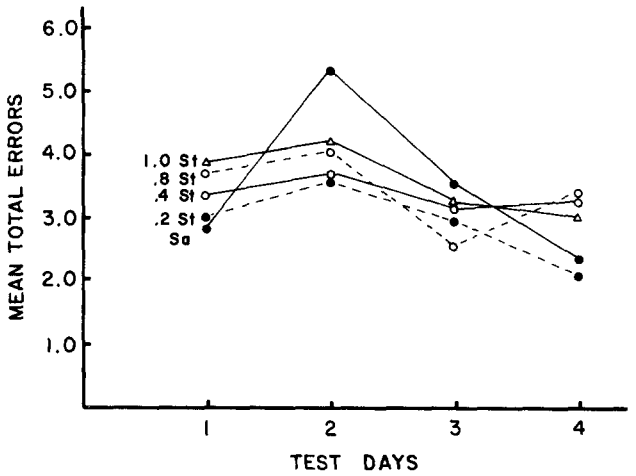


FIG. 3. Mean total errors across test days for all treatment groups.

not only did facilitation fail to occur on test day 1, but if anything, the SA animals appeared to perform better than animals in the strychnine injected groups. These results suggest that the failure to obtain facilitation in Experiments 1 and 2 was not due to the use of an inappropriate dose of strychnine.

## GENERAL DISCUSSION

The present experiments represent a failure to replicate the facilitation effect found in the Alpern-Crabbe studies using strychnine. It is felt that the present findings represent a rather strong negative case against such an effect for a variety of reasons. First, evidence from Experiments 1 and 2 indicated that some learning does in fact occur during the 2 training days in the maze task employed in these studies. Thus, it is not argueable that strychnine failed to produce facilitation because no prior learning had occurred.

Secondly, all 3 experiments provided evidence for continued improvement of performance across the 4 retention test days. These findings suggest that performance on the first retention test day was not asymptotic. Thus, it is implausible to suggest that strychnine failed to produce facilitated retention because of ceiling performance levels attained on the 2 training days by all groups.

Thirdly, this failure to obtain the facilitation effect cannot be accounted for easily by suggesting that inappropriate doses of the drug were used. Experiment 3 demonstrated that no facilitation could be produced even when a range of strychnine doses were employed. Such results do however, raise the question of whether the drug used in the present studies was biologically active within the range of doses employed. In answer to this question, at least three points should be noted. First, just prior to Experiment 1 a small group of animals was administered a 2 mg/kg dose of strychnine to test the potency of the drug. All of these animals exhibited typical strychnine – induced seizures followed shortly by death. Secondly, following Experiment 3 the same supply of strychnine used throughout all experiments was used to compute a LD-50 for female mice of the C57BL/6J strain. The LD-50 proved to be a dose of 1.7 mg/kg, and again, all mice given a dose of 2 mg/kg convulsed and died. Aside from these data which attest to the potency and biological activity of the drug at higher dose levels, the behavioral effects produced by strychnine

in Experiments 2 and 3 should be noted. In both studies there was a clear tendency for strychnine-injected animals to perform more poorly than saline-injected animals on day 1 of retention testing. While, this effect is statistically substantiated only in Experiment 2 (see group St-10), the tendency of strychnine-injected mice to exhibit performance deficits suggests that the drug was biologically active.

Finally, it should be noted that the experiments reported here represent only part of the total work directed toward this problem in our laboratory. Under no circumstances have we have been able to obtain this effect even in terms of measures not reported in the present paper (e.g., difference scores between Trial 2 of training and Trial 1 of testing and trials-to-criterion measures).

Certainly, the original findings of Alpern and Crabbe are important in their implications for memory research. Yet, the results of the present studies suggest that the phenomenon of facilitating the long-term memory store is difficult to demonstrate. Given the potential importance of this facilitation effect for models of memory, it will be necessary for subsequent research to determine if this effect is generally repeatable, and if so, under what specific conditions it can be obtained.

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