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Blockade of Spontaneous Posttraining Performance Improvement in Mice by NMDA Antagonists

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MÉLAN, C., D. EICHENLAUB, A. UNGERER, C. MESSIER AND C. DESTRADE. *Blockade of spontaneous posttraining performance improvement in mice by NMDA antagonists.* PHARMACOL BIOCHEM BEHAV **56**(4) 589–594, 1997.—We investigated the effects of immediate post-training systemic administration of γ-L-glutamyl-L-aspartate (γ-LGLA) and 3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonate (CPP), antagonists at the *N-methyl*-D-aspartate receptor, in a lever-press task in two inbred strains of mice. When retention performance was tested in control animals 24 h after partial acquisition of the task, BALB/c mice exhibited a spontaneous performance improvement whereas C57BL/6J mice did not. γ-LGLA at doses of 2.5 and 25 μmol/kg and CPP at doses ranging between 0.025 and 2.5 μmol/kg blocked the spontaneous performance improvement found in BALB/c mice but had no apparent effects on the retention performance of C57BL/6J mice. These data suggest that retention impairment induced by CPP and γ-LGLA in BALB/c mice results from an interference with posttraining memory processes. © 1997 Elsevier Science Inc.

Memorization CRF γ-L-Glutamyl-L-aspartate 3-(2-Carboxypiperazine-4-yl)propyl-1-phosphonate *N*-Methyl-D-aspartate receptor Mouse

CONVERGENT data indicate that memory traces are not in their definite form at the end of learning acquisition. On one hand, numerous reports indicate that memory traces can be considerably modified during the hours following acquisition by inferences, addition of information, or modulation of endogenous systems (19). On the other hand, memory processing does not appear to develop monotonically over time. Thus, retention performance, when tested at increasing delays after partial acquisition of a task, enhances correlatively to the delay, before stabilizing at a high level after hours or days (14,18,21). Because this performance increment occurs without complementary training, it is called "spontaneous posttraining performance improvement." This phenomenon is thought to reflect an organization of memory traces allowing subsequent long-term storage (36). It has been observed in various appetitive and aversive tasks, depending on factors such as strength of learning, task complexity, species, and strain (13,18,21,35). In mice, for instance, performance improvement varies considerably across strains according to task. Thus, retention performance enhances progressively in BALB/c mice between 1 and 24 h after partial acquisition of an appetitive lever-press task but not in an active avoidance task in a Y-maze, whereas in the same conditions C57BL/6J mice exhibit the opposite response profile, that is, spontaneous performance improvement in the Y-maze task but not in the lever-press task (9,40).

The mechanisms underlying this memory process are far from being understood but likely require functional plasticity of the central nervous system. In favour of this hypothesis, it has been shown that posttraining improvement of performance can be modulated by hippocampal activity and more especially by activation of the hippocampal cholinergic system (20). Indeed, electrical stimulation of the dorsal hippocampus at low intensities immediately after partial acquisition of a lever-press task shortened the onset of performance improvement and increased its amplitude in BALB/c mice (8–10). Correlatively to this modulation of the memory trace, the hippocampal choline acetyltransferase activity increased (20).

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However, more recent studies have revealed that compounds acting as competitive antagonists at the NMDA subtype of glutamate receptors suppressed posttraining performance increment in a Y-maze avoidance learning task (39). This was first demonstrated by using γ-L-glutamyl-L-aspartate (γ-LGLA), a pseudopeptide that almost completely inhibits binding of ^{3}H-CPP in a hippocampal membrane preparation (39) and selectively blocks the clonic–tonic seizures induced by NMDA while being devoid of apparent effects on seizures induced by quisqualate or kainate (25). Consequently, γ-LGLA has the pharmacological properties of an NMDA antagonist. Its systemic administration immediately after acquisition of the active avoidance task blocks spontaneous performance improvement normally observed in C57BL/6J mice between 1 and 24 h after training. In contrast, performance in BALB/c mice, which do not exhibit spontaneously enhanced retention, was not impaired (40). In C57BL/6J mice, the impairment appeared to be very selective, as it concerned only retention of the temporal component of the task (leave the start alley of the maze within 5 s), which improved significantly over time in this strain, whereas it had no effect on retention of the spatial component (choose the left alley of the maze), which did not improve over time (40).

The competitive NMDA antagonists 3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonate (CPP) and D-2-amino-5-phosphonovalerate (D-AP5) induced selective behavioural effects similar to those seen for γ-LGLA in Swiss mice submitted to the avoidance task (26,39). Conversely, neither γ-LGLA nor CPP had any apparent effect on spatial recognition memory in an alternation task in which Swiss mice did not exhibit spontaneous performance improvement (39). Taken together, these results suggest a specific action of NMDA antagonists on memory processing during the hours following acquisition of the avoidance learning task.

The aim of the present study was to determine whether the hypothesis of an involvement of NMDA receptor activation in posttraining improvement of performance could be generalized to an operant lever-press task. Therefore, we investigated the effects of γ-LGLA and CPP on retention performance of BALB/c and C57BL/6J mice in such a task. Because BALB/c but not C57BL/6J control mice show a significant posttraining improvement of performance 24 h after training [(9,20); see above], both compounds should affect retention performance of the former but not of the latter strain.

METHOD

Subjects

A total of 144 BALB/c and 90 C57BL/6J male mice were used. They were maintained at 23°C on a 12:12 hour light: dark cycle (lights on at 0800 h) and were housed individually with food and water ad lib for 1 week prior to testing.

Apparatus

The test cage was made of translucent Plexiglas (14 cm square and 18 cm high); it was dimly illuminated (10 lux) and placed in an experimental room with white noise (60 dB). The conditioning box contained a bar (3 × 2 cm) and a food cup separated by a 5-cm-long partition such that, after a bar-press, the mouse had to go around the partition to collect a 5-mg food pellet. A continuous reinforcement schedule (CRF1) was applied; bar-presses and the presence of the animal in front of the food cup or in front of the bar were recorded on calibrated paper.

Procedure

Four days before training, food was removed from home cages and the food ration was adjusted individually such that, on the day of the test, the weight loss of the subjects corresponded, respectively, to 17–19% and 21–23% of the ad lib weight of the BALB/c and C57BL/6J mice. This weight loss was achieved by decreasing the food ration on consecutive days from 2 g to 1.5 g and 0.5 g in C57BL/6J mice and from 3 g to 2 g and 1 g in BALB/c mice. This has been shown to produce optimal learning in each strain (8).

During training, each animal remained in the test cage until it made 15 reinforced responses. A reinforced response was defined as a bar-press followed within 30 s by food consumption. Retention of the bar-pressing task was tested in a 30-min session 24 h after training. Animals received a food ration adjusted such that their weight remained the same during training and testing. Spontaneous performance improvement was determined by comparing the number of reinforced lever-presses during the last 5 min of training and during the first 5 min of retention testing. Training and testing took place during the light period.

Treatment

Chemicals. CPP was purchased from Tocris Neuramin (Buckhurst Hill, UK), and γ-LGLA was synthesized and purified in the laboratory. In both experiments, drugs and saline were administered systemically immediately after training. Subjects were assigned to groups matched for performance during acquisition.

Experiment I. Thirty BALB/c and 30 C57BL/6J male mice received a post-training IP injection of either normal saline (0.9% NaCl, 25 ml/kg) or 2.5 or 25 μmol/kg of γ-LGLA (dissolved in saline). For both strains, each of the three treatment conditions included 10 animals.

Experiment II. Sixty C57BL/6J and 60 BALB/c mice trained and tested as in experiment I received an IP administration of either 0.9% NaCl or CPP at doses of 0.025, 0.25, or 25 μmol/kg immediately after the learning session. A noninjected control group was also included in experiment II. Each group comprised 12 animals. This experiment was replicated with BALB/c mice using one placebo control group (n = 14) and four groups (n = 10) treated with 0.025, 0.25, 2.5, and 25 μmol/kg CPP, respectively.

Statistics.

Interstrain comparison of performance during acquisition, expressed by the latency to perform the first bar-press, the time to complete 15 reinforced bar-presses, and the number of reinforced bar-presses recorded during the last 5 min, was analyzed by two-way ANOVAs (strain × group). Spontaneous performance improvement was analyzed for each strain separately by two-way ANOVAs with repeated measures (session × group) followed by post hoc Newman–Keuls tests. When indicated, each treatment group was compared separately to controls.

RESULTS

Experiment I

The mean latency to make the first reinforced bar-press during acquisition did not differ between the two strains (Table

TABLE 1

ACQUISITION OF AN OPERANT LEVER-PRESS TASK IN BALB/c AND C57BL/6J MICE (MEANS ± SEM), EXPERIMENT I

	Latency (s) to First Bar-Press	Total Time (s) for 15 Bar-Presses	Number of Bar-Presses
BALB/c	121.3 (15.0)	777.3 (35.5)	7.8 (0.4)
C57BL/6J	110.0 (10.4)	916.0 (26.4)	6.7 (0.3)

1), indicating comparable reactivities to the bar-pressing task (9,20). However, C57BL/6J mice were slower to reach 15 reinforced bar-presses [$F(1, 54) = 10$, $p < 0.003$] and as a consequence they also made a smaller number of reinforced bar-presses during the last 5 min of training [$F(1, 54) = 4.88$, $p < 0.031$]. The different experimental subgroups within each strain did not differ from each other in either of these parameters.

Comparison, for each strain, of the mean number of bar-presses made during the last 5 min of the training period and during the first 5 min of the retention test (Fig. 1) revealed a peptide effect only for the BALB/c mice [$F(2, 27) = 5.83$, $p < 0.008$]. The spontaneous memory improvement expressed in controls by an increase of reinforced bar-presses was completely abolished by both doses of γ-LGLA ($p < 0.05$).

The C57BL/6J strain did not show any time-dependent memory improvement in this task, but did display a time-dependent memory decrement between training and the retention test as expressed by a global decrease of reinforced lever-presses [$F(1, 27) = 35.6$, $p < 0.0001$].

Experiment II

As was observed in experiment I, during acquisition, BALB/c mice made more reinforced bar-presses during the last 5 min of training (mean ± SEM: 6.12 ± 0.21) than did the C57BL/6J mice [4.3 ± 0.15; $F(1, 110) = 46.39$, $p < 0.0001$] and needed less time to reach the partial acquisition criterion (mean ± SEM: 804.5 ± 25.1 s) compared with C57BL/6J mice [1162.3 ± 339.9 s; $F(1, 110) = 71.17$, $p < 0.0001$]. The latencies to perform the first reinforced bar-press did not differ between the two strains (mean ± SEM: BALB/c, 69 ± 7.8 s; C57BL/6J, 61 ± 4.6 s).

The mean number of reinforced bar-presses made by BALB/c mice during the first 5 min of the retention test did not differ between injected and noninjected controls (Table 2). The dose–response effects of CPP were nonlinear, so each CPP group was compared separately with the NaCl group. The lowest dose of CPP (0.025 μmol/kg) significantly reduced the performance improvement observed 24 h after training ($p < 0.02$), whereas no significant effect was found for the other two doses. This quite unexpected result led us to replicate the experiment in BALB/c mice by completing the dose range of CPP with a 2.5-μmol/kg group.

The results obtained in the replication experiment (Fig. 2) revealed comparable bar-press performance in the different groups of BALB/c mice during the last 5 min of training, and demonstrated a reliable effect of treatment on bar-pressing during the first 5 min of the retention test [$F(4, 49) = 5.31$, $p < 0.001$]. This effect was due to a performance decrement of the 0.025-, 0.25-, and 2.5-μmol/kg CPP groups compared with the control group ($p < 0.05$). No impairment occurred in the 25-μmol/kg group.

In C57BL/6J mice, a significant performance decrement was observed between training and testing that was similar to the one observed in experiment I: the number of reinforced bar-presses decreased overall between training and the retention test [$F(1, 55) = 22.03$, $p < 0.0001$]. CPP did not produce any effect on C57BL/6J performance, as shown by the absence of any difference between the CPP-treated and saline-injected animals.

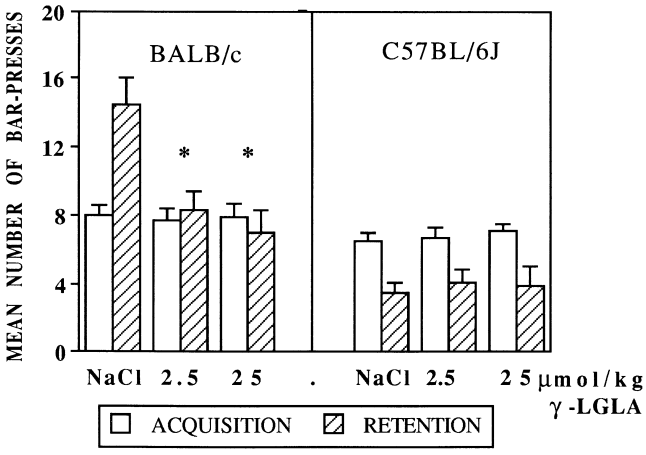

FIG. 1. Effects, in an operant bar-pressing task, of γ-LGLA on the number of reinforced bar-presses (mean ± SEM) made by BALB/c and C57BL/6J mice during the last 5 min of training and during the first 5 min of the retention test 24 h later. The evolution of performance between the two sessions was compared between groups. *$p < 0.05$, post hoc Newman–Keuls test.

DISCUSSION

These results show that γ-LGLA and CPP effectively blocked the posttraining performance increment in BALB/c mice in a lever-press task but had no effect on retention in C57BL/6J mice, which do not exhibit improved retention performance. The present results are to be compared with those obtained in C57BL/6J and BALB/c mice in an active avoidance task in a Y-maze (40). Following partial acquisition of this task, spontaneous performance enhancement occurred for the C57BL/6J strain only. Impairment of retention performance 24 h after posttraining administration of γ-LGLA was restricted to C57BL/6J mice in the Y-maze task and to BALB/c mice in the operant task. The disrupting effects of γ-LGLA occurred at the same doses for both tasks (40). Conversely, the compound was devoid of effects in either strain when no such performance increment was evident.

Moreover, γ-LGLA and AP5 suppressed the posttraining performance increment observed in Swiss mice in both tasks (27,39). CPP administered under the same conditions in the Y-maze task had comparable effects on retention performance in Swiss mice (39). Moreover, the dose–effect curve found in the Y-maze avoidance task was very similar to the dose range antagonizing enhanced retention of operant learning in BALB/c; high doses of CPP (25–200 μmol/kg) did not affect retention performance of avoidance and operant learning.

In both tasks, the retention deficits induced by γ-LGLA and CPP are restricted to those strains of mice demonstrating posttraining performance improvement. In addition, for a given strain of mice, performance is only affected in those

TABLE 2

EFFECTS OF POST-TRAINING ADMINISTRATION OF CCP ON THE NUMBER OF REINFORCED BAR-PRESSES (MEANS ± SEM) DURING THE FIRST 5 MIN OF RETENTION TESTING IN BALB/c AND C57BL/6J MICE, EXPERIMENT II

	Controls		Dose of CPP (μmol/kg)		
	Non-injected	NaCl	0.025	2.5	25
BALB/c	14.7 (1.7)	14.3 (1.4)	9.9 (1.5)	13.8 (3.0)	11.2 (1.9)
C57BL/6J	3.5 (0.7)	3.0 (0.6)	2.6 (0.4)	3.0 (0.5)	2.9 (0.5)

tasks in which it improves spontaneously after training. Taken together, the results strongly support the hypothesis of a mediation by NMDA receptors of some mechanism underlying spontaneous performance improvement.

The strain-dependent treatment effects raise the question of strain-specific learning in the operant task. BALB/c mice more readily associated the bar-pressing and the delivery of food, as indicated by the smaller amount of time required to complete the acquisition criterion, and showed enhanced lever-press performance after the 24-h delay. As the opposite evolution of retention performance was observed in the two strains in the Y-maze avoidance task, a strain-dependent sensitivity to various factors may be inferred. For instance, it is noteworthy that BALB/c and C57BL/6J mice are known, respectively, as "emotional" and "nonemotional" strains, reacting differently to agonists of the benzodiazepine receptor (5). Treated BALB/c mice exhibited reduced neophobia in a free-exploratory paradigm, whereas responses of C57BL/6J mice toward novelty remained unchanged (16). In contrast, posttrial administration of corticosterone or a posttrial stressful experience (e.g., constraint) improved retention of passive avoidance in C57BL/6J mice but not in DBA mice (4). Thus, interstrain variations of retention performance reflect, at least partially, differences of behaviour according to memory load and/or emotional factors differing between tasks.

Spontaneous enhancement of retention performance is further dependent on a number of factors such as strength of learning and task complexity, in addition to genetic differences (13,18,35). Whether interstrain differences of behavioural alterations by NMDA antagonists reflect genetic differences in excitatory amino acid systems, especially in NMDA receptors, remains unclear. No difference in glutamate binding to the NMDA receptor was found between the BALB/c and the C57BL/6J strains in whole sections of brain tissue (24,33). These data are in agreement with a preliminary study carried out in our laboratory indicating that γ-LGLA displaced [^{3}H]L-glutamate on hippocampal membranes in the two strains, without revealing significant differences of site densities or dissociation constants (40).

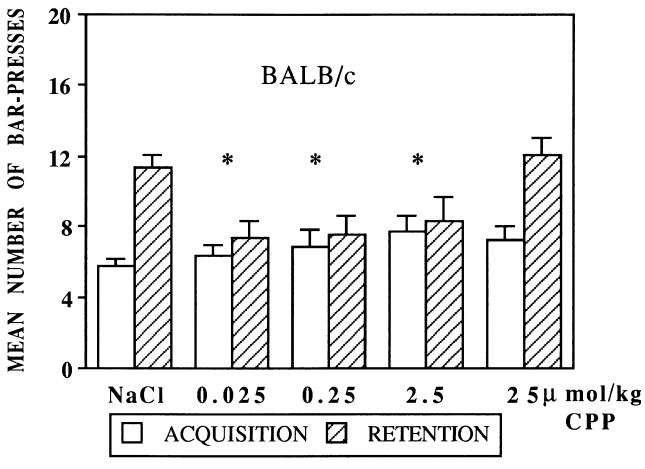

FIG. 2. Effects of CPP on the number of reinforced bar-presses (mean ± SEM) made by BALB/c mice during the last 5 min of training and during the first 5 min of the retention test 24 h later. The evolution of performance between the two sessions was compared between groups. *$p < 0.05$, post hoc Newman–Keuls test.

During the last 5 years, numerous experiments have explored the involvement of NMDA receptors in learning and memory processes. Most of them have investigated the effects of NMDA antagonists on memory formation (7), as they were shown to block induction of hippocampal long-term potentiation, an experimental model thought to reflect processes comparable to those encountered during learning (3). In view of this hypothesis, the blockade of NMDA receptors by administration of competitive antagonists prior to training or by their perfusion during training has been shown to produce very different effects on memory processes, depending on a number of factors such as the mode of action and application of the compounds and response requirements (6,43). Thus, chronic ICV infusion of AP5 impairs acquisition of place learning without affecting visual discrimination learning in a water-maze task in rats (30), whereas daily pretraining systemic administration of CPP retards acquisition of both versions of a water-maze task in mice (41) and retention of well-learned place and cue tasks in a radial-arm maze in rats (23,42). Similarly, the competitive NMDA antagonist CGS 19775, when administered prior to passive avoidance training, disrupts retention performance of mice in a step-through but not in a step-down protocol (22). Retention of the former task was impaired and that of the latter improved following pretraining administration of AP7, which was devoid of effects in either task when administered after training (29). These conflicting results make it difficult to draw general conclusions about the precise nature of the mnesic process requiring intact NMDA function.

On the other hand, Freed and Wyatt (11), suggesting for the first time that antagonism at glutamate receptors impairs learning, showed that pretraining administration of the nonselective antagonist glutamic acid diethyl ester (GDEE; 240 or 480 ng/kg IP) impaired acquisition and, transiently, retention of a noncontingently reinforced bar-pressing task in rats. GDEE did not affect performance when administered to previously trained rats. In well-trained rats, ICV perfusion of AP5 or IP administration of noncompetitive NMDA antagonists resulted however in a persistent impairment in a DRL sched-

ule (34,38). However, animals must withhold responses in this task for a certain period of time in order to be reinforced, and the results obtained do not allow differentiation of a specific effect on short-term memory from effects on the timing ability of animals or on their ability to refrain from responding. Further, various NMDA antagonists have been shown to increase lever-press responses suppressed by punishment procedures (34) and to affect conditional emotional procedures (17), thereby suggesting antianxiety effects.

Anxiolytic-like effects of competitive NMDA antagonists (CPP, 3 mg/kg; and 2-amino-7-phosphonoheptanoate, 30 mg/kg) have indeed been reported (1). In addition, retention deficits after pretraining administration of NMDA antagonists may result from an interference with nonspecific factors. Working memory impairments (32,42) have been reported at doses of CPP and CGS19955 (>2.5 and 4 mg/kg, IP, respectively) eliciting motor disturbances and ataxia (23,39). Moreover, intrathecal CPP, AP5, and AP7 act as analgesics in the mouse hot-plate and formalin models of pain (15,31). Performance decrease of rats in a delayed conditional auditory discrimination after posttraining administration of CPP revealed disruption of stimulus discriminability rather than increased forgetting (37). These studies provide some evidence of an involvement of NMDA receptors in early stages of memory consolidation that may already take place during acquisition. Elsewhere, they stress the importance of controlling for nonassociative factors (2) in addition to specific mnesic effects (4,6,12).

The procedure used in the present experiments, consisting of drug administration following partial acquisition of a task, focuses its action on memory trace rather than on performance-related events (4,43). Drugs were administered to groups matched according to acquisition performance, so interference with acquisition processes as such may be ruled out and effects on memorisation and retrieval may be distinguished easily. Indeed, as long as a spontaneous performance improvement occurs, ongoing memory formation may be reasonably inferred. Conversely, performance stabilization probably reflects the outcome of memory trace consolidation. According to this view, analysis of the data obtained with γ-LGLA and CPP points to a role of NMDA receptors in formation of long-term memory occurring during the hours following training. These effects appear to be specific in that efficient doses of CPP (2.5 μmol/kg, corresponding to 0.63 mg/kg) are significantly lower than those reported in the literature to induce ataxic or anxiolytic effects (23,29). At the doses used, the two compounds did not produce apparent ataxic effects. As shown previously for γ-LGLA (28), treated animals consumed the food reward as quickly as controls. Thus, it seems unlikely that the behavioural effects of γ-LGLA and CPP in the lever-press task result from an interference with motivational processes or general activity.

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