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Gabapentin, an antiepileptic drug, improves memory storage in mice

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Abstract

Male CF-1 mice were tested 48 h after training in a one-trial step-through inhibitory avoidance task. Immediately post-training i.p. injections of the antiepileptic drug gabapentin (1-aminomethyl cyclohexaneacetic acid) (GBP; 5, 10, 50, and 100 mg/kg) induced a dose-dependent enhancement of retention performance. Gabapentin did not affect response latencies in mice not given the footshock on the training trial, indicating that the actions of GBP on retention were not due to non-specific proactive effects on response latencies. The effects of GBP (10 mg/kg) were time-dependent, and the administration of GBP (10 mg/kg) 30 min before training also enhanced retention performance. However, the administration of GBP (10 mg/kg) 30 min prior to the retention test did not modify retention latencies of mice that had received either saline or GBP (10 mg/kg) immediately after training. Altogether, the results suggest that GBP influences retention by modulating time-dependent processes involved in memory storage, although the mechanism(s) of this action remain to be established.

Keywords: Gabapentin; Antiepileptics; Anticonvulsants; (1-aminomethyl) cyclohexane acetic acid; Memory; Inhibitory avoidance; Retention; Memory storage

Gabapentin, (1-(aminonomethy) cyclohexaneatic acid) (GBP), is a novel anticonvulsivant drug that is active in a variety of animal seizures models [19] and currently in clinical use as an add-on therapy in patients exhibiting partial seizures resistant to other antiepileptic drugs [12]. GBP also possess antihyperalgesic and anxiolytic-like actions [17]. Although there is some evidence of slight improvement in psychomotor function in healthy volunteers that had received GBP, and also spontaneous reports of improved memory and perception from some treated epileptic patients [8,13], to the best of our knowledge there are no reported data concerning learning and/or memory actions of GBP from animals studies. We reported here that intraperitoneal administration of low doses of GBP facilitates retention performance of a one trial step-through inhibitory avoidance response in mice.

Albino male CF-1 mice (25–30 g, Gilardoni–Cabañas Farms, Argentina) were cages in groups of 10–15 with food and water ad lib., and maintained on a 12-h light–dark cycle (lights on 06:00 h) at constant temperature for at least 3 days prior to the experiments. The mice were trained in a one-trial step-through inhibitory avoidance task [2] using a 0.80 mA, 50 Hz, 1-s footshock, and were tested for retention 48 h later. A ceiling score of 300 was recorded on the retention trial.

GBP was a generous gift of C.P. Taylor (Parke–Davis Pharmaceutical Research, USA). The drug was dissolved in saline immediately before been used, and was administered intraperitonealy (10 ml/kg). Controls received the same volume of saline. Drug dosages were selected on the basis of pilot experiments, and all were conducted blind with respect to the drug treatments and according to international principles and the local regulations concerning the care and use of laboratory animals.

In the first experiment, we examined the effects of the immediate post-training, injections of saline or GBP (5, 10, 50 and 100 mg/kg) to mice that had ($n = 15$ mice/group) or had not received ($n = 10$ mice/group) the footshock during

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the training trial. Additional groups of shocked ($n = 15$ mice/group) and unshocked ($n = 10$ mice/group) mice were injected with saline or GBP 30 min before training (10 mg/kg). In a second experiment, the effects, on retention, of delayed injections of saline or GBP (10 mg/kg) were studied. Thus, four different groups of 15 mice each were training and were injected with saline or GBP (10 mg/kg) immediately or 180 min after training. Finally, mice ($n = 15$ mice/group) were trained on the inhibitory avoidance task and given post-training injections of saline or GBP (10 mg/kg). A second injection of saline or GBP (10 mg/kg) was administered 30 min prior to the 48-h retention test. In these experiments, appropriate unshocked control mice ($n = 10$ mice/group) were also included. The retention test latencies are expressed as medians and interquatile ranges, and were analyzed, when it was necessary, by the Kruskal–Wallis analysis of variance; differences between groups were estimated by individual Mann–Whitney *U*-test (two-tailed) (Siegel, 1956). *P*-values less than 0.05 were considered significant.

There was an overall significant dose effect ($H_{(4)} = 9.92$; $P < 0.05$) of GBP on retention performance of mice that had received the footshock during the training trial (Fig. 1A). Post-training GBP facilitated retention performance in a dose-related manner, and statistical significance was reached at the doses of 10 and 50 mg/kg ($P < 0.01$ and $P < 0.05$, respectively). The lower and the higher doses of GBP were ineffective ($P > 0.05$, in both cases) and, furthermore, the latencies to step-through of the mice that did not receive the footshock, but were injected with saline or GBP immediately after training, did not differ significantly from each other ($H_{(4)} = 3.61$; $P > 0.05$). There were no differences in the initial step-through response latencies of mice trained 30 min after saline or GBP (10 mg/kg) (Saline: 5 (4–7) s, and GBP: 6 (4–8) s; $H_{(1)} = 2.22$; $P > 0.05$). In contrast, during the retention test the mice that had received GBP 30 min before training showed retention latencies significantly higher than those saline control groups ($P < 0.01$) (Fig. 1B). Pre-training GBP did not affect retention performance ($P > 0,05$) of unshocked mice during training (data not shown).

Gabapentin administered immediately, but not 180 min after training, significantly enhanced ($P < 0.01$) retention performance (Fig. 2). Finally, as shown in Fig. 3, the administration of GBP prior to the retention test did not affect retention latencies of mice given post-training injections of either saline ($P > 0.05$, as compared with the saline/saline control group) or the same dose of GBP ($P < 0.01$, as compared with the GBP/saline injected group). No drug effects ($H_{(3)} = 4.44$; $P > 0.05$) on unshocked mice were observed in these experiments (data not shown).

Our results demonstrate probably for the first time, that the post-training intraperitoneal administration of gabapentin, an antiepileptic drug currently in clinical use [12] enhances retention performance of a one-trial step-through inhibitory avoidance response in mice. Dose response curve

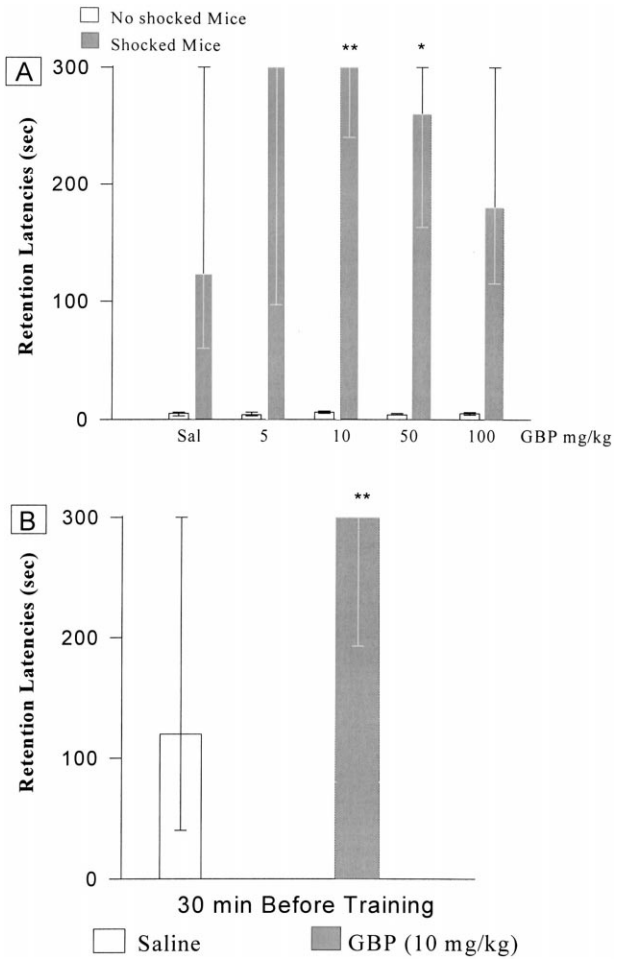

Fig. 1. (A) Effects of immediate post-training injections of gabapentin (GBP) on the latencies to step-through during retest. $**P < 0.01$, and $*P < 0.05$, compared with saline control group. Each bar represents the medians and interquartile ranges for 15 mice (shocked) or 10 mice (unshocked) per group. (b) Effect of pre-training administration of gabapentin (GBP) on retention. The drug was injected 30 min before training. Data are expressed as medians and interquartile ranges for $n = 15$ mice/group. $**P < 0.01$, compared with saline-treated mice.

was bell-shaped, and maximal response to post-training GBP were attained at doses of 10 and 50 mg/kg. It is of interest that the effective doses of GBP in the present experiment were significantly lower than those producing antiseizure activity in animal seizure models [14]. The effects of GBP on retention performance were not attributable to nonspecific influences on response latencies; that is, GBP did not affect either training-response latencies when administered prior to training or retention response latencies of unshocked controls mice when administrated either immediately after training or prior to the retention test. Further, the effects of GBP on retention performance varied with the training-treatment interval; retention was not improved in mice injected with the anticonvulsivant 180 min after training. The time dependent nature of GBP effects on retention

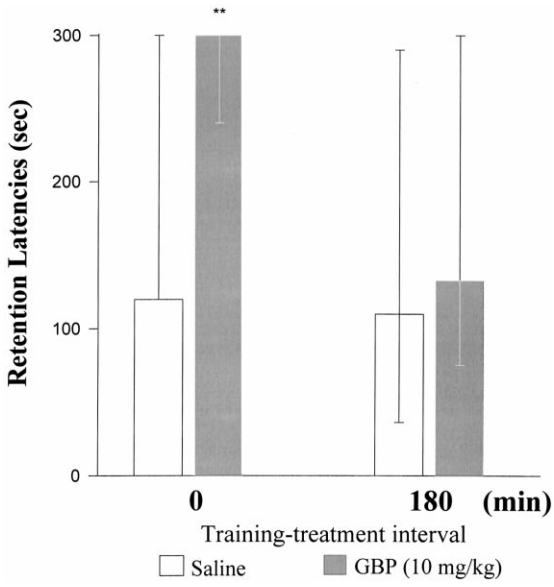

Fig. 2. Effects of delayed injections of saline or gabapentin (GBP) on retention. Data are expressed as medians and interquartile ranges for $n = 15$ mice/group. $^{**}P < 0.01$, compared with its respective control group.

suggests an influence on endogenous mechanisms that retroactively regulate the storage of new information [6,10].

This suggestion is further supported by the following findings. Pre-training GBP injection improves retention performance of shocked mice, and the effect was of the same magnitude of that produced by an equal dose of the drug administered immediately after training. Further, the administration of GBP prior to the retention test did not affect the retention latencies of mice, which were given either saline or the active dose of the drug immediately after training. These results indicate that GBP does not influence memory retrieval [10] and also argue against the interpretation that the post-training facilitatory effects of GBP on retention might result from state-dependency [11] rather than from the enhancement of memory storage [3].

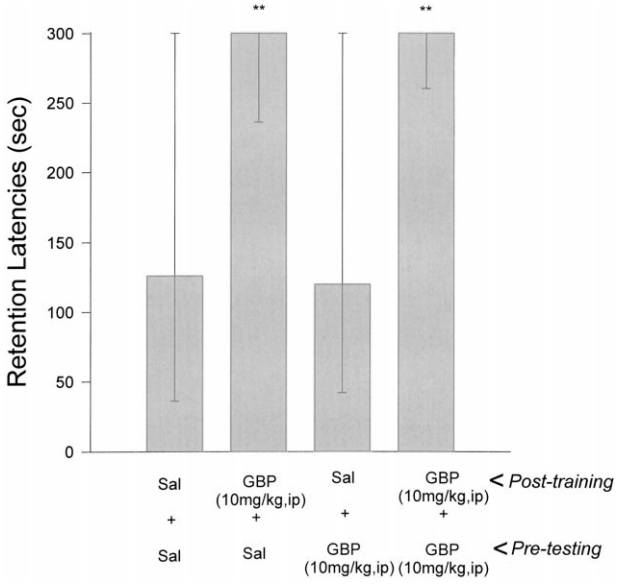

Fig. 3. Effects on retention of saline or gabapentin (GBP) administered post-training and prior to retention test. The treatments were given immediately after training and 30 min before the retention test. Data are expressed as medians and interquartile ranges for $n = 15$ mice/group. $^{**}P < 0.01$, in contrast with all groups given saline post-training.

Although originally synthesized as a lipophilic analogue of the inhibitory amino acid neurotransmitter γ-amino butyric acid (GABA) [7] capable of penetrating the blood–brain barrier [15], GBP does not possess high affinity for either $GABA_A$ or $GABA_B$ receptors, or GABA uptake carriers [20]. On the other hand, the data regarding the participation of GABA on memory, indicate that drugs that facilitate GABAergic neurotransmission at $GABA_A$ or $GABA_B$ receptors, impair memory in experimental animals and humans [4], whereas drugs that reduce neurotransmission at $GABA_A$ receptors improve memory in rodents [1,5]. Altogether, these findings suggest that the memory enhancing effects of GBP reported here, may not be associated with a direct interaction of the drug with central GABAergic mechanisms.

Gabapentin treatments alters the metabolism or concentration of glutamate, glycine or GABA in brain tissues [19,20] and, like that of several endogenous amino acids, also interact with the $alpha_2$ delta auxiliary sub-unity of voltage-gates Ca^{2+} channels [9]. This finding suggests that GBP may modulate certain types of Ca^{2+} currents [18] and that the inhibition by GBP on monoamine neurotransmitter release [16] may be caused by an interaction with Ca^{2+} channels [19]. The evidence summarized above suggests that several potential mechanisms may account for the activity of GBP as an enhancer of retention performance in mice. The present experiments were not aimed to clarify this question, however, further studies are in progress to do just that.

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