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Behavioral Effects of NBQX, a Competitive Antagonist of the AMPA Receptors

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FILLIAT, P., I. PERNOT-MARINO, D. BAUBICHON AND G. LALLEMENT. *Behavioral effects of NBQX, a competitive antagonist of the AMPA receptors.* PHARMACOL BIOCHEM BEHAV **59**(4) 1087–1092, 1998.—NBQX, a specific and potent AMPA receptor antagonist has been found to be neuroprotective in various models of ischemia and to have anticonvulsant properties in different models of epilepsy. In this experiment, the neurobehavioral effects of NBQX were studied. In an open field, an important ataxia was emphasized at a dose of 60 mg/kg. In a swimming task, an increase of the escape latencies was noted on the third day at a dose of 40 mg/kg. In a Morris water maze task, doses devoid of effects on locomotion were used (10, 20, and 30 mg/kg). There was no effect on the acquisition of the task at 10 mg/kg and a slight impairment at 20 mg/kg, but the rats did not learn the task at 30 mg/kg. This impairment was reversible, as shown by the increasing performance of this group without treatment. No impairment was noted in the retention phase of the Morris water maze task. The results are discussed relative to the role of the AMPA receptor in memory processes. © 1998 Elsevier Science Inc.

NBQX AMPA receptors Morris water maze Spatial memory Motor behavior Open field Rats

GLUTAMATE is considered as the major excitatory neurotransmitter in the central nervous system. On the other hand, an excess of glutamate can induce pathologic processes. So, there as been, for many years, a great interest in the development of glutamate antagonists (competitive or noncompetitive) of the *N*-methyl-D-aspartate (NMDA) subtype of ionotropic glutamate receptor. This was due to a lack of selective antagonists for the other types of receptors to the glutamate: non-NMDA [(S)-a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid = AMPA and kainate] and metabotropic receptors. The recent discovery of 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo (F) quinoxaline (NBQX), a potent, selective, competitive AMPA/kainate antagonist (14,29) with very low affinity for the glycine site of the NMDA receptor (28,29,39) allowed to test its effects in various models of glutamate pathology.

NBQX has been found to be neuroprotective in various models of focal (7,13) and global ischemia (2,6,19,20,29,30). It also affords anticonvulsant properties in different models of epilepsy. NBQX is able to terminate (37) and to prevent (38) an electrically induced status epilepticus. NBQX is effective against audiogenic-, AMPA-induced seizures (9) and soman-induced seizures (17,18). In kindling, it is more effective than NMDA antagonists (8) and, in contrast with NMDA antagonists (21,22) exerts potent anticonvulsant activity without concomitant phencyclidine (PCP)-like behavior (24,25).

NBQX has therapeutic properties in spasticity (34), spinal cord injury (35,36), dystonia, and some models of Parkinson (16) but it does not counteract neuroleptic-induced catalepsy (40).

Despite these numerous sudies, little is known about the neurobehavioral effects of the administration of NBQX, especially concerning the effects on memory. Only Parada et al. (27) showed that NBQX did not influence alternation in a Y-maze and did not impair learning in a passive avoidance test.

In the present experiment, the effects of NBQX on locomotor activity are studied in an open field and in a water maze and the effects on learning and memory using the Morris water maze test.

METHOD

Animals

Forty male Wistar rats weighing 200–220 g at the beginning of the experiment were used as subjects. Rats were main-

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tained in hanging cages (five per cage) with food and water freely available in a light-controlled animal room (lights on from 0700 to 1900 h). All tests were conducted during the light portion of the cycle. The same rats were used during the entire experiment.

Apparatus

The Morris water maze consisted of a circular pool (diameter: 140 cm, depth: 45 cm). The pool was filled to a depth of 25 cm with water at 21°C (± 2°C) rendered opaque by the addition of milk. The hidden platform was a circular Plexiglas stand (diameter: 11 cm) submerged 2 cm below the water surface so that it was invisible at water level. The visible platform was identical except that it was 1 cm above the water surface.

The open field consisted in a 90 × 90 × 40 cm flat black Poly Vinyl Carbonat (PVC) box.

The rats behavior was recorded and analyzed by two CCD cameras (one for the water maze and the other for the open field) connected to a computer-assisted image processor (video-track, View-Point, Lyon, France).

Drugs

NBQX (a generous gift of Dr. Lars Nordholm, Novo Nordisk, Denmark) was dissolved in a minimum quantity of 1 M NaOH, diluted with distilled water, and adjusted to pH 8.0. Three dosages of NBQX were chosen: 20, 40, and 60 mg/kg, the second dosage corresponding to the ED_{50} for antiepileptic and neuroprotective efficacy against chemically induced seizures (17). NBQX or its vehicle was administrated IP daily, 15 min before each trial except for the effects of the drug on retention in the Morris water maze test where all the groups learned the task without treatment.

Procedure

The experiment consisted in four parts separated by a washout phase of 10 days to allow the elimination of the product.

TABLE 1

DISTANCE TRAVELED IN THE OPEN-FIELD BY CONTROL- AND NBQX-TREATED RATS (n = 10 FOR EACH GROUP)

	Control	NBQX 20 mg/kg	NBQX 40 mg/kg	NBQX 60 mg/kg
Distance traveled (cm)	19073	3468*	5490*	2756*

*$p < 0.001$ significantly different from control group.

Phase 1: habituation. During 1 week the animals were habituated by being handled twice a day.

Phase 2: the open field. Fifteen minutes after the injection each animal was placed in the open field and the recording system analyzed the distance covered during 30 min by phases of 5 min. During the first minute of each 5-min phase, the degree of ataxia was noted according to a scale derived from that of Sturgeon et al. (33): 0—inactive or coordinated movements; 1—awkward or jerky movements or loss of balance while rearing; 2—frequent falling or partial impairment of antigravity reflexes; 3—inability to move beyond a small area, and support of body weight on haunches or abdomen; 4—inability to move except for twitching movements.

Phase 3: swimming test. Rats were allowed to swim freely until they found a visible platform located in the center of the pool. If a rat failed to climb on the platform within 60 s, it was placed on it by the experimenter and remained on it for 15 s. There were four trials each day, the starting point being always the same, against the wall of the pool, nose facing the platform. The time to reach the platform (latency) was recorded. This parameter was averaged for each block of four trials and for each rat whose performance was thus characterized.

Phase 4: the Morris water maze test. Rats were allowed to swim freely until they found a submerged platform, and it remained on it for 15 s. If a rat failed to find the escape platform

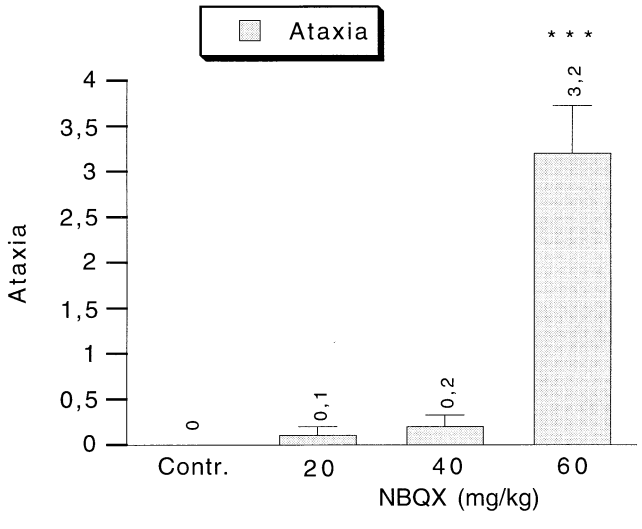

FIG. 1. Evolution of the ataxia degree for control and NBQX-treated rats (n = 10 for each group). (The degree of ataxia was noted according to a scale derived from this of Sturgeon et al., cf. procedure). ***$p < 0.001$, significantly different from the three other groups.

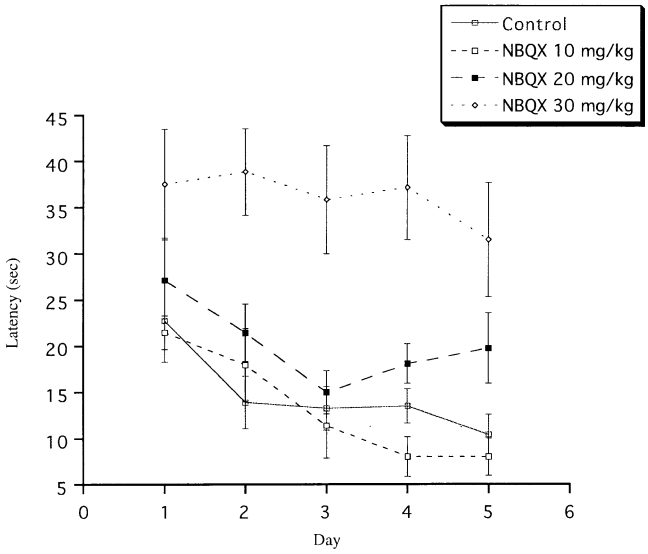

FIG. 2. Escape latency for control and NBQX-treated rats. Values represent the mean + SEM for each group (n = 10 for each group). **$p < 0.001$, significantly different from the three other groups.

within 60 s, it was placed on it by the experimenter. Each rat did a trial from each of the four starting points each day until an acquisition criterion was reached by its group (stable escape latency over 2 consecutive days). For each trial the rat was placed in the pool at one of four randomly determined starting locations; those locations were identical for all rats of all groups. The platform was located in a fixed position midway between the center and the edge of the pool (in the middle of quadrant 1, southwest). The time to reach the platform (latency), the distance traveled, and the swimming speed were recorded. Those parameters were averaged for each block of trials and for each rat, whose daily performance was thus characterized. When the acquisition criterion was reached, animals performed a spatial probe trial. It consisted of removing the platform from the pool and allowing the rat to swim for 60 s in search of it. If the animal showed a persistent preference during this trial to swim in the pool quadrant where the platform had previously been placed, this was taken to indicate that the rat had acquired the spatial task and remembered it. The number of crossings of the previous place of the patform was also registered.

Morris water maze test, retention. The same rats were used and the procedure was identical except that the rats learned the task without treatment (after the washout phase of 10 days). One day after the reaching of the acquisition criterion, the rats were injected and the probe test performed 15 min later.

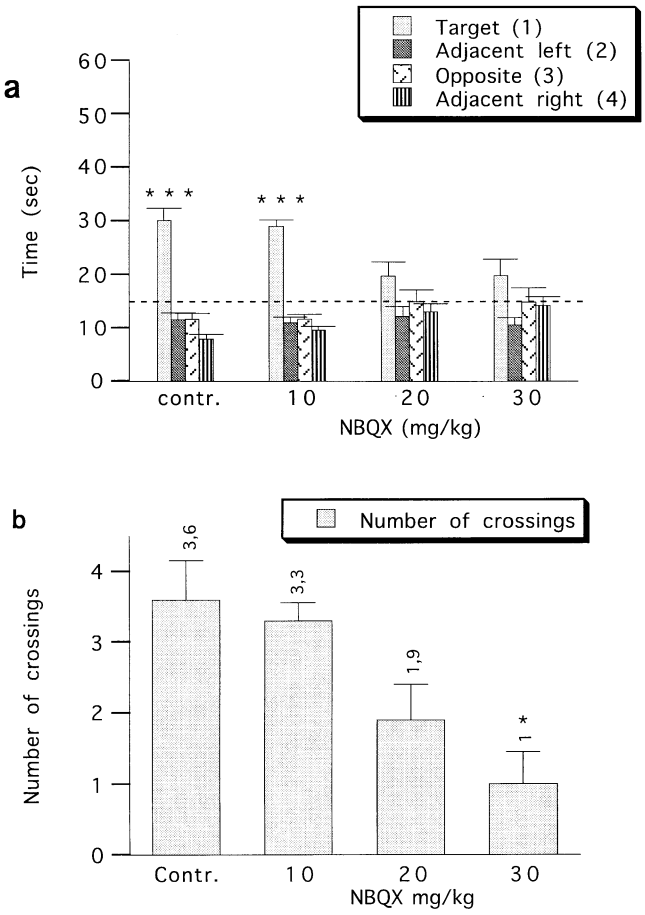

FIG. 3. (a) Swimming time of control and NBQX-treated rats in each of the quadrants of the pool without a platform. Horizontal line represents the chance level (15 s). Values represent the mean + SEM for each group ($n = 10$ for each group). $^{**}p < 0.001$, significantly different from chance level (Bonferroni test, $n = 10$ for each group). (b) Number of crossings of the previous place of the platform for the control and NBQX-treated rats. Values represent the mean + SEM for each group ($n = 10$ for each group). $^{*}p < 0.05$, significantly different from the 10 and the control groups.

Statistical Analysis

The data were analyzed by the Kruskal–Wallis test or by ANOVA followed by the Bonferroni test. Significance was set at $p < 0.05$.

RESULTS

Open Field

The difference between the 60 mg/kg NBQX group and the three other groups (Fig. 1) was significant, $F(3, 36) = 30.865$, $p < 0.001$.

The distance traveled by all the groups treated with NBQX was significatively less than the distance traveled by the control group, $F(3, 36) = 23.048$, $p < 0.001$. There was no difference between the three groups treated with NBQX (Table 1).

Visible Platform Test

Due to the severe ataxia observed in the previous part of this study, the maximal dosage of 60 mg/kg was discarded for this test, which was conducted with 40, 20, and 10 mg/kg NBQX.

On the third day, half of the rats treated with 40 mg/kg were unable to swim. This test was thus interrupted.

There was no difference between the escape latencies of the three other groups (20 and 10 mg/kg and control).

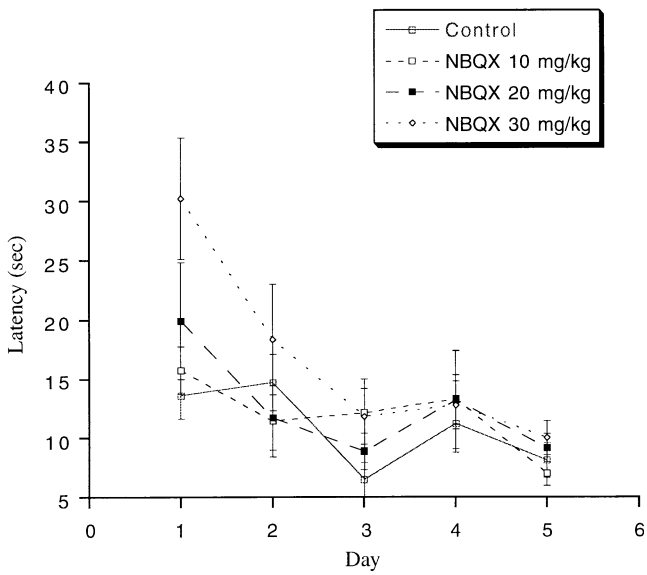

FIG. 4. Escape latency for control and NBQX-treated rats. Values represent the mean + SEM for each group ($n = 10$ for each group).

Water Maze Test, Acquisition

Swimming speed. The swimming speed of the 30 mg/kg group differed (decreased) from that of the 10 and 20 mg/kg groups but not from that of the control group, $F(3, 36) = 5.703$, $p = 0.0027$ (data not shown).

Latency. There was a main effect of the treatment and a main effect of the time without day × treatment interaction, $F(3, 36) = 14.121$, $p < 0.0001$) (Fig. 2). The results of the 30 mg/kg group differed from the results of the three other groups. The results were the same for the distance (data not shown).

During the probe test, there was no difference between the swimming speeds of the different groups, $F(3, 36) = 2.808$, $p = 0.056$. Control, $F(3, 36) = 45.683$, $p < 0.0001$, and 10 mg/kg-treated, $F(3, 36) = 87.643$, $p < 0.0001$, rats swam preferentially in quadrant 1, where the platform had previously been located during the training, than in the three other quadrants but rats treated with 20, $F(3, 36) = 2.58$, $p = 0.0686$, or 30 mg/kg, $F(3, 36) = 2.818$, $p = 0.0527$, NBQX did not swim preferentially in quadrant 1. The number of crossings was significatively less for the 30 mg/kg group than for the control and the 10 mg/kg group, $F(3, 36) = 7.082$, $p = 0.0007$) (Fig. 3).

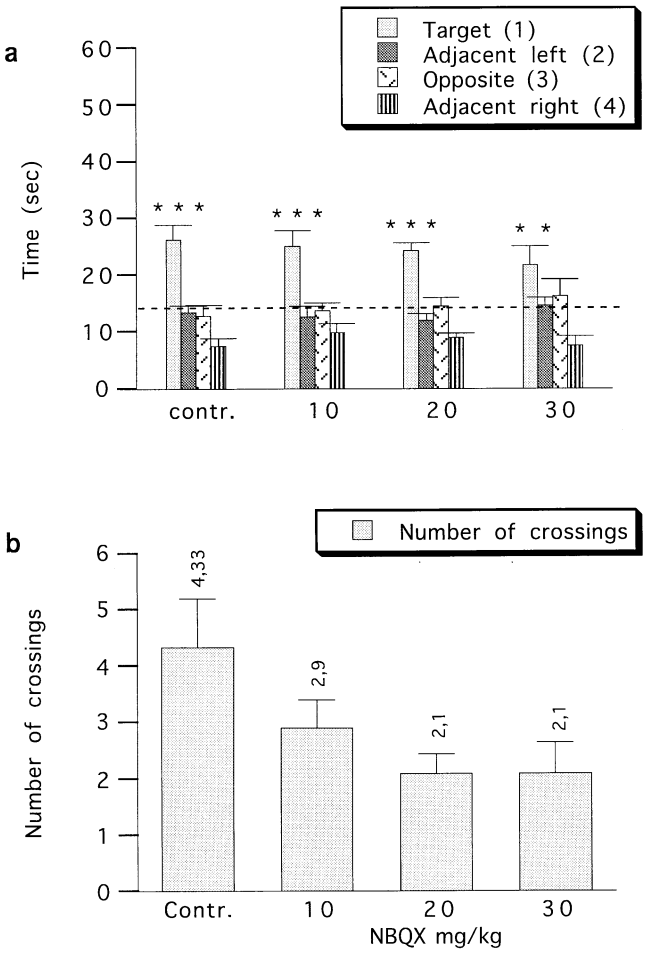

FIG. 5. (a) Swimming time of control and NBQX-treated rats in each of the quadrants of the pool without a platform. Horizontal line represents the chance level (15 s). Values represent the mean + SEM for each group ($n = 10$ for each group). ***$p < 0.001$ and **$p < 0.01$, significantly different from chance level (Bonferroni test, $n = 10$ for each group). (b) Number of crossings of the previous place of the platform for the control and NBQX-treated rats. Values represent the mean + SEM for each group ($n = 10$ for each group).

Water Maze Without Treatment

Swimming speed. There was no difference between the swimming speed of the different groups, $F(3, 36) = 1.464$, $p = 0.2411$.

Latency. There was no effect of the previous treatment administered during the acquisition, $F(3, 36) = 1.383$, $p = 0.264$, an effect of the day, $F(4, 36) = 18.05$, $p < 0.0001$, and a significant day × treatment interaction, $F(12, 36) = 2.39$, $p = 0.0077$: the latency of the 30 mg/kg group, initially different from the latency of the three other groups, became no different from the third day (Fig. 4). The results were the same for the distance (data not shown).

Retention

Swimming speed. There was no difference between the swimming speed of the different groups, $F(3, 36) = 2.625$, $p = 0.0658$.

All groups. Control, $F(3, 36) = 19.45$, $p < 0.0001$), 10, $F(3, 36) = 10.885$, $p < 0.0001$, 20 mg/kg, $F(3, 36) = 26.937$, $p < 0.0001$, and 30 mg/kg-treated rats, $F(3, 36) = 5.347$, $p = 0.0038$, swam preferentially in quadrant 1, where the platform was previously located during the training, rather than in the three other quadrants. There was no difference between the four groups in the number of crossings (Bonferroni test nonsignificant) (Fig. 5).

If we compare the results of the control group during the acquisition with those of the 30 mg/kg during the procedure without treatment (Fig. 6), we can see that there was no difference between the latencies of the two groups, $F(1, 18) < 1$. The results were the same for the distance (data not shown).

DISCUSSION

In the open field, an ataxia was noted for 60 mg/kg. This ataxia was important, the degree of ataxia being 4 for 80% of the rats. NBQX has been found to induce ataxia in rats at

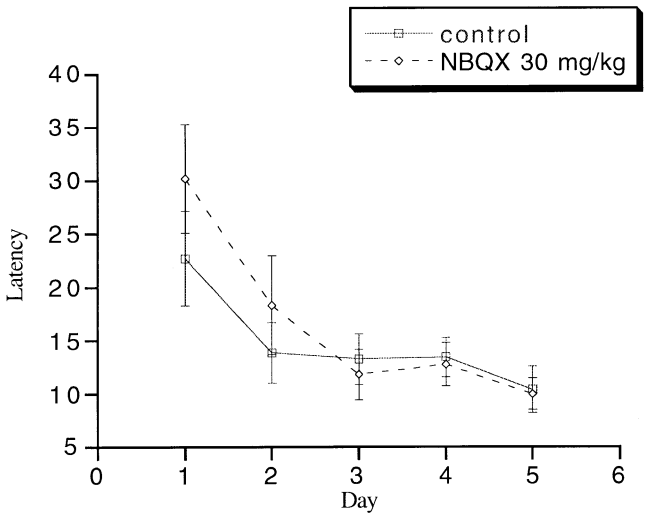

FIG. 6. Comparaison of the escape latencies of the control group during the acquisition phase and the escape latencies of the 30 mg/kg NBQX treated groups. Values represent the mean + SEM for each group ($n = 10$ for each group).

doses equal to (11) or equal or above 40 mg/kg (23), but not up to 30 mg/kg (10). Chapman et al. (8) found a dose-related incidence of mild to moderate ataxia, at doses of 20–82 mg/kg NBQX in mice. It thus seems that NBQX induces an ataxia for doses above 40 mg/kg in rats.

All the groups treated with NBQX presented an important hypolocomotion in comparison with the control group. Similarly, NBQX was found to decrease in a dose-dependent manner locomotor activity in mice in an Y-maze as from 20 mg/kg (27), but not to affect exploratory mobility at doses up to 30 (16) or 34 mg/kg (34). Comparatively, in the rotarod test, NBQX did not seem to affect the performance at 30 mg/kg in rats (25) but caused impairment at a dose of 62 mg/kg in mice (9).

The present hypolocomotion could be in relation with a sedation that was previously observed by many authors from 30 (3–5) or 40 mg/kg (23).

The swimming test had to be interrupted because of an inability of the 40 mg/kg NBQX group to swim on the third day. Two explanations are possible: a greater sensitivity of the pool to detect fine locomotor troubles comparatively to the open field or more likely a cumulative effect of the doses. This possible cumulative effect was not apparent for the inferior doses of 20 and 10 mg/kg NBQX, the swimming speed of these groups being no different from that of the control group.

In the acquisition phase of the Morris water maze test, NBQX 30 mg/kg-treated rats swam slower than NBQX 10 and 20 mg/kg-treated rats, but it is important to note that there was no difference with the control group. Furthermore, during the spatial probe trial, there was no difference between the four groups in terms of swimming speed. Thus, it can be assumed that no locomotor trouble was observed in the water maze for those doses.

The 20 mg/kg group had the same pattern as control and NBQX 10 mg/kg-treated rats. Furthermore, their number of crossings was not significatively different. Nevertheless, it did not manifest a bias for the target quadrant in the spatial probe trial. Thus, it can be said that they manifested a slight memory impairment.

For the 30 mg/kg NBQX group, the data of the escape latency and distance, the lack of bias for the target quadrant in the spatial probe test and the fewer number of crossings of the initial location of the platform (comparatively to control and 10 mg/kg-treated rats) show that these animals had not learned the task.

In the washout phase of the Morris water maze test, the lack of effect of the treatment and the presence of a main effect of the day and a significative day $\times$ treatment interaction can be explained by an increased performance of the NBQX 30 mg/kg-treated group (which was previously treated with 30 mg/kg) with the time, the performance of this group becoming no different from the other groups from the third day.

The results of the NBQX 30 mg/kg-treated group seem not to be different from those of a control naive group. If we compare the results of the control group in the acquisition phase (naive rats, without knowledge of the Morris water maze test and without treatment) to the results of the NBQX 30 mg/kg-treated rats in the washout phase, it can be observed that there was no difference between those two groups. Thus, the effects of repeated injections of 30 mg/kg NBQX are reversible, confirming that there was no learning in the acquisition phase of the task for this group, even latent, because their performance (in the washout phase) was not better than the initial performance of the control group (which had no knowledge of the Morris water maze test).

In the retention phase of the water maze, although the 30 mg/kg NBQX-treated rats did not manifest a real bias for the target quadrant, their performance did not differ from those of the three other groups in terms of number of crossings. It can thus be said that the retention of the 30 mg/kg NBQX-treated rats was not affected.

Although the role of AMPA receptors in synaptic plasticity is less well established than that of NMDA receptors, some evidence implicates AMPA receptors in learning and memory.

ICV injection of the AMPA antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) immediately after a T-maze training impaired retention for foot shock training (12). Maldonado-Irizarry and Kelley (26) showed that injection of DNQX into core and shell subregions of the nucleus accumbens impaired acquisition and retention of a free-choice discrimination task. For the authors, it can be said that "both NMDA and non-NMDA (AMPA and/or kainate) receptors within the nucleus accumbens mediate spatial learning and performance."

Similarly, ICV injection of an other AMPA antagonist: 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) in day-old chick impaired retention in a one-trial passive avoidance task (32).

Moreover, increased affinity of AMPA receptors has been found to be associated with longer term memory (6.5 h after training) for passive avoidance training in chicks (32).

Recently, a new series of benzamide compounds has been reported to potentiate AMPA receptor-mediated currents in hippocampal cell cultures (1) as well as enhance fast synaptic responses in rat hippocampus (1,15,31). Those compounds have been shown to cause an improvement in memory encoding in a two-oder discrimination task, a water maze task (31), or in a radial arm maze (15,31).

Although all these experimental data argue in favor of a participation of AMPA receptors in learning and memory, it can be said that DNQX and CNQX are not specific AMPA antagonists and that their effects on memory can be at least partially mediated by an action on NMDA receptors. Comparatively, our results, using a specific AMPA antagonist, clearly put forward the evidence of a role of the AMPA receptors in learning and memory.

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