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The effects of NMDA receptor antagonists at anticonvulsive doses on the performance of rats in the water maze task

Aarne Ylinen [a,b,*], Mervi Pitkänen [a], Jouni Sirviö [a,b], Tiina Hartikainen [a], Juhani Sivenius [a], Esa Koivisto [a], Paavo J. Riekkinen, Sr. [a,b]

[a] *Department of Neurology, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland*
[b] *A.I. Virtanen Institute, Kuopio, Finland*

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Abstract

In the present study we investigated the effects of two competitive NMDA receptor antagonists, CGP 37849 (DL-(*E*)-2-amino-4-methyl-phosphono-3-pentonoic acid) and CGP 39551 (carboxyethyl ester of CGP 37849) as well as MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenz(*a*,*d*)cycloheptene-5,10-imine hydrogen maleate), a non-competitive antagonist, administered systemically before training, on the acquisition of a water maze task used to assess spatial learning and memory in rats. The competitive NMDA receptor antagonists dose dependently impaired water maze acquisition (increased escape distance), but did not significantly affect swimming speed in rats. MK-801 induced clear behavioral effects and impaired the acquisition of the water maze task. However, as training advanced drug-treated rats did show a decrease in distance swum per trial before encountering the platform in the water pool. This suggests that drug treatments did not abolish learning. When the anticonvulsive properties of the drugs were determined, MK-801 did not show any protection in the maximal electroshock (MES) test at doses already impairing the acquisition of the water maze task while the two competitive NMDA receptor antagonists protected the rats against seizures at doses not impairing acquisition. This result suggests a wider therapeutic range for CGP 39551 and especially for CGP 37849 than for MK-801 in the treatment of epilepsy.

Keywords: Epilepsy; NMDA receptor antagonist; CGP 39551; CGP 37849; MK-801; Spatial learning

1. Introduction

The receptors of excitatory amino acids (L-glutamate, L-aspartate) can be classified into non-NMDA and NMDA receptors (Dingledine et al., 1990). The ionotropic non-NMDA receptors induce fast depolarization of neurons whereas the activation of NMDA receptors causes slow depolarization of neurons in the mammalian forebrain. NMDA receptors, whose activation is dependent on prior membrane depolarization, are regulated by both ligand binding and allosteric sites (Williams et al., 1991).

According to the excitotoxic hypothesis, excessive release of excitatory amino acids and/or prolonged stimulation of the receptors of excitatory amino acids play a role in the neuropathology associated with ischemia (Schmidt-Kastner and Freund, 1991) and epileptic seizures (Olney, 1983; Dingledine et al., 1990) as well as in some neurodegenerative diseases (Greenamyre and Young, 1989; Meldrum and Gartwaite, 1990). Both competitive and non-competitive NMDA receptor antagonists have been shown to diminish neuronal damage in experimental models of stroke (Albers et al., 1989; Schmidt-Kastner and Freund, 1991) and epilepsy (Rogers et al., 1989; Rogers and Tilson, 1989; Ylinen et al., 1991; Lahtinen et al., 1993). Furthermore, several NMDA receptor antagonists have been shown to have anticonvulsive properties in both in vitro and in vivo models of epilepsy (Wong et al., 1986; Koek and Colpaert, 1990; Mintz et al., 1990; Schmutz et al., 1990). In recent studies, NMDA receptor antagonists have also been shown to prevent epileptogenesis (Stasheff et al., 1989). However, NMDA receptor antagonists exert only a weak effect in the amygdala-kindling model of epilepsy when studied in fully kindled rats (Löscher and Hönack, 1991; Cotterell et al., 1992).

* Corresponding author. Fax 358-71-162048.

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NMDA receptor-mediated mechanisms are involved in the neural plasticity underlying learning and memory (Collinridge et al., 1983). Intracerebral administration of NMDA receptor antagonists impairs long-term potentiation in the hippocampus and spatial learning without any apparent side effects in rats (Morris et al., 1986; Davis et al., 1992). Furthermore, systemic administration of non-competitive and competitive NMDA receptor antagonists impairs the performance of rats in several behavioral tasks assessing learning and memory (Danysz et al., 1988; Butelman, 1989; Heale and Harley, 1990; McLamb et al., 1990; Parada-Turska and Turski, 1990; Venable and Kelly, 1990; Ward et al., 1990; Wozniak et al., 1990).

New competitive antagonists which are also orally active have been developed (Fagg et al., 1990; Pozza et al., 1990). These compounds have shown antiepileptogenic effects in some experimental models of human epilepsies (Schmutz et al., 1990). Other studies have also investigated the effects of these compounds on psychomotor activity in kindled rats and their effects on brain neurochemistry in rats (Löscher et al., 1991). The present experiments were undertaken to investigate whether two such agents, CGP 39551 and CGP 37849, affect learning in rats. Thus, the effects of different anticonvulsive doses of these compounds on the acquisition of the water maze task, which measures spatial representational memory, were studied for evaluating the therapeutic range of the compounds. MK-801, which binds to the ion channel in the NMDA receptor/ion channel complex, was used as a reference compound, because its antiepileptic and behavioral effects are well known (Wong et al., 1986; Ferkany et al., 1989; Tricklebank et al., 1989; Heale and Harley, 1990; Mintz et al., 1990; Wozniak et al., 1990).

2. Materials and methods

Adult male Kuo:Wistar rats (250–300 g) (National Animal Center, Kuopio, Finland) were used in these studies. The rats were housed in Makrolon cages (2 or 3 rats/cage) in a temperature (20°C) and humidity (50–60%) controlled environment. Lights were on from 7 a.m. to 9 p.m. Water and food pellets were given ad libitum.

2.1. Spatial learning

CGP 37849 (DL-(*E*)-2-amino-4-methyl-phosphono-3-pentenoic acid) and CGP 39551 (carboxyethyl ester of CGP 37849) (Ciba-Geigy, Basel, Switzerland) were dissolved in saline. Drug solutions were injected 4 h before behavioral training (once a day, 4 ml/kg). Treated groups consisted of saline ($n = 8$), CGP 39551 2.8 mg/kg ($n = 8$), 5.6 mg/kg ($n = 7$) and 11.2 mg/kg ($n = 8$) as well as CGP 37849 2.5 mg/kg ($n = 8$), 5.0 mg/kg ($n = 8$) and 10.0 mg/kg ($n = 8$). One rat treated with 5.6 mg/kg CGP 39551 died during the experiments. The lowest dose of the compounds corresponds to the ED_{50} dose in the maximal electroshock (MES) test (Schmutz et al., 1990). Although these competitive NMDA receptor antagonists are also orally active, the intraperitoneal route was used for administration to permit a valid comparison with the reference compound, MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenz(*a*,*d*)cycloheptene-5,10-imine hydrogen maleate, dizocilpine) (Research Biochemicals International, Natick, MA, USA), which was also dissolved in saline. Drug solutions were injected (4.0 ml/kg) 45 min before behavioral testing. Treated groups consisted of saline ($n = 8$), 0.075 mg/kg ($n = 8$) and 0.15 mg/kg ($n = 8$). The higher dose corresponds to the ED_{50} in the MES test.

For the assessment of spatial learning, we used a modified version of the Morris water maze task (black pool filled with clear water) (Riekkinen et al., 1990; Sirviö et al., 1991). The water-maze pool was a circular fiber-glass tank, 150 cm in diameter, 74 cm deep, and filled to a height of 52 cm with water at room temperature. The platform was made of a Plexiglas tube and the top surface was composed of black rubber and was 1.5 cm below the water line. The pool was divided into 4 quadrants of equal surface area. The starting locations were called north, south, east and west and they were located arbitrarily at equal distances on the pool rim. The platform was located in the south-west quadrant on each training day. The swim paths were monitored by a video camera linked to a computer through an image analyzer. The computer calculated the total time (s) and distance (pixels, which were computerized to cm) swum. The timing of the latency was started and ended by the experimenter.

The rats were placed into the water, with the nose pointing toward the wall, at one of the four starting points, which were ordered in a semi-random manner. The first and third swims of the day were always started from one of the points located farthest from the platform (north/east) and the starting location for the second swim of the day was chosen between south and west. Testing consisted of 5 consecutive training days. On each trial (three/day), the rats were allowed a maximum of 70 s to find the hidden platform. If the rat found the platform, it was allowed to stay there for 10 s. The rats that failed to find the platform within 70 s were placed on it for 10 s. A 30-s recovery period was used between daily trials. After the third trial of each training day, the rats were dried with a towel and placed in their home cage.

Water maze data (escape distance as well as swimming speed (distance/latency)) were evaluated using analysis of variance for repeated measurements

(MANOVA, SPSS/PC + program; Norusis, 1986) with treatment and training day as the two factors. Post-hoc MANOVA was used for pair-wise comparisons between different groups. The results are expressed as group means of three daily training trials; all data of each rat in three different trials were combined in each treatment group for each day.

2.2. Behavioral activity

For the assessment of behavioral activity, we used a water maze staying-on-platform task. The rat was placed into the water as in the normal water maze task. If the rat found the hidden platform, it was allowed to stay on it for 20 s. If the rat failed to find the platform, it was placed on it (maximum 10 times in order to meet the criterion 20 s). The testing consisted of 5 training days (two trials/day, maximum 20 s on the platform, 60 s recovery between daily training trials). The computerized system calculated the mean time (maximum 20 s) each rat stayed on board.

The effects of the drugs were tested in adult rats (250–350 g) in a counterbalanced order every third day. The rats were treated 45 min (MK-801) or 4 h (CGP 39551 and CGP 37849) before behavioral testing.

Staying-on-platform data (mean duration to stay on the platform) was evaluated using a series of within-subjects repeated measures multivariate analyses of variance designs (MANOVA), using the averaged F-ratios. If MANOVA revealed an overall treatment effect, post-hoc MANOVA was used to analyze differences between treatments (saline versus different doses of a drug).

2.3. Anticonvulsive effects

The dosage used for the assessment of spatial learning was originally based on the ED_{50} values in the MES test from the literature. To test whether these are valid also in our strain of rats, the MES tests were performed in our laboratory for MK-801 (administered intraperitoneally 45 min before testing), CGP 39551 and CGP 37849 (administered intraperitoneally 4 h before testing). The values for CGP 39551 and CGP 37849 were determined using the corresponding doses of the active enantiomers of the drugs (Fagg et al., 1990). The ED_{50} values for our strain of rats are presented in Table 1. They were either approximately the same (CGP 39551 and MK-801) or lower (CGP 37849) than those previously reported for different strains of animals (see above). They were determined using maximal threshold seizures (tonic extension of the hind limbs) induced by an electrical apparatus similar to that described by Woodbury and Davenport (1952). The 60 Hz current was delivered for 0.2 s via corneal electrodes (Topical Testing, Salt Lake City, UT, USA). Maximal seizure patterns are best studied in the rat after an electric shock induced by application of 150 mA current. Since the rats used in our behavioral experiments and also in our MES tests were

Table 1
The effects of MK-801, CGP 39551 and CGP 37849 in the MES test

	Dose (mg/kg)	Protection (%)	ED_{50} mg/kg (95% confidence)
MK-801	0.075	2/10 (20)	
	0.15	4/10 (40)	0.14
	0.30	19/20 (95)	(0.09–0.18)
CGP 39551	0.7	2/10 (20)	
	1.4	4/10 (40)	2.52
	2.8	4/10 (40)	(1.17–7.91)
	5.6	8/10 (80)	
CGP 37849	0.625	3/10 (30)	
	1.25	6/10 (60)	1.04
	2.5	8/10 (80)	(0.50–1.52)
	5.0	10/10 (100)	

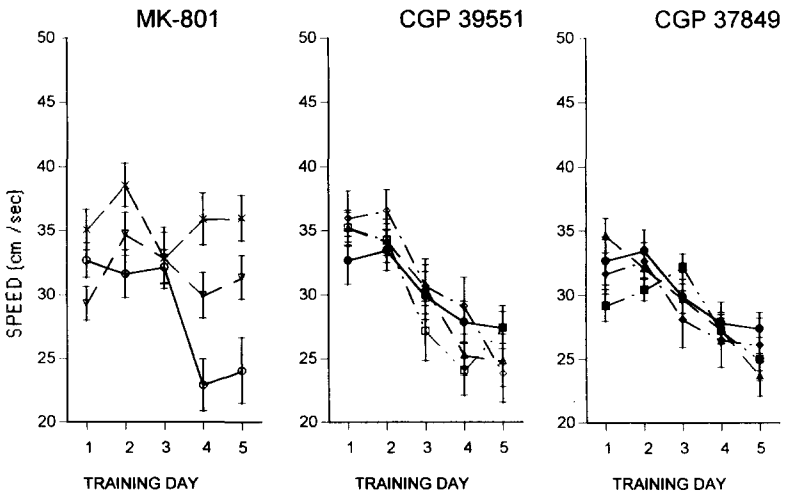

Fig. 1. The speed of swimming of saline-, MK-801-, CGP 39551- or CGP 37489-treated rats during the acquisition of the water maze task. The results are expressed as the group means ± S.E.M. of daily training trials. Symbols: Saline (○) or (●), MK-801 0.075 mg/kg (×), MK-801 0.15 mg/kg (▽), CGP 39551 2.8 mg/kg (△), 5.6 mg/kg (◇), 11.2 mg/kg (□), CGP 37849 2.5 mg/kg (▲), 5.0 mg/kg (◆) and 10.0 mg/kg (■).

heavier than usually is the case, we used a current of 200 mA.

3. Results

3.1. Behavioral activity

MANOVA revealed a significant overall treatment ($F(2,21) = 5.9$, $P < 0.01$) and training day ($F(4,340) = 4.4$, $P < 0.01$) effects in swimming speed in the group of saline- or MK-801-treated rats. At the dose of 0.075 mg/kg, MK-801 increased the speed of swimming as compared to that of saline-treated rats ($F(1,14) = 19.7$, $P = 0.001$) (Fig. 1). MK-801 0.150 mg/kg did not affect swimming speed significantly ($P > 0.1$), but the rats treated with 0.150 mg/kg MK-801 did not stay on the escape platform for the 10-s reinforcement period at the beginning of water maze training. At the doses used, CGP 39551 and CGP 37849 did not significantly affect swimming speed in rats (MANOVA revealed a non-significant overall treatment effect in swimming speed of rats treated with saline or CGP 39551 or CGP 37849 ($P > 0.1$) (Fig. 1).

When staying-on-platform was tested separately, MANOVA revealed a significant overall treatment effect on the staying-on-platform durations of rats treated with saline or different doses of MK-801 ($F(2,16) = 30.26$, $P < 0.001$) or CGP 39551 ($F(3,24) = 8.40$, $P = 0.001$) or CGP 37849 ($F(3,24) = 7.84$, $P = 0.001$). Post-hoc MANOVA analysis showed that smaller doses of CGP 39551 (2.8 or 5.6 mg/kg) or CGP 37849 (2.5 or 5.0 mg/kg) did not significantly affect staying-on-platform durations between treatments ($P > 0.05$). However, 11.2 mg/kg CGP 39551 and 10.0 mg/kg CGP 37849 shortened the staying-on-platform durations ($F(1,8) = 16.87$, $P < 0.01$ and $F(1,8) = 21.21$, $P < 0.01$, respectively). MK-801 shortened the durations at the dose of 0.075 mg/kg ($F(1,8) = 9.19$, $P < 0.05$) and more significantly at the dose of 0.15 mg/kg ($F(1,8) = 494.34$, $P < 0.001$) (Table 2).

3.2. Spatial learning

Because MK-801-treated rats had increased swimming speeds, the escape distance to the hidden platform was used as an index for the acquisition of the water maze task. MANOVA revealed significant overall treatment ($F(2,21) = 8.4$, $P < 0.01$) and training day ($F(,340) = 27.3$, $P < 0.001$) effects in the escape distance of rats treated with saline or MK-801. The interaction between treatment and training day was not significant ($P > 0.1$). Post-hoc treatment group comparisons revealed that the rats treated with 0.075 ($F(1,14) = 7.0$, $P < 0.05$) or 0.15 mg/kg ($F(1,14) = 20.8$, $P < 0.001$) MK-801 had significantly longer escape distances than saline-treated controls (Fig. 2).

Table 2
Effects of MK-801, CGP 39551 and CGP 37849 in the staying-on-platform task. Max. 20 s

	Dose (mg/kg)	n	Stayed on board (s)
MK-801	0.075	10	12.6 ± 1.9 [a]
	0.15	10	3.3 ± 1.0 [c]
Saline		10	19.0 ± 1.0
CGP 39551	2.8	10	18.8 ± 1.2
	5.6	10	13.4 ± 2.4
	11.2	10	91.0 ± 2.2 [b]
Saline		10	19.2 ± 0.8
CGP 37849	2.5	10	18.7 ± 0.8
	5.0	10	15.8 ± 1.5
	10.0	10	10.1 ± 2.0 [b]
Saline		10	18.8 ± 1.0

The results are expressed as means ± S.E.M.
[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ as compared to saline using MANOVA.

MANOVA revealed a significant overall treatment effect ($F(3,27) = 6.8$, $P = 0.001$) on the escape distance of rats treated with saline or CGP 39551 (Fig. 3). The interaction between treatment and training day effects was significant ($F(12,108) = 2.1$, $P < 0.05$). Post-hoc MANOVA tests between treatments showed that 2.8 mg/kg CGP 39551 did not affect the escape distance ($P > 0.1$), but the rats treated with 5.6 mg/kg CGP 39551 ($F(1,13) = 4.9$, $P < 0.05$) or 11.2 mg/kg CGP 39551 ($F(1,14) = 7.6$, $P < 0.05$) had significantly increased escape distances when compared to those of the controls (Fig. 3). The treatment and training day interaction was significant between saline and 11.2 mg/kg CGP 39551 treatments ($F(4,56) = 3.5$, $P < 0.05$). The CGP 39551-induced impairment was most marked at the beginning of the training period (Fig. 3).

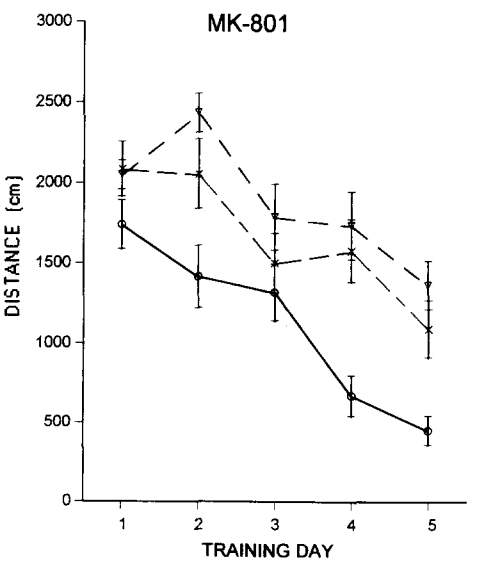

Fig. 2. The acquisition of the water maze task (expressed as escape distance) by saline- or MK-801-treated rats. The results are expressed as the group means ± S.E.M. of daily training trials. Symbols: Saline (○), MK-801 0.075 mg/kg (×), MK-801 0.15 mg/kg (▽).

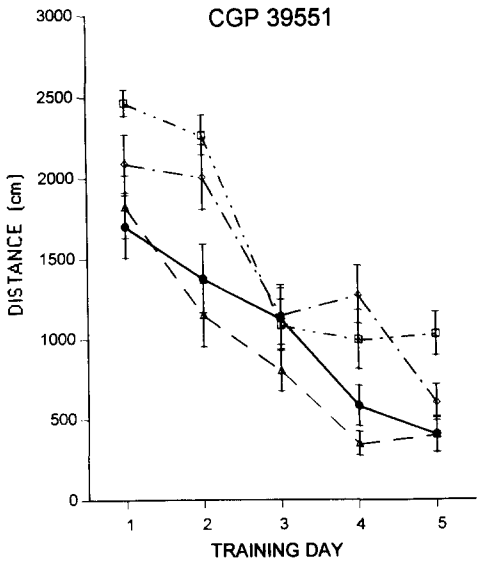

Fig. 3. The acquisition of the water maze task (expressed as escape distance) by saline- or CGP 39551-treated rats. The results are expressed as the group means ± S.E.M. of daily training trials. Symbols: Saline (●), CGP 39551 2.8 mg/kg (△), 5.6 mg/kg (◇), 11.2 mg/kg (□).

MANOVA revealed a significant overall treatment effect ($F(3,28) = 6.5$, $P < 0.01$) on the escape distance of rats treated with saline or different doses of CGP 37849 (Fig. 4). The interaction between treatment and training day effects was significant ($F(12,112) = 1.9$, $P < 0.05$). Post-hoc MANOVA tests between treatments showed that 2.5 mg/kg CGP 37849 and 5.0 mg/kg CGP 37849 did not affect escape distances ($P > 0.1$), but CGP 37849 markedly increased the escape distance at the dose of 10.0 mg/kg ($F(1,14) = 10.3$, $P < 0.01$) (Fig. 4). The treatment and training day interaction tended to be statistically significant between saline and 10.0 mg/kg CGP 37849 treatments ($F(4,56) = 2.3$, $P = 0.07$). The CGP 37849-induced impairment of the water maze task was more evident as the training sessions proceeded (Fig. 4).

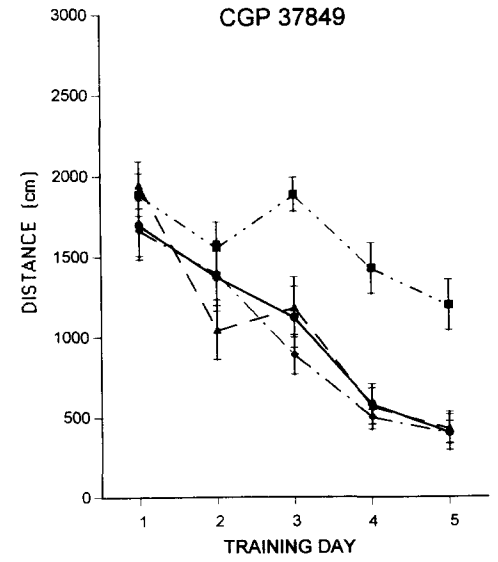

Fig. 4. The acquisition of the water maze task (expressed as escape distance) by saline- or CGP 37849-treated rats. The results are expressed as the group means ± S.E.M. of daily training trials. Symbols: Saline (●), CGP 37849 2.5 mg/kg (▲), 5.0 mg/kg (◆) and 10.0 mg/kg (■).

4. Discussion

The present study investigated whether NMDA receptor antagonists can affect spatial learning in rats at antiepileptic doses. MK-801, a non-competitive NMDA receptor antagonist, impaired the performance of rats in the water maze task at the doses 0.075 and 0.15 mg/kg, which agrees with previous studies (Heale and Harley, 1990). The higher dose of MK-801 corresponds to the ED_{50} in the MES test (Table 1). Previously, it has been suggested that MK-801 impairs acquisition but not recall of spatial or non-spatial memory tasks (Heale and Harley, 1990; McLamb et al., 1990; Parada-Turska and Turski, 1990; Venable and Kelly, 1990). Furthermore, it has been proposed that spatial learning deficits induced by MK-801 are due to the blockade of hippocampal NMDA receptors (Butelman, 1989).

Competitive NMDA receptor antagonists impaired the acquisition of the water maze task dose dependently in rats. Neither of the compounds impaired spatial learning at the doses corresponding to the ED_{50} in the MES test, which have been measured in another laboratory with a different rat strain (Schmutz et al., 1990). When we determined the ED_{50} values for our strain of rats, they were found to be either the same or lower than those previously reported (2.5 mg/kg for CGP 39551 and 1.0 mg/kg for CGP 37849). CGP 39551 slightly increased the escape distance of rats in the water maze task at double this dose. However, CGP 37849 did not increase the escape distance at a dose 5 times the ED_{50} in the MES test. According to our previous data, CGP 39551 (5.0 mg/kg i.p.) partly alleviates the functional deficits of a limbic seizure model, the so-called perforant pathway stimulation in rats (Ylinen et al., 1991). In the present study both CGP compounds impaired water maze acquisition at the highest dose used. The highest dose (10.0 mg/kg) of CGP 37849 tended to induce the kind of training day-dependent impairment which is suggestive of a spatial learning deficit. In contrast, the highest dose (11.2 mg/kg) of CGP 39551 induced a more variable deficit, because the escape distance was increased on the first and second, but not on the third day of the

training period. However, there was also some increase in escape distance on the last two days of the training period as compared to those of the saline treatment group. Whether this kind of impairment is due to tolerance to the drug is not known. However, this could be explained by the finding that the acquisition curves of the different groups seemed to reflect mainly how many rats are moving up from a 'poorly performing' subgroup to a 'well performing' subgroup on each training day. Some controls show an improved escape to the platform already on the first day. It is important to note that the drug-treated rats did show a decrease in distance swum per trial before encountering the platform in the water pool. This suggests that learning was not totally abolished.

In addition to an interference with learning and memory, the impairment of water maze acquisition could be due to impaired sensory and motor processes (Willets et al., 1990). MK-801 induced marked hyperactivity already at the lowest anticonvulsive doses, as reflected in the increased swimming speed of rats and their inability to stay on the escape platform during the reinforcement period. This was also confirmed in the separate staying-on-platform test. It is interesting to note that MK-801-treated rats did not show any marked decrease in swimming speed during training, which is in contrast to the performance of the rats treated with saline or competitive NMDA receptor antagonists. The competitive antagonists did not impair the acquisition of the water maze task nor cause any hyperactivity at the lowest anticonvulsive doses. However, it is important to note that epileptic rats may be more sensitive to the motor side effects of NMDA receptor antagonists than non-epileptic rats (Löscher et al., 1991).

A recent study investigated the effects of MK-801, CGP 39551 and CGP 37849 on different spatial orientation tasks using the 8-arm radial maze. Only MK-801 increased the locomotion of the rats. The higher doses of CGP compounds and MK-801 impaired the acquisition of an egocentric orientation task and an allocentric reversal task (Bischoff and Tiedtke, 1992). Because the water maze task is considered to assess allocentric spatial learning/memory, the present data are in line with these findings.

In conclusion, competitive NMDA receptor antagonists, CGP 39551 and CGP 37849, dose dependently impaired the acquisition of the water maze task by rats. However, neither the lowest anticonvulsive dose of CGP 39551 nor the dose of CGP 37849 that induced 100% protection in the MES test induced any cognitive impairment. MK-801, a non-competitive antagonist, induced clear behavioral effects and impaired spatial learning already at half of the lowest anticonvulsive dose. The results suggest a larger therapeutic window for CGP 39551 and especially for CGP 37849 than for MK-801.

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