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LY 300164, a novel antagonist of AMPA/kainate receptors, potentiates the anticonvulsive activity of antiepileptic drugs

Stanisław J. Czuczwar [a,b,*], Mariusz Świąder [a], Hubert Kuźniar [a], Maciej Gasior [a,1], Zdzisław Kleinrok [a]

[a] *Department of Pharmacology and Toxicology, Medical University School, Jaczewskiego 8, 20-090 Lublin, Poland*
[b] *Department of Clinical Toxicology, Institute of Agricultural Medicine, Jaczewskiego 2, 20-090 Lublin, Poland*

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Abstract

LY 300164 [7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7*H*-1,3-dioxolo(4,5*H*)-2,3-benzodiazepine], administered intraperitoneally up to 2 mg/kg, did not influence the threshold for electroconvulsions. In doses of 2.5–4 mg/kg, LY 300164 significantly raised the threshold. In subprotective doses against electroconvulsions, this excitatory amino acid receptor antagonist enhanced the protective activity of intraperitoneally given valproate, carbamazepine and diphenylhydantoin against maximal electroshock-induced convulsions in mice. The anticonvulsive action of phenobarbital was potentiated by LY 300164 only at 2 mg/kg. The non-*N*-methyl-D-aspartate receptor antagonist did not affect the plasma levels of the antiepileptic drugs, so a pharmacokinetic interaction is not probable. Combined treatment with LY 300164 (2 mg/kg) and the antiepileptics studied (providing 50% protection against maximal electroshock) did not impair the motor performance of mice, evaluated in the chimney test. Valproate, at its ED_{50} of 280 mg/kg against maximal electroshock, produced motor impairment. As shown in the passive avoidance task, combination of LY 300164 (2 mg/kg) with valproate or diphenylhydantoin resulted in impairment of long-term memory. Alone among the antiepileptics, valproate (280 mg/kg) and phenobarbital (28.5 mg/kg) disturbed long-term memory. The results suggest that blockade of glutamate-mediated events via non-NMDA receptors leads to enhancement of the anticonvulsive activity of conventional antiepileptics. Some combinations of LY 300164 with antiepileptic drugs were superior to these antiepileptics alone in terms of their lack of adverse effects.

Keywords: Antiepileptics; LY 300164; Seizure; AMPA/kainate receptor

1. Introduction

Glutamate serves as a major excitatory neurotransmitter in the vertebrate central nervous system and its involvement in the generation of seizure activity has been well-documented (Johnston, 1973; Meldrum, 1984; Collingridge and Lester, 1989). The excitation exerted by glutamate may be mediated by either ionotropic or metabotropic receptors. NMDA and non-NMDA receptors belong to the first group. Non-NMDA receptors are further classified into AMPA and kainate receptors (Watkins et al., 1990). More than a decade ago, the anticonvulsive properties of NMDA receptor antagonists were documented, against both chemically induced seizures and electroconvulsions (Croucher et al., 1982; Czuczwar and Meldrum, 1982; Czuczwar et al., 1985; Turski et al., 1990). Later, it became evident that AMPA/kainate receptor antagonists also possessed anticonvulsive activity in a variety of experimental models of epilepsy (Smith et al., 1991; Turski et al., 1992; Löscher et al., 1993; Borowicz et al., 1995; Czuczwar et al., 1995).

Apart from ifenprodil, the excitatory amino acid receptor antagonists, blocking either NMDA- or AMPA/kainate-mediated excitation, potentiated the protective activity of conventional antiepileptic drugs against maximal electroshock-induced seizures in mice (Czuczwar et al., 1984; Czechowska et al., 1993; Pietrasiewicz et al., 1993; Żarnowski et al., 1994a,b). Interestingly, 1-(4-ami-

* Corresponding author. Tel.: +48-81-747-89-24; Fax: +48-81-532-89-03; E-mail: czuczwar@galen.imw. lublin.pl

[1] Present address: Preclinical Pharmacology Laboratory, National Institute on Drug Abuse, Addiction Research Center, NIH, 5500 Nathan Shock Drive, Baltimore, MD 212244, USA.

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nophenyl)-4-methoxy-7,8-methylene-dioxy-5*H*-2, 3-benzodiazepine chloride (GYKI 52466) enhanced the protection offered by carbamazepine, diphenylhydantoin, and valproate, but not that by phenobarbital (Borowicz et al., 1995).

The clinical potential of some NMDA receptor antagonists may obviously be hampered by a number of adverse effects on long-term memory and motor performance. The undesirable effects were observed both after peripheral administration alone at anticonvulsive doses or when combined (at reduced doses) with conventional antiepileptic drugs (Parada-Turska and Turski, 1990; Żarnowski et al., 1994a,b). Epileptic subjects (amygdala-kindled rats) were particularly susceptible to the NMDA receptor antagonist-induced adverse actions (Löscher and Hönack, 1991). Evidence shows that AMPA/kainate receptor antagonists possess less adverse potential than agents blocking NMDA receptors (Parada et al., 1992; Danysz et al., 1994). Initial studies confined to the combined treatment with AMPA/kainate receptor antagonists and conventional antiepileptic drugs have indicated that the enhanced protective activity of the latter was not associated with serious side effects (Żarnowski et al., 1993; Borowicz et al., 1995).

There are data available suggesting that LY 300164 (7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7*H*-1,3-dioxolo-4,5*H*-2,3-benzodiazepine hydrochloride; a novel antagonist of AMPA/kainate receptors) is 2.3 to 3-fold more potent as an antagonist of AMPA-mediated currents than the parent compound, GYKI 52466 (Donevan et al., 1994; Rammes et al., 1996). Also, some differences were noted in the influence of LY 300164 and GYKI 52466 on dopamine-mediated behaviors in mice (Vanover, 1998). Consequently, we decided to examine the influence of LY 300164 on the anticonvulsive effects of valproate, carbamazepine, diphenylhydantoin or phenobarbital against maximal electroshock-induced convulsions in mice. These studies were accompanied by an evaluation of adverse effects of combined treatment with LY 300164 and antiepileptic drugs. Finally, the effect of LY 300164 on the free plasma levels of antiepileptic drugs was evaluated.

2. Material and methods

2.1. General

The experiments were conducted on female Swiss mice 20–25 g in weight. The animals were housed in colony cages with food (chow pellets) and tap water ad libitum. The laboratory temperature was 21 ± 1°C and the mice were kept on a natural light–dark cycle. The experimental groups consisting of 8–12 animals were made up at random. The experimental procedures were carried out between 10:00 a.m. and 2:00 p.m. and each mouse was used only once.

2.2. Electroconvulsions

Electroconvulsions were produced according to Swinyard et al. (1952) with ear-clip electrodes and alternating current delivered by a Hugo Sachs (Type 221, Freiburg, Germany) stimulator. The stimulus duration was 0.2 s. Full tonic extension of both hind limbs was taken as the endpoint. The convulsive threshold was evaluated as CS_{50}, which is the current strength (in mA) required to produce tonic hindlimb extension in 50% of the animals tested. To calculate the convulsive threshold, at least three groups of mice (consisting of 8–10 animals per group) were challenged with electroshocks of various intensities. An intensity–response curve was calculated with a computer, taking into consideration the percentage of animals convulsing in experimental groups. To calculate the respective ED_{50} values for the antiepileptic drugs used, the mice were challenged with maximal electroshock (25 mA; four- to five-fold higher than the CS_{50} value in untreated animals). At least four groups of mice, (8–10 animals per experimental group), were used to estimate each ED_{50} value.

2.3. Drugs

The antiepileptic drugs used were: valproate magnesium (Dipromal, Polfa, Rzeszów, Poland), carbamazepine (Amizepin), diphenylhydantoin (Phenytoinum) and phenobarbital sodium (Luminalum Natrium, all three antiepileptics from Polfa, Warsaw, Poland). Valproate and phenobarbital were dissolved in sterile saline. Carbamazepine and diphenylhydantoin were suspended in a 1% solution of Tween 81 (Loba Chemie, Vienna, Austria).

LY 300164 (7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7*H*-1,3-dioxolo-4,5*H*-2,3-benzodiazepine hydrochloride; kindly supplied by Eli-Lilly, Indianapolis, IN, USA) was dissolved in sterile saline. All drugs were injected i.p., in a volume of 10 ml/kg valproate magnesium, carbamazepine 30 min, phenobarbital 60 min, diphenylhydantoin 120 min, and LY 300164 15 min before the tests. The doses of LY 300164, phenobarbital and valproate refer to their free forms.

2.4. Chimney test

The effects of antiepileptic drugs alone or combined with LY 300164 on motor performance were evaluated with the chimney test of Boissier et al. (1960). The animals had to climb backwards up a plastic tube (3 cm i.d., 25 cm length). Motor impairment was indicated by the inability of mice to climb backwards up the tube within 60 s and the results are shown as the percentages of animals that failed to perform in the test.

2.5. Passive avoidance acquisition and retention testing

The animals were put into an illuminated box ($10 \times 13 \times 15$ cm) connected to a large dark box ($25 \times 20 \times 15$

cm). The large box was equipped with an electric grid floor. Entrance into the dark box was punished by an electric footshock (0.6 mA for 2 s; facilitation of acquisition). The mice that did not enter the dark compartment within 180 s on the first experimental day, were excluded from the experiment. On the next day (24 h later), the same animals were placed into the illuminated box and those avoiding the dark compartment for over 180 s were regarded as remembering the task. Retention was evaluated as the mean time (in s) required to enter the dark box. According to Venault et al. (1986), the step-through passive avoidance task is recognized as a measure of long-term memory.

2.6. Estimation of the free plasma levels of antiepileptic drugs

The animals were given one of the antiepileptic drugs studied (+saline) or combinations of LY 300164 with one of these drugs. The mice were decapitated at times scheduled for the convulsive test and blood samples of approximately 1 ml were collected into Eppendorf tubes. Samples of blood were centrifuged at 10 000 rpm (Abbott centrifuge, Irving, TX, USA) for 3 min and plasma samples of 200 μl were pipetted into a micropartition system, MPS-1 (Amicon, Danvers, MA, USA), for separation of free from protein-bound microsolutes. Then, the MPS-1 tubes were centrifuged at 3000 rpm (MPW-360 centrifuge; Mechanika Precyzyjna, Warsaw, Poland) for 10 min and 50-μl filtrate samples were pipetted into original Abbott system cartridges which were subsequently put into a carousel for up to 20 samples. Control plasma samples of an antiepileptic were placed at the beginning and end of each carousel for verification of the calibration. The free plasma levels of antiepileptic drugs were estimated by immunofluorescence, with an Abbott TDx analyzer (Abbott, Irving, TX, USA). Plasma levels were expressed in μg/ml as means ± S.D. of at least seven determinations.

2.7. Statistics

Both CS_{50} and ED_{50} values and their statistical comparisons were calculated by computer probit analysis, according to Litchfield and Wilcoxon (1949). The results from the passive avoidance task were statistically verified in the Mann–Whitney test. The data obtained in the chimney test were compared statistically by using Fisher's exact probability test. An unpaired Student's *t*-test was employed for the statistical evaluation of the plasma levels of antiepileptic drugs.

3. Results

3.1. Influence of LY 300164 on the threshold for electroconvulsions

LY 300164 (2.5, 3 and 4 mg/kg) dose dependently raised the threshold for electroconvulsions. At 0.75, 1 and 2 mg/kg, LY 300164 did not affect the electroconvulsive threshold (Fig. 1).

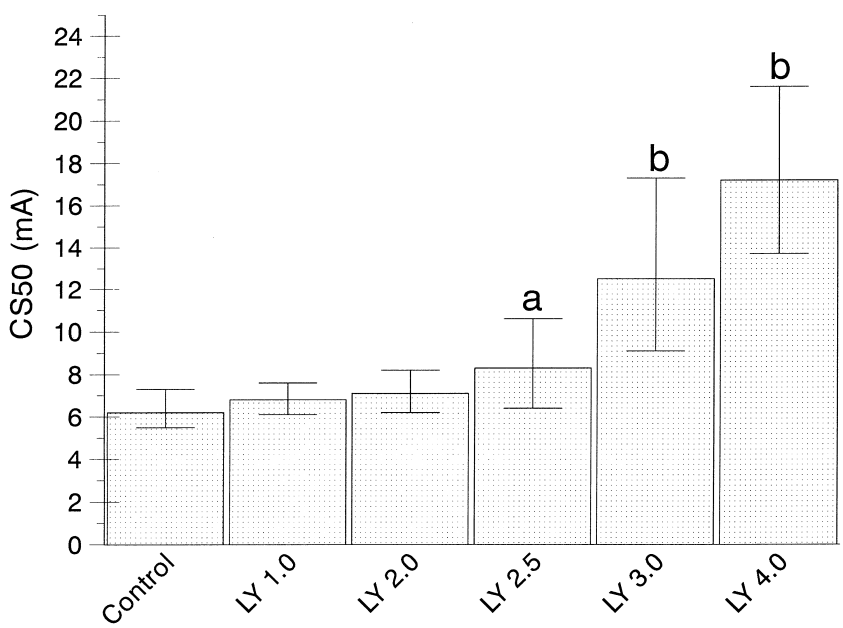

Fig. 1. Influence of LY 300164 on the threshold for electroconvulsions. Bars represent CS_{50} values in mA with 95% confidence limits indicated by error bars. LY 300164 was administered intraperitoneally in a single dose 15 min prior to the test. The doses of LY 300164 are shown below each bar in mg/kg. The CS_{50} values and statistical comparisons were calculated according to Litchfield and Wilcoxon (1949). The number of animals used for the calculation of the CS_{50} values: 24 (control and LY 300164 in a dose of 3 mg/kg), 26 (LY 300164 in a dose of 2.5 mg/kg) and 32 (LY 300164 in doses of 1, 2 and 4 mg/kg). $^{a}P < 0.05$, $^{b}P < 0.001$ vs. control group.

Table 1
Influence of LY 300164 on the anticonvulsant action of valproate, carbamazepine, diphenylhydantoin and phenobarbital against maximal electroshock-induced seizures in mice

Treatment	LY 300164 (mg/kg)				
	0	0.5	0.75	1.0	2.0
Valproate	280 (267–293)	278 (251–308)	260[a] (246–275)	222.5[a] (196–253)	165[a] (147–184)
Carbamazepine	15.8 (14.9–16.9)	15.1 (13.4–16.9)	12.9[a] (11.3–14.7)	12.7[a] (11.5–13.9)	5.0[a] (3.9–6.3)
Diphenylhydantoin	11.9 (10.3–13.7)	11.3 (10.0–12.8)	11.6 (10.0–13.4)	9.3[a] (8.0–10.8)	3.6[a] (2.2–5.8)
Phenobarbital	28.5 (25.5–31.8)	24.9 (21.9–28.4)	24.1 (20.9–27.8)	24.5 (21.4–28.1)	10.1[a] (15.1–20.0)

All drugs were administered i.p., DPH 120 min, PB 60 min, VPA and CBZ 30 min, LY 300164 15 min prior to the test.
The data are ED_{50} values (in mg/kg) with 95% confidence limits in parentheses.
ED_{50} values and statistical analysis of the data were calculated according to Litchfield and Wilcoxon (1949).
[a] P at least < 0.05 vs. respective control group.

3.2. Effect of LY 300164 upon the anticonvulsive action of antiepileptic drugs against maximal electroshock-induced seizures in mice

LY 300164 (0.75–2 mg/kg) reduced the respective ED_{50} values for carbamazepine and valproate. When combined with diphenylhydantoin, the AMPA/kainate receptor antagonist potentiated the protective activity of this antiepileptic drug when given at 1 and 2 mg/kg. The anticonvulsive action of phenobarbital was enhanced by LY 300164 only at 2 mg/kg (Table 1).

3.3. Influence of LY 300164 co-administered with antiepileptic drugs on motor performance of mice

When given alone at their ED_{50} values against maximal electroshock-induced convulsions, carbamazepine (15.8 mg/kg), diphenylhydantoin (11.9 mg/kg), or phenobarbital (28.5 mg/kg) did not affect the performance of mice in the chimney test. Valproate (at its ED_{50} of 280 mg/kg) caused motor impairment in 33% of the animals (Table 2). In no case did the combined treatment with LY 300164 (2 mg/kg) and antiepileptic drugs (providing 50% protection against maximal electroshock) result in significant motor impairment. Similarly, LY 300164 alone at 2 mg/kg did not affect the performance of mice in this test (Table 2).

3.4. Dark avoidance task

Among antiepileptic drugs, carbamazepine and diphenylhydantoin, given at their ED_{50} values against maximal electroshock, did not influence retention in the passive avoidance task. Valproate and phenobarbital, at their

Table 2
Motor impairment after administration of antiepileptic drugs, LY 300164 or a combination of LY 300164 with an antiepileptic

Treatment (mg/kg)	Percentage of mice impaired (%)
Vehicle	0
LY 300164 (2.0)	0
Valproate (280)	33.3[a]
Valproate (165)	0
Valproate (165) + LY 300164 (2.0)	8.3
Carbamazepine (15.8)	0
Carbamazepine (5.0)	8.3
Carbamazepine (5.0) + LY 300164 (2.0)	16.7
Diphenylhydantoin (11.9)	0
Diphenylhydantoin (3.6)	0
Diphenylhydantoin (3.6) + LY 300164 (2.0)	0
Phenobarbital (28.5)	0
Phenobarbital (10.1)	0
Phenobarbital (10.1) + LY 300164 (2.0)	16.7

The results are expressed as percentage of animals (12 per group) that failed to perform in the chimney test (see Section 2). Antiepileptics at higher doses and combined treatments provided 50% protection against maximal electroshock. See also legend to Table 1.
[a] $P < 0.05$ vs. control group (Fisher's exact probability test).

Table 3
Effect of antiepileptic drugs, LY 300164 or a combination of an antiepileptic with LY 300164 on the retention time of a passive avoidance task by mice

Treatment (mg/kg)	Retention time (s)
Vehicle	180 (180, 180)
LY 300164 (2.0)	180 (180, 180)
Valproate (280)	70 (42.3, 150)[a]
Valproate (165)	69 (41.3, 180)[a]
Valproate (165) + LY 300164 (2.0)	135 (42.5, 180)[a]
Carbamazepine (15.8)	170 (159.3, 180)
Carbamazepine (5.0)	175 (81.8, 180)
Carbamazepine (5.0) + LY 300164 (2.0)	180 (180, 180)
Diphenylhydantoin (11.9)	180 (120, 180)
Diphenylhydantoin (3.6)	180 (141.3, 180)
Diphenylhydantoin (3.6) + LY 300164 (2.0)	147.5 (73.8, 180)
Phenobarbital (28.5)	90 (63.8, 152)[a]
Phenobarbital (10.1)	90 (62.5, 180)[a]
Phenobarbital (10.1) + LY 300164 (2.0)	180 (180, 180)[b]

Retention reflects a median and semiquartiles (25 and 75 percentiles) for avoidance of the dark compartment (see Section 2).
[a] P at least < 0.05 vs. vehicle.
[b] $P < 0.01$ vs. PB (28.5 mg/kg) group (Mann–Whitney test).
See also Table 1.

Table 4
Influence of LY 300164 on the free plasma levels of antiepileptic drugs in mice

Treatment (mg/kg)	Plasma levels
Valproate (165)	157 ± 13.6
Valproate (165) + LY 300164 (2.0)	146 ± 17.9
Carbamazepine (5.0)	0.85 ± 0.097
Carbamazepine (5.0) + LY 300164 (2.0)	0.84 ± 0.14
Diphenylhydantoin (3.6)	0.19 ± 0.031
Diphenylhydantoin (3.6) + LY 300164 (2.0)	0.20 ± 0.038
Phenobarbital (10.1)	10.3 ± 0.95
Phenobarbital (10.1) + LY 300164 (2.0)	10.2 ± 0.53

Table data are the means (in μg/ml of plasma) of at least seven determinations ± S.D. Unpaired Student's *t*-test was used for statistical comparisons. For abbreviations and treatment times see legend to Table 1.

ED_{50} values of 280 mg/kg and 28.5 mg/kg, respectively, impaired retention (Table 3). LY 300164 (2 mg/kg) produced no statistically significant worsening of long-term memory. The combined treatment with LY 300164 (2 mg/kg) and carbamazepine (5 mg/kg), diphenylhydantoin (3.6 mg/kg), or phenobarbital (10.1 mg/kg), providing 50% protection against maximal electroshock-induced seizures, also did not impair retention. However, co-administration of LY 300164 (2 mg/kg) with valproate (165 mg/kg) resulted in worsening of long-term memory (Table 3).

3.5. Effect of LY 300164 on the free plasma levels of antiepileptic drugs

LY 300164 (2 mg/kg) in no case affected the free plasma levels of carbamazepine (5 mg/kg), diphenylhydantoin (3.6 mg/kg), phenobarbital (10.1 mg/kg), or valproate (165 mg/kg; Table 4).

4. Discussion

Existing evidence indicates that AMPA/kainate receptor antagonists may potentiate the anticonvulsive activity of antiepileptic drugs. 2,3-Dihydroxy-6-nitro-7-sulfamoylbenzo-(F)quinoxaline (NBQX; a competitive antagonist) enhanced the protective action of carbamazepine, diphenylhydantoin, phenobarbital and valproate against maximal electroshock-induced convulsions in mice. Motor impairment and disturbed long-term memory were only observed with a combination of NBQX and valproate (Żarnowski et al., 1993). 1-(4-Aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466; a non-competitive antagonist) increased the anticonvulsive activity of carbamazepine, diphenylhydantoin, and valproate, but not that of phenobarbital against maximal electroshock. The combined treatment with GYKI 52466 and antiepileptic drugs did not affect motor performance, and a memory deficit was only seen when this AMPA/kainate receptor antagonist was co-administered with valproate (Borowicz et al., 1995). Neither NBQX nor GYKI 52466 seemed to exert their effects on antiepileptic drugs through a pharmacokinetic mechanism, although free plasma levels of antiepileptic drugs were only measured in the case of GYKI 52466 (Żarnowski et al., 1993; Borowicz et al., 1995).

LY 300164 is structurally closely related to GYKI 52466 and, similarly to this compound, enhanced the protective action of carbamazepine, diphenylhydantoin, and valproate. Unlike GYKI 52466, LY 300164 also potentiated the anticonvulsive potency of phenobarbital. However, the potentiating effect was only observed at the highest dose of LY 300164 (2 mg/kg) used for the combined treatment. In this context, LY 300164 more resembles NBQX (Żarnowski et al., 1993), nevertheless, the latter produced a quantitatively generally weaker effect. It is remarkable that the combined treatment with LY 300164 and antiepileptic drugs, providing a 50% protection against maximal electroshock-induced seizures, was free from adverse effects as regards motor performance. Among antiepileptic drugs alone at their ED_{50} values, valproate impaired motor performance. Phenobarbital and valproate alone impaired long-term memory in the passive avoidance task, while only a combination of LY 300164 with valproate resulted in disturbed retention. Interestingly, no impairment of retention was observed when LY 300164 was combined with phenobarbital. According to Löscher and Hönack (1994), the anticonvulsive effects of 2,3-benzodiazepines are unlikely to be mediated via benzodiazepine receptors, so this mechanism may also have been of no importance in our experiments. Other possible mechanisms, discussed in detail by Borowicz et al. (1995), may involve the simultaneous blockade of NMDA and AMPA/kainate receptor-produced events since carbamazepine, diphenylhydantoin, and valproate were reported to diminish glutamatergic neurotransmission in the NMDA receptor complex.

The initial attempts to use excitatory amino acid receptor antagonists, dizocilpine (MK-801; an uncompetitive NMDA receptor antagonist) or D-3-(2-carboxypiperazine-4-yl)-1-propenyl-1-phosphonic acid (D-CPP-ene; a competitive NMDA receptor antagonist), as an add-on therapy in epileptic patients were not successful. Although within the first month of the clinical trial, dizocilpine decreased seizure frequency in 55% of the patients, this effect tended to fade gradually over the months following, in spite of the four-fold increase in the dose of dizocilpine after 10 months (Troupin et al., 1986). Moreover, according to Porter (1990), dizocilpine induced confusion in epileptic patients and further clinical evaluation of dizocilpine as an add-on therapy to antiepileptics was discontinued. The competitive NMDA receptor antagonist, D-CPP-ene, added to conventional antiepileptic drugs, did not reduce seizure

frequency in patients with complex partial seizures. The lack of any therapeutic benefit was associated with profound adverse effects, including amnesia, ataxia, poor concentration, and sedation (Sveinbjornsdottir et al., 1993). These clinical data correlate to a certain extent with the results of experimental studies. Dizocilpine enhanced the protective action of both phenobarbital and valproate against electroconvulsions and this combined treatment was free from side-effects on motor performance and long-term memory (Urbańska et al., 1991). Actually, at the beginning of dizocilpine administration to epileptic patients, the incidence of adverse reactions was very low (Troupin et al., 1986). Combinations of D-CPP-ene with antiepileptic drugs generally resulted in severe impairment of motor coordination and long-term memory (Żarnowski et al., 1994a,b). Consequently, it is reasonable to assume, on the basis of data presented, that AMPA/kainate receptor antagonists may prove of clinical significance in epileptic patients. It is noteworthy that the excitatory amino acid receptor antagonists blocking AMPA/kainate-mediated events (GYKI 52466 and NBQX) produced no major changes in the open field test in rats (Danysz et al., 1994). According to Parada et al. (1992), AMPA/kainate receptors play a marginal role in memory processes when compared to NMDA receptors (Parada-Turska and Turski, 1990). Although some combinations of antiepileptic drugs with NMDA receptor antagonists could seem promising from the experimental point of view (Czechowska et al., 1993; Pietrasiewicz et al., 1993), considerable side-effects were noted in a number of cases (Urbańska et al., 1992; Żarnowski et al., 1994a,b; Borowicz et al., 1996). In addition, one has to consider that epileptic subjects (for instance, amygdala-kindled rats) are considerably more sensitive to the adverse potential of NMDA receptor antagonists than naive animals (Löscher and Hönack, 1991).

Although LY 300164 seems to be a more potent blocker of AMPA currents than GYKI 52466 in cultured hippocampal neurons and cultured superior colliculus neurons (Donevan et al., 1994; Rammes et al., 1996), it enhanced the protective activity of carbamazepine and diphenylhydantoin to a comparable degree. However, LY 300164 (2 mg/kg) lowered the ED_{50} value of valproate by 41% while GYKI 52466 (in a subprotective dose of 5 mg/kg against the threshold electroconvulsions) lowered it by 68% (Borowicz et al., 1995). This may indicate that the interaction of GYKI 52466 with valproate may also involve some other mechanisms, not necessarily related to AMPA/kainate receptor blockade. On the other hand, the LY 300164-induced enhancement of the anticonvulsive activity of phenobarbital, and a total ineffectiveness of GYKI 52466 in this regard, might result from the differences between the two compounds as AMPA receptor blockers (Donevan et al., 1994; Rammes et al., 1996).

In conclusion, this paper provides further evidence for the enhancement by excitatory amino acid receptor antagonists of the AMPA/kainate type of the anticonvulsive activity of conventional antiepileptic drugs. The combinations of LY 300164 with phenobarbital or valproate were superior to these antiepileptics alone in terms of lack of adverse effects.

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