ELSEVIER

European Journal of Pharmacology 281 (1995) 319–326

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The non-competitive AMPA/kainate receptor antagonist, GYKI 52466, potentiates the anticonvulsant activity of conventional antiepileptics

Kinga K. Borowicz, Maciej Gasior, Zdzisław Kleinrok, Stanisław J. Czuczwar *

Department of Pharmacology and Toxicology, Lublin Medical University School, Jaczewskiego 8, 20-090 Lublin, Poland

Received 3 November 1994; revised 21 April 1995; accepted 28 April 1995

Abstract

1-(4-Aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine hydrochloride (GYKI 52466), up to 5 mg/kg, did not influence the electroconvulsive threshold but potentiated the anticonvulsant activity of valproate, carbamazepine and diphenylhydantoin against maximal electroshock-induced convulsions in mice. No potentiation was observed in the case of phenobarbital. Moreover, this non-NMDA receptor antagonist did not influence the plasma levels of the antiepileptic drugs studied, so a pharmacokinetic interaction, in terms of total and free plasma levels, is not probable. The combined treatment of GYKI 52466 with either carbamazepine or diphenylhydantoin (providing a 50% protection against maximal electroshock) was devoid of significant side effects (motor and long-term memory impairment). Valproate applied at a dose equal to its ED_{50} caused serious worsening of motor coordination and long-term memory. It is noteworthy that the combined treatment of GYKI 52466 with valproate was superior to valproate alone, as regards adverse effects. The results suggest that concomitant administration of GYKI 52466 with some conventional antiepileptic drugs may offer a novel approach in the treatment of epilepsy.

Keywords: Anti-epileptic; GYKI 52466; Seizure

1. Introduction

The excitatory amino acids are thought to act as major neurotransmitters in the vertebrate central nervous system (Collingridge and Lester, 1989). In general, there are three different subtypes of glutamate receptors: NMDA and non-NMDA ones, which incorporate an ion channel within the receptor complex, and one subtype, which is a metabotropic receptor. Furthermore, non-NMDA receptors are classified into α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and kainate receptors (Watkins et al., 1990). All of the ionotropic channels are involved in mediating excitatory synaptic transmission. In electrophysiological studies, it has been recognized that AMPA and kainate receptors mediate most of the rapid excitatory post-synaptic potential (fast EPSP) and conduct mainly Na^+ currents, whereas NMDA receptor channels display a voltage-dependent Ca^{2+} permeability, which results in slow synaptic transmission (late EPSP), depending on a release of an Mg^{2+} blockade (Monaghan et al., 1989).

Existing body of evidence indicates that excitatory amino acids play a prominent role in the initiation of seizures and their propagation (Delgado-Escueta et al., 1986; Meldrum, 1992). First data on the anticonvulsive efficacy of NMDA receptor antagonists were reported more than a decade ago (Croucher et al., 1982; Czuczwar and Meldrum, 1982). Although most attention, as regards seizure activity, has been directed so far to NMDA receptors, more recent research points to a potential role for non-NMDA (AMPA/kainate) receptors (Meldrum et al., 1992; Turski et al., 1992; Löscher et al., 1993; Żarnowski et al., 1993).

Most of competitive and non-competitive NMDA receptor antagonists, apart from their own anticonvulsive properties, 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, only ifenprodil (an antagonist of the polyamine recognition site within the NMDA receptor complex) remained

* Corresponding author. Tel./fax +48-81-77-89-24.

Elsevier Science B.V.
SSDI 0014-2999(95)00266-9

without any effect on standard antiepileptics (Żarnowski et al., 1994b). Furthermore, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(*F*)quinoxaline (NBQX), a selective, competitive AMPA/kainate receptor antagonist, was proved to possess some protective efficacy against electroconvulsions (Turski et al., 1992), sound-induced seizures (Chapman et al., 1991; Smith et al., 1991) and a number of chemoconvulsants (Turski et al., 1990; Lallement et al., 1994). In addition, it was demonstrated that NBQX considerably potentiated the anticonvulsant action of conventional antiepileptic drugs (Żarnowski et al., 1993).

Unfortunately, the potential clinical utility of some NMDA receptor antagonists may be limited by their adverse effects (long-term memory and motor impairment), which appeared either after per se administration at anticonvulsive doses or in combination (at reduced doses) with antiepileptic drugs (Flood et al., 1990; Parada-Turska and Turski, 1990; Żarnowski et al., 1994a). Interestingly, NBQX alone (Parada et al., 1992) and the combinations of NBQX with carbamazepine, diphenylhydantoin or phenobarbital were devoid of side effects evaluated in the chimney test and passive avoidance task in mice (Żarnowski et al., 1993). A great body of evidence indicates that AMPA receptors are not critically involved in the formation of spatial working memory and acquisition (storage) in the passive avoidance and have no effect on recall (retrieval) from long-term memory (Flood et al., 1990; Parada et al., 1992).

1-(4-Aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine hydrochloride (GYKI 52466) shares anticonvulsant and central muscle relaxant activity with classical 1,4-benzodiazepines. According to Tarnawa et al. (1990), these effects are not, however, mediated via the GABA-benzodiazepine receptor complex. Actually, GYKI 52466 antagonizes excitation mediated by non-NMDA glutamate receptors and is a highly selective, non-competitive antagonist of the AMPA/kainate receptor responses (Tarnawa et al., 1990).

Herein, we report the influence of GYKI 52466 on the protection offered by valproate, carbamazepine, diphenylhydantoin or phenobarbital against maximal electroshock-induced convulsions in mice. Moreover, the effects of the combined treatment of antiepileptic drugs with GYKI 52466 on the performance of mice in the chimney test and passive avoidance task were studied.

2. Material and methods

2.1. General

The experiments were carried out on female Swiss mice weighing 20–25 g. The animals were housed in colony cages with free access to food (chow pellets) and tap water. The experimental temperature was 21 ± 1°C and mice were on a natural light-dark cycle. The experimental groups consisting of 8–12 animals, were chosen by means of a randomized schedule. The convulsive and behavioral tests were performed 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) using ear-clip electrodes and alternating current delivered by a Hugo Sachs (Type 221, Freiburg, Germany) stimulator, the stimulus duration being 0.2 s. Tonic hindlimb extension was taken as the endpoint. The convulsive threshold was evaluated as CS_{50}, which is the current strength (in mA) necessary to produce tonic hindlimb extension in 50% of the animals tested. To estimate the convulsive threshold, at least four groups of mice (8–10 animals per group) were challenged with electroshocks of various intensities. Subsequently, an intensity-response curve was calculated on the basis of the percentage of mice convulsing. Mice pretreated with antiepileptic drugs were challenged with maximal electroshock (25 mA) in order to evaluate the respective ED_{50} values (in mg/kg). Again, at least four groups of mice, consisting of 8–10 animals, were used to estimate each ED_{50} value.

2.3. Drugs

The following antiepileptic drugs were used: 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 brought into solution with sterile saline whilst carbamazepine and diphenylhydantoin were suspended in a 1% solution of Tween 81 (Loba Chemie, Vienna, Austria).

GYKI 52466 (1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine hydrochloride) (Institute for Drug Research, Budapest, Hungary) was dissolved in sterile saline. All drugs were administered i.p., in a volume of 0.1 ml/kg –valproate magnesium, carbamazepine 30 min, phenobarbital 60 min, diphenylhydantoin 120 min, and GYKI 52466 15 min prior to the test. The doses of GYKI 52466, phenobarbital and valproate refer to their free forms.

2.4. Chimney test

The effects of antiepileptic drugs alone or in combination with GYKI 52466 on motor impairment were quantified with the chimney test of Boissier et al.

(1960). In this test animals had to climb backwards up the plastic tube (3 cm inner diameter, 25 cm length). Motor impairment was indicated by the inability of the animals to climb backwards up the tube within 60 s and the results are shown as a percentage of animals which failed to perform the test.

2.5. Passive-avoidance acquisition and retention testing

The mice were placed in an illuminated box (10 × 13 × 15 cm) connected to a large dark box (25 × 20 × 15 cm) which 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 60 s were excluded from the experiment. On the next day (24 h later), the same animals were put into the illuminated box and those avoiding the dark compartment for over 60 s were regarded as remembering the task. Retention was evaluated as the percentage of mice that did not 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 plasma levels of antiepileptic drugs

The animals were administered either saline + one of the antiepileptic drugs or GYKI 52466 + one of these drugs. The mice were killed by decapitation at times scheduled for the convulsive test and samples of blood of approximately 1 ml were collected into Eppendorf tubes. Samples of blood were centrifuged at 10000 r.p.m. (Abbott centrifuge, Irving, TX, USA) for 3 min and plasma samples of 70 μl were transferred into Abbott System cartridges and the rest of the plasma was pipetted to 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 r.p.m. (MPW-360 centrifuge; Mechanika Precyzyjna, Warsaw, Poland) for 10 min and the filtrate samples of 70 μl were put into Abbott system cartridges. The total and free plasma levels of antiepileptic drugs were estimated by immunofluorescence, using an Abbott TDx analyzer (Abbott, Irving, TX, USA). Plasma levels were expressed as means ± S.D. of at least 7 determinations.

2.7. Statistics

Both CS_{50} and ED_{50} values and statistical analysis of the results, obtained in the electroconvulsive tests, were estimated by computer probit analysis, according to Litchfield and Wilcoxon (1949). The results from the passive avoidance and chimney tests were compared statistically by using Fisher's exact probability test. Plasma levels of antiepileptic drugs alone or in combination with GYKI 52466 were evaluated with unpaired Student's *t*-test.

3. Results

3.1. Effects of GYKI 52466 upon the electroconvulsive threshold

GYKI 52466 (10 mg/kg), administered 15 min before the test, raised the electroconvulsive threshold from 5.6 to 15.3 mA. At the dose of 5 mg/kg it did not influence the threshold.

3.2. Influence of GYKI 52466 upon the protective activity of antiepileptic drugs against maximal electroshock-induced seizures in mice

GYKI 52466 (0.625, 1.25, 2.5 and 5.0 mg/kg), when applied together with valproate, significantly reduced its ED_{50} from 272 to 240, 170, 130 and 88 mg/kg,

Table 1
Influence of GYKI 52466 upon the anticonvulsant activity of valproate, carbamazepine, diphenylhydantoin and phenobarbital against maximal electroshock

Treatment	GYKI 52466 (mg/kg)					
	0	0.3125	0.625	1.25	2.5	5.0
Valproate	272 (252–293)	257 (241–274)	240 (225–255)	170 [b] (152–157)	130 [b] (112–152)	88 [b] (74–104)
Carmazepine	13.3 (12.2–14.5)	N.D.	11.9 (10.3–13.7)	10.2 [a] (8.7–12)	8.5 [b] (8.2–10)	4.8 [b] (3.4–6.6)
Diphenylhydantoin	9.5 (8.2–11)	N.D.	N.D.	8.4 (7–9.8)	5.4 [b] (4.6–6.3)	3.9 [b] (3.2–4.8)
Phenobarbital	16.1 (14–18.4)	N.D.	N.D.	N.D.	N.D.	14.6 (12.7–16.8)

All drugs were administered i.p., diphenylhydantoin 120 min, phenobarbital 60 min, valproate and carbamazepine 30 min, GYKI 52466 15 min prior to the test. Table 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] $P < 0.01$, [b] $P < 0.001$ vs. respective control group. N.D., not determined.

Table 2
Motor impairment after administration of antiepileptic drugs, GYKI 52466 or a combination of GYKI 52466 with an antiepileptic

Treatment (mg/kg)	*n*	Mice impaired (%)
Vehicle	12	0
Valproate (272)	12	58.3 [a]
Valproate (88)	12	0
Valproate (88) + GYKI 52466 (5.0)	12	25
GYKI 52466 (5.0)	12	16.6
GYKI 52466 (1.25–2.5)	12	0
Carbamazepine (13.3)	12	8.3
Carbamazepine (4.8)	12	0
Carbamazepine (4.8) + GYKI 52466 (5.0)	12	16.6
GYKI 52466 (5.0)	12	25
Diphenylhydantoin (9.5)	12	16.6
Diphenylhydantoin (3.9)	12	0
Diphenylhydantoin (3.9) + GYKI 52466 (5.0)	12	25
GYKI 52466 (5.0)	12	25

The results are expressed in percentage of animals that failed to perform the chimney test (see Material and methods). [a] $P < 0.001$ vs. vehicle (Fisher's exact probability test). *n*, number of animals. Antiepileptics at higher doses and combined treatments provide a 50% protection against maximal electroshock. See also legend of Table 1.

respectively. GYKI 52466 (1.25, 2.5 and 5.0 mg/kg), administered together with carbamazepine also potentiated its protective activity (ED_{50} value was reduced from 13.3 to 10.2, 8.5 and 4.8 mg/kg, respectively). Co-administration of GYKI 52466 (2.5 and 5.0 mg/kg) and diphenylhydantoin reduced its respective ED_{50} value from 9.5 to 5.4 and 3.9 mg/kg. However, GYKI 52466 (5.0 mg/kg) remained without effect upon the antielectroshock efficacy of phenobarbital (Table 1).

3.3. Chimney test

When applied at doses equal to their ED_{50} values against maximal electroshock-induced convulsions, carbamazepine (13.3 mg/kg) and diphenylhydantoin (9.5 mg/kg) did not influence the performance of mice in the chimney test. In contrast, valproate (272 mg/kg) caused a strong motor impairment in 58% of the animals (Table 2). When GYKI 52466 was given in doses of 1.25–2.5 mg/kg, all animals performed the test correctly (result not shown in Table 2) whilst at 5 mg/kg it produced insignificant disturbances. The combined treatment of GYKI 52466 (1.25, 2.5 and 5.0 mg/kg) with valproate (170, 130 and 88 mg/kg, respectively), providing a 50% protection against maximal electroshock, resulted in a reduced motor impairment, when compared with valproate alone, given at its ED_{50} value of 272 mg/kg against maximal electroshock. In all three cases 25% of mice did not complete the test. The combined treatment of GYKI 52466 (5.0 mg/kg)

Table 3
Effect of antiepileptic drugs, GYKI 52466 or a combination of an antiepileptic with GYKI 52466 on the retention of a passive avoidance task by mice

Treatment (mg/kg)	*n*	Retention (% of control)
Vehicle	12	91.7
Valproate (272)	12	16.6 [a]
Valproate (88)	12	100
Valproate (88) + GYKI 52466 (5.0)	12	66.6 [b]
Vehicle	12	100
Carbamazepine (13.3)	11	90.9
Carbamazepine (4.8)	12	100
Carbamazepine (4.8) + GYKI 52466 (5.0)	12	75
Vehicle	12	100
Diphenylhydantoin (9.5)	12	75
Diphenylhydantoin (3.9)	12	100
Diphenylhydantoin (3.9) + GYKI 52466 (5.0)	12	75
GYKI 52466 (5.0)	12	75

The retention was quantified as a percentage of animals avoiding the dark compartment for over 60 s (see Material and methods). [a] $P < 0.001$ vs. saline-treated group, [b] $P < 0.05$ vs. valproate (272 mg/kg)-treated group (Fisher's exact probability test). See also legends of Tables 1 and 2.

with carbamazepine (4.8 mg/kg) or diphenylhydantoin (3.9 mg/kg), also providing the same degree of protection, did not significantly affect the motor performance of mice (Table 2).

3.4. Dark avoidance task

Carbamazepine and diphenylhydantoin, when applied at doses equal to their ED_{50} values against maximal electroshock, did not influence retention in the passive avoidance task. On the contrary, administration of valproate at its ED_{50} of 272 mg/kg against maximal electroshock, caused strong impairment of long-term memory in 83% of mice (Table 3). GYKI 52466 (1.25 mg/kg) produced no worsening of the performance of mice in memory tasks whilst at 2.5 mg only one mouse out of 12 tested showed memory deficit (results not shown in Table 3). GYKI 52466 (5 mg/kg) impaired memory in 25% of mice, which did not reach the level of significance. The combined treatment of GYKI 52466 (1.25, 2.5 and 5.0 mg/kg) with valproate (170, 130 and 88 mg/kg, respectively), providing a 50% protection against maximal electroshock, resulted in the reduced impairment of long-term memory when compared with valproate alone given at its ED_{50} against maximal electroshock. Specifically, a combination of GYKI 52466 (1.25 mg/kg) with valproate (170 mg/kg) induced memory deficit in 33% of mice whilst that of GYKI 52466 (2.5 mg/kg) with valproate (130 mg/kg) –in 45% of animals (results not shown in Table 3). Co-administration of GYKI 52466 (5.0 mg/kg) with carbamazepine (4.8 mg/kg) or diphenylhydantoin (3.9 mg/kg), also providing a 50% protection against maximal electroshock, did not significantly affect retention in the passive avoidance task (Table 3).

3.5. Influence of GYKI 52466 on the plasma levels of antiepileptic drugs

GYKI 52466 (5.0 mg/kg) did not alter either the total or free plasma levels of valproate (88 mg/kg), carbamazepine (4.8 mg/kg) or diphenylhydantoin (3.9 mg/kg; Table 4).

4. Discussion

The present study demonstrated that GYKI 52466 exerted an anticonvulsant action per se, elevating the threshold for electroconvulsions in mice. Furthermore, GYKI 52466 (at the subthreshold dose of 5.0 mg/kg) significantly enhanced the protective activity of valproate, carbamazepine or diphenylhydantoin, but not that of phenobarbital against maximal electroshock-induced seizures. It is remarkable that GYKI 52466 (5.0 mg/kg) reduced the ED_{50} value of valproate more than 3-fold. Interestingly, a pharmacokinetic interaction, in terms of total and free plasma levels, does not seem probable for the enhanced protection of antiepileptic drugs by GYKI 52466, since plasma levels of these drugs remained unchanged in the presence of this excitatory amino acid antagonist. Nevertheless, a possibility that GYKI 52466 may interfere with the metabolism or pharmacokinetics of antiepileptic drugs studied at different times or when used chronically, cannot be excluded.

It is widely accepted that GYKI 52466 is a highly selective AMPA/kainate receptor antagonist and appears to act by a novel non-competitive, allosteric mechanism. It exerts anticonvulsant effects following systemic administration which supports a role for the involvement of non-NMDA receptors in the generation of seizure activity (Donevan and Rogawski, 1993; Zorumski et al., 1993; Osipenko et al., 1994). AMPA/kainate-gated channels are permeable to Na^+ and K^+ and with some exceptions they have low permeability to Ca^{2+} (Heinemann et al., 1991; Mayer and Miller, 1991).

The mechanism responsible for the protective efficacy of a number of antiepileptic drugs might be associated with several processes. According to some reports, valproate (McLean and Macdonald, 1986a), car-

Table 4
Influence of GYKI 52466 on the total and free plasma levels of antiepileptic drugs in mice

Treatment	Plasma levels	
	Total	Free
Valproate (88)	88.2 ±21.1	64.2 ±9.2
Valproate (88) + GYKI 52466 (5.0)	92.7 ± 3.9	67.6 ±9.0
Carbamazepine (4.8)	3.51 ± 0.51	0.58 ± 0.05
Carbamazepine (4.8) + GYKI 52466 (5.0)	3.68 ± 0.57	0.57 ± 0.1
Diphenylhydantoin (3.9)	3.68 ± 0.58	0.32 ± 0.05
Diphenylhydantoin (3.9) + GYKI 52466 (5.0)	3.17 ± 0.52	0.32 ± 0.04

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

bamazepine (McLean and Macdonald, 1986b) and diphenylhydantoin (McLean and Macdonald, 1983) are able to suppress the Na^+ channel-dependent high-frequency firing of cultured central neurons. However, K^+ channels also may contribute to carbamazepine, but not valproate or diphenylhydantoin anticonvulsive effects (Zona et al., 1990). On the other hand, it was shown in biochemical investigations that carbamazepine reduced the [^{3}H]L-glutamate release. Also in electrophysiological studies carbamazepine was documented to reduce excitatory transmission in the hippocampal formation (Olpe et al., 1985). Further, it was reported that this antiepileptic drug blocked NMDA-activated currents in cultured spinal neurons (Lampe and Bigalke, 1990). Some evidence was also provided that valproate suppressed NMDA-evoked transient depolarization in the rat neocortex, in vitro (Zeise et al., 1991). Finally, recent evidences indicate that diphenylhydantoin blocks NMDA responses in mouse central neurons (Wamil and McLean, 1993). These data may suggest that all three antiepileptic drugs mentioned above inhibit glutamate transmission, at least in in vitro conditions. Diphenylhydantoin and carbamazepine are hypothesized to act as non-competitive antagonists or to be novel modulatory site agents of NMDA receptors (Steppuhn and Turski, 1993). Actually, dizocilpine (MK-801, a non-competitive NMDA receptor antagonist) failed to potentiate the anticonvulsant action of both diphenylhydantoin and carbamazepine (Urbańska et al., 1991), whose protective effects against maximal electroshock were enhanced by a number of competitive NMDA receptor antagonists (Pietrasiewicz et al., 1993; Żarnowski et al., 1994a). This may point that the two antiepileptics are likely to interact with the dizocilpine binding site in vivo within the NMDA receptor channel. Consequently, the beneficial interaction between GYKI 52466 and valproate, carbamazepine or diphenylhydantoin can result from the simultaneous impairment of NMDA and AMPA/kainate receptor-mediated events. Actually, Löscher et al. (1993) have revealed that NMDA receptor antagonists (at low doses) synergistically potentiated the anticonvulsive action of NBQX in the kindling model of epilepsy. It is worth mentioning that the results achieved after co-administration of NMDA receptor antagonists [D-3-(2-carboxypiperazine-4-yl)-1-propenyl-1-phosphonic acid and MK-801) with AMPA/kainate receptor antagonists (NBQX, GYKI 52466) were shown to be quite encouraging in the electroconvulsive test in mice (Czuczwar et al., 1995). Having in mind that the anticonvulsive activity of phenobarbital was readily increased by a competitive AMPA/kainate receptor antagonist, NBQX (Żarnowski et al., 1993), and not affected by GYKI 52466, one can assume that this antiepileptic may compete for the same binding site with GYKI 52466.

GYKI 52466, at subprotective doses against electroconvulsions, did not cause any side effects (motor or long-term memory impairment). These findings seem to support the hypothesis that AMPA/kainate receptors are not required for the induction of long-term potentiation (Parada et al., 1992), which is believed to underline the storage of information in the brain. The combinations of GYKI 52466 and valproate, providing a 50% protection against maximal electroshock seizures, in contrast to valproate alone applied at its ED_{50} against maximal electroshock, did not exert statistically significant unwanted effects evaluated in the chimney test and passive avoidance task. Similarly, combinations of GYKI 52466 with either diphenylhydantoin or carbamazepine exerted no adverse effects. According to Danysz et al. (1994), agents either blocking NMDA or non-NMDA receptors produced qualitatively different behavioral consequences. Generally, NMDA receptor antagonists disturbed locomotor activity to a considerably greater degree than GYKI 52466 or NBQX did. Actually, these AMPA/kainate receptor antagonists, up to 30 mg/kg, produced no major changes in the open field test in rats (Danysz et al., 1994). It is thus of importance to evaluate the influence of the combined treatment of individual excitatory amino acid antagonists, acting at NMDA or non-NMDA receptors, with conventional antiepileptics on the motor performance of mice in the open field test. A possibility exists that the differences in the profile of NMDA or non-NMDA receptor antagonists in this test (Danysz et al., 1994) may persist when these drugs are combined with standard antiepileptics.

Summing up, our previous report indicated that a competitive antagonism at AMPA/kainate receptors resulted in the pronounced potentiation of the anti-electroshock activity of conventional antiepileptics, with no adverse effects in some cases (Żarnowski et al., 1993). Now, we provide evidence that a non-competitive antagonism at this receptor site leads generally to comparable effects, which can offer a novel approach in the treatment of epilepsy.

Acknowledgements

The results of this study were presented during the 36th Spring Meeting of the German Pharmacological Society held at Mainz, Germany (March 14–17, 1995) (Czuczwar et al. (1995) Naunyn-Schmied. Arch. Pharmacol. 351 (Suppl.), R161).

The generous gifts of GYKI 52466 by Dr. I. Tarnawa (Lab. for Drug Research, Budapest, Hungary) and valproate magnesium (Polfa, Rzeszów, Poland) are greatly appreciated.

This study was supported by a grant from Lublin Medical University School.

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