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β-Adrenoceptor blockade enhances the anticonvulsant effect of glutamate receptor antagonists against maximal electroshock

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Abstract

In this study, we evaluated whether β-adrenoceptor antagonists may modify the protective efficacy of dizocilpine (MK-801), a NMDA receptor antagonist, and 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466), a non-NMDA (AMPA/kainate) receptor antagonist, against maximal electroshock-induced seizures in mice. Propranolol, acebutolol, metoprolol and atenolol were used in doses that did not alter the electroconvulsive threshold. Propranolol potentiated the anticonvulsant activity of MK-801 and GYKI 52466, significantly lowering their ED_{50} values from 0.38 and 15.0 to 0.15 ($P < 0.001$) and 8.4 mg/kg ($P < 0.001$), respectively. Similarly, metoprolol lowered the ED_{50} of MK-801 and GYKI 52466 from 0.38 and 15.0 to 0.17 ($P < 0.05$) and 11.2 mg/kg ($P < 0.05$). Acebutolol enhanced the protective action of GYKI 52466, lowering its ED_{50} value from 15.0 to 12.2 mg/kg ($P < 0.05$), but not that of MK-801. Atenolol, not penetrating the blood–brain barrier, did not affect the anticonvulsive efficacy of MK-801 and GYKI 52466. In conclusion, β-adrenoceptor antagonists may act synergistically with excitatory amino acid receptor antagonists to inhibit generalised tonic-clonic seizures.

Keywords: β-Adrenoceptor antagonist; Propranolol; Metoprolol; Excitatory amino acid receptor antagonist; Seizure; Electroshock, maximal

1. Introduction

The alteration of excitatory amino acids-mediated neurotransmission is considered as one of the major factors contributing to the initiation, propagation and maintenance of epileptic activity (Meldrum, 1994). Extracellular glutamate was shown to rise prior to the onset of an epileptic attack in the hippocampus of patients with complex partial seizures (During and Spencer, 1993). Intracerebral and systemic administration of excitatory amino acid receptor agonists, such as NMDA, AMPA, quisqualate or homocysteate leads to seizures that occur in the form of generalised tonic-clonic convusions or wild running episodes (Meldrum, 1994). Moreover, glutamate receptor antagonists of the NMDA or non-NMDA (AMPA/kainate) type are potent antiepileptic compounds in a variety of experimental seizures including chemically induced, genetically determined, and to a lesser extent, in the kindling model of epilepsy and electroconvulsions (Löscher, 1998; Urbanska et al., 1998; Meldrum and Chapman, 1999).

Apart from the well-documented clinical cardiovascular and non-cardiovascular applications of β-adrenoceptor antagonists, there is a growing body of data showing that the activation of central β-adrenoceptors may also be involved in the development/progress of epileptic phenomena. The highest density of β-adrenoceptors occurs in all subfields of the hippocampus (Reznikoff et al., 1986), known for its low seizure threshold and dominant role in the propagation of seizures (McNamara, 1994). Recent studies show that central β-adrenoceptor activation may lead to the facilitation of excitatory amino acids release and, hence, modulate synaptic transmission (Herrero and Sanchez-Prieto, 1996). Moreover, some β-adrenoceptor antagonists display anticonvulsant actions under experimental conditions and could potentiate the protective activity of classical antiepileptics (Fischer and Müller, 1988).

Thus, in this study we aimed to evaluate the effect of β-adrenoceptor antagonists on the protective efficacy of dizocilpine (MK-801), a NMDA receptor antagonist, and

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1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466), a non-NMDA receptor antagonist, against generalised tonic-clonic seizures in mice.

2. Materials and methods

2.1. Animals

The experiments were carried out on male Albino Swiss mice, weighing 20–25 g, and kept in colony cages at room temperature, under a natural light–dark cycle. Food pellets and tap water were supplied ad libitum. Experimental groups, consisting of 10–12 animals, were assigned according to a randomised schedule. The control groups of animals were always tested on the same day as the respective experimental groups. Experimental procedures were approved by the local Ethical Committee and are in agreement with European Communities Council Directives.

2.2. Drugs

Metoprolol tartrate (Polpharma, Starogard Gdanski, Poland), atenolol (RBI, Natick, MA, USA) and GYKI 52466 (Sigma, St. Louis, MO, U.S.A) were suspended in a 1% solution of Tween 80. Propranolol (Sigma, St. Louis, MO, USA), acebutolol (Polfa, Grodzisk, Poland) and MK-801 (RBI, Natick, MA, USA) were dissolved in sterile saline. All drugs were administered intraperitoneally (i.p.): GYKI 52466 15 min, propranolol, metoprolol and acebutolol 30 min, MK-801 45 min and atenolol 60 min prior to the test. The injection volume was always 0.1 ml/10 g of body weight. Control animals received equivalent volumes of the solvent at the respective times before the test.

2.3. Electroconvulsions

The electroconvulsions were evoked according to the method of Swinyard et al. (1952). The electroshock was applied via ear-clip electrodes and generated with a Hugo-Sachs stimulator (Type 221, Freiburg, Germany), which produced an alternating current (50 Hz); the stimulus duration was 0.2 s. To evaluate the convulsive threshold (CS_{50}), i.e. the current strength (in mA) necessary to induce tonic hind limb extension in 50% of the mice tested, at least three groups of mice, consisting of 10–12 animals each, were subjected to electrical shocks of various intensities. Maximal electroshock-induced seizures were evoked with a current of 25 mA intensity.

2.4. Chimney test

The influence of β-adrenoceptor antagonists on the motor impairment evoked by the glutamate receptor antagonists was evaluated according to Boissier et al. (1960). Motor impairment was indicated by the inability of animals to climb backwards in a plastic tube (3 cm inner diameter, 25 cm length) within 60 s.

2.5. Statistics

Calculations of CS_{50} and ED_{50} (the dose of drug (in mg/kg) required to protect 50% of mice against maximal electroshock-induced tonic hind limb extension) values with their respective 95% confidence limits, and statistical comparisons of the results were performed by computerized linear regression analysis, according to the method of Litchfield and Wilcoxon (1949). Fisher's exact probability test was used for statistical analysis of the results concerning motor performance of mice.

3. Results

3.1. Effects of β-adrenoceptor antagonists on the electroconvulsive threshold

Propranolol (10 mg/kg), acebutolol (150 mg/kg), metoprolol (100 mg/kg) and atenolol (25 mg/kg) raised the CS_{50} value from 6.3, 6.0, 6.7 and 6.6 to 8.2 ($P < 0.05$), 7.9 ($P < 0.001$), 8.1 ($P < 0.001$) and 7.9 mA ($P < 0.001$), respectively (Fig. 1). Propranolol, acebutolol, metoprolol and atenolol applied at the doses of 7.5, 100, 75 and 10 mg/kg (i.p.), respectively, did not influence the CS_{50} and these doses of drugs were used for experiments with the maximal electroshock test (Fig. 1).

3.2. Effects of β-adrenoceptor antagonists on maximal electroshock-induced seizures

Propranolol and metoprolol displayed a marked dose-related anticonvulsant activity against maximal electroshock-induced seizures. The estimated ED_{50} value for propranolol was 14.8 mg/kg and for metoprolol 186.7 mg/kg (Table 1). Acebutolol and atenolol, up to 175 and 300 mg/kg, respectively, did not affect maximal electroshock-evoked convulsions (Table 1).

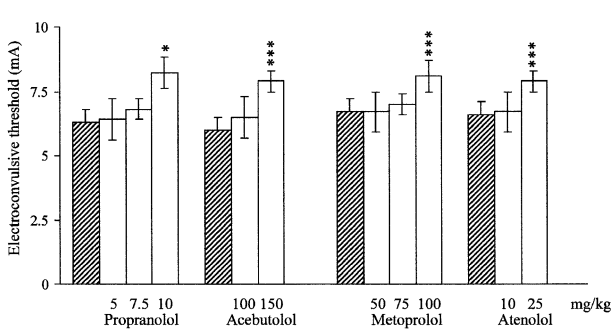

Fig. 1. Influence of β-adrenoceptor antagonists on the electroconvulsive threshold (CS_{50}). Data are presented as the CS_{50} values (in mA, with 95% confidence limits). Filled bars represent control groups given only saline. The calculation of CS_{50} values and statistical analyses of the data were performed according to the method of Litchfield and Wilcoxon (1949). $^{*}P < 0.05$, $^{***}P < 0.001$ vs. saline-treated group.

Table 1
Anticonvulsant activity of β-adrenoceptor antagonists against maximal electroshock-induced seizures

Treatment	ED_{50} (mg/kg)
Propranolol	14.8 [13.9–15.7]
Metoprolol	186.7 [166.8–208.9]
Acebutolol	> 175
Atenolol	> 300

All drugs were administered i.p.: propranolol, acebutolol and metoprolol 30 min, and atenolol 60 min prior to the test. Data are presented as ED_{50}, i.e. dose of a drug (in mg/kg, with 95% confidence limits) required to protect 50% of the mice against maximal electroshock (25 mA)-induced tonic hind limb extension. ED_{50} values were calculated and statistical comparisons performed by computerized linear regression analysis, based on the method of Litchfield and Wilcoxon (1949).

3.3. Influence of β-adrenoceptor antagonists on the protective efficacy of MK-801 and GYKI 52466

The anticonvulsant activity of GYKI 52466 against maximal electroshock-evoked seizures was potentiated by propranolol, acebutolol and metoprolol, which lowered its ED_{50} from 15.0 to 8.4 ($P < 0.001$), 12.2 ($P < 0.05$) and 11.2 mg/kg ($P < 0.05$), respectively (Fig. 2). Propranolol and metoprolol, but not acebutolol, also enhanced the protective efficacy of MK-801, lowering its ED_{50} from 0.38 to 0.15 ($P < 0.001$) and 0.17 mg/kg ($P < 0.05$), respectively (Fig. 3). Atenolol did not influence the anticonvulsant effect of GYKI 52466 or of MK-801 in the maximal electroshock test (Figs. 2 and 3).

3.4. Motor impairment

β-adrenoceptor antagonists, given in the doses used for concomitant application with GYKI 52466 and MK-801, did not themselves induce motor impairment, as shown by the chimney test. The administration of propranolol (7.5 mg/kg), together with GYKI 52466 or MK-801, did not affect the motor performance of mice. Metoprolol (75 mg/kg) given together with MK-801 also did not alter

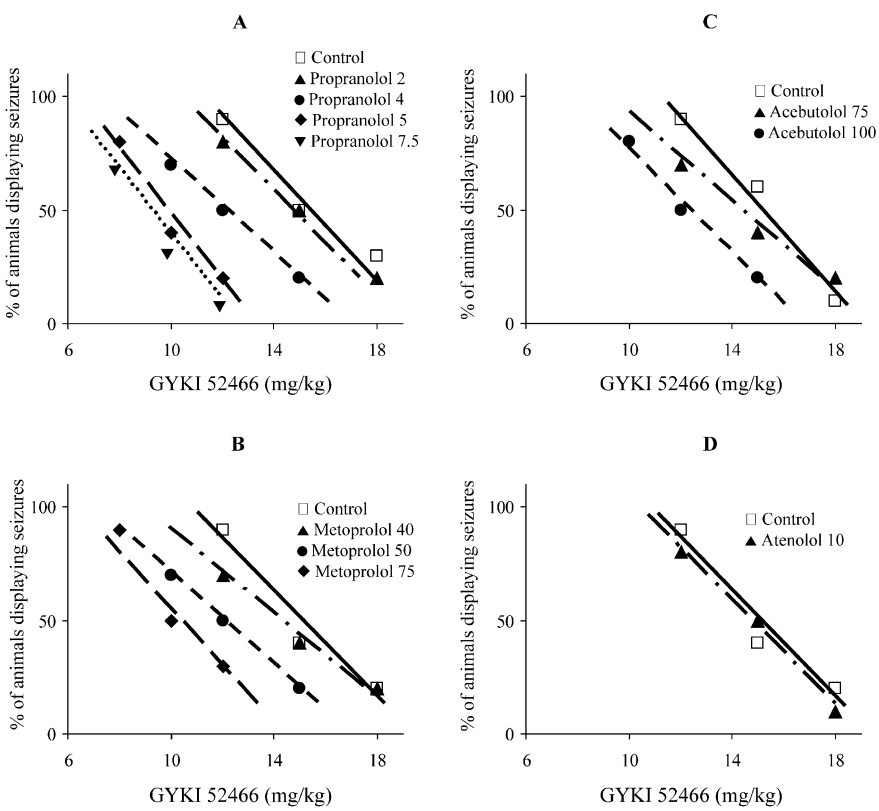

Fig. 2. Influence of β-adrenoceptor antagonists on the protective efficacy of GYKI 52466 against maximal electroshock-induced seizures. Data are presented as percentages of animals displaying seizures given various concentrations of GYKI 52466 with saline (control) or with the respective β-adrenoceptor antagonist. The calculation of ED_{50} values and statistical analyses of the data were performed according to the method of Litchfield and Wilcoxon (1949). Dose regression curves were calculated using GraphPAD software. (A) Control: $y = -10.0x + 206.7$, $r = -0.98$; Propranolol 2 mg/kg: $y = -10.0x + 200.0$, $r = -1.0$; Propranolol 3 mg/kg: $y = -10.0x + 170.0$, $r = -1.0$ ($P < 0.05$); Propranolol 5 mg/kg: $y = -15.0x + 196.7$, $r = -0.98$ ($P < 0.001$); Propranolol 7.5 mg/kg: $y = -15.0x + 186.7$, $r = -0.98$ ($P < 0.001$). (B) Control: $y = -11.7x + 225.0$, $r = -0.97$; Metoprolol 40 mg/kg: $y = -8.3x + 168.3$, $r = -0.99$; Metoprolol 50 mg/kg: $y = -10.0x + 170.0$, $r = -1.0$ ($P < 0.05$); Metoprolol 75 mg/kg: $y = -15.0x + 206.7$, $r = -0.98$ ($P < 0.05$). (C) Control: $y = -13.3x + 253.3$, $r = -0.99$; Acebutolol 75 mg/kg: $y = -8.3x + 168.3$, $r = -0.99$; Acebutolol 100 mg/kg: $y = -11.8x + 196.1$, $r = -0.99$ ($P < 0.05$). (D) Control: $y = -11.7x + 225.0$, $r = -0.97$; Atenolol 10 mg/kg: $y = -11.7x + 221.7$, $r = -1.0$.

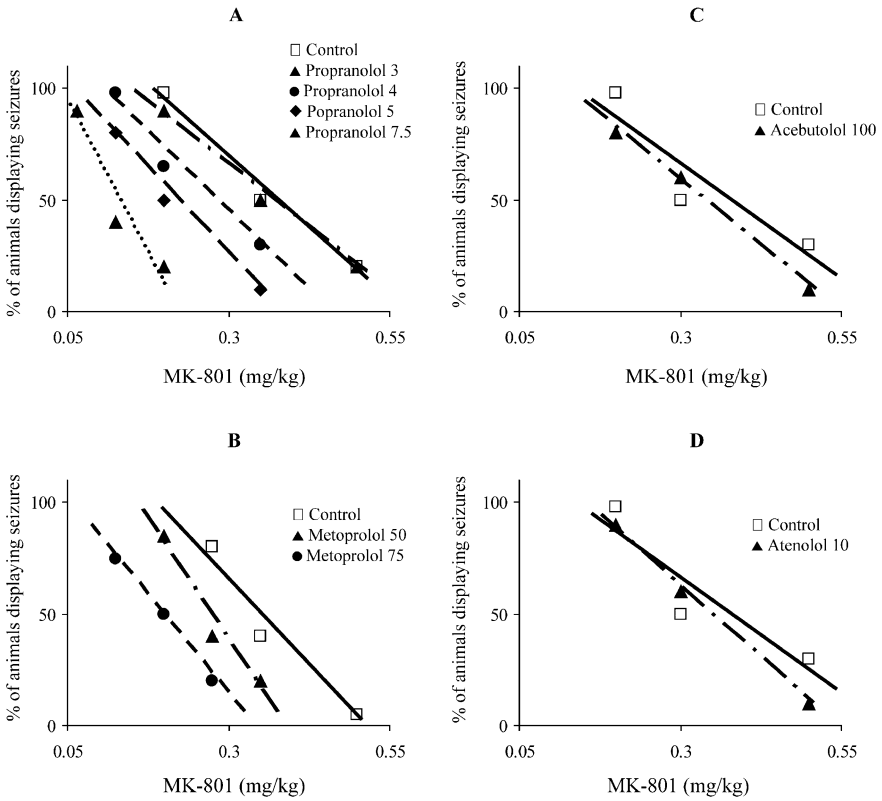

Fig. 3. Influence of β-adrenoceptor antagonists on the protective efficacy of MK-801 against maximal electroshock-induced seizures. Data are presented as percentages of animals displaying seizures given various concentrations of MK-801 with saline (control) and MK-801 or with the respective β-adrenoceptor antagonist. The calculation of ED_{50} values and statistical analysis of the data were performed according to the method of Litchfield and Wilcoxon (1949). Dose regression curves were calculated using GraphPAD software. (A) Control: $y = -260.0x + 147.0$, $r = -0.99$; Propranolol 3 mg/kg: $y = -233.0x + 135.0$, $r = -1.0$; Propranolol 4 mg/kg: $y = -292.4x + 130.1$, $r = -0.99$ ($P < 0.05$); Propranolol 5 mg/kg: $y = -304.8x + 115.2$, $r = -0.99$ ($P < 0.01$); Propranolol 7.5 mg/kg: $y = -508.2x + 116.1$, $r = -0.95$ ($P < 0.001$). (B) Control: $y = -319.1x + 161.3$, $r = -0.97$; Metoprolol 50 mg/kg: $y = -433.3x + 167.5$, $r = -0.98$; Metoprolol 75 mg/kg: $y = -366.7x + 121.7$, $r = -1.0$ ($P < 0.05$). (C) Control: $y = -208.6x + 128.9$, $r = -0.91$; Acebutolol 100 mg/kg: $y = -235.7x + 128.6$, $r = -1.0$. (D) Control: $y = -208.6x + 128.9$, $r = -0.91$; Atenolol 10 mg/kg: $y = -264.3x + 141.4$, $r = -1.0$.

locomotor activity. In contrast, co-administration of metoprolol (75 mg/kg) or acebutolol (100 mg/kg), with GYKI 52466 caused motor impairment (Fig. 4).

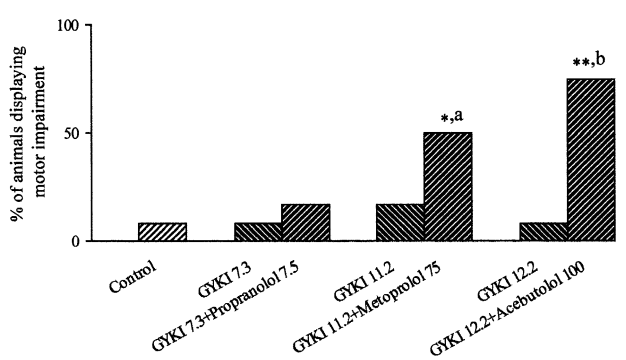

Fig. 4. Motor performance of mice after administration of GYKI 52466 alone or co-administered with propranolol, metoprolol or acebutolol. Motor impairment was estimated according to Boissier et al. (1960), and indicated by the inability of animals to climb backwards, in a plastic tube (3 cm inner diameter, 25 cm length), within 60 s. The results are expressed as percentages of animals that failed to perform in the test. Statistical analysis of results was performed with Fisher's exact probability test. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control; $^{a}P < 0.05$, $^{b}P < 0.01$ vs. respective dose of GYKI 52466.

4. Discussion

The results of our study indicated that β-adrenoceptor blockade enhances the protective activity of the NMDA receptor antagonist, MK-801, and of the non-NMDA receptor antagonist, GYKI 52466. The protective action of GYKI 52466 and MK-801 against maximal electroshock-induced convulsions was markedly potentiated by a β_1/β_2-adrenoceptor antagonist, propranolol, and a selective β_1-adrenoceptor antagonist, metoprolol, applied at doses which themselves did not affect the electroconvulsive threshold. Anticonvulsant effects of GYKI 52466 were also augmented by the selective β_1-adrenoceptor antagonist, acebutolol. However, acebutolol did not influence the anti-seizure efficacy of MK-801. A selective β_1-adrenoceptor antagonist, that does not penetrate the blood–brain barrier, atenolol, did not affect the activity of any anticonvulsants now studied.

MK-801 is a non-competitive antagonist that binds rapidly and dissociates slowly from the ion channel (high-affinity blocker) of the NMDA receptor complex, whereas GYKI 52466 has been identified as a highly selective,

non-competitive antagonist of non-NMDA receptors (Meldrum and Chapman, 1999). Both drugs display potent anticonvulsant properties in various experimental models including seizures evoked by the excessive activation of excitatory amino acid receptors, impaired γ-aminobutyric acid (GABA)-related inhibition, enhanced cholinergic transmission, kindling, hypoglycemia or electroshock (Löscher, 1998; Urbanska et al., 1998).

Increasing evidence suggests that central β-adrenergic neurotransmission might also play a modulatory role in epileptic phenomena (Rutecki, 1995). McIntyre and Wong (1986) observed the potentiation of epileptiform abnormalities in slices of pyriform cortex obtained from kindled animals following β-adrenoceptor agonists application. Similarly, β-adrenoceptor activation increased the rate of spontaneous epileptiform discharges in hippocampal slices (Mueller and Dunwiddie, 1983; Rutecki, 1995). The involvement of central β-adrenoceptors in genetically programmed seizures has also been demonstrated (Lints and Nyquist-Battie, 1984; Khanna et al., 1989). Moreover, β-adrenoceptor antagonists, especially propranolol, display anticonvulsant effects, raising the threshold for electroconvulsions and protecting against maximal electroshock- and pentylenetetrazol-induced seizures (Louis et al., 1982; Fischer et al., 1985).

There are single reports indicating that β-adrenoceptor antagonists may also potentiate the activity of certain classical antiepileptic drugs. Co-administration of diazepam with atenolol increases the activity of the latter against aminophylline-evoked seizures (Chugh et al., 1991). Propranolol, pindolol and alprenolol were shown to enhance the anticonvulsant activity of phenobarbital in the maximal electroshock test (Fischer and Muller, 1988). Recently, we have demonstrated that propranolol and metoprolol augment the anticonvulsant action of valproate and diazepam, but not that of phenytoin and carbamazepine, against maximal electroshock-induced seizures (Luchowska et al., in press).

Either pre- or/and postsynaptic β-adrenoceptor effects may be responsible for the potentiation of the anticonvulsant activity of excitatory amino acid receptor antagonists. The stimulation of β-adrenoceptors leads to the activation of adenylyl cyclase and subsequent phosphorylation of key target proteins by cAMP-dependent protein kinase (Hein and Kobilka, 1995; Scholich et al., 1999). β-Adrenoceptor-mediated increases in cAMP formation have been shown to augment the activity of voltage-dependent Ca^{2+} channels in hippocampal neurones (Gray and Johnston, 1987). Parfitt et al. (1992) reported that β-adrenergic/cAMP-mediated activation of cAMP-dependent protein kinase enhances the phosphorylation of a synaptic vesicle-associated protein, synapsin. Hypothetically, either of these actions could influence synaptic transmission. Indeed, increased cAMP formation within the nerve terminals of the cerebral cortex induces spontaneous action potentials and leads to Ca^{2+}-dependent glutamate release (Herrero and Sanchez-Prieto, 1996). It has also been demonstrated that the augmented cAMP-dependent protein kinase activity enhances both NMDA-mediated (Raman et al., 1996) and AMPA/kainate-mediated postsynaptic responses (Greengard et al., 1991; Raymond et al., 1993). Thus, diminished synthesis of cAMP and decreased cAMP-dependent protein kinase-mediated processes, due to β-adrenoceptor antagonists used, may impair glutamate release via the reduction of nerve terminal excitability or interference with vesicular release mechanisms, or may reduce postsynaptic responses. In such scenarios, the glutamatergic blockade would be augmented by the application of β-adrenoceptor antagonists, which indeed was the case here.

It is not clear whether β-adrenoceptor antagonists may directly block glutamate receptors at high doses. One of the antagonists, carvedilol, was demonstrated to inhibit NMDA-related responses (Lysko et al., 1998), but to our knowledge there are no data regarding such an action displayed by propranolol or metoprolol.

A contribution of sodium channel blockade, characteristic of some β-adrenoceptor antagonists, to the effects observed cannot be excluded. It is well documented that propranolol exerts strong local anaesthetic activity (van Zwieten and Timmermans, 1983). As regards metoprolol, the vast majority of studies indicate that it lacks membrane stabilizing properties (Takeo et al., 1990; Kendall, 1997; Soriano et al., 1997). In contrast, only few reports show that high doses of metoprolol might cause some sodium channel blockade (Boucher et al., 1992). In our study, both propranolol and metoprolol were able to potentiate the protective activity of MK-801 and GYKI 52466, implying that β-adrenoceptor blockade per se and not the sodium channel blockade might be responsible for the potentiation observed.

The doses of β-adrenoceptor antagonists that we used may seem relatively high, however, it was shown by others that, e.g. the experimental application of propranolol, in similar doses, does not affect haemodynamic parameters in animals (Brenner et al., 1984; Moreau et al., 1997). Moreover, we show that all of the β-adrenoceptor antagonists now investigated, up to the highest dose used in the maximal electroshock test, do not themselves influence the locomotor activity of animals, as shown in the chimney test. Also, the co-administration of propranolol with GYKI 52466 or MK-801 and metoprolol with MK-801 did not alter the motor performance of mice. Nevertheless, metoprolol and acebutolol given with GYKI 52466 impaired motor performance. However, atenolol, which is known not to penetrate the blood–brain barrier, did not influence the anticonvulsant potential of GYKI 52466 or MK-801, which argues against the involvement of peripheral β-adrenergic blockade in the potentiation we observed.

Finally, we should consider whether the interactions observed are not of a pharmacokinetic nature. This seems rather unlikely, since neither propranolol nor metoprolol changed the free plasma or brain levels of other anticon-

vulsants, such as diazepam and valproate (Luchowska et al., in press).

In conclusion, β-adrenoceptor antagonists may enhance the anticonvulsant potential of glutamate receptor antagonists in the model of generalised tonic-clonic seizures. This effect does not seem to correlate with the peripheral action or membrane stabilizing activity of β-adrenoceptor antagonists. It could be hypothesised that β-adrenoceptor blockade augments the effects evoked by excitatory amino acid receptor antagonists via diminished formation of cAMP, which leads to either the inhibition of presynaptic release of glutamate, or the reduction of postsynaptic cAMP-dependent protein kinase-related actions.

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