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Weak blockade of AMPA receptor-mediated depolarisations in the rat cortical wedge by phenytoin but not lamotrigine or carbamazepine

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Abstract

The effects of the anticonvulsants, lamotrigine, phenytoin and carbamazepine, were investigated on NMDA and non-NMDA receptor agonist-evoked responses and against spontaneous epileptiform discharges, in the in vitro rat cortical wedge. Lamotrigine weakly attenuated responses to (RS)-α-amino-3-hydroxy-5-methoxy-4-isoxazole propionic acid (AMPA) and quisqualate (IC_{50} values $\gg$ 100 μM), but was without effect on responses to NMDA. Phenytoin weakly, but concentration-dependently, attenuated responses to AMPA and quisqualate, but much less potently attenuated responses to NMDA (IC_{50} values 163, 248 and $\gg$ 300 μM, respectively). Carbamazepine (3–100 μM) significantly attenuated responses to NMDA and at 100 μM attenuated responses to AMPA and quisqualate. These effects were not concentration dependent, with the IC_{50} values $\gg$ 100 μM. Lamotrigine and phenytoin weakly, but concentration-dependently, reduced the frequency (IC_{50} values 254 and $>$ 300 μM, respectively) and amplitude (IC_{50} values 141 and $>$ 300 μM, respectively) of spontaneous epileptiform discharges, whereas carbamazepine had no effect. The results show that the anticonvulsant effects of these antiepileptics are unlikely to involve antagonism of ionotropic glutamate receptors, although blockade of non-NMDA responses may play a role in the anticonvulsant profile of phenytoin. Furthermore, the data show that clinically effective anticonvulsants do not necessarily attenuate spontaneous epileptiform discharges in the rat cortical wedge. © 1997 Elsevier Science B.V.

Keywords: NMDA receptor; Non-NMDA receptor; Antiepileptic; Cortical wedge

1. Introduction

Lamotrigine, carbamazepine and phenytoin are antiepileptic drugs the primary actions of which are believed to involve the voltage- and use-dependent blockade of voltage-sensitive Na^+ channels (Leach et al., 1986; McLean and MacDonald, 1986). This activity results in the inhibition of neurotransmitter release (principally glutamate), thus reducing neuronal excitability and stabilising neuronal membranes. Lamotrigine, like phenytoin and carbamazepine, inhibits the binding of [^{3}H]batrachotoxinin A 20 α-benzoate to a Na^+ channel site related to activation of Na^+ channel ion fluxes (Willow and Catterall, 1982; Leach et al., 1986). Lamotrigine and phenytoin both inhibit the veratrine-induced release of the neurotransmitters glutamate, aspartate and γ-aminobutyric acid (GABA) (Leach et al., 1986, 1991), whereas carbamazepine produces a mixed inhibition of veratridine-activated channels (Willow et al., 1983).

Although there is widespread agreement on the effects of these three drugs on Na^+ channels, there remains some confusion concerning their actions on excitatory amino acid receptors. Thus, it has been argued that lamotrigine does not act on the NMDA receptor because it does not block post-synaptic ligand-gated ion channels (Baxter et al., 1990) and does not inhibit NMDA-stimulated formation of cyclic GMP (Leach et al., 1991). There have been mixed reports on the actions of phenytoin at NMDA receptors. Lampe and Bigalke (1990) reported that at concentrations up to 50 μM, phenytoin was without effect on NMDA-activated currents in cultured spinal cord neurones. This finding was confirmed by Laffling et al. (1995) who determined the effects of phenytoin on NMDA-mediated population spikes in the rat hippocampus. However, a number of other workers have reported that phenytoin inhibits NMDA-mediated responses (Wamil and McLean, 1993; Brown et al., 1994; Kawano et al., 1994). Carbamazepine has been reported to block NMDA-mediated

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currents in cultured spinal cord neurones (Lampe and Bigalke, 1990) and to inhibit NMDA-induced depolarisations in DBA/2 mouse cortical wedges (Lancaster and Davies, 1992).

The rat cortical wedge preparation has been used extensively to investigate the effects of antiepileptics on responses evoked by excitatory amino acids (Harrison and Simmonds, 1985; Lodge et al., 1988; Sheardown et al., 1989; Grimwood et al., 1991; Palmer and Lodge, 1991; Robichaud et al., 1991; Lodge and Palmer, 1994). By removing Mg^{2+} from the bathing medium, it is also possible to generate spontaneous epileptiform discharges in the cortical wedge, which result from the removal of the voltage-dependent block of the NMDA receptor. The cortical wedge preparation, therefore, also allows the effects of drugs on epileptiform activity to be determined. We have used this robust preparation to compare the effects of lamotrigine, carbamazepine and phenytoin on responses to NMDA and non-NMDA receptor agonists. In addition, the effects of these antiepiliptics on spontaneous epileptiform discharges was investigated.

2. Materials and methods

2.1. Wedge preparation and recording

Neocortical wedges were prepared largely as described by Harrison and Simmonds (1985). Male CD rats (80–120 g; Charles River) were decapitated under halothane anaesthesia and their brains removed and placed in gassed (95% O_2, 5% CO_2) artificial cerebrospinal fluid (aCSF) with the following composition in mM: NaCl, 124; KCl, 3.3; KH_2PO_4, 1.2; $NaHCO_3$, 25.5; D-glucose, 10; $CaCl_2$, 2.5 and $MgSO_4 \cdot 7H_2O$, 1.0. Coronal slices (500 μm) were cut at room temperature in gassed aCSF using a vibroslice (Campden Instruments). The slices were allowed approximately 30 min to recover before being cut into wedges 1.5–2.0 mm wide at the cortical side and 1 mm wide at the callosal side. Each wedge was placed in a two-compartment bath separating the cortex from the callosum by a greased barrier (Harrison and Simmonds, 1985). Each compartment was perfused independently at 2 ml/min with continuously gassed aCSF. After allowing 1 h for recovery, the perfusate to both sides of the wedge was changed to Mg^{2+}-free aCSF. The dc potential between the two compartments was monitored via Ag/AgCl electrodes embedded in Sylgard. The signal was amplified, filtered using Neurolog system ac–dc amplifiers and filters (Digitimer) and displayed using a MacLab data acquisition system and Chart software on a Power Macintosh 6100/66 computer.

2.2. Drug application

Drugs were dissolved in double distilled, de-ionised water at stock concentrations of 1×10^{-2} M unless otherwise stated. Stock solutions were kept frozen until use and

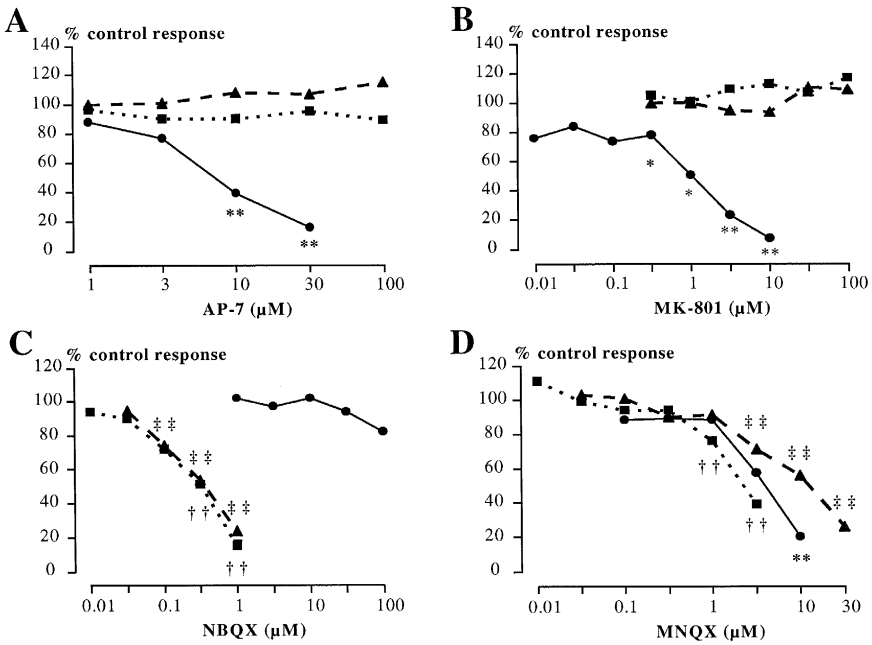

Fig. 1. Effects of ionotropic glutamate receptor antagonists on NMDA and non-NMDA receptor agonist-evoked responses. (A–D) Responses to 10 μM AMPA (· · · ■ · · ·), 10 μM quisqualate (- - - ▲ - - -) and 30 μM NMDA (—●—) in the presence of (A) AP-7; (B) MK-801; (C) NBQX and (D) MNQX. *, † and ‡ indicate significance at the 5% level, **, †† and ‡‡ indicate significance at the 1% level for NMDA, AMPA and quisqualate, respectively. Although error bars are not shown on the axis, S.E. values = 4–65% of mean.

dilutions were made in gassed Mg^{2+}-free aCSF. All the drugs were applied to the cortical side of the preparation only. Carbamazepine, lamotrigine, phenytoin and 5,7-dinitroquinoxaline-2,3-dione (MNQX) were dissolved in dimethylsulphoxide (DMSO) at 1×10^{-2} M and diluted in gassed Mg^{2+}-free aCSF. DMSO alone, at comparable concentrations, was without effect on any of the agonist responses and did not affect spontaneous epileptiform discharges.

Excitatory amino acid receptor agonists were applied for 1 min with 15–20 min between applications. Excitatory amino acid receptor antagonists or anticonvulsants were applied 10 min before agonist applications and continued for 10 min after withdrawal of agonist. An increasing series of agonist concentrations was used to determine the concentration giving 50% of maximum response (EC_{50}). This EC_{50} concentration of agonist was then used to determine the effects on the agonist response of an increasing series of antagonist or anticonvulsant concentrations.

In experiments where the effects on frequency and amplitude of spontaneous epileptiform discharges were investigated, drugs were tested in an increasing concentration series, with each concentration being applied for a 10 min period.

2.3. Data analysis

Depolarisation amplitude was used to quantitate agonist responses. The treatment-induced response was converted to a percent of control (mean pre-intervention response). Data were log transformed then analysed by two-way analysis of variance. Comparisons against control were made using Williams' test. Data are reported as mean % control ± standard error (S.E.M.). Experiments investigating effects on the frequency and amplitude of spontaneous epileptiform discharges were quantified over the final 4 min of the 10 min treatment interval for each concentration applied, by which time the response had stabilised. Control values were quantified using the 4 min immediately prior to the initial application of drug. Statistical analysis of these data were as described above, except that data was not log transformed before two-way analysis of variance.

2.4. Drugs

The following drugs were used: (*RS*)-α-amino-3-hydroxy-5-methoxy-4-isoxazole propionic acid (AMPA), D,L-2-amino-7-phosphonoheptanoic acid (AP7), MNQX, 6-nitro-7-sulphamoylbenzo(f)-quinoxaline-2,3-dione (NBQX), *N*-methyl-D-aspartic acid (NMDA), L-quisqualic acid, (Sigma); carbamazepine, (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (MK-801), phenytoin (R.B.I.) and lamotrigine (gift from Wellcome Foundation).

3. Results

3.1. Effects of glutamate receptor antagonists on glutamate receptor agonist-evoked responses

The application of NMDA and non-NMDA receptor agonists caused concentration-dependent depolarisations with the following EC_{50} values (95% confidence limits): NMDA, 36 μM (20.7, 62.8); AMPA, 7.8 μM (5.9, 10.3) and quisqualate, 20.4 μM (14.8, 28.1). These EC_{50} concentrations were then used to select the agonist concentration which would give approximately 50% of maximum response. The selective NMDA receptor antagonists, AP7 (Fig. 1A) and MK-801 (Fig. 1B), concentration-dependently blocked responses to NMDA (30 μM) (IC_{50} values (95% confidence limits) 8.1 μM (4.5, 14.5, $n = 8$) and 0.95 μM (0.7, 1.4, $n = 3–6$), respectively), but both AP7

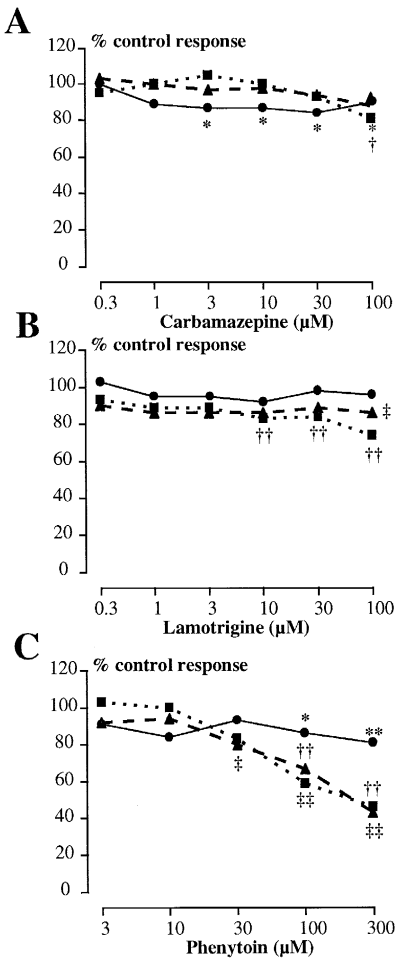

Fig. 2. Effects of antiepileptics on glutamate agonist-evoked responses. (A–C) Responses to 10 μM AMPA (· · · ■ · · ·), 10 μM quisqualate (- - - ▲ - - -) and 30 μM NMDA (— ● —) in the presence of increasing concentrations of (A) carbamazepine; (B) lamotrigine and (C) phenytoin. *, † and ‡ indicate significance at the 5% level, **, ††, and ‡‡ indicate significance at the 1% level, for NMDA, AMPA and quisqualate, respectively. Although error bars are not shown on the axis, S.E. values = 1–20% of mean.

and MK-801 were without effect on responses to the non-NMDA receptor agonists, AMPA (10 μM) and quisqualate (10 μM). NBQX, a selective antagonist at non-NMDA receptors, attenuated responses to AMPA (IC_{50} (95% confidence limits): 0.3 μM (0.1, 0.7, $n = 5–7$)) and quisqualate, (IC_{50} (95% confidence limits): 0.4 μM (0.2, 0.8, $n = 7$)) in a concentration-dependent manner, but was without effect on NMDA-evoked responses ($IC_{50} > 100$ μM ($n = 7–9$)) (Fig. 1C). MNQX, an antagonist at both NMDA and AMPA receptors, concentration-dependently attenuated responses evoked by the non-NMDA receptor agonists AMPA and quisqualate, (IC_{50} values (95% confidence limits) 2 μM (1.5, 2.6, $n = 4$) and 10.2 μM (5.6, 18.5, $n = 3–4$), respectively) and responses evoked by NMDA, (IC_{50} (95% confidence limits): 3.5 μM (2.6, 4.7, $n = 4$)) (Fig. 1D).

3.2. Effects of antiepileptics on glutamate agonist-evoked responses

Carbamazepine at concentrations up to 30 μM failed to block responses to AMPA and quisqualate, although at 100 μM, responses to AMPA and quisqualate were weakly attenuated (by 19 and 12%, respectively; $P < 0.01\%$ and $P < 0.05\%$, respectively). However, at concentrations of 3–100 μM, carbamazepine weakly attenuated the response to NMDA. This effect was approximately similar (10–16% reduction; $p < 0.05\%$) over the range of concentrations stated. Lamotrigine had no effect on NMDA-evoked responses at concentrations up to 100 μM and only weakly (IC_{50} values $\gg 100$ μM, $n = 4–8$) attenuated responses to the non-NMDA receptor agonists AMPA and quisqualate (Fig. 2B). By contrast, phenytoin concentration-dependently decreased responses to the non-NMDA receptor agonists AMPA and quisqualate (IC_{50} values (95% confident limits): 163 μM (63, 421, $n = 4$) and 248 μM (125, 491, $n = 4$), respectively). Responses to NMDA were much less potently ($IC_{50} \gg 300$ μM, $n = 4$) attenuated by phenytoin (Fig. 2C).

3.3. Effects of glutamate receptor antagonists on spontaneous epileptiform discharges

The selective NMDA receptor antagonists AP7 and MK-801 concentration-dependently reduced the frequency (IC_{50} values (95% confidence limits): 0.6 μM (0.2, 1.9, $n = 3–7$) and 4.2 μM (1.3, 13.7, $n = 3$)) and amplitude (IC_{50} values (95% confidence limits): 10.6 μM (7.2, 15.6, $n = 3–7$) and 18.1 μM (0.7, 464, $n = 3$)) of spontaneous epileptiform discharges (Fig. 3A and B).

The potent and selective non-NMDA antagonist NBQX had no effect on either the frequency or amplitude of spontaneous epileptiform discharges at concentrations which block non-NMDA receptors (i.e., < 10 μM). At higher concentrations (10–100 μM), NBQX weakly (16%) attenuated the frequency of spontaneous epileptiform discharges ($IC_{50} > 100$ μM, $n = 4$) but was without effect on spontaneous epileptiform discharge amplitude (Fig. 3C).

MNQX, an antagonist at both the glycine site of the NMDA receptor and at the AMPA/kainate receptor, con-

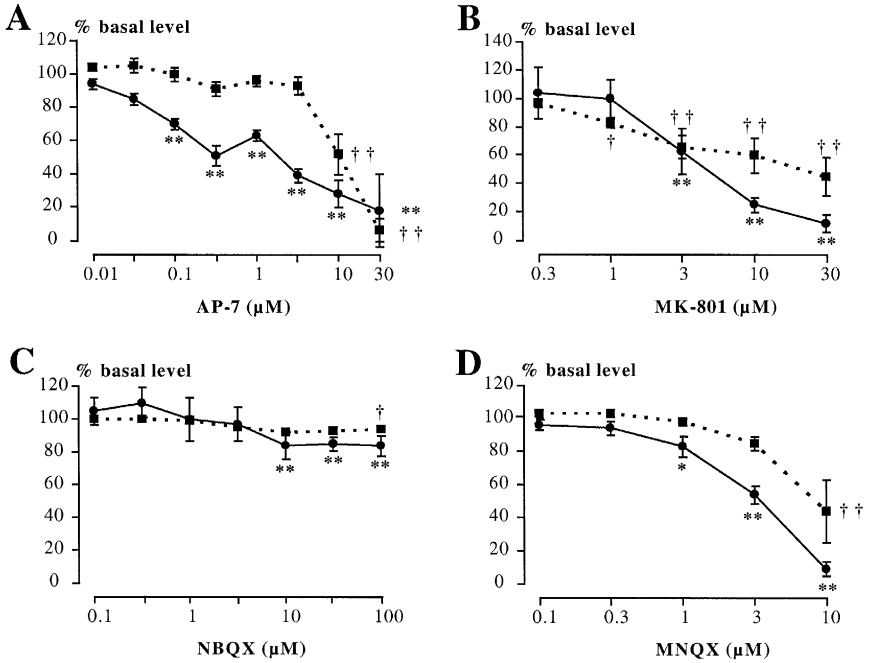

Fig. 3. Effects of glutamate receptor antagonists on spontaneous epileptiform discharges. (A–D) % Change from control frequency (—●—) and amplitude (· · · ■ · · ·) was determined over the final 4 min for each 10 min application of antagonist: (A) AP-7; (B) MK-801; (C) NBQX and (D) MNQX. * and † indicate significance at the 5% level, ** and †† indicate significance at the 1% level for frequency and amplitude, respectively.

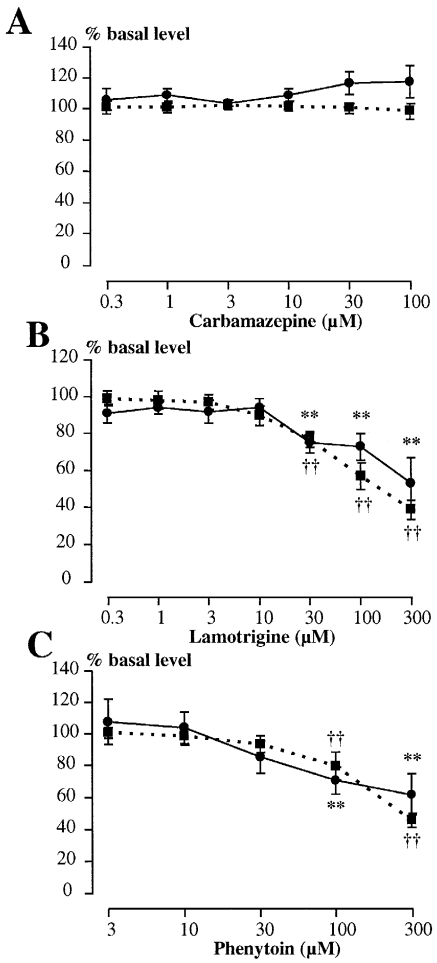

Fig. 4. Effects of anticonvulsants on spontaneous epileptiform discharge frequency and amplitude. (A–C) % Change from control spontaneous epileptiform discharges frequency (—●—) and amplitude (· · · ■ · · ·) was determined over the final 4 min for each 10 min application of: (A) carbamazepine; (B) lamotrigine and (C) phenytoin. ** and †† indicate significance at the 1% level for frequency and amplitude, respectively.

centration-dependently reduced both the frequency (IC_{50} (95% confidence limits): 3.2 μM (2.5, 4.2, $n = 6$)) and amplitude (IC_{50} (95% confidence limits): 7.5 μM (4.6, 12.3, $n = 6$)) of the spontaneous epileptiform discharges (Fig. 3D).

3.4. Effects of carbamazepine, lamotrigine and phenytoin on spontaneous epileptiform discharges

Carbamazepine had no effect on spontaneous epileptiform discharge frequency or amplitude at concentrations up to 100 μM (Fig. 4A). Lamotrigine concentration-dependently reduced both the frequency (IC_{50} values (95% confidence limits) 254 μM (152, 425, $n = 5$)) and amplitude (141 μM (81, 246, $n = 5$)) of spontaneous epileptiform discharges (Fig. 4B). Phenytoin also concentration-dependently reduced both the frequency and amplitude of spontaneous epileptiform discharges. However, the IC_{50} values were greater than 300 μM (Fig. 4C).

4. Discussion

The principal findings of this study, using the rat cortical wedge preparation, were as follows. Firstly, we confirmed that a number of selective and non-selective antagonists at NMDA and AMPA receptors blocked the depolarisation responses evoked by the appropriate selective agonists at these receptors. Secondly, we were able to demonstrate that the spontaneous epileptiform discharges elicited by removal of Mg^{2+} from the aCSF, were selectively attenuated by NMDA, but not AMPA receptor antagonists, confirming the role of Mg^{2+} in voltage-dependent NMDA receptor blockade and the control of spontaneous epileptiform discharges. Thirdly, the data presented here demonstrate that phenytoin, but not lamotrigine or carbamazepine, attenuate AMPA receptor-mediated depolarisations; however, none of these anticonvulsant drugs was able to fully antagonise responses to NMDA at concentrations less than 100 μM. Finally, although lamotrigine and phenytoin were not effective NMDA receptor antagonists, both drugs were able to attenuate the spontaneous epileptiform discharges following removal of Mg^{2+} from the aCSF. We deduce from this, that removing Mg^{2+} may facilitate spontaneous epileptiform discharge generation; however, the process probably occurs by both an NMDA and a non-NMDA receptor dependent mechanism that is sensitive to lamotrigine and phenytoin. Interestingly, despite the well known anticonvulsant actions of carbamazepine in animal models and in the clinic, it did not affect the spontaneous epileptiform discharges observed in the experimental conditions used here. However, the ability of lamotrigine and phenytoin to attenuate spontaneous epileptiform discharges generated by the removal of the voltage-dependent blockade of NMDA receptors by Mg^{2+} must therefore illustrate differences in the pharmacological actions of the three anticonvulsants tested.

Lodge et al. (1988), and subsequently Grimwood et al. (1991), have reported that AP-7 selectively antagonises NMDA receptor-mediated responses, with an IC_{50} of 11.1 μM and a pA_2 value of 5.3, respectively, in these two studies. In our experimental conditions, AP7 also selectively abolished NMDA receptor-mediated responses, with an IC_{50} of 8.1 μM, in close agreement with the above studies. Similarly, our finding that MK-801 selectively attenuated NMDA-induced depolarisations with an IC_{50} of 0.95 μM is in close agreement with the findings of Davies et al. (1988). MNQX potently blocked the responses to NMDA and the non-NMDA receptor agonists, AMPA and quisqualate. Consistent with the hypothesis that the spontaneous epileptiform discharges observed in this preparation are due to disinhibition of the NMDA receptor (Robichaud et al., 1991; Sheardown et al., 1989), the selective NMDA antagonists, AP7 and MK-801 and the non-selective NMDA receptor glycine site and AMPA receptor antagonist, MNQX, attenuated both the frequency (IC_{50} values 0.6, 4.2 and 3.2 μM, respectively) and amplitude (IC_{50}

values 10.1, 18.1 and 7.5 μM, respectively) of the spontaneous epileptiform discharges. These IC_{50} values for effects on spontaneous epileptiform discharges are concordant with the IC_{50} values for these compounds antagonising NMDA receptor-mediated responses. Conversely, the selective AMPA receptor antagonist, NBQX, potently antagonised responses to AMPA and quisqualate (IC_{50} values 0.3 and 0.4 μM, respectively), but had no effects on NMDA-elicited responses, nor did it alter spontaneous epileptiform discharges. These findings are in agreement with those of Palmer and Lodge (1991), Robichaud et al. (1992) and Lodge and Palmer (1994).

There were clear differences in the effects of the three anticonvulsants used in this study on NMDA and non-NMDA receptor-mediated responses. Lamotrigine had no effect on NMDA-evoked depolarisations. Baxter et al. (1990) has also reported that lamotrigine did not inhibit NMDA-evoked responses in drug discrimination and working memory tests in rats. Similarly, Leach et al. (1991) found that lamotrigine did not inhibit NMDA-stimulated formation of cyclic GMP in immature rat cerebellum. Additionally, AMPA receptor-mediated responses were only weakly altered by 100 μM lamotrigine (26% reduction of response to 10 μM AMPA). The present data, therefore, are in agreement with previously published observations using different paradigms.

The effect of phenytoin on NMDA-mediated responses was very weak ($IC_{50} \gg 300$ μM). This lack of effect of phenytoin on NMDA receptor-mediated responses is in good agreement with the findings of Lampe and Bigalke (1990) using cultured mouse spinal cord neurones, Laffling et al. (1995) using rat hippocampus in vitro and Kawano et al. (1994) using *Xenopus* oocytes that translated ddY-stock mouse brain mRNA. By contrast, Wamil and McLean (1993) reported that phenytoin concentration-dependently (0.8–80 μM) blocked responses to NMDA in cultured mouse spinal cord neurones, and Brown et al. (1994) reported that phenytoin concentration-dependently inhibited NMDA-stimulated [^{3}H]norepinephrine efflux from rat brain cortical slices, although significance was only obtained at 0.1 mg/ml (equivalent to 300 μM) Overall, however, the data favour the view that phenytoin has no effect on NMDA receptor-mediated responses.

Without question, phenytoin was, however, more potent in its blockade of responses to non-NMDA receptor agonists than against NMDA, a finding in agreement with Kawano et al. (1994). This may be an important feature in the anticonvulsant profile of phenytoin, as it has been suggested that non-NMDA glutamate receptor blockade results in the considerable enhancement of the efficacy of antiepileptic drugs (Zarnowski et al., 1993) and also, that even a weak blockade of non-NMDA receptors would attenuate seizures because of the interaction between non-NMDA and NMDA receptors (Kawano et al., 1994). To our knowledge, there is no comparative data on the effect of phenytoin on responses to AMPA/quisqualate.

Carbamazepine weakly attenuated responses to both NMDA and non-NMDA receptor agonists. The weak effect of carbamazepine at NMDA receptors (maximum of 16% at 30 μM) is not strikingly dissimilar to the findings of Lampe and Bigalke (1990) who reported that carbamazepine attenuated the response to NMDA by approximately 50% at 50 μM. Lancaster and Davies (1992), found that carbamazepine produced a marked reduction of responses to NMDA. This anomaly may be due to the techniques employed by the different investigators, Lancaster and Davies employed cortical wedges prepared from genetically epilepsy prone DBA/2 mice (21–30 days). Cortical wedges prepared from these DBA/2 mice may indicate that NMDA receptor function in these animals is a better reflection of the underlying mechanisms involved in epileptogenesis.

The differences in the ability of the three antiepileptics to attenuate spontaneous epileptiform discharge frequency and amplitude highlights a limitation of the rat cortical wedge preparation in predicting anticonvulsant efficacy in the clinic, because carbamazepine was without effect on epileptiform activity. Of the other compounds tested, lamotrigine was the most potent at attenuating both frequency and amplitude of spontaneous epileptiform discharges. This effect is unlikely to be due to the weak antagonism of non-NMDA glutamate receptors by lamotrigine, because we have shown that the potent non-NMDA receptor antagonist, NBQX, is without effect on spontaneous epileptiform discharge frequency or amplitude at concentrations which block non-NMDA receptors. The same is also true for phenytoin, which weakly attenuated responses to non-NMDA receptor agonists. However, it is possible that the ability of phenytoin to attenuate spontaneous epileptiform discharge frequency and amplitude may be due to its very weak attenuation of NMDA receptor-mediated responses. Carbamazepine was totally without effect on spontaneous epileptiform discharges, even though it significantly attenuated responses to NMDA at concentrations as low as 3 μM. However, the attenuation of NMDA responses by carbamazepine was only weak (10% reduction of the response to 30 μM NMDA at 100 μM carbamazepine) and it appears that this weak effect is insufficient to overcome the NMDA-driven spontaneous epileptiform activity.

In conclusion, the three antiepileptics investigated vary in their abilities to antagonise responses to NMDA or non-NMDA receptor agonists. Furthermore, these capabilities are unrelated to the blockade of spontaneous epileptiform discharges. Therefore, it seems likely that the mode of action of phenytoin, lamotrigine or carbamazepine in ambulant patients does not involve the antagonism of ionotropic glutamate receptors. However, the blockade of non-NMDA receptors by high concentrations of phenytoin may play a role in the anticonvulsant efficacy of phenytoin at high doses in status epilepticus. It is also apparent that compounds with potent anticonvulsant activity (e.g., carba-

mazepine) need not necessarily attenuate spontaneous epileptiform discharges in the rat cortical wedge, indicating that this particular model may not identify all potential anticonvulsant compounds.

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