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Gabapentin potentiation of the antiepileptic efficacy of vigabatrin in an *in vitro* model of epilepsy

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1 An enhancement of promoted release of γ-aminobutyric acid (GABA) and a change in GABA-metabolism have been suggested as mechanisms of action of gabapentin. Vigabatrin is supposed to act mainly via inhibition of GABA-transaminase but it also interferes with GABA-release and GABA-uptake. On the basis of these mechanisms of action, a pharmacodynamic interaction of the two antiepileptic drugs could be supposed which might be of relevance in the sense of a rational polypharmacy.

2 To address the aforementioned hypothesis, experiments were carried out on hippocampal slices ($n=107$) of guinea-pigs ($n=70$). Epileptiform field potentials (e.f.p.) were induced by omission of magnesium from the bath solution and recorded in the stratum pyramidale of the CA3 region. Gabapentin (30–600 μM; 5.1–102.72 μg ml^{-1}), vigabatrin (50–200 μM, 6.45–25.8 μg ml^{-1}) and the $GABA_A$-receptor antagonist bicuculline (100 μM) were added to the bath solution for 3 h.

3 Gabapentin, in concentrations up to 600 μM, failed to decrease the repetition rate or duration of e.f.p. ($n=19$). However, vigabatrin, evoked a dose-dependent reduction of the repetition rate of e.f.p. For a concentration of 100 μM (12.9 μg ml^{-1}) there was a reduction down to 48±5% (mean±s.e.mean) of the initial value within 3 h ($n=11$). With simultaneous administration of vigabatrin (100 μM) and gabapentin (60 μM) for 3 h ($n=15$), the repetition rate of e.f.p. decreased down to 8±3%, which is significantly different from the values obtained after administration of 100 μM vigabatrin alone ($P<0.0001$). Both, the antiepileptic effect of vigabatrin alone and the enhancement by gabapentin were blocked by the $GABA_A$-receptor antagonist bicuculline (100 μM, $n=16$).

4 These results demonstrate that gabapentin is able to augment the antiepileptic effects of vigabatrin significantly. It is possible that a change in the GABA-release machinery is induced by vigabatrin which then can be augmented by gabapentin.

Keywords: Vigabatrin; gabapentin; antiepileptic drugs; pharmacodynamic interactions; rationale polypharmacy; γ-aminobutyric acid (GABA); *in vitro* epilepsy model

Introduction

It is generally accepted that the gold standard of antiepileptic drug therapy is a monotherapy based on the accurate seizure diagnosis and delivered at the maximal tolerated dose which is necessary to control seizures. However, if monotherapy fails, polypharmacy is indicated for such difficult to treat epilepsies, which will account for about 20 to 30% of patients suffering from epilepsy. In order to choose the optimal combinations of antiepileptic drugs, pharmacokinetic and pharmacodynamic interactions have to be considered. An optimal combination of two antiepileptic drugs should be supra-additive concerning seizure protection and infra-additive concerning side effects (Bourgeois & Dodson, 1989). Recently, several new antiepileptic drugs have been released which are mostly tested as add-on therapy in patients with difficult to treat epilepsies. From clinical studies and *in vivo* animal experiments up to now, there has been little information available as to the pharmacodynamic interactions of new and conventional antiepileptic drugs or combinations of different new antiepileptic substances (Gordon *et al*., 1993; Perucca, 1995; DeSarro *et al*., 1996; McDonnell & Morrow, 1996). In this context, *in vitro* epilepsy models may be suitable to investigate the pharmacodynamic interactions of antiepileptic drugs. The *in vitro* models offer the chance to investigate in more detail the mechanism of action involved in the pharmacodynamic interactions. They might also provide the basis for the more invasive animal experiments *in vivo*, which can predict the side effects of combinations of antiepileptic drugs.

The aim of the present study was to examine the pharmacodynamic interaction of gabapentin and vigabatrin in an *in vitro* model of epilepsy, since their mechanisms of action make such an interaction very likely. Both an increase in γ-aminobutyric acid (GABA)-synthesis (Löscher *et al*., 1991; Bloms-Funke & Löscher, 1996) and GABA-release (Götz *et al*., 1993) have been suggested as mechanisms of action of gabapentin. The increase in GABA-release applies especially to situations where the equilibrium of the GABA-transport-system has been altered, resulting in a calcium-independent release of GABA (Kocsis & Honmou, 1994; Honmou *et al*., 1995a,b). Moreover, gabapentin has been shown to inhibit GABA-transaminase which metabolizes GABA to succinic semialdehyde and glutamate (Goldlust *et al*., 1995). However, it is not clear to what extent the reversible competitive and noncompetitive inhibition of the enzyme might be involved in the antiepileptic action of gabapentin, as a significant inhibition of the GABA-transaminase only occurs with high concentrations of gabapentin. The irreversible inhibition of the GABA-transaminase is believed to be the main anticonvulsant mechanism of vigabatrin (Jung *et al*., 1977). Nevertheless,

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vigabatrin has also been shown to increase GABA-release (Abdul-Ghani *et al*., 1980; Gram *et al*., 1989), to inhibit GABA-uptake (Löscher, 1980) and be a substrate for the GABA-transporter (Schousboe *et al*., 1986). As a whole, the proposed mechanisms of actions of the two antiepileptic drugs favour the assumption of a pharmacodynamic interaction. To verify this hypothesis, the effects of combinations of the two drugs on epileptiform activity induced in hippocampal slices of guinea-pigs were tested.

Methods

The experiments were performed on hippocampal slices ($n=107$) of guinea-pigs ($n=70$) weighing 300–400 g. The animals were deeply anaesthetized with methohexital (250 mg kg^{-1} body weight), the hippocampus was exposed and transverse slices of 500 μm thickness were cut with a McIlwain tissue chopper.

The slices were preincubated in warm (28°C) physiological solution (PS) equilibrated with 5% CO_2 in O_2. The PS contained (in mM): NaCl 124, KCl 4, NaH_2PO_4 1.24, $MgSO_4$ 1.3, $NaHCO_3$ 26, glucose 10 and $CaCl_2$ 1.0. After a pre-incubation period of 1 h, the slices were transferred to a submersion recording chamber. The slices were superfused with warm (32°C) PS, the composition of which was the same as above except that the $CaCl_2$ concentration was increased to 2.0 mM. The bath fluid was exchanged three to five times per minute. The pH values of all solutions were continuously monitored in the recording chamber and ranged between 7.4 and 7.5.

Field potentials were recorded from the stratum pyramidale of the CA3-region by use of glass micropipettes (filling solution: 150 mM NaCl; resistance 1 MΩ) and stored by means of a digital oscilloscope.

Epileptiform activity was induced by omitting magnesium from the control solution. Regular epileptiform activity was monitored for at least two hours before the addition of antiepileptic drugs. The antiepileptic drugs gabapentin (30–600 μM, 5.1–102.72 μg ml^{-1}; a gift from Parke-Davis, Freiburg, Germany) and vigabatrin (50–200 μM, 6.45–25.8 μg ml^{-1}, a gift from Hoechst Marion Roussel, Cincinnati, U.S.A.) and the $GABA_A$-receptor antagonist bicuculline (100 μM; Serva, Heidelberg, Germany) were added to the bath solution for 3 h and washed for 1 h.

All experimental data are given as mean ± s.e.mean and were tested for significant differences with Student's t test or Mann Whitney rank sum test at the level of $P=0.05$.

Results

Low magnesium-induced epileptiform discharges

As has been shown previously, the omission of magnesium from the control solution induced spontaneous epileptiform field potentials (e.f.p.) which were recorded in the stratum pyramidale of the CA3 region of hippocampal slices (Figures 1–4; Thompson & West, 1986; Mody *et al*., 1987; Tancredi *et al*., 1988; 1990; Traub *et al*., 1994). In most cases, e.f.p. appeared with regular repetition rate, and grouped activity developed only in some slices. Only slices with a regular discharge frequency were selected for further investigations. The e.f.p. were monophasic or biphasic (duration 272 ± 15 ms, peak-to-peak amplitude: 1.3 ± 0.1 mV) were sometimes superimposed by population spikes and occurred with a regular repetition rate of 10 ± 0.8 min^{-1} ($n=107$). In control experiments ($n=8$), the slices were incubated in magnesium-free solution for five hours. The epileptiform field potentials remained unchanged in duration and amplitude over this period of time. However, there was a significant increase in discharge frequency to about 200 ± 26% when the values obtained after two and five hours exposure to magnesium-free solution were compared (data not shown).

Effects of gabapentin on low-magnesium-induced epileptiform discharges

Application of gabapentin in concentrations of 30 and 60 μM for 3 h produced no antiepileptic effect (Figure 1, $n=9$ and 11, respectively). Thus, the amplitude and duration of e.f.p. remained unchanged (Figure 5b). However, there was a significant increase in the discharge frequency. With 30 μM gabapentin, the discharge frequency increased to 218 ± 33% and with 60 μM to 207 ± 26% of the initial value (Figure 5a). These effects were not reversible and also occurred in the control experiments mentioned in the first paragraph of the Results section. As there was no statistically significant difference between the control experiments and the experiments after addition of gabapentin, the increase in discharge frequency was not mediated by gabapentin. An elevation of the gabapentin concentration to 600 μM did not reveal an antiepileptic effect ($n=6$, data not shown).

Effects of vigabatrin on low-magnesium-induced epileptiform discharges

In contrast to gabapentin, vigabatrin dose-dependently suppressed low-magnesium-induced epileptiform discharges. Thus, at a concentration of 50 μM, vigabatrin reversibly reduced the repetition rate of e.f.p. down to 57 ± 13% of the initial value

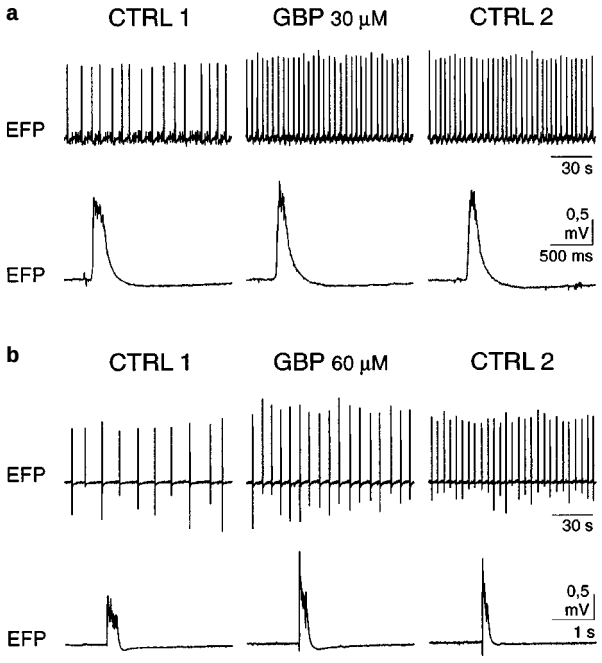

Figure 1 Missing antiepileptic effects of gabapentin (GBP; (a) 30 μM, (b) 60 μM) on epileptiform activity induced by omission of Mg^{2+} in hippocampal slices of guinea-pigs. Epileptiform field potentials (EFP) were recorded in the stratum pyramidale of the CA3 region and stored by a digital oscilloscope. CTRL1 and CTRL2 represent activity recorded before and 1 h after administration of gabapentin for 3 h, respectively. Scale bars apply to upper and lower traces.

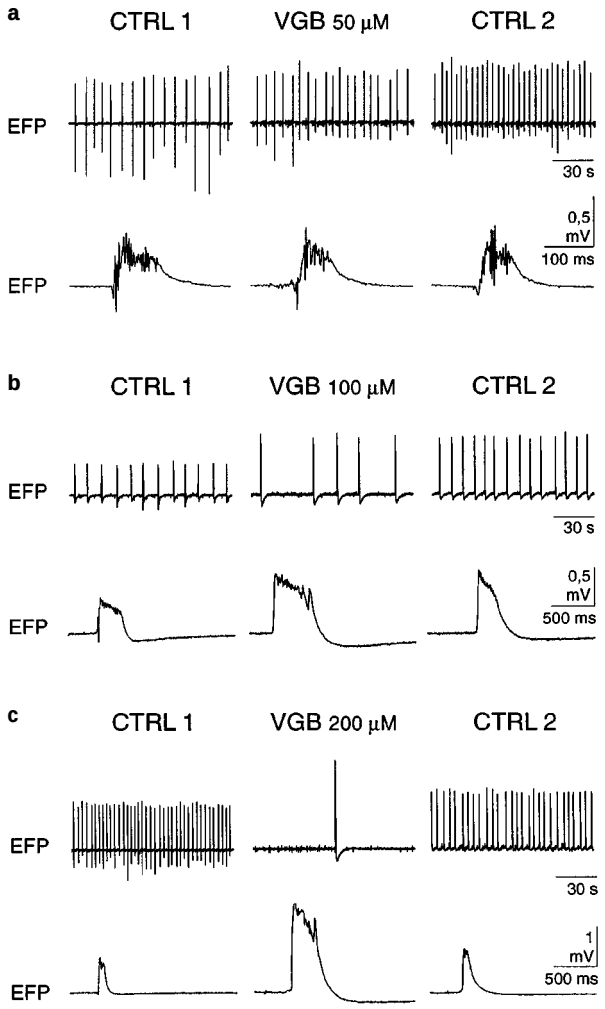

Figure 2 Dose-dependent antiepileptic effects of vigabatrin (VGB; (a) 50 μM, (b) 100 μM and (c) 200 μM) on epileptiform activity induced by omission of Mg^{2+} in hippocampal slices of guinea-pigs. Epileptiform field potentials (EFP) were recorded in the stratum pyramidale of the CA3 region and stored by a digital oscilloscope. CTRL1 and CTRL2 represent activity recorded before and 1 h after administration of vigabatrin for 3 h, respectively. Scale bars apply to upper and lower traces.

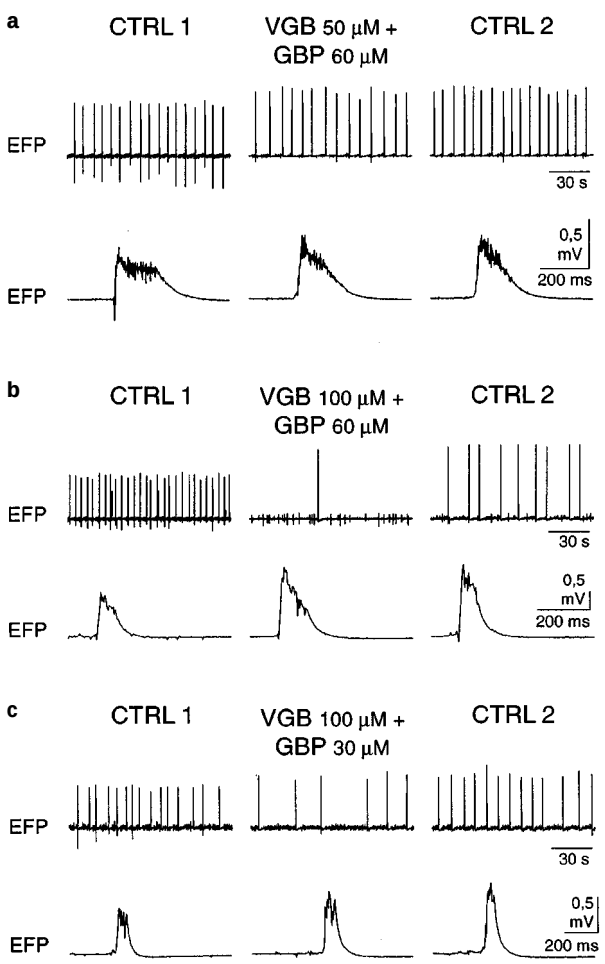

Figure 3 Antiepileptic effects of combined administration of vigabatrin (VGB) and gabapentin (GBP) in different concentrations on epileptiform activity induced by omission of Mg^{2+} in hippocampal slices of guinea-pigs. (a) VGB 50 μM and GBP 60 μM; (b) VGB 100 μM and GBP 60 μM; (c) VGB 100 μM and GBP 30 μM. Epileptiform field potentials (EFP) were recorded in the stratum pyramidale of the CA3 region and stored by a digital oscilloscope. CTRL1 and CTRL2 represent activity recorded before and 1 h after administration of vigabatrin and gabapentin for 3 h, respectively. Scale bars apply to upper and lower traces.

(Figure 2a and 5a, $n=8$). This effect was marginally significant ($P=0.05$). The amplitude or duration of e.f.p. remained unchanged (Figures 2a and 5b). Increasing the vigabatrin concentration to 100 μM evoked a significant and partly reversible reduction of the discharge frequency down to $47\pm5\%$ of the initial value (Figures 2b and 5a, $n=11$). This was accompanied by a significant but irreversible increase in the duration of e.f.p. to $140\pm13\%$ of the initial value (Figures 2b and 5b). A further elevation of the vigabatrin concentration to 200 μM enhanced the antiepileptic effects. Thus, the discharge frequency decreased to $10\pm6\%$ of the initial value (Figures 2c and 5a, $n=7$). As with 100 μM vigabatrin, this effect was highly statistically significant and partly reversible and was associated with a significant but irreversible increase in the duration of e.f.p. to $278\pm55\%$ of the initial value (Figures 2c and 5b).

Effects of simultaneous administration of gabapentin and vigabatrin on low-magnesium-induced epileptiform discharges

Even though gabapentin alone had no antiepileptic effect in the low-magnesium epilepsy model, it was able to enhance the antiepileptic effects of vigabatrin drastically. Thus, the addition of gabapentin (60 μM) to a solution containing 100 μM vigabatrin reduced the repetition rate of e.f.p. down to $7.4\pm2.5\%$ of the initial value (Figures 3b and 5a, $n=15$). This was a significant potentiation of the antiepileptic effects of vigabatrin alone, as in this concentration vigabatrin alone only reduced the discharge frequency down to $47\pm5\%$ (Figures 2b and 5a). The effect was only partly reversible as a wash of the two drugs only led to an increase of the discharge frequency to $31\pm7\%$ of the initial value (Figures 3b and 5b). The reduction of the discharge frequency induced by the combined administration of vigabatrin and gabapentin was accompanied by a significant but not reversible increase in the duration of e.f.p. to $175\pm24\%$ (Figures 3b and 5b). The enhancement of the antiepileptic efficacy of vigabatrin by gabapentin could not be observed with combinations of the two drugs in other concentrations. Thus, the antiepileptic efficacy of the combined administration of 50 μM vigabatrin and 60 μM gabapentin was not significantly different from the antiepileptic effects of 50 μM vigabatrin alone (Figures 3a and 5a,b; $n=6$). In contrast, there was a tendency towards a reduction of the antiepileptic effects of vigabatrin by gabapentin, since the

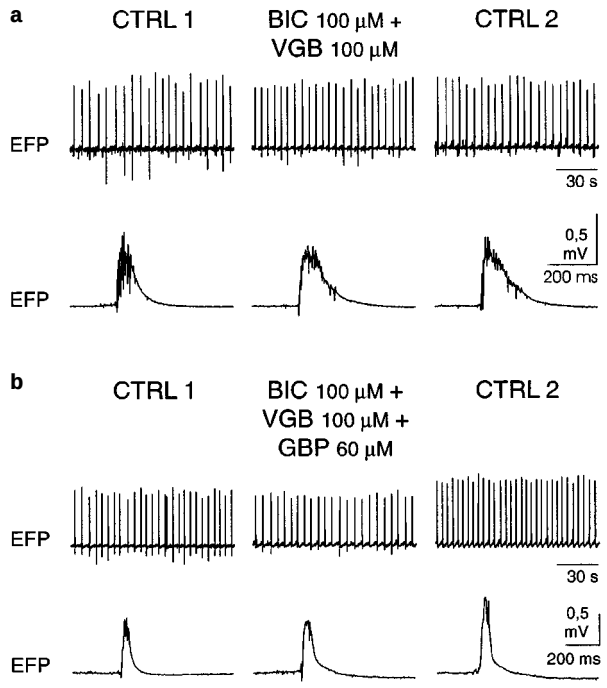

Figure 4 Blockade of antiepileptic effects of vigabatrin alone and vigabatrin (VGB) in combination with gabapentin (GBP) by the $GABA_A$-receptor antagonist bicuculline (Bic). (a) Bic 100 μM and VGB 100 μM; (b) Bic 100 μM, VGB 100 μM and GBP 60 μM. Epileptiform field potentials (EFP) were induced by omission of Mg^{2+} in hippocampal slices of guinea-pigs. They were recorded in the stratum pyramidale of the CA3 region and stored by a digital oscilloscope. CTRL1 and CTRL2 represent activity recorded before and 1 h after administration of the substances for 3 h, respectively. Scale bars apply to upper and lower traces.

combined administration of the two drugs in these concentrations did not evoke a significant antiepileptic effect, whereas the application of vigabatrin (50 μM) alone led to a marginally significant reduction of the discharge frequency. The same applies in principle to the combination of 100 μM vigabatrin and 30 μM gabapentin. On average, the repetition rate of e.f.p. was reduced to $57 \pm 17\%$ of the initial value (Figures 3c and 5a,b; $n = 7$), which was not significantly different from the antiepileptic effects of vigabatrin (100 μM) alone. However, the reduction in discharge frequency induced by the combined administration of 100 μM vigabatrin and 30 μM gabapentin was not statistically significant. This was due to the fact that in two of the seven slices tested there was no antiepileptic effect, whereas in two other slices there was a very strong reduction of the discharge frequency down to about 10% of the initial value. With this combination of the two drugs in some slices gabapentin had a tendency to reduce the antiepileptic effects of vigabatrin, whereas in others it enhanced the effects.

Effects of $GABA_A$-receptor blockade on antiepileptic efficacy of vigabatrin and gabapentin

To shed light on the mechanisms involved in the antiepileptic effects of vigabatrin and its combination with gabapentin in this epilepsy model, the role of the $GABA_A$-receptor was examined by adding bicuculline (100 μM) to the antiepileptic drugs. Bicuculline blocked the antiepileptic effect of vigabatrin (100 μM) alone and of vigabatrin (100 μM) in combination with gabapentin (60 μM). Thus, on addition of bicuculline to the antiepileptic drugs, no significant change in the repetition rate of e.f.p. could be observed (Figures 4a,b and 5a; $n = 6$ and $n = 10$, respectively). However, there was a significant and reversible increase in the duration of e.f.p. As mentioned

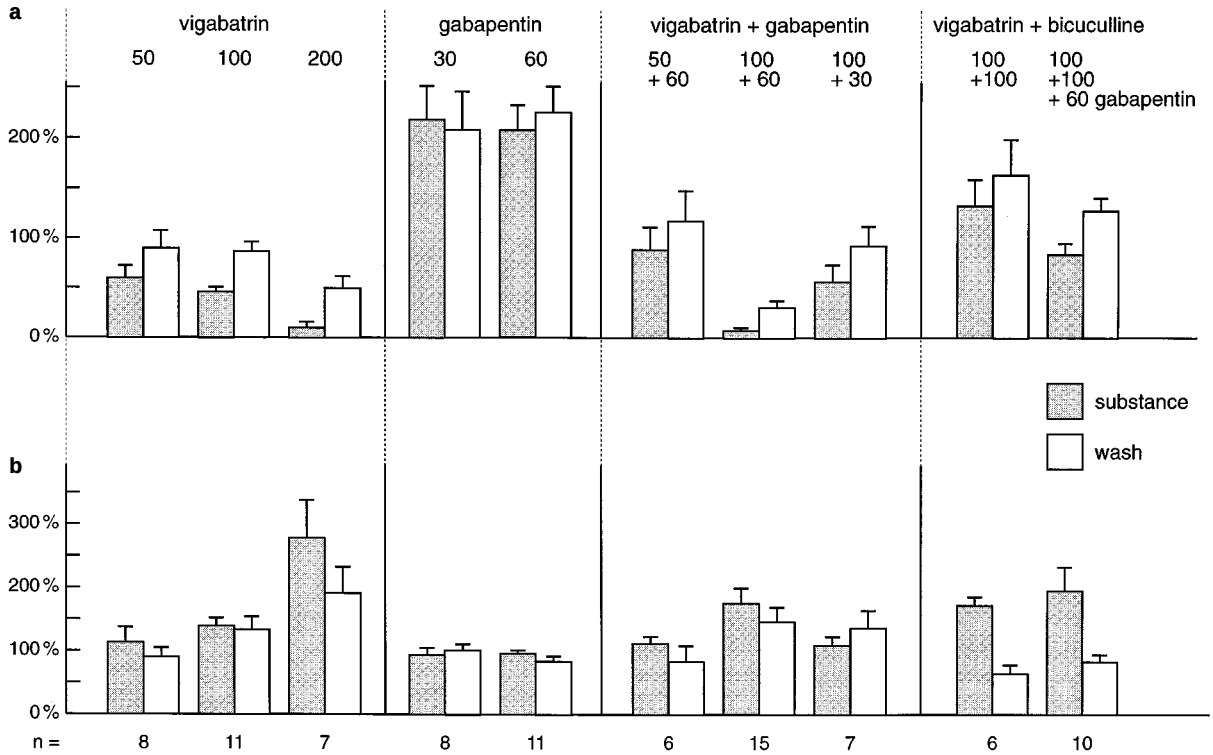

Figure 5 Statistical evaluation of the antiepileptic effects of vigabatrin, gabapentin, their combination and the simultaneous administration of the $GABA_A$-receptor antagonist bicuculline. Stippled columns indicate the percentage of the control value obtained after administration of the different drugs for 3 h and open columns after 1 h wash. (a) The effects on the repetition rate of e.f.p. and (b) the effects on the duration of e.f.p. Concentrations of the substances are given in μM. Each column shows the mean $\pm$ s.e.mean.

above, the increase in duration of e.f.p. occurred also after administration of vigabatrin alone or vigabatrin and gabapentin in combination. Compared with the data from these experiments, the increase in duration of e.f.p. was not significantly changed by addition of bicuculline. Administration of bicuculline (100 μM, 3 h) alone also had effects on the shape and repetition rate of e.f.p. Thus, the duration of e.f.p. increased significantly to $160 \pm 21\%$ and the repetition rate to $195 \pm 34\%$ of the initial values ($n = 8$, data not shown).

Discussion

The lack of any antiepileptic effects of gabapentin in the low-magnesium epilepsy model

In the low-magnesium epilepsy model, gabapentin even in supratherapeutic concentrations did not exert an antiepileptic effect. The increase in discharge frequency which occurred on the application of gabapentin cannot be interpreted as a proepileptic effect of gabapentin, as it was not reversible and also occurred in control experiments. Rather it seems that with prolonged omission of Mg^{2+} the epileptiform activity increases in severity (Dreier & Heinemann, 1990; Zhang *et al*., 1995; Whittington *et al*., 1995). Nevertheless, in different *in vivo* animal models gabapentin has been shown to prevent seizures. This applies especially to tonic extensor seizures induced by different chemical agents and to seizures induced by maximal electroshock (Taylor, 1995). In the low-magnesium epilepsy model an increase in the activity of the N-methyl-D-aspartate (NMDA)-receptor and a reduction of inhibitory responses play an important role (Traub *et al*., 1994; Whittington *et al*., 1995). Thus, a blockade of NMDA-responses (Mody *et al*., 1987; Tancredi *et al*., 1990) and an enhancement of $GABA_A$-mediated potentials blocks epileptiform discharges in this epilepsy model (Pfeiffer *et al*., 1996). From this it can be supposed that blockage of NMDA-responses or enhancement of GABA-mediated processes is not a major antiepileptic mechanism of gabapentin. The first conclusion is in good agreement with other data from the literature showing no consistent effect of gabapentin on NMDA-mediated responses (Rock *et al*., 1993). However, there are data indicating that gabapentin might indeed increase in one way or another the inhibitory system. This involves an increase in GABA-synthesis (Löscher *et al*., 1991; Bloms-Funke & Löscher, 1996) or GABA-release (Götz *et al*., 1993; Kocsis & Honmou, 1994; Honmou *et al*., 1995a,b). In the epilepsy model used here, these effects do not seem to be sufficient to suppress the epileptiform discharges. To compare the efficacy of gabapentin with other conventional antiepileptic drugs it should be borne in mind that the recurrent short discharges induced by omission of Mg^{2+} in hippocampal slices are sensitive to valproic acid, but do not respond to benzodiazepines, barbiturates, carbamazepine and phenytoin at clinically relevant concentrations (Heinemann *et al*., 1994).

Antiepileptic effects of vigabatrin in the low-magnesium epilepsy model

In contrast to gabapentin, vigabatrin exerted a dose-dependent antiepileptic effect on epileptiform discharges induced by omission of Mg^{2+} in hippocampal slices. The effect was marginally significant with vigabatrin concentrations of 50 μM, but very clear with 100 and 200 μM. A concentration of 100 μM (13 μg ml^{-1}) corresponds quite well to serum levels found in patients. As mentioned above, in this *in vitro* model of epilepsy, vigabatrin is more effective than most other antiepileptic drugs, except valproic acid. An increase of the inhibitory system induced by vigabatrin (Jung *et al*., 1997; Löscher, 1980; Abdul-Ghani *et al*., 1980; Schousboe *et al*., 1986) accords with the epileptogenic processes being of relevance in the low-magnesium model of epilepsy (Whittington *et al*., 1995; Pfeiffer *et al*., 1996). Furthermore, this is underlined by the finding that the antiepileptic effects of vigabatrin were blocked by simultaneous administration of bicuculline, as observed in the present study. However, investigations of the acute actions of vigabatrin on inhibitory potentials in hippocampal slices revealed that superfusion of vigabatrin in a concentration of 100 μM for 60 min resulted in a decrease of paired pulse inhibition and the appearance of multiple population spikes in the second response of a double pulse stimulation (Jackson *et al*., 1994). Furthermore, at a concentration of 500 μM vigabatrin induced a reduction in the amplitude of the inhibitory postsynaptic potential (i.p.s.p.) though vigabatrin evoked an increase in the total GABA-concentration of the slices by about 50% (Neal & Shah, 1990; Wadman & Nunes Filipe, 1992). These observations are in contrast to the hypothesis that vigabatrin mediates its antiepileptic effects via an increase of the inhibitory system. An explanation for this discrepancy might be as follows: firstly, it should be noted that the increase in excitability found with vigabatrin in the above quoted publications occurred after about 30 min, whereas we observed significant antiepileptic effects only after 2 to 3 h, which is in line with a maximal inhibiton of the GABA-transaminase. Secondly, another important point is that both studies mentioned examined inhibitory responses induced by electrical stimulation. The reduction in amplitude of electrically evoked IPSP brought about by vigabatrin is supposed to be due to the fact that vigabatrin is taken up into GABAergic terminals and produces dishinhibition by acting as a false transmitter, as it competes with GABA for release (Schousboe *et al*., 1986; Jackson *et al*., 1994). It might indeed be possible that evoked inhibitory potentials are reduced while for instance the frequency of spontaneous inhibitory potentials is increased. Thirdly, it has been shown that the effects of GABA-uptake on GABA-ergic inhibition are strongly frequency-dependent, as with low frequencies there is nearly no effect or even a reduction in amplitude of i.p.s.p. (Dingledine & Korn, 1985) and with high frequencies there is a strong enhancement of inhibition (Capek & Esplin, 1993). Probably the latter situation simulates the conditions during epileptiform discharges. However, the two studies mentioned above, did not use high frequency-stimulation so that it is difficult to apply their results to the conditions occurring with epileptiform discharges.

In the present study, two effects were striking with regard to the antiepileptic effect of vigabatrin in this epilepsy model: firstly, the antiepileptic effect was reversible and secondly, the reduction in discharge frequency went along with an increase in duration of epileptiform discharges. The reversibility of the antiepileptic effects of vigabatrin is in contrast to the irreversible inhibition of the GABA-transaminase induced by vigabatrin (Jung *et al*., 1997). This could mean that the effects of vigabatrin on GABA-uptake and GABA-release are more involved in the antiepileptic action of vigabatrin in this epilepsy model, since they have been shown to be reversible. On the other hand, washout of GABA induced by permanent superfusion of the slice could be involved in the reversibility of the antiepileptic effects. To answer this question, further neurochemical investigations are necessary, in which the concentration of GABA and the activity of the GABA-transaminase is determined at different phases of the

experiments. As mentioned above, it has already been shown that vigabatrin induces an increase in the GABA concentration of the whole slice (Neal & Shah, 1990; Wadman & Nunes Filipe, 1992), but it is not known what happens during washout of vigabatrin.

The reduction in frequency by vigabatrin was accompanied by an increase in duration of e.f.p. This inverse relationship between duration of e.f.p. and its frequency of occurrence is a well-known phenomenon which has been found previously (Tancredi & Avoli, 1987; Neuman *et al*., 1988; Tancredi *et al*., 1990). It has been suggested that depolarizing and hyperpolarizing afterpotentials, which follow the epileptiform discharges, are responsible for the cessation of epileptiform discharges and for the duration of the interval between the epileptiform discharges (Witte, 1994). The afterpotentials are to a great extent mediated by $GABA_A$- and $GABA_B$-receptors. A blockade of $GABA_A$-receptors has different effects upon the duration and frequency of e.f.p. depending on the concentration used. Thus, with 10 μM bicuculline the frequency of occurrence of e.f.p. induced by omission of Mg^{2+} increased (Pfeiffer *et al*., 1996), while with 20 μM there was a reduction in discharge frequency associated with an increase in duration of e.f.p. (Tancredi *et al*., 1990). In the present study, with a bicuculline concentration of 100 μM, we observed an increase in duration of e.f.p. along with an increase in discharge frequency. It is astonishing that the blockade of $GABA_A$-receptors induced by biculline as well as the increase in GABA-concentration evoked by vigabatrin are both associated with an increase in duration of e.f.p. However, the increase in GABA-concentration evoked by vigabatrin might induce a desensitization of $GABA_A$-receptors (Numan & Wong, 1984; Huguenhard & Alger, 1986) and/or a feedback inhibition of GABA-release due to the activation of presynaptic $GABA_B$ autoreceptors (Deisz & Prince, 1989). Moreover, vigabatrin being a substrate for the GABA-transporter might produce disinhibition by acting as a false transmitter, as mentioned above. The blockade of $GABA_A$-receptors induced by bicuculline and the disinhibition induced by vigabatrin could both be involved in a reduction of $GABA_A$-receptor-mediated afterpotentials and thus, result in an increase in the duration of e.f.p.

Nevertheless, it is still possible that the antiepileptic effect of vigabatrin is mediated by the enhancement of the GABAergic system as it might selectively reinforce inhibition during hyperactivity, as has been shown for other GABA-uptake inhibitors (Capek & Esplin, 1993).

Enhancement of antiepileptic effects of vigabatrin by gabapentin

The addition of gabapentin (60 μM) to a solution containing 100 μM vigabatrin led to a strong increase in antiepileptic efficacy of vigabatrin. It is very likely that this is not a simple additive effect of the two drugs, since a combination of 50 μM vigabatrin and 60 μM gabapentin had no synergistic effect with regard to antiepileptic efficacy. For a positive interaction of vigabatrin and gabapentin it seems necessary that, firstly, vigabatrin induces a change in the GABA-release machinery which might then be potentiated by gabapentin. In this context, vigabatrin, similar to nipecotic acid, is known to be a substrate for the GABA-transporter (Schousboe *et al*., 1986) and has been shown to have an intrinsic GABA releasing action (Abdul-Ghani *et al*., 1980). As has been shown for nipecotic acid and gabapentin (Kocsis & Honmou, 1994, Honmou *et al*., 1995a,b), it is possible that the increase in release of GABA induced by vigabatrin is augmented by gabapentin. In addition, vigabatrin and gabapentin could have an additive effect with regard to the inhibition of GABA-transaminase, since gabapentin has also been shown to inhibit this enzyme (Goldlust *et al*., 1995). However, in this context it has been shown that the inhibition of GABA-transaminase by gabapentin only occurs at high concentrations and at lower concentrations gabapentin probably has no significant effect on GABA-transaminase. Further neurochemical experiments, in which the GABA content of the slices and activity of GABA-transaminase are determined, are needed to clarify the mechanisms of the interaction between gabapentin and vigabatrin.

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