

The effect of valproate on silent period and corticomotor excitability

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ABSTRACT – Objective. To investigate, by transcranial magnetic stimulation, the effects of valproate on silent period and corticomotor excitability. **Methods:** thirty patients with generalized epilepsy were studied at baseline, and re-examined 4 (S1) and 25 (S2) weeks after the administration of valproate (mean dose: 1040 ± 284 mg). Transcranial magnetic stimulation was performed with a figure of eight coil (recording, first dorsal interosseous). Threshold was measured at 1% steps. Silent period was measured using a recently described protocol. Briefly, silent periods were elicited at 5% increments from 0 to 100% maximum stimulus intensity. At each stimulus intensity, 4 silent periods were obtained and the average value of silent period duration was used to construct a stimulus/response curve of stimulus intensity versus silent period. The resulting curves were then fitted to a Boltzman function and were statistically compared. The motor-evoked potential recruitment curve was constructed under active conditions and analyzed in a similar way. **Results.** Valproate increased threshold from $36.5 \pm 5.99\%$ at baseline to $41.02 \pm 7.84\%$ at S1 ($p < 0.0001$, paired t-test). The maximum value of the silent period curve decreased from 257.5 ± 3.9 ms at baseline to 230.3 ± 3.9 ms at S1 ($p < 0.0001$, F-test and AIC) while the other best-fit values (V_{50} , slope, threshold) were not significantly affected. Regarding the motor-evoked potential recruitment curve, the maximum value decreased significantly post-drug (from 0.449 ± 0.007 to 0.392 ± 0.009 , $p < 0.01$, F-test and AIC test), whereas the rest of the best-fit values remained unaffected. **Conclusion.** In patients with idiopathic generalized epilepsy, valproate increases threshold and reduces the maximum values of the silent period curve and the motor-evoked potential recruitment curve. These findings probably reflect valproate's effects on voltage-dependent Na^+ channels, as well as an activation of GABA_A receptors.

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Transcranial magnetic stimulation (TMS) is a non-invasive, neurophysiological technique considered to be highly promising as an *in vivo* test of the effects of antiepileptic drugs (AEDs) on cortical excitability. In its most simple version, it involves the generation of a brief, time-varying magnetic field over the head. The magnetic field, unattenuated by the scalp and skull, induces an electric field within the cerebral cortex that depolarizes cortical neurons, including those of central motor pathways. As a result, a motor-evoked potential (MEP), as well as inhibitory phenomena such as silent period (SP) may then be recorded from limb muscles.

Over the last 15 years, a number of TMS studies have established that AEDs produce different patterns of effects on various TMS parameters, and suggested that these patterns may correlate with the basic modes of action of these drugs. For instance, AEDs which enhance the action of GABA (*i.e.* vigabatrin) increase intracortical inhibition but have no effect on corticomotor threshold. In contrast, AEDs which block voltage-gated sodium or calcium channels (*i.e.* phenytoin) increase corticomotor threshold without significant effects on intracortical excitability (Ziemann 2005).

Valproate (VPA) is one of the most commonly used drugs in the treatment of epilepsy, in migraine prophylaxis, as well as in the therapy of mood disorders. Despite the extensive clinical use of VPA, its effects on human CNS excitability have not been studied in detail with TMS. Accordingly, the present study was designed in order to investigate, by TMS, the effects of VPA on silent period (SP) and corticomotor excitability in patients suffering from idiopathic generalized epilepsy (IGE).

Subjects and methods

Thirty, newly diagnosed patients with IGE (16 females, median age 25 yrs, range:16-41) entered the study after giving informed consent for the procedures which were approved by an institutional review board. Using the new diagnostic International League Against Epilepsy scheme (Engel and International League Against Epilepsy (ILAE) 2001), seven patients were diagnosed with juvenile myoclonic epilepsy (JME), 10 patients with idiopathic generalized epilepsy with generalized tonic-clonic seizures only, three with juvenile absence epilepsy, and the rest as suffering from idiopathic generalized epilepsy syndromes that could not be better defined.

Patients were studied at baseline and re-examined 4 ± 1 weeks after commencement of VPA therapy (study session S1, mean dose: 1040 ± 284 mg). Twenty-three patients were additionally examined 24.9 ± 7.5 weeks post-drug (session S2) and were divided into a subgroup receiving identical VPA doses at S1 & S2 ($n = 14$, mean dose: 984 ± 285 mg), and a subgroup which received increased

VPA doses at S2 compared to S1 ($n = 9$, mean dose: 1158 ± 187 mg at S2 versus 717 ± 218 mg at S1).

The parameters investigated in the study included corticomotor threshold, silent period (SP) and the motor-evoked potential (MEP) recruitment curves.

Corticomotor threshold was measured in all patients and compared with reference values obtained using identical methodology in 82, neurologically normal subjects (39 females, median age = 19 yrs, range: 12-65) as previously reported in a repeatability study of threshold measurements (Kimiskidis *et al.* 2004). SP and the MEP recruitment curves were recorded in 14 patients (6 females, median age 26 yrs, range: 17-40), including 7 patients with JME and 7 IGE patients with generalized tonic-clonic seizures only. The results of the patient group were compared with a control group comprising 13 healthy, age-matched subjects (5 females, median age 29 yrs, range: 19-44). All electrophysiological examinations were performed at least 72 hours after the occurrence of an epileptic seizure so as to minimize the effect of post-ictal threshold changes (Delvaux *et al.* 2001). None of the participants was taking centrally acting drugs, save for VPA, and in all cases both hemispheres were examined at approximately the same time of day (14:00-16:00) so as to increase the repeatability of the measurements.

MEPs were recorded with surface electrodes from the first dorsal interosseous muscle (FDI). Transcranial magnetic stimulation was performed with a Magstim 200 stimulator (Magstim, Dyfed, Wales) and a 70 mm diameter figure-of-eight coil (Magstim type 9925). The center of the linear contiguous segment of the coil was placed 5 cm lateral to the vertex on the interaural line and then the coil was angled 45° to the parasagittal level so that current in the central segment flowed toward the midline. It has been previously shown that this positioning and orientation is the optimum for the excitation of the motor hand area (Mills *et al.* 1992).

Corticomotor threshold was defined at rest in 1% steps using the method of Mills and Nithi (Mills and Nithi 1997) which determines two stimulus intensity levels designated lower (LT) and upper (UT) threshold. Briefly, LT corresponds to the highest intensity which evokes motor-evoked potentials (MEPs) with a probability of zero, whereas UT is the lowest intensity that evokes MEPs with a probability of unity. Mean threshold (MT) is the arithmetic mean of UT and LT.

SPs were obtained by the following procedure. Subjects performed an isometric contraction at 50% maximum voluntary contraction (MVC) and were specifically instructed to maintain the force constant after the magnetic stimulus until requested to relax. Stimuli were given 3 s after the target force was attained and were repeated every 15 s. To avoid the occurrence of fatigue, left and right hemisphere stimulation was alternated. To measure the duration of SP, its onset was defined as the onset of the

MEP and the endpoint coincided with the recurrence of EMG activity in individual trials.

The SP data were analyzed using a recently described method (Kimiskidis *et al.* 2005). Briefly, stimulus/response (S/R) curves of SP duration against stimulus intensity (SI) were constructed using a wide range of SIs (from 5 to 100% maximum SI in 5% increments). At each SI, 4 SPs were obtained and the average value of SP duration was used to construct the S/R curve. Stimuli of different intensity were applied in random order to avoid serial order effects. As recently shown, the resulting S/R curves are sigmoidal (Kimiskidis *et al.* 2005). Therefore, the Boltzman function was used to fit these data by the Levenberg–Marquard, non-linear, least-mean-square algorithm. The Boltzman function is given by the equation:

$$Y = \text{Min} + (\text{Max} - \text{Min}) / \left(1 + e^{\frac{V_{50}-x}{\text{slope}}} \right)$$

where Y is SP duration and X is SI, Min and Max are the minimum and maximum values of SP duration, V_{50} is the SI at which SP duration is halfway between Min and Max, and slope is a measure of the steepness of the curve. The threshold for eliciting SPs (SP Θ) was estimated by fitting the data on the steepest part of the Boltzman curve by a straight line. SP threshold, essentially the x-intercept, was then calculated from linear regression analysis.

The MEP recruitment curve was constructed under active conditions, as previously described (Kimiskidis *et al.* 2005). Briefly, magnetic stimulation was performed in 5% steps from 5–100% maximum stimulator output and at each SI, four MEPs were obtained. In addition, the ulnar nerve was supramaximally stimulated at the wrist bilaterally, and the amplitude of the resulting compound motor action potentials (CMAPs) was measured. MEP/CMAP amplitude ratios were calculated and used for the construction of normalized MEP recruitment curves. The data were then fitted with a Boltzman function and the best-fit values (Max, V_{50} , slope, threshold) were calculated.

Statistical analysis was performed using commercially available statistical packages (SPSS for Windows version 11; SPSS, Chicago, IL, USA and GraphPad Prism version 4, San Diego, CA, USA). Normality of data distribution was tested using the Kolmogorov-Smirnov test. Corticomotor threshold comparisons between the patient and the control group were performed using a Welch corrected unpaired t-test. The effects of VPA on threshold (Thr) were tested by repeated-measures analysis of variance (ANOVA) and the paired t-test. In order to control for the effect of multiple comparisons, the Bonferroni adjustment was applied. The SP curves and the MEP recruitment curves before and after VPA administration were compared using an F-test and Akaike's Information Criterion (AIC) (Motulsky and Christopoulos 2003). Differences were considered significant if $p < 0.05$.

Results

At baseline, UT, MT and LT in the patient group were significantly lower compared to the control group ($40.28 \pm 6.69\%$ versus $45.69 \pm 8.31\%$, $36.5 \pm 5.99\%$ versus $41.08 \pm 7.85\%$ and $32.51 \pm 5.77\%$ versus $36.49 \pm 7.67\%$, respectively, $p < 0.01$, Welch corrected unpaired t-test).

After VPA administration, UT, LT and MT increased significantly (table 1). For instance, MT increased from $36.5 \pm 5.99\%$ at baseline to $41.02 \pm 7.84\%$ at S1 ($p < 0.0001$, paired t-test). These data prove that VPA increased corticomotor threshold at a group level by approximately 5% maximum stimulator output. However, they do not give us any information regarding threshold changes on an individual level. In particular, they do not answer the clinically important question of, in which specific subjects did VPA elevate threshold significantly? The only way to answer this question is to use the measurement error, which is the value below which the difference in duplicate measurements will lie with a probability

Table 1. VPA-induced corticomotor threshold changes.

Whole group (n = 30)	Baseline	S1	S2
UT(%)	40.28 ± 6.69	$45.77 \pm 8.08^{***}$	
MT(%)	36.5 ± 5.99	$41.02 \pm 7.84^{***}$	
LT(%)	32.51 ± 5.77	$36.79 \pm 7.52^{***}$	
Stable dose surgroup (n = 14)			
UT(%)	40.74 ± 7.1	$44.77 \pm 8.55^*$	46.29 ± 9.37
MT(%)	36.63 ± 6.4	$40.35 \pm 7.8^*$	42.01 ± 8.45
LT(%)	32.4 ± 6.14	$35.88 \pm 7.57^*$	37.77 ± 8.05
Increasing dose surgroup (n = 9)			
UT (%)	40.9 ± 4.9	$45.88 \pm 6.1^{***}$	$49.78 \pm 7.3^{**}$
MT(%)	37 ± 3.3	$41.7 \pm 5.6^{***}$	$45.55 \pm 6.8^{**}$
LT(%)	33.07 ± 3.9	$37.38 \pm 5.2^{***}$	$41.12 \pm 6.4^{**}$

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

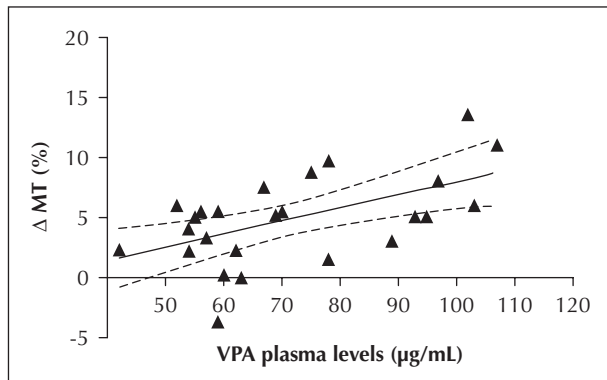


Figure 1. Correlation and regression line with 95% confidence interval between plasma VPA levels and Δ MT ($n = 25$ subjects, $y = -2.9 + 0.1x$, $r = 0.56$, $p < 0.005$).

of 95%. Then, the percentage of subjects with MT changes (Δ MT) exceeding this particular value can be calculated. It has recently been shown that the MT measurement error is 8 (Kimiskidis *et al.* 2004), and therefore VPA increased threshold significantly in 20.7% of the patient population. Mean Δ MT was 5% with maximum and minimum values of -4% and 20%, respectively.

Δ MT did not correlate with the daily VPA dose (Spearman $r = -0.038$, 95% CI: -0.330 to +0.259, $p > 0.05$) but correlated moderately with plasma VPA levels (Pearson's $r = 0.56$, 95% CI: 0.12 to 0.81, $p < 0.005$) (figure 1).

In the subgroup of patients who were re-examined twice at a stable VPA dose ($n = 14$), MT increased from $36.63 \pm 6.4\%$ at baseline to $40.35 \pm 7.8\%$ at S1 ($p < 0.05$), while no further increases occurred at S2 ($42.01 \pm 8.45\%$, $p > 0.05$, ANOVA and Tukey-Kramer post-test).

In contrast, in the subgroup of patients ($n = 9$) who were repeatedly studied at increasing VPA doses, corticomotor threshold was progressively elevated. MT, for instance, increased from $37 \pm 3.3\%$ at baseline to $41.7 \pm 5.6\%$ at S1 and $45.55 \pm 6.8\%$ at S2 (baseline versus S1, $p < 0.001$ and S1 versus S2, $p < 0.01$; ANOVA and Tukey-Kramer post-test).

The MT increase in the VPA-treated subjects was not the result of test repetition, as in the control group the duplicate measurements were very repeatable with the mean Δ MT being -0.03% at S1 (95% CI: -1.12 to $+1.06$) and 0.15 at S2 (95% CI: -0.98 to $+1.28$) (paired t-test, $p > 0.05$).

At baseline, the SP S/R curve of the patients was significantly different compared to 13, age-matched controls ($p < 0.0001$, F-test and AIC). In particular, the Max value of the patients' curve was 257.5 ± 3.98 ms versus 221.4 ± 2.89 ms in the controls ($p < 0.0001$) and V_{50} was 46.95 ± 0.71 versus 51.03 ± 0.57 ($p < 0.0001$), whereas slope was not significantly different (9.94 ± 0.58 versus 10.09 ± 0.46 , $p > 0.05$).

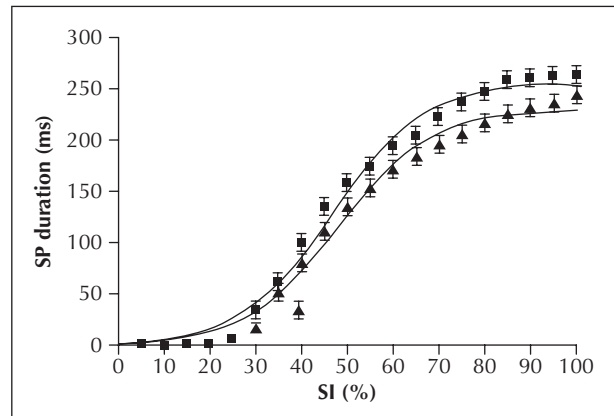


Figure 2. Silent period (SP) stimulus/response (S/R) curves before (■) and after (▲) the administration of valproate (VPA).

Following the administration of VPA, the Max value of the S/R curve decreased from 257.5 ± 3.9 ms at baseline to 230.3 ± 3.9 ms at S1 ($p < 0.0001$, F-test and AIC) (figure 2). The other best-fit values of the S/R curves (V_{50} , slope, threshold) were not significantly affected (46.95 ± 0.71 versus 47.95 ± 0.77 , 9.94 ± 0.58 versus 9.88 ± 0.64 and 24.68% versus 25.51% ; $p > 0.05$, F-test). The active MEP recruitment curve (figure 3) of the patients at baseline had the following best-fit values: Max = 0.4497 ± 0.007 , $V_{50} = 38.71 \pm 0.61$, slope = 4.457 ± 0.53 and threshold = 27.32% . Drug administration decreased significantly the Max value (0.3920 ± 0.009 ; $p < 0.01$, F-test and AIC test), whereas the rest of the best-fit values remained unaffected ($V_{50} = 38.93 \pm 0.85$, slope = 3.765 ± 0.64 , threshold = 28.81% , $p > 0.05$). Visual inspection of the MEP curve suggests that the effect of VPA was maximal at the higher range of stimulus intensities ($> 50\%$).

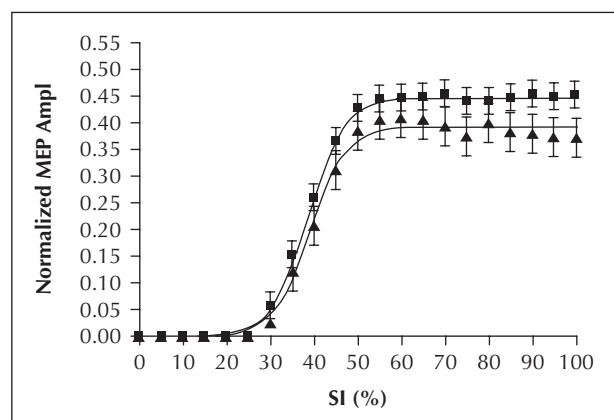


Figure 3. Active motor evoked potential (MEP) recruitment curves at baseline (■) and following valproate (VPA) (▲) administration.

Discussion

The present TMS study demonstrated that VPA, when chronically administered in patients with IGE, induces changes in SP and corticospinal excitability. In particular, corticomotor threshold increases post-drug, and the Max value of the SP S/R curve and the MEP recruitment curve is reduced. The other best-fit values of the S/R curves remained unaffected.

A number of previous studies investigated the effects of VPA on corticospinal excitability (Reutens *et al.* 1993, Nezu *et al.* 1997, Ziemann *et al.* 1998). From a methodological point of view, these studies can be classified according to the duration of drug administration (*i.e.* acute versus chronic studies), and the population under study (*i.e.* epileptic patients versus healthy volunteers). Pharmacology-TMS studies involving healthy subjects are theoretically preferable as any observed effects should be ascribed to a drug action *per se* rather than to brain pathology. On the other hand, studies with healthy subjects are usually performed in the acute setting because of the obvious ethical concerns associated with the prolonged administration of a drug at clinically used doses purely for scientific purposes. The results of these acute studies, however, may not be applicable to clinical practice given the various changes induced by the chronic administration of a drug for instance in receptor density or the rate of metabolism (Lee *et al.* 2005). This issue is particularly relevant to VPA studies as experimental and clinical observations suggest that the maximum antiepileptic action of this drug occurs with significant hysteresis compared to the attainment of therapeutic drug levels (Lockard and Levy 1976, Rowan *et al.* 1979, Bourgeois *et al.* 1987). Accordingly, chronic pharmacology-TMS studies in patients with epilepsy may offer useful information provided their limitations are taken into account.

In the present study, the chronic administration of VPA in patients with IGE resulted in elevation of the corticomotor threshold. This finding is in accord with the results by Reutens *et al.* (Reutens *et al.* 1993), who investigated 10 patients with generalized epilepsy before and 4 months after commencement of valproate therapy and observed a threshold increase of $8 \pm 2\%$. Nezu *et al.* (Nezu *et al.* 1997) investigated 4 previously untreated patients with benign childhood epilepsy with centro-temporal spikes, before and within the month after the administration of valproate and observed an increase in threshold of $15 \pm 4.1\%$ (range: 10-20%). In contrast to the above studies, Ziemann *et al.* (Ziemann *et al.* 1998), reported that the acute administration of 1200 mg VPA *p.o.* in healthy volunteers did not affect motor system excitability as assessed by various TMS measures including corticomotor threshold. The authors suggested that the lack of an effect may be explained by a too low loading dose and by the delayed antiepileptic effect of VPA. This discrepancy highlights the importance of performing chronic pharmacology-

TMS studies, in addition to acute ones, when investigating the effects of AEDs.

The observation that VPA elevates corticomotor threshold is similar to the findings of previous acute TMS studies with phenytoin (Chen *et al.* 1997), carbamazepine (Ziemann *et al.* 1996) and lamotrigine (Ziemann *et al.* 1996, Boroojerdi *et al.* 2001), as well as a single chronic study of carbamazepine and lamotrigine in healthy volunteers (Lee *et al.* 2005). Threshold is thought to reflect axonal excitability, which depends primarily on ion channel conductivity (Ziemann 2005). Phenytoin, carbamazepine and lamotrigine cause a voltage- and frequency- dependent block of sodium-dependent action potentials, which stabilizes neuronal membranes and increases threshold. The mode of action of VPA has not been fully elucidated. Although most experimental studies emphasized the effect of VPA on the GABA system, the drug has multiple *in vitro* pharmacological actions including blockade of sodium currents and high-frequency repetitive firing (McLean and McDonald 1986). The similar effects of VPA and sodium channel blockers on corticomotor threshold may suggest therefore that membrane stabilization via sodium channel inhibition is a relevant mechanism of action of VPA *in vivo*.

The VPA-induced elevation of corticomotor threshold correlated with the plasma levels. This correlation, however, is moderate, as previously noted in other studies (Reutens *et al.* 1993, Nezu *et al.* 1997), possibly due to the high diurnal variation of VPA plasma levels, the presence of active metabolites or a poor correlation between brain and plasma concentrations.

In the subgroup of patients who were re-examined twice at stable VPA plasma levels, no threshold changes were detected between the two sessions. The impetus for serially investigating this subgroup of patients was provided by an interesting phenomenon associated with the clinical use of VPA. As Bourgeois *et al.* (Bourgeois *et al.* 1987) first noted in a large study of 118 patients with IGE, the cumulative percentage of patients achieving seizure control, as well as the percentage of EEGs devoid of paroxysmal discharges, increase in time despite maintaining stable VPA blood levels. These investigators observed that between two follow-up visits, at least 6 months apart, the percentage of pathological EEGs was reduced from 48% to 32% and the cumulative percentage of seizure-free patients increased from 60% to 83% while VPA serum levels were unchanged (61.2 ± 19.6 and 63.8 ± 14.6 $\mu\text{g/ml}$, respectively). Subsequent experiments investigating the mechanisms underlying this phenomenon concluded that whereas the rapid anticonvulsant action of VPA is due to an effect on extracellular sites (*i.e.* ion channels), the late anticonvulsant effect of the drug is most likely explained by slow access to intracellular sites of action (for instance affecting the synthesis of GABA) (Löscher 2002).

The present study was not designed to investigate the correlation between clinical efficacy and drug-induced

electrophysiological changes. However, a progressive improvement in clinical and EEG parameters did occur in our patient population and therefore our results indicate that the improvement is not accompanied by progressive changes in corticomotor threshold in patients with stable VPA blood levels. This finding implies that the late anti-epileptic action of VPA is not closely correlated with threshold changes as indeed would be expected for a phenomenon that is not mediated by an effect on ion channels. It remains to be seen whether other TMS parameters affected by VPA (*vide infra*) are better electrophysiological markers of the clinical efficacy of the drug.

The shortening of SP following VPA administration in epileptic patients is an intriguing finding not previously reported. Other studies investigating the influence of VPA on SP have either found no effect, when performed in healthy volunteers (Ziemann *et al.* 1998) or were inconclusive in this respect, as in the study by Ertas *et al.* (Ertas *et al.* 2000). In this latter study, the absence of pre-drug measurements of SP renders the results difficult to interpret.

One can only speculate about the etiology of the shortening of SP induced by VPA. According to current thinking, SP represents a TMS-evoked intracortical inhibition mediated principally by GABA_B receptors (Ziemann 2005). Basic neurophysiology studies suggest that the amplitude of GABA_B IPSPs is compromised by the concurrent activation of GABA_A receptors (Thomson and Destexhe 1999, Crunelli *et al.* 1988, Lopantsev and Schwartzkroin 1999). Various mechanisms have been put forward to explain this latter phenomenon including blockade by raised intracellular Cl⁻ of the G-protein activation of the K⁺ channels associated with the GABA_B receptors, or by Cl⁻ channel shunting of lower conductance events such as GABA_B IPSPs.

Interestingly, a reduction in SP duration has been described previously with diazepam, a GABA_A receptor-positive, allosteric modulator (Inghilleri *et al.* 1996). An action of VPA at the GABA_A receptor is considered equivocal (Löscher 2002). Nevertheless a number of recent studies have provided evidence supporting such an effect and focusing particularly on the benzodiazepine regulatory site. For instance, VPA prolongs GABA currents in hippocampal and cerebellar granule neurones, and similarly to the benzodiazepine clonazepam, reverses the inhibition of these currents induced by β -carbolines (Rigo *et al.* 2002). In addition, VPA prolongs the decay time of sIPSCs in entorhinal cortex neurons and, most importantly, this effect is occluded by the benzodiazepine agonist, zolpidem (Cunningham *et al.* 2003). These observations led Cunningham *et al.* (2003) to conclude that VPA can potentiate postsynaptic GABA_A responses, possibly by an interaction with the benzodiazepine regulatory site of the GABA_A receptor. It could therefore be hypothesized that the shortening of SPs following VPA administration reflects

a curtailing of GABA_B IPSPs as a result of GABA_A receptor potentiation by VPA.

The effects of VPA on the MEP recruitment curves have not been previously reported. The MEP recruitment curves are constructed by plotting the amplitude of motor-evoked potentials as a function of increasing stimulus intensities. These curves are sigmoidal and it is generally thought that the initial part of the curve corresponds to the activation of low-threshold corticospinal neurons, whereas the plateau phase reflects the activation of high-threshold neurons (Ziemann 2005). The present data suggest that VPA reduces the Max value of the MEP curve, leaving the other best-fit values unaffected. The effect of VPA on MEPs may be attributed to the drug's action on sodium channels and/or GABA_A receptors. Boroojerdi *et al.*, (2001) have previously shown that lamotrigine, a voltage-gated Na⁺ and Ca²⁺ channel blocker and lorazepam, a GABA_A receptor positive modulator acting at the benzodiazepine site, depressed the MEP recruitment curves. Interestingly, the effect of lorazepam was maximal at the highest stimulus intensities, as observed in the present study with VPA. In conclusion, VPA, in common with other Na⁺ channel blockers, increases the corticomotor threshold in patients with IGE. In addition, it reduces the Max values of the SP S/R curve and the MEP recruitment curve. These findings probably reflect VPA's effects on voltage-dependent Na⁺ channels as well as an activation of GABA_A receptors. □

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