AMMONIA-INDEPENDENT MODIFICATIONS OF THE BACKGROUND EEG SIGNAL AND PARADOXICAL ENHANCEMENT OF EPILEPTIC ABNORMALITIES IN EEG AFTER ACUTE ADMINISTRATION OF VALPROATE TO EPILEPTIC PATIENTS

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Summary—The effects on the background quantitative EEG (power spectral analysis) and concentration of valproate in plasma were studied after single-dose (14.3–33.3 mg/kg) oral administration in 12 epileptic patients with generalized nonconvulsive or partial seizures. An increase of the amplitude of the background EEG (diffuse and preponderant on anterior scalp areas) and a decrease of the 12.5–32.0 Hz relative power (limited to the posterior electrode deviations) were observed; the increase in the EEG total power was paralleled by a definite increment in incidence of epileptic phenomena in the EEG. Both effects proved unrelated to shifts in vigilance or changes in the concentration of ammonia or serum glucose in plasma and confirm previous observations from superimposable study designs. These findings are qualitatively opposite to those observed during long-term treatment at comparable doses and are suggested to reflect a direct CNS action of acute administration of valproate.

Key words—valproate, EEG power spectral analysis, epileptic EEG abnormalities, drug plasma concentration, ammonia, glucose serum concentration, epilepsy.

Valproic acid is a compound widely used in the treatment of the epilepsies (Levy, 1984; Gram and Bentsen, 1985). Conventional recordings and computer-assisted analysis after exclusion of signal epochs with epileptic abnormalities indicate that valproic acid modifies the background electroencephalogram (EEG), independent of its therapeutic action on seizures and interictal EEG abnormalities (e.g. spike and wave discharges) (Miribel and Marinier, 1968; Adams, Luders and Pippenger, 1978; Sackellares, Satom, Dreifuss and Penry, 1980). Opposite effects on the background EEG were observed in epileptic patients after acute 8.2–13.2 mg/kg oral administration and during single-drug long-term treatment at the same daily dose. These effects were the increase of the total power of the EEG and the reduction of total and 12.5–45.0 Hz power, respectively; the incidence of spike and wave abnormalities in the EEG paralleled the changes in total power (Sannita, Gervasio and Zagnoni, 1989). These acute effects of valproic acid were interpreted as secondary to disposition, metabolism and/or pharmacological mechanisms of the drug, differing from those that result in an antiepileptic action during long-term treatment. A role in the paradoxical enhancements of clinical seizures or EEG epileptic abnormalities, that occasionally occur at the onset of therapy with valproic acid is also conceivable (Chadwick, Cumming, Livingstone and Cartlidge, 1979; Marescaux, Warter, Michelotti, Rumbach, Coquillet and Kurtz, 1982; Zaret, Beckner, Marini, Wagle and Passarelli, 1982). Valproic acid-induced hyperammonemia has been indicated as a possible cause for this side effect (Coulter and Allen, 1980; Williams, Tiefenback and McReynolds, 1984), whereas a direct action of valproic acid on the CNS was proposed based on the results of in vitro studies (Slater and Johnston, 1978; Hackman, Grayson and Davidoff, 1981) and on EEG observations (Marescaux et al., 1982; Sannita et al., 1989). The observed effects of acute administration of valproic acid on the quantitative EEG (Sannita et al., 1989) could support either hypothesis. The small dose administered and the lack of control on ammonemia were, however, limitations that warranted the present study on the effects of larger acute doses of valproic acid.

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METHODS

Twelve outpatients (7 females and 5 males, ranging in age from 14 to 38 years; mean 20.9 ± 7.4 years), with a history of generalized non-convulsive seizures (8 subjects) or partial complex seizures (4 patients), were studied. Occasional generalized tonic-clonic convulsive seizures were associated in four cases. Three patients were photosensitive. Generalized bursts of spike- and/or polyspike and wave activity with anterior scalp preponderance and no evidence of secondary bilateral synchrony were observed in all cases at the visual inspection of standard EEG recordings. Focal spikes were detectable in four patients with ambiguous indications of focality. Macroscopic brain lesions were excluded based on neuroradiological evidence, including CT scan and/or MRI and the standard haematological parameters were in the range of normality in all cases. Four patients had not been previously exposed to antiepileptic drugs, while eight had been treated and the therapy had been discontinued for 1–3 months. All patients were considered for single-drug treatment with valproic acid in accordance with its therapeutic indications (Levy, 1984). Consistent with this program, a pharmacological and electrophysiological study with multiple pre- and postdrug EEG recordings (1, 2, 3, 4, 5 and 7 hr) after administration of a single oral dose of valproic acid in the range suggested by the attending physician, was performed to test individual tolerance. Patients were aware of the purpose of the study, drug administered and recording procedures and signed an informed consent; they also agreed to avoid other neuroactive medications during the 72 hr preceding the experimental session. Experimental design and setting, administration of drug and data acquisition were consistent with the Helsinki recommendations for clinical research and the guidelines suggested for EEG studies in human neuropharmacology (Dumermuth, Ferber, Herrmann, Kinrichs and Kunkel, 1987). Systolic and diastolic blood pressures and heart rate were measured following each pre- and postdrug EEG recording. The subjects were requested to report subjective symptoms, both informally and according to a reduced Abramson Symptom Questionnaire comparing pre- and postdrug subjective drowsiness, fatigue, restlessness, mood, etc. (Fink, Irwin and Sibony, 1975). Samples of venous blood were collected after each pre- and postdrug EEG recording for determinations of valproic acid, glucose and ammonia.

The EEG signal was processed off-line by power spectral analysis of consecutive 2-sec epochs, after acquisition through a multiplexed ADC processing, by sequential equidistant sampling (amplitude resolution: 12 bit) and after analogue to digital conversion at 128 sample/sec. Signal epochs with EEG abnormalities or technical artefacts were identified visually and excluded from further analyses. Mean power values and standard deviation for each EEG recording and electrode were computed with a 0.5 Hz resolution on the 0.5–32.0 Hz frequency interval. The EEG total power value (0.5–32.0 Hz) and the relative power values on the following predetermined bandwidths were computed: 0.5–4.0, 4.5–8.0, 8.5–12.0 and 12.5–32.0 Hz. Epileptic EEG abnormalities were independently identified upon visual inspection of the conventional recording by two authors trained in clinical electroencephalography. The temporal incidence was rated for each electrode as the number of spikes per 5 min recording; whenever ratings were inconsistent, the recordings were re-examined and an agreement between observers was reached. Generalized spike/polyspike and wave activity and focal spikes were counted separately. Focal spikes were detected in 4 patients only, with erratic scalp distribution and were counted regardless of topography.

The concentration of valproic acid was determined by high pressure liquid chromatography in serum, esterified with 4-bromophenacyl bromide and heated at 70°C (Balbi, Sottofattori, Mazzei and Sannita, 1991). The quantification system included a Perkin Elmer, a Lambda 3 UV-adapter detector (wavelength: 254 nm) and a Date Station 3700. A Hibar (Merck) column with 5 microm Lichrosorb RP-18 (Merck) was used. The range referred to as “therapeutic” (i.e. associated with a high probability of control of seizures by valproic acid is 40–110 μg/ml, when using this analytical method. Concentrations of
ammonia and glucose were assessed by the glutamate dehydrogenase (GLDH) enzymatic method (van Anken and Shiporst, 1974) and the hexokinase/G6P-DH assay (Schmidt, 1961), respectively in plasma and serum. The ranges of physiological variability of estimates of glucose and ammonia in blood are 55–110 mg/dl and 25–65 µg/dl, respectively.

The hypothesis of no difference between the pre- and postdrug quantitative values of the EEG and incidence of epileptic spikes was tested by paired t-test computed on each EEG parameter for each postdrug recording and electrode. The statistical correlation between variables was tested by regression analysis (Winer, 1971). Nonlinear regression models were used when appropriate but were in no case found to fit the distribution of data more conveniently than, or to reach statistical probability levels significantly different from linear regression. The concentration of valproic acid in plasma was an exception in this regard, due to the compound kinetics. The reported statistical correlations between variables refer to linear regression analysis.

**RESULTS**

Changes in blood pressure, heart rate and reports of subjective symptoms after administration of drug were inconsistent among subjects and over time. Significant variations in alertness were never detected by observation of the behaviour of the subjects or by visual inspection of the EEG recordings. Four patients reported subjective drowsiness or fatigue, with inconsistent postdrug timing. In no case were epileptic phenomena of clinical relevance observed.

**Concentrations of valproic acid, glucose and ammonia**

The concentrations of valproic acid in serum were in the range commonly observed during long-term administration at therapeutic doses. The C_{max} and the area under the curve (AUC) ranged from 68 to 139 µg/ml (mean: 92.9 ± 21.6 µg/ml) and from 312.3 to 703.5 µg/ml·hr (mean: 442.9 ± 116.2), respectively, with a T_{max} of 2–5 hr (mean: 3.3 ± 1.1 hr) and without any correlation with dose (Table 1). Concentration values below the lower limit of the therapeutic range (40–110 µg/ml) were not detected after the second postdrug control, while values exceeding the upper limit were observed occasionally (Fig. 1). The concentration of valproic acid in serum correlated with time after administration (P < 0.0001) but not with dose of the drug (Table 1). The concentration of glucose in serum decreased with time and the trend was significant across subjects (linear regression; slope: −2.12; t: −2.75; P < 0.01), although in no case did the concentrations exceed the range of physiological variability (55–110 mg/dl). Values for ammonemia above the physiological range (25–65 µg/dl) were not detected at baseline and were occasionally observed after administration of drug, without any systematic trend of variation across subjects or over time. Concentrations of ammonia and glucose were not correlated with each other or with the concentration of valproic acid (Table 1).

**EEG**

The administration of valproate was followed by a systematic increase of the total power of the EEG and by a decrement of the relative power on the 12.5–32.0 Hz frequency interval (Fig. 2). The increase in total power was generalized over the scalp but was observed earlier on anterior than on posterior electrode locations. The modifications in 12.5–32.0 Hz power were restricted to posterior scalp areas (occipital; posterior temporal) (Fig. 2). A transient power increment of the low frequency (0.5–4.0 Hz) EEG activity was observed at the 2nd–3rd postdrug controls. No other modification of the EEG was detected.

The incidence of spike/polyspike and wave activity with generalized scalp distribution increased systematically from the 2nd to the 5th hr after administration of valproate. This effect varied between subjects and reached its maximum at the 3rd and 5th postdrug controls (Fig. 3). A comparable trend was observed for the incidence of focal epileptic activity, though with limited statistical significance due to the smaller number of patients with EEG abnormalities of this type. Changes in morphology, duration and/or scalp distribution of the spike/polyspike and wave bursts or focal spikes were not observed upon visual inspection of the conventional EEG recordings. A correlation between the valproic acid-related changes in the total power of the EEG and incidence of spike/polyspike and wave activity was observed in frontal (t: 3.058; P < 0.01) and central (t: 4.395; P < 0.001) electrode locations.

**Table 1. Correlations between the plasma/serum concentrations of valproic acid, glucose and ammonia, the AUC of valproic acid, the dose of valproate and the time after administration**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum Concentration</th>
<th>Plasma Concentration</th>
<th>Serum Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Slope</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>11.15</td>
<td>6.405</td>
<td>0.000001</td>
</tr>
<tr>
<td>Valproate dose (mg/kg)</td>
<td>Slope</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>0.67</td>
<td>0.96</td>
<td>0.36</td>
</tr>
<tr>
<td>Valproate serum concentration</td>
<td>Slope</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>−0.08</td>
<td>1.80</td>
<td>0.07</td>
</tr>
<tr>
<td>Glucose serum concentration</td>
<td>Slope</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>−0.13</td>
<td>1.54</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Table 2. Correlations between the mean EEG values before and after valproate administration**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum Concentration</th>
<th>Plasma Concentration</th>
<th>Serum Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate acid</td>
<td>Slope</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>0.96</td>
<td>0.57</td>
<td>0.37</td>
</tr>
<tr>
<td>(AUC; area under the curve)</td>
<td>t</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Linear regression; slope, t values; and statistical significance.
Fig. 1. Concentrations of valproic acid, glucose and ammonia in plasma/serum as a function of time after administration of a single oral 14.3–33.3 mg/kg dose of magnesium valproate. Twelve patients; venous blood. Mean across subjects and standard deviation. A linear correlation with time was found for the glucose in serum (slope of the regression function: $-2.116$; $t: -2.754$; $P < 0.01$) and the valproic acid in serum (slope of the regression function: $11.15$; $t: 6.405$; $P < 0.00001$) but not for the concentration of ammonia in plasma.

Correlations between the EEG and concentrations of glucose, ammonia and valproic acid

The valproic acid-related postdrug modifications in the total power and 12.5–32.0 Hz power, paralleled over time the variations in the concentrations of drug in serum but $T_{\text{max}}$ and maximum EEG effects were not correlated and the peak effect in the EEG anticipated the $T_{\text{max}}$. A direct correlation between postdrug changes in total power of the EEG and levels of valproic acid in serum was observed, limited to the anterior scalp electrode locations (frontal; central; anterior temporal; middle temporal) (Table 2; Fig. 4). No correlation with the serum level of drug was found for the 12.5–32.0 Hz power postdrug variations or the temporal incidence of generalized and focal epileptic EEG abnormalities (Table 2). Neither the valproic acid-related postdrug modifications of the total power of the EEG or 12.5–32.0 Hz power nor the increased incidence of epileptic EEG potentials were correlated with levels of ammonia or glucose. A positive correlation with levels of glucose and a negative correlation with ammonemia of the 12.5–32.0 Hz power values was
detected on frontal and central electrodes, at locations where the postdrug changes of this EEG parameter were not systematic or consistent across subjects (Table 2).

DISCUSSION

The effects on the background EEG of acute administration of valproic acid were comparable, as to extent of variation, with those of most neuroactive compounds when administered at acute therapeutic doses, including antiepileptic drugs (Fink, 1969, 1978; Itil, 1974; Saletu, 1976; Herrmann, 1983; Sannita, 1986). Individual variability conceivably reflects in these experimental conditions differences between subjects in age, clinical history, type of epilepsy, previous treatment with drugs, etc., that could not be studied independently without generating subgroups of subjects, inadequate in size. For this reason it is mandatory in human studies that the attribution of postdrug modifications of the EEG to the action of

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Fig. 2. Topographic distribution of valproic acid-induced modifications of EEG total power (---) and 12.5-32.0 Hz relative power (—), expressed as percent variations from baseline determination. Mean across subjects; standard deviations are reported whenever postdrug changes were different from baseline (paired t-test). Statistical significance is indicated. Left hemisphere.
the drug be also grounded on criteria with biological relevance, such as consistency with the kinetics of the drug, repeatability, topographic distribution, etc. (Kunkel, 1982; Herrmann, 1982). The attribution of postdrug EEG changes to the action of valproic acid is supported in this study by the confirmation of the increase in total power of the EEG and incidence of epileptic abnormalities that was observed under comparable experimental conditions after administration of smaller doses of valproic acid (8.2-13.2 mg/kg) (Sannita et al., 1989). In agreement with systematic indications that topographic distribution of drug-induced EEG modifications is a critical factor in neuropharmacological studies (Kunkel, 1982), the correlation between valproic acid-related increment in total power and levels of drug in serum was restricted to the anterior areas, although this effect on the EEG was evident and comparable as to extent

**Table 2. Correlations between the postdrug modifications of total power of the EEG and 12.5–32.0 Hz power (expressed as percent variations from normalized baseline) and the plasma/serum concentrations of valproic acid, glucose and ammonia**

<table>
<thead>
<tr>
<th>Electrode derivation</th>
<th>EEG total power</th>
<th>Valproic acid</th>
<th>Glucose</th>
<th>Ammonia</th>
<th>EEG 12.5–32.0 Hz power</th>
<th>Valproic acid</th>
<th>Glucose</th>
<th>Ammonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontopolar</td>
<td>Slope</td>
<td>0.15</td>
<td>-0.34</td>
<td>0.12</td>
<td>0.03</td>
<td>-0.04</td>
<td>-0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>1.51</td>
<td>-0.94</td>
<td>1.58</td>
<td>0.53</td>
<td>-0.61</td>
<td>-0.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
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<tr>
<td>Frontal</td>
<td>Slope</td>
<td>0.24</td>
<td>-0.16</td>
<td>0.01</td>
<td>0.04</td>
<td>0.14</td>
<td>-0.57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>2.96</td>
<td>-1.18</td>
<td>0.24</td>
<td>1.21</td>
<td>2.61</td>
<td>-2.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.005</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0.01</td>
<td>0.05</td>
<td></td>
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<tr>
<td>Central</td>
<td>Slope</td>
<td>0.23</td>
<td>-0.24</td>
<td>0.04</td>
<td>0.02</td>
<td>0.23</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>2.59</td>
<td>-1.68</td>
<td>0.62</td>
<td>0.61</td>
<td>2.58</td>
<td>2.79</td>
<td></td>
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<tr>
<td></td>
<td>P</td>
<td>0.01</td>
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<tr>
<td>Parietal</td>
<td>Slope</td>
<td>0.23</td>
<td>-0.09</td>
<td>0.12</td>
<td>-0.23</td>
<td>0.02</td>
<td>-0.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>1.02</td>
<td>-0.96</td>
<td>0.84</td>
<td>-0.44</td>
<td>0.98</td>
<td>1.12</td>
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<tr>
<td></td>
<td>P</td>
<td>n.s.</td>
<td>n.s.</td>
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<td>n.s.</td>
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<tr>
<td>Occipital</td>
<td>Slope</td>
<td>0.19</td>
<td>-0.11</td>
<td>0.12</td>
<td>0.02</td>
<td>0.08</td>
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</tr>
<tr>
<td></td>
<td>t</td>
<td>1.38</td>
<td>-0.59</td>
<td>1.64</td>
<td>0.65</td>
<td>1.44</td>
<td>1.17</td>
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<tr>
<td></td>
<td>P</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
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<td>Slope</td>
<td>0.22</td>
<td>-0.34</td>
<td>0.02</td>
<td>0.04</td>
<td>0.19</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t</td>
<td>2.94</td>
<td>-1.94</td>
<td>0.39</td>
<td>0.84</td>
<td>1.72</td>
<td>1.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
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<td>n.s.</td>
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<tr>
<td>Middle temporal</td>
<td>Slope</td>
<td>0.31</td>
<td>-0.19</td>
<td>-0.03</td>
<td>0.09</td>
<td>0.15</td>
<td>-0.02</td>
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</tr>
<tr>
<td></td>
<td>t</td>
<td>3.59</td>
<td>-1.27</td>
<td>-0.88</td>
<td>1.62</td>
<td>1.02</td>
<td>1.06</td>
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<tr>
<td></td>
<td>P</td>
<td>0.001</td>
<td>n.s.</td>
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<tr>
<td>Posterior temporal</td>
<td>Slope</td>
<td>0.19</td>
<td>-0.27</td>
<td>0.06</td>
<td>0.02</td>
<td>0.17</td>
<td>-0.02</td>
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<tr>
<td></td>
<td>t</td>
<td>1.82</td>
<td>-1.66</td>
<td>0.96</td>
<td>0.03</td>
<td>1.44</td>
<td>1.02</td>
<td></td>
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<tr>
<td></td>
<td>P</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
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<td>n.s.</td>
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</tr>
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</table>

**Left hemisphere. Linear regression: slope; t values; and statistical significance.**
EEG effects of valproate

Fig. 4. Correlation (linear regression analysis) between the postdrug percent variations in total power and the concentration of valproic acid in serum. Frontal electrode location: slope of the regression function: 0.24; t: 2.96; P < 0.005. Central electrode location: 0.23; t: 2.59; P < 0.01. See also Table 2.

A comparison between the effects on the EEG at the 14.3–33.3 mg/kg dose and those reported at 8.2–13.2 mg/kg (Sannita et al., 1989) allows some inference on the effect of dose and treatment modalities and suggest differences among EEG parameters in sensitivity to the action of valproic acid. The decrease of fast frequency power in the EEG after chronic treatment with 8.2–13.2 mg/kg doses of valproic acid also occurred after acute administration, when the dose was increased to 14.3–33.3 mg/kg and is conceivably dose-related, while being apparently independent of the modality (acute versus chronic) of administration of drug. This by contrast is a possible dose-independent factor in the generation of the postdrug changes in total power and incidence of spike and wave, that both increased after acute administration and decreased during chronic treatment with valproic acid, regardless of dose. The postdrug increment in the total power at the 14.3–33.3 mg/kg dose was the only EEG parameter correlating with the concentration of the drug in serum, suggesting some specificity of this effect on the EEG with respect to the compound administered.

A paradoxical enhancement of clinical seizures and/or epileptic abnormalities in the EEG occasionally occurs at the beginning of therapy with valproic acid.
acid. Episodes of impaired vigilance (ranging in severity from reduced performance in neuropsychological tests, to stupor or coma) are also described, for which an epileptic origin was suggested, based on observations of greater incidence of epileptic abnormalities in the EEG than prior to therapy with valproic acid or after discontinuation of drug (Chadwick et al., 1979; Koskineni and Hakamies, 1979; Marescaux et al., 1982). Though undetermined, the antiepileptic action of valproic acid is presumed to be mediated by indirect mechanisms resulting in modifications of levels of γ-aminobutyric acid (GABA), 5-hydroxytryptamine or dopamine in the CNS or depending on benzodiazepine agonist properties (Bruinvels and van der Laan, 1989; Fariello and Smith, 1989). No one of these mechanisms is likely to be operative 2–3 hr after acute administration and to account for the generation of the EEG effects observed in the present study with this delay after administration. Studies on gerbils with spontaneous reflex epilepsy suggest that paradoxical epileptogenic effects also occur during treatment with other antiepileptic compounds, such as phenobarbitaline (Watanabe, Schain and Bailey, 1978) and are independent of dysfunctions of the GABA system (Cutler and Horton, 1988) in cortical areas where seizures are thought to originate in these animals (Loskota and Lomax, 1975). Overdosing with valproic acid, hyperammonemia, alterations of glucose metabolism or a direct action of the drug on the CNS, were alternatively and independently suggested to play a role in the generation of both stuporous states and paradoxical enhancement of epileptic symptoms (Chadwick et al., 1979; Sackellaes, Lee and Dreifuss, 1979; Marescaux et al., 1982; Zaret and Cohen, 1986). A mild impairment of consciousness was documented by neuropsychological testing in healthy volunteers after acute administration of valproic acid (Thompson and Trimble, 1983). At the doses used in the present study, however, the effects on the EEG occurred in the absence of measurable behavioural or shifts in vigilance in the EEG, while the concentration of valproic acid in serum did not exceed the therapeutic levels and only the increase in the total power in the EEG correlated with levels of valproic acid in serum. The concentration of glucose was within normal limits throughout the whole experimental session, with variations after administration of valproic acid that were neither correlated with the concentration of the drug or its effects on the EEG nor of any clinical significance. The correlation with the concentration of glucose of the variations in 14.5–32.0 Hz relative power in the EEG was restricted to areas of the scalp where the modifications of this measure of the EEG were neither systematic nor attributable to the action of the drug. This observation suggests that this metabolic factor can independently affect the electrophysiology of the human brain independent of administration of drugs (Davis, 1943; Creutzfeld and Meisch, 1963; Sannita, Balestra, Di Bon, Hassan and Rosadini, 1992) or that valproic acid is active on the metabolism of glucose in the CNS (Koch, Wilensky and Levy, 1989; Leiderman, Balish, Bromfield and Theodore, 1991) regardless of changes in the availability of glucose in the peripheral compartments. The suggested role of hyperammonemia in inducing a valproic acid-related paradoxical enhancement of epileptic abnormalities in the EEG is grounded on evidence that ammonia blocks postsynaptic inhibitory neurotransmission in animal models (Lux, Lorache and Neher, 1970; Raabe and Gumnit, 1975) and affects metabolism in the brain (Banister and Cameron, 1990). Neuropsychological symptoms of impaired vigilance, comparable to those of hepatic precoma, were described in normal subjects after exogenous administration of ammonia salts yielding arterial levels of ammonia ranging from 2 to 5 μg/ml (Eichler, 1964). Venous levels of ammonia ranging from 116 to 334 μg/dl (Zaccara, Paganini, Campostrini, Arnetoli, Zappoli and Moroni, 1984) or from 66 to 289 μM (Williams, Tiefenbach and McReynolds, 1984) were assessed in epileptic patients on therapy with valproic acid. An impairment of vigilance was observed in both studies, but epileptic seizures and epileptic abnormalities in the EEG worsened only in a limited proportion of patients. Ammonemia was seldom above the upper normal limit (65 μg/dl) in the present study and the effects of valproic acid on the EEG were observed in the absence of significant changes in vigilance, systematic variations of ammonemia over time or correlations between ammonemia and valproic acid-related modifications of the EEG.

It remains undefined whether the effects of valproic acid on the quantitative background EEG and incidence of epileptic abnormalities, as observed in this study, are qualitatively equivalent to the reported exacerbation of epileptic symptomatology in the EEG and involve mechanisms of action in the CNS that are shared by the compound at toxic doses. Several mechanisms involving extrasynaptic functions in single neurones or changes in the level of activation of neural networks are believed to play a relevant role in the action of valproic acid. Increased potassium conductance of the neural membrane, reduced neural firing and reduced bursting pacemaker activity were observed in vitro in animal models (Slater and Johnston, 1978; Hackman et al., 1981) and indicate inhibitory effects of valproic acid on neural activity, independent of the indirect mechanisms of action that are believed to result in the antiepileptic effect of the drug (Bruinvels and van der Laan, 1989; Fariello and Smith, 1989). A direct epileptogenic action can be hypothesized, based on observations on animals with spontaneous epilepsy (Cutler and Horton, 1988) and on the increase in excitability of neurones induced by iontophoretic application of valproic acid (Blume, Lamoour, Arnauld, Layton and Renault, 1979). Recent studies in vitro (Altrup, Gerlach, Reith, Said and
membrane hyperpolarization and increased resist-
epileptogenic) effects of valproic acid induced by
Speekmann, 1992; Altrup, Reith and Speckmann,
ante at the intracellular level or transient paroxysmal
depolarization shift at the extracellular level, respect-
ibly. This epileptogenic effect has shorter latency
duced by large concentration of hydrogen ions or
idiosyncrasies, such as hypersensitivity to the drug,
tibility to seizures. Contingencies and/or individual
iosyncrasies, such as hypersensitivity to the drug,
may also be at the origin of events of greater clinical
relevance. Within the limits of comparison between
human and in vitro animal data, the observed val-
proic acid-induced modifications of the epileptic ab-
normalities in the EEG and background EEG signal
are consistent with the implications of the in vitro
observations.

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