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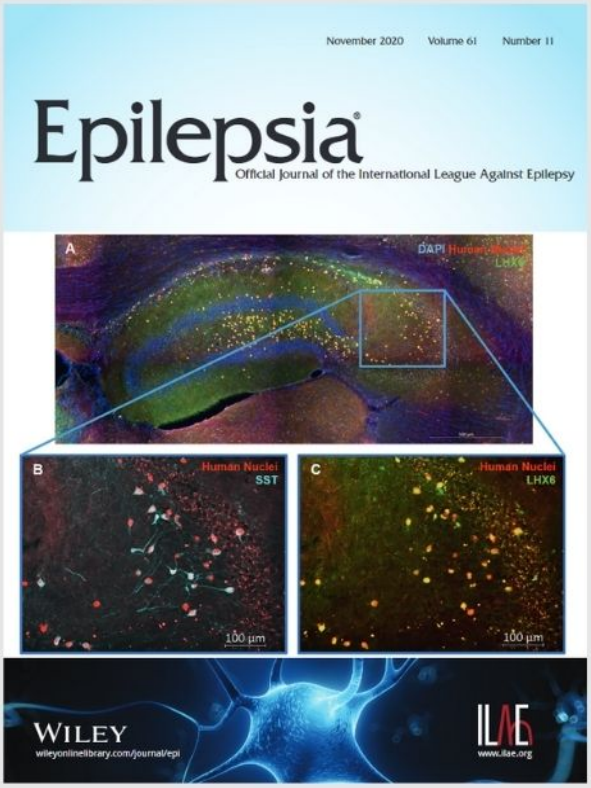

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Effect of Valproate on Cerebral Metabolism and Blood Flow: An ^{18}F-2-Deoxyglusose and ^{15}O Water Positron Emission Tomography Study

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Summary: We compared the effect of valproate (VPA) on cerebral metabolic rate for glucose (CMRGlc) and cerebral blood flow (CBF), measured with ^{18}F-2-deoxyglucose (^{18}FDG) and ^{15}O water positron emission tomography (PET), in 10 normal volunteers. Mean VPA dose was 17.7 mg/kg, and mean VPA level was 82.1 mg/L (±16.5) for 4 weeks. VPA reduced global CMRGlc by 9.4% (9.60 ± 0.76 vs. 8.59 ± 1.02 mg Glc/min/100 g, $p < 0.05$) and regionally in all anatomic areas ($p < 0.05$ for 11 of 26 areas). VPA diminished global CBF by 14.9% (56.55 ± 6.70 vs. 47.48 ± 4.42 ml/min/100 g, $p < 0.002$) and regionally in all anatomic areas ($p < 0.05$ for 12 of 26 areas). No significant correlation was noted between VPA level and either global CMRGlc or CBF. The effect of VPA on global CMRGlc is similar to that of carbamazepine (CBZ) and phenytoin but less than that of phenobarbital, valium, or combination therapy with VPA and CBZ. VPA reduced regional CBF (rCBF) but not CMRGlc in the thalamus, an effect that may be associated with VPA's mechanism of action against generalized seizures. **Key Words:** Valproate—Positron emission tomography—Cerebral blood flow—Cerebral metabolism.

Antiepileptic drugs (AEDs) impair cognitive function and decrease cerebral metabolism to varying degrees (1–4). In a previous study, we noted that valproate (VPA) decreased cerebral metabolism by 22% in epilepsy patients treated concomitantly with carbamazepine (CBZ) (5). To measure the effect of VPA alone on cerebral function, we studied cerebral glucose metabolism (CMRGlc) and cerebral blood flow (CBF) in normal volunteers before and after administration of VPA using ^{18}F-2-deoxyglucose positron emission tomography (FDG-PET) and ^{15}O water PET ([^{15}O]-PET).

METHODS

Ten normal volunteers (6 men and 4 women) with a mean age of 29.2 years (±8.6, range 20–43 years) were enrolled by the Clinical Epilepsy Section, Epilepsy Research Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health (NINDS, NIH) after approval was granted by the NIH Institutional Review Board and the subjects had given informed consent. All subjects had normal neurologic examinations, complete blood count liver function tests, and 1.5-T magnetic resonance imaging (MRI General Electric Signa). They underwent FDG-PET and [^{15}O]PET before and after administration of VPA (Depakote). Subjects were titrated to maintenance for 1 week, after which weekly trough levels were obtained for a minimum of 4 weeks. The mean dose of VPA was 17.7 mg/kg ± 3.74 (range 13.2–24.9), which maintained mean trough levels at 82 mg/L ± 16.5 (range 58.5–110.8). VPA was administered for a mean duration of 33 days (range 28–54 days, but only 1 subject received VPA >35 days).

PET studies were performed on the Scanditronix 2048-15B scanner with a full-width half-maximum axial and in-plane resolution of 5.5 mm. Subjects were scanned in the resting awake state with eyes patched, ears plugged, and heads immobilized by a thermoplastic mask. Scans were obtained oriented

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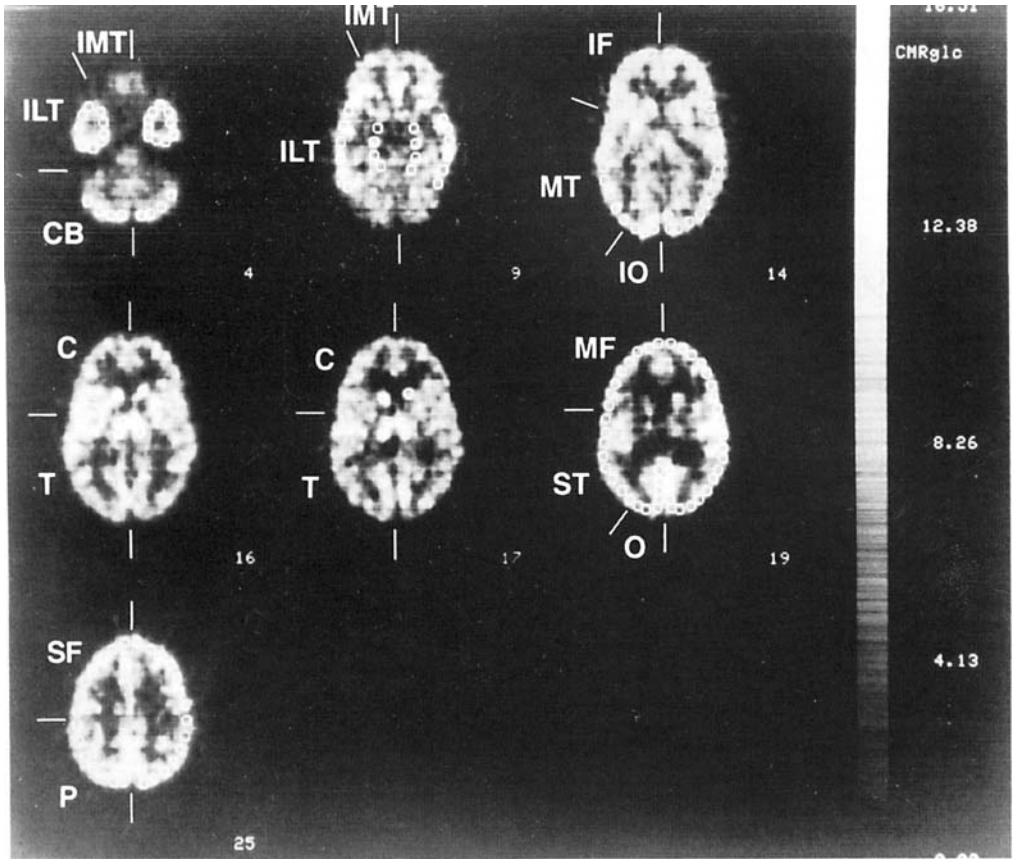

FIG. 1. Region of interest template placed on ^{18}F-2-deoxyglucose positron emission tomography study. Areas: ILT, inferolateral temporal; IMT, inferomesial temporal; MT, midtemporal; ST, superotemporal; IF, inferofrontal; MF, midfrontal; SF, superofrontal; P, parietal; IO, inferior occipital; O, occipital; C, caudate; T, thalamus; CB, cerebellum.

along the canthomeatal plane. After a measured ^{68}Gallium attenuation scan was made, 30 mCi ^{15}O-labeled water was injected by intravenous bolus and data were collected for 4 min. This procedure was repeated 12 min later with the head position advanced 3.3 mm. Immediately after data acquisition for the second ^{15}O water scan, 5.0 mCi FDG was injected. After a 30-min uptake period, data were acquired for two 15-min intervals with head position matching that in water studies. Arterial sampling was performed to quantitate local CMRGlc (LCMRGlc) and regional CBF (rCBF) (6,7).

Data analysis

Data were analyzed with a standard template of 176 regions, each 48 mm^2, grouped into 13 paired anatomic areas. The template was superimposed and placed directly on seven PET slices from the FDG study (Fig. 1), and regions of interest (ROIs) were adjusted as necessary to fit each slice; the template was then superimposed on the water images by an investigator blinded to scan conditions. Mean values of LCMRGlc (mg Glc/min/100 g) and rCBF (ml/min/100 g) were calculated for each anatomic area. Statistical analysis was performed with the Statview statistical package on a Macintosh IIX PC. Two-tailed Student's *t* tests and nonparametric tests (Wilcoxon ranked sum) were performed to determine significant differences between the two conditions for each area and for global measures. We hypothesized that there would be global changes in CMRGlc and CBF as a result of drug administration.

Drug-related regional CMRGlc and CBF effects were also studied with SPM (MRC Cyclotron Unit, London, U.K.) and MEDx (Sensor Systems, Sterling, VA, U.S.A.). The analysis procedure consisted of spatial normalization followed by statistical parametric map (SPM) generation, which allowed intersubject averaging and quantitative assessment of change significance (8–10). The scans were individually reoriented, rescaled and reformatted to generate a stereotaxically normalized image corresponding

TABLE 1. *Effect of VPA on LCMRGlc*

Region	Without VPA	With VPA	*t* Test	Wilcoxon ranked-sum test
Inferolateroltemporal				
L	8.70 ± 0.76	7.63 ± 1.00	0.01	0.02
R	8.38 ± 0.59	7.77 ± 0.93	0.18	0.17
Inferomesiotemporal				
L	6.67 ± 0.68	6.26 ± 0.78	0.29	0.26
R	6.76 ± 0.75	6.30 ± 0.74	0.32	0.37
Cerebellum				
L	8.24 ± 0.61	7.52 ± 1.08	0.12	0.11
R	8.35 ± 0.90	7.55 ± 1.11	0.12	0.14
Inferofrontal				
L	10.51 ± 1.19	9.03 ± 1.27	0.02	0.05
R	10.24 ± 0.92	9.05 ± 1.35	0.07	0.09
Midtemporal				
L	9.95 ± 0.86	8.88 ± 1.03	0.03	0.04
R	9.42 ± 0.63	8.86 ± 1.09	0.23	0.21
Inferior occipital				
L	8.97 ± 0.96	8.29 ± 0.81	0.19	0.21
R	8.95 ± 0.70	8.40 ± 1.17	0.32	0.26
Thalamus				
L	10.97 ± 0.88	9.72 ± 1.65	0.09	0.11
R	10.56 ± 1.09	9.73 ± 1.65	0.30	0.31
Caudate				
L	10.44 ± 1.13	9.79 ± 1.45	0.45	0.44
R	10.45 ± 1.20	9.61 ± 1.46	0.31	0.17
Midfrontal				
L	10.71 ± 0.83	9.20 ± 1.05	0.01	0.02
R	10.26 ± 0.95	8.93 ± 0.98	0.02	0.04
Superotemporal				
L	10.03 ± 0.75	8.83 ± 1.04	0.02	0.14
R	9.68 ± 0.94	8.65 ± 1.07	0.06	0.02
Occipital				
L	10.34 ± 1.03	9.11 ± 1.21	0.02	0.04
R	10.13 ± 1.29	9.20 ± 0.91	0.04	0.04
Superofrontal				
L	10.76 ± 1.10	9.22 ± 1.47	0.02	0.04
R	10.46 ± 1.03	9.31 ± 1.25	0.06	0.05
Parietal				
L	10.03 ± 1.13	8.74 ± 1.23	0.03	0.04
R	9.79 ± 0.76	8.59 ± 1.02	0.05	0.05
Global				
	9.60 ± 0.76	8.59 ± 1.02	0.05	0.05

VPA, valproate; LCMRGlc, cerebral metabolic rate of glucose metabolism (mg/min/100 g).
Values are mean ± SD.

to the stereotaxtic atlas of Talairach and Tournoux (9,11). Analysis of change significance was performed with a pixel-by-pixel analysis of covariance to remove the confounding effect of intersubject variation in CMRGlc or CBF, followed by planned linear comparisons of the adjusted mean images (12). This procedure removed global effects of drug administration from the analysis. Comparison (with drug minus without drug) eliminated activity common to both conditions, the remaining areas of difference reflecting local drug effect (13). The value of *t* for each pixel in each comparison was calculated and then transformed to a normal standard distribution (*Z*-values). The significance level for detecting effect of drug and areas of decreased or increased CBF and CMRGlc was set up at $p < 0.01$ (13).

RESULTS

VPA reduced global CMRGlc by 9.4% (±7.5, $p < 0.05$). Decreases in CMRGlc were evident in all areas examined and were significant ($p < 0.05$) in 11 of 26 areas (Table 1). Subcortical areas, cerebellum, and inferior temporal areas showed no consistent significant changes. VPA diminished global CBF by 14.9% (±10.4, $p < 0.002$). Reductions in CBF were noted in all areas examined and were significant ($p < 0.05$) in 12 of 26. Alterations in CBF generally paralleled that for FDG except for thalamus and cerebellum, which had significantly decreased rCBF (Table 2). Nonparametric tests (Wilcoxon ranked sum) showed significant changes in CMRGlc and CBF, which confirmed the *t* tests and

TABLE 2. *Effect of VPA on rCBF*

Region	Without VPA	With VPA	*t* Test	Wilcoxon ranked-sum test
Inferolateroltemporal				
L	49.77 ± 12.45	43.30 ± 5.84	0.09	0.09
R	48.38 ± 11.09	42.74 ± 6.27	0.06	0.09
Inferomesiotemporal				
L	47.72 ± 11.61	43.28 ± 7.31	0.18	0.17
R	46.33 ± 9.28	43.14 ± 9.03	0.29	0.14
Cerebellum				
L	56.55 ± 8.65	47.44 ± 5.55	0.03	0.04
R	56.08 ± 11.35	46.42 ± 5.22	0.03	0.06
Inferofrontal				
L	53.31 ± 7.20	48.93 ± 6.12	0.14	0.19
R	54.04 ± 7.06	48.56 ± 6.08	0.12	0.11
Midtemporal				
L	53.70 ± 7.41	50.20 ± 5.17	0.21	0.14
R	51.37 ± 7.81	49.90 ± 5.89	0.61	0.80
Inferior occipital				
L	50.37 ± 12.23	48.97 ± 7.64	0.70	0.96
R	50.90 ± 7.89	49.93 ± 5.06	0.64	0.65
Thalamus				
L	68.19 ± 11.39	53.48 ± 5.98	0.01	0.01
R	66.00 ± 8.42	54.18 ± 7.87	0.01	0.03
Caudate				
L	56.16 ± 12.76	46.22 ± 7.77	0.11	0.07
R	57.88 ± 7.93	48.64 ± 7.59	0.03	0.04
Midfrontal				
L	61.27 ± 7.68	49.93 ± 5.83	0.01	0.01
R	58.40 ± 8.02	50.76 ± 5.49	0.07	0.09
Superotemporal				
L	58.42 ± 7.79	49.62 ± 6.21	0.03	0.04
R	55.19 ± 6.34	47.66 ± 5.74	0.02	0.03
Occipital				
L	60.77 ± 8.93	52.63 ± 7.66	0.05	0.05
R	58.21 ± 9.42	52.66 ± 8.96	0.23	0.33
Superofrontal				
L	59.52 ± 13.38	48.83 ± 5.90	0.04	0.05
R	59.68 ± 11.99	47.87 ± 5.65	0.03	0.03
Parietal				
L	57.66 ± 14.96	45.58 ± 5.66	0.05	0.06
R	57.06 ± 11.44	46.56 ± 7.38	0.06	0.06
Global				
	56.55 ± 6.70	47.48 ± 4.42	0.002	0.01

VPA, valproate; rCBF, regional cerebral blood flow (ml/min/100 g).
Values are mean ± SD.

support a broad and modest drug effect. SPM analysis, controlling for global effects, identified region-specific decreased CBF in the thalamic regions and, to a lesser extent, in some prefrontal cortical areas (Fig. 2). SPM analysis of CMRGlc data did not show changes at the $p < 0.01$ level. No areas of increased CBF or metabolism were noted. No significant correlation was noted between VPA serum concentration and global CMRGlc or CBF ($r = 0.091$, $p = 0.238$).

In a previous study, 7 patients with complex partial seizures of temporal lobe origin had two FDG scans without a drug change (5). Global mean CMRGlc did not change (7.52 ± 2.06 vs. 7.68 ± 2.54, $F = 0.312$). Mean global variance for the scan–scan difference was 1.12; no individual variance was >2.5. We also examined the regional variances for both scans in the 7 patients. Across-patient comparisons are much less valuable than within-patient comparisons due to the marked differences between individuals in resting CMRGlc. Nevertheless, variance was >4.32 in only 7 of 26 regions and was <4.32 in all regions if one outlying subject was not included.

DISCUSSION

Our results show a modest effect of VPA in reducing global CMRGlc and CBF. The 9.4% reduction in global CMRGlc in the present study was similar to that noted with CBZ (9.6%) and phenytoin (PHT, 11.5%) but less than that noted with phenobarbital (PB, 27.0%) or valium (20%) (1–4). In a previous study, using VPA, we noted a decrease in global CMRGlc of 22% (5). However, that study was per-

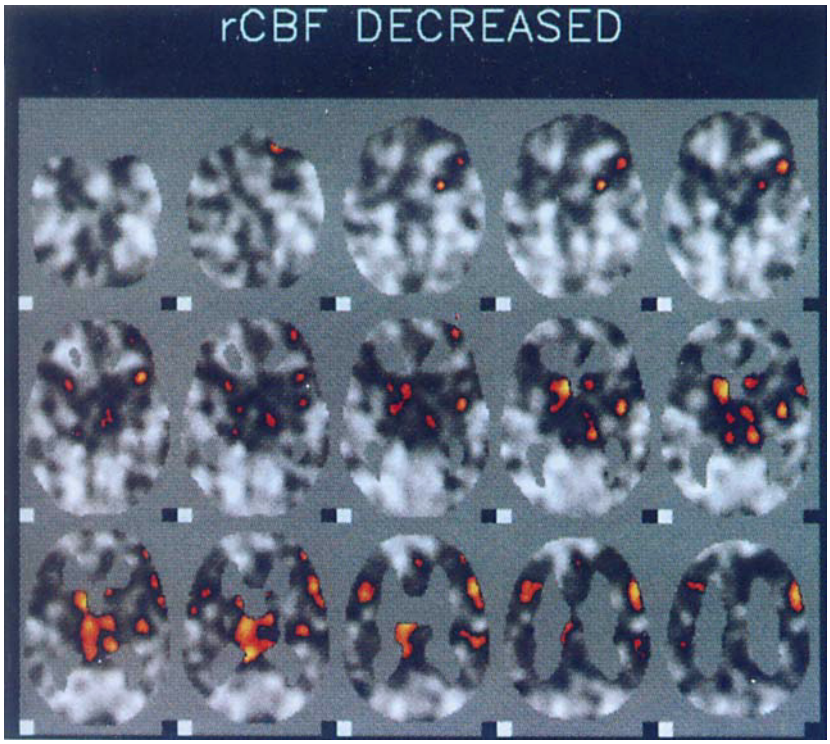

FIG. 2. Statistical parametric map analysis of valproate drug effect. Colored regions represent regions of decreased regional blood flow during drug treatment as compared with no drug ($p < 0.01$).

formed in epilepsy patients who were concurrently treated with CBZ. CBZ in conjunction with VPA may have had a synergistic effect, resulting in greater decrease in CMRGlc than would have been caused by either drug alone. CBZ levels were unchanged, but CBZ metabolites were not measured. Valproate reduces the clearance rate of CBZ and its epoxide metabolites, and CBZ epoxide levels may have increased (14,15). In addition, although levels of VPA were lower (52 vs. 82 mg/L), duration of VPA administration was longer (75 vs. 33 days) in the first study (5). Some evidence indicates a cumulative CNS effect of VPA since seizure reduction may lag behind initiation of VPA administration (16).

The effect of AEDs on global CNS metabolism parallels their effect on cognitive performance and may be associated with their mechanism of action (17). PB, in therapeutic concentrations, impairs attention, concentration, and memory (18–21). PHT, CBZ and VPA produce subtle cognitive effects that are less pronounced than those produced by PB but that may be more readily apparent at higher drug concentrations (21–25).

Polytherapy results in greater cognitive impairment than any single AED along (25,26). This observation is of note in light of our finding that VPA decreased CMRGlc to a greater degree in patients receiving CBZ than in normal volunteers. AEDs that act at the γ-aminobutyric acid (GABA) receptor may decrease cerebral metabolism more than AEDs that alter sodium ion membrane conductance (17). PHT and CBZ inhibit voltage- and frequency-dependent sodium channels; PB and benzodiazepines potentiate GABAergic-mediated activation of inhibitory chloride channels (4,17–30).

The mechanism of action of VPA is unknown. Brain and cerebrospinal fluid GABA is increased after VPA administration, which may block the degradative enzymes GABA transaminase and succinic semialdehyde dehydrogenase or the citric acid cycle α-ketoglutarate dehydrogenase complex (31–35). However, increased GABA levels may not imply increased release or interaction with postsynaptic receptors. Moreover, results in animal models may not always be applicable to, or occur at, clinically relevant drug concentrations (27,35,36). Evidence that VPA enhances the effect of GABA-mediated alterations in chloride conductance is conflicting (27,30,36,37). An alternative hypothesis suggests that VPA alters voltage-dependent sodium conductance, decreasing sustained repetition (27, 36,38–40).

Our results may have been influenced by our scan sequence and differences in ligand half-life. We obtained all baseline scans before administering VPA. However, our previous study showed no scan order effect in assessing LCMRGlc in subjects with serial FDG-PET (3). In the absence of a sham scan, a scan

effect between first and second ^{15}O water injections might have influenced our template-based results (41). However, using the second scan images for the SPM analysis controls for this possible effect. Minor regional differences may be attributed to the larger area of cortex encompassed in template regions and to mild head movement effect on template analysis, which is reduced by the head fitting algorithm of SPM. Because CMRGlc and CBF do not vary independently in each brain region, it is difficult to choose the proper correction for multiple comparisons. Our results are strengthened by converging analysis for CMRGlc and for CBF, as well as by the low variance for scan–scan difference in a patient group.

FDG-PET studies with PHT, CBZ, PB, and VPA showed no region-specific cortical effects, which may reflect an effect on a ubiquitous ion channel (e.g., sodium) or neurotransmitter system (e.g., GABA). Some of the variability between our metabolism and CBF data may reflect differences in the higher energy of the ^{15}O to ^{18}F positron and the longer half-life and uptake period of FDG as compared with that of ^{15}O water.

The effect of VPA in moderately reducing LCMRGlc and CBF was similar in all cortical regions and suggests that VPA may not have a significant GABAergic effect at therapeutic levels. However, VPA did appear to have a greater effect on subcortical thalamic CBF. This may be related to the drug's greater efficacy against generalized rather than partial epilepsies (42–44). Further studies are warranted to ascertain whether the effects observed in normal volunteers are applicable to a population with generalized epilepsy. In recent studies, SPM analysis demonstrated greater increases in thalamic CBF than in global CBF during absence seizures (45).

The thalamus is essential in facilitating and maintaining cortically initiated paroxysmal activity and in the oscillating electrical activity associated with spike and wave discharges in the generalized epilepsies (46–48). Ethosuximide (ESM), an effective and specific antiabsence anticonvulsant, reduces the low-threshold voltage-dependent Ca^{2+} current of thalamic neurons, which mediates the phasic firing associated with absence discharges and spindle generation (30,48–51). VPA may have a similar region-specific activity underlying its efficacy in treatment of generalized epilepsies. Both VPA and ESM reduce corticothalamic-mediated evoked responses (52–54), and VPA reduces cortical excitability in subjects with generalized epilepsy (54). Although no action similar to that of ESM has been observed with VPA in disassociated thalamic neuron studies, VPA inhibits the T-type calcium current in rat nodose neurons (49,55). VPA's accentuated thalamic decrease of rCBF may help explain its mechanism of action. If our observations regarding VPA are valid, ESM may show similar metabolic and CBF patterns, and VPA may have a more robust thalamic effect in patients with newly diagnosed primary generalized epilepsy.

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