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Valproate treatment normalizes EEG functional connectivity in successfully treated idiopathic generalized epilepsy patients

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Summary
Aim: To investigate the effect of chronic VPA treatment of EEG functional connectivity in successfully treated idiopathic generalized epilepsy (IGE) patients.
Patients and methods: 19-channel waking, resting-state EEG records of 26 IGE patients were analyzed before treatment (IGE) and after the 90th day of treatment (VPA), in seizure-free condition. Three minutes of artifact-free EEG background activity (without epileptiform potentials) was analyzed for each patient in both conditions. A group of 26 age-matched healthy normative control persons (NC) was analyzed in the same way. All the EEG samples were processed to LORETA (Low Resolution Electromagnetic Tomography) to localize multiple distributed sources of EEG activity. Current source density time series were generated for 33 regions of interest (ROI) in each hemisphere for four frequency bands. Pearson correlation coefficients (R) were computed between all ROIs in each hemisphere, for four bands across the investigated samples. R values corresponded to intrahemispheric, cortico-cortical functional EEG connectivity (EEGfC). Group and condition differences were analyzed by statistical parametric network method.

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Main results: $p < 0.05$, corrected for multiple comparisons: (1) The untreated IGE group showed increased EEGfC in the delta and theta bands, and decreased EEGfC in the alpha band (as compared to the NC group); (2) VPA treatment normalized EEGfC in the delta, theta and alpha bands; and (3) degree of normalization depended on frequency band and cortical region.
Conclusions: VPA treatment normalizes EEGfC in IGE patients.

Introduction

Valproate (VPA) is an effective antiepileptic drug for idiopathic generalized epilepsy (IGE) syndromes. Its anticonvulsive mechanisms were thoroughly investigated at the molecular and cellular levels. Classic pharmacological research demonstrated that VPA binds to several neuronal and glial targets and modifies electric activity of these cells (Cotariu et al., 1990; Löscher, 2002; Capek and Esplin, 1990). However, the results do not explain the full therapeutic effect of VPA. The best argument for this is the so-called delayed or carryover effect of VPA (Löscher, 2002) that contributes to its superior therapeutic efficacy in IGE (Nicolson et al., 2004). The delayed effect suggests that VPA causes rearrangement of cerebral structure and/or function, which protects against seizures and is independent of the momentary serum level of the drug (Burr et al., 1984; Stefan et al., 1984). Recently, a few other studies supported the enduring effect of VPA on cerebral connectivity, which may give rise to beneficial or adverse effects. VPA inhibits effective connectivity among motor areas in healthy volunteers (Li et al., 2011). VPA alters expression of multiple genes in the CNS in rats (Fukuchi et al., 2009) and epilepsy patients as well (Tang et al., 2004). VPA modifies cortical excitability by modifying neuron—glia relationship (Wang et al., 2012), influences myelin production, repairs and alters neuronal connectivity (Rosenzweig et al., 2012). IGEs are increasingly realized as network disorders, so it is reasonable to suppose that VPA modifies abnormal cerebral connectivity.

The aim of this study was to investigate the effect of chronic VPA administration on functional EEG connectivity (EEGfC) in IGE patients. The key-lock principle of pharmaco-EEG (Saletu et al., 2002) suggests that if epilepsy results from abnormal cortical function, normalization of that function results in clinical improvement. We have tested the hypothesis that VPA reverses abnormal resting-state intrahemispheric, cortico-cortical EEGfC in successfully treated IGE patients. Targeting this part of cerebral connectivity is justified because abnormal intrahemispheric connectivity is the neurophysiological basis of seizure-prone state and ictogenesis in experimental models (Timofeev and Steriade, 2004) and IGE syndromes as well (Holmes et al., 2004, 2010; Clemens et al., 2013).

Patients and methods

Patients and control persons

The study design was approved by the Local Research Ethics Committee of Kenézy Gyula County Hospital, Debrecen, Hungary. All unmedicated IGE patients, who visited one of the collaborating epilepsy outpatient services, were potential candidates for the study. Patients with recent-onset IGE were diagnosed according to generally accepted criteria (Panayiotopoulos, 2005). No diagnostic procedure was indicated, missed, or postponed for study purposes only. Therapeutic decision has done after correct diagnosis was stated. The patients were informed about risks and benefits of the drug treatment, with special reference to VPA-related risk for females of childbearing age. VPA was not the drug of first choice for those who desired to be pregnant within a few years. Also patients who had a well-documented, longer history of IGE but did not take medication for any reason were potentially eligible for the study. Risk-benefit estimation was exposed to them as well and individual experience with prior drug treatment was taken into consideration.

Inclusion criteria were: first seizure after the fifth year of life; clinically and electrographically unequivocal findings indicating one of the common IGE syndromes: idiopathic childhood absence or juvenile absence epilepsy (ABS), juvenile myoclonic epilepsy (JME), epilepsy with generalized tonic—clonic seizures exclusively (GTC); the decision to treat the patient with VPA monotherapy. Exclusion criteria were: significant neurological or psychiatric comorbidity, metabolic disorders, alcohol or substance abuse and any other medical condition that is known to significantly modify EEG activity. Patients having a generalized tonic—clonic seizure in the five days prior EEG investigation were excluded. 26 patients entered the study (ABS = 14, JME = 7, GTC = 5). Age-and sex distribution were: 11 males, 15 females, 7—54 years of age, mean age: 17.2 years. 17 patients had recent-onset IGE, 4 patients had long-lasting IGE, disease onset was uncertain in 5 patients.

Baseline clinical and EEG evaluations were carried out at entry visit. Initial daily dose of VPA was 300 to 500 mg. The dose was increased until seizure freedom was reached. The final daily dose of VPA was 300 to 1500 mg. The second EEG was recorded 3 month after the first one because the initial, transient EEG effects of the drug disappear by this time (Sannita et al., 1989). The patients' general and neurological condition did not change from initial to control evaluation. No patient reported complaints indicating neurotoxicity.

To evaluate the baseline EEGfC abnormality in the patient group, a group of healthy, normal control persons (NC) was created. Each patient was matched to a NC person of same age and sex. Mean age for the NC group was 16.9 years.

EEG recording and sample selection

EEG recordings were carried out in the morning, after a night of sufficient sleep, in a semi-isolated room, with the same type of digital equipment, by trained personnel. Silver-silver chloride electrodes were placed according to the 19 sites of