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Glutamate concentrations vary with antiepileptic drug use and mental slowing

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ABSTRACT

Objective: Although antiepileptic drugs (AEDs) are effective in suppressing epileptic seizures, they also induce (cognitive) side effects, with mental slowing as a general effect. This study aimed to assess whether concentrations of MR detectable neurotransmitters, glutamate and GABA, are associated with mental slowing in patients with epilepsy taking AEDs.
Methods: Cross-sectional data were collected from patients with localization-related epilepsy using a variety of AEDs from three risk categories, i.e., AEDs with low, intermediate, and high risks of developing cognitive problems. Patients underwent 3T MR spectroscopy, including a PRESS (n = 55) and MEGA-PRESS (n = 43) sequence, to estimate occipital glutamate and GABA concentrations, respectively. The association was calculated between neurotransmitter concentrations and central information processing speed, which was measured using the Computerized Visual Searching Task (CVST) and compared between the different risk categories.
Results: Combining all groups, patients with lower processing speeds had lower glutamate concentrations. Patients in the high-risk category had a lower glutamate concentration and lower processing speed compared with patients taking low-risk AEDs. Patients taking intermediate-risk AEDs also had a lower glutamate concentration compared with patients taking low-risk AEDs, but processing speed did not differ significantly between those groups. No associations were found between the GABA concentration and risk category or processing speed.
Conclusions: For the first time, a relation is shown between glutamate concentration and both mental slowing and AED use. It is suggested that the reduced excitatory action, reflected by lowered glutamate concentrations, may have contributed to the slowing of information processing in patients using AEDs with higher risks of cognitive side effects.

1. Introduction

Although antiepileptic drugs (AEDs) are effective in suppressing epileptic seizures, they may also induce side effects. These side effects can strongly affect the quality of life of patients, with slowing of central information processing speed as the dominant cognitive effect of most AEDs and also the first sign of cognitive adverse effects [1,2]. Cognitive side effects are commonly seen among the different AED regimes, but the occurrence and severity vary between different AEDs. The newer AEDs lamotrigine and levetiracetam are suggested to have no adverse, and maybe even beneficial, cognitive effects, while topiramate is known for its deleterious cognitive effects. Other AEDs, such as valproate or carbamazepine, are associated with milder cognitive effects [1,3,4].

Antiepileptic drugs aim to control epileptic seizures via a number of distinct mechanisms of action, which can be subdivided in suppression

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of the excitatory mechanisms or enhancement of inhibitory mechanisms [5]. Although cognitive side effects are likely to result from the anticonvulsant activity of the AEDs, these effects cannot be linked to any particular mechanism of action, and other mechanisms might be involved as well [6]. It has been hypothesized that, especially, AEDs with mechanisms acting on the γ-aminobutyric acid (GABA) system cause cognitive side effects, but similar side effects are also induced by AEDs with other mechanisms of action [7]. Furthermore, it is currently not possible to predict which patients will suffer from these side effects and who will not. However, compliance to AED therapy relies on efficacy as well as tolerance to side effects.

In vivo measurements of the main inhibitory and excitatory neurotransmitters GABA and glutamate can be provided by proton magnetic resonance spectroscopy (^{1}H-MRS). In healthy individuals, higher GABA concentrations and lower glutamate concentrations have been associated with better cognitive performance [8–10]. Previous studies also showed that AED treatment can be associated with altered neurotransmitter concentrations [11]. Although several studies have been performed to associate GABA and glutamate concentrations with seizure control [12–14], to our knowledge, the association with cognitive side effects has not been investigated yet. The aim of this cross-sectional study was to assess whether GABA and glutamate concentrations can be linked to cognitive functioning, in terms of decreased processing speed, in patients with epilepsy on long-term AED treatment.

2. Material and methods

2.1. Patients

Patients with localization-related epilepsy, recruited from our tertiary epilepsy referral center, were included in this study. Inclusion criteria were an age between 18 and 70 years and no contraindications for MRI (metal implants, claustrophobia, or pregnancy). This study was approved by the local medical ethical committee, and written informed consent was obtained from all patients before the examination.

To obtain a variation in information processing speed, three groups of patients using different AEDs were included. The groups were defined according to Samarasekera et al. [15], based on the known risk of developing cognitive side effects: a low-risk category (levetiracetam and lamotrigine), an intermediate-risk category (valproate, carbamazepine, oxcarbazepine, and phenytoin), and a high-risk category (topiramate). Both patients on mono- and polytherapy were included, but patients took maximal two different AEDs. Patients on polytherapy were classified according to the AED in the highest-risk category.

2.2. Neuropsychological investigation

Information processing speed was used as a measure for cognitive side effects, as slowing of central information processing speed is the most common side effect of AEDs [2]. For this, the Computerized Visual Searching Task (CVST) was used [16]. In this task, a centered grid pattern has to be compared with 24 surrounding grid patterns. Participants have to find the grid pattern identical to the centered pattern. The score is the average time needed to complete this task. Additionally, as global cognitive abilities are assumed to be unaffected by AEDs [2], the Raven Standard Progressive Matrices was performed to correct for possible variation in cognitive abilities between the patients [17]. This is a nonverbal reasoning test, in which participants have to identify the figure that is required to fulfill a series of eight other figures.

2.3. Data acquisition

The MR data were acquired on a 3.0T MR scanner equipped with an 8-channel head coil (Philips Achieva, Philips Medical Systems, Best, The Netherlands). Glutamate concentrations were measured using a PRESS sequence (T_E/T_R: 35/2000 ms, 128 averages, VAPOR water suppression). The GABA-edited MR spectra were acquired using a MEGA-PRESS sequence (T_E/T_R 68/2000 ms, 320 averages, with editing pulses at 1.9 (ON) and 7.46 ppm (OFF) interleaved in 40 blocks, MOIST water suppression). Both spectra were acquired from the same $3 \times 3 \times 3$-cm^3 voxel located around the parietooccipital sulcus (Fig. 1). This location has an optimal signal-to-noise ratio and is commonly selected in MRS studies [18]. To estimate the water signal, separate scans without water suppression were made directly after the PRESS and MEGA-PRESS scans (with T_E/T_R 35/2000 ms and 128 averages or T_E/T_R 68/2000 ms and 8 averages, respectively). Additionally, a T1-weighted scan was made to determine the voxel composition (voxel size: $1 \times 1 \times 1$ mm, flip angle: 8°, 3D fast spoiled gradient echo sequence, $T_E/T_I/T_R$ 4.8/1022/8.3 ms, 180 slices).

2.4. Data analysis

The PRESS spectra were analyzed using LCModel (version 6.3-1L). LCModel fits the spectrum with a linear combination of individual metabolite spectra [19]. A standard basis set with sixteen different simulated metabolite spectra was used in this analysis, and spectra were analyzed within the resonance frequency range from 0.2 to 4.0 ppm. In addition to glutamate, tNAA (N-acetyl aspartate + N-acetylaspartylglutamate), tCho (phosphorylcholine + glycerophosphorylcholine), and tCr (creatine + phosphocreatine) concentration estimates were collected for further analyses.

Gannet (version 2.0) was used for the preprocessing and quantification of the GABA+ concentration (i.e., GABA and coedited macromolecules) [20]. The GABA peak is fitted to a Gaussian model curve. Gannet is designed for GABA+ quantification but also enables Glx quantification from MEGA-PRESS spectra [21]. Gannet has the advantage that it also includes frequency and phase corrections [22,23]. The MEGA-PRESS scans are more vulnerable for field drifts and movement artifacts than typical PRESS scans because of the addition of an editing pulse and subtraction of ON and OFF scans to obtain difference spectra, potentially leading to subtraction artifacts. Frequency correction can reduce quantification errors [22]. All spectra were visually inspected on subtraction artifacts and adequate noise levels.

Repeatability of these methods was tested in five healthy volunteers (age: 29 ± 4 year, four male), who underwent two PRESS and MEGA-PRESS scans immediately after each other. The results showed a coefficient of variation of 2.9%, 5.2%, and 8.1% for glutamate (using PRESS/LCModel), Glx (using MEGA-PRESS/Gannet) and GABA+, respectively. Because of the better coefficient of variation of glutamate estimations with PRESS than Glx estimations with MEGA-PRESS and because of a moderate concordance between these measurements in the included patients (Pearson correlation coefficient = 0.31, $p = 0.046$), only glutamate measurements with PRESS were considered in this study.

All concentrations are reported relative to the unsuppressed water signal from the same volume. The voxel composition, in terms of gray matter, white matter, and cerebral spinal fluid (CSF), was determined with FMRIB's Automated Segmentation Tool (FAST), part of FSL (version 5.0.1), was applied to determine the voxel composition in terms of gray matter, white matter, and cerebral spinal fluid (CSF) content [24,25]. Assuming that the neurometabolites are only present in the gray and white matter, the concentrations relative to the water signal were corrected for the CSF content of the voxel. Therefore, the neurometabolite concentrations were divided by the sum of the gray and white matter fractions.

2.5. Statistical analysis

Associations between the neurometabolite concentrations (i.e., glutamate, GABA+, tNAA, tCho, and tCr) and CVST were tested with linear regression analysis, with CVST as dependent variable and the concentrations as independent variables. Separate analyses were performed for each neurometabolite. Besides the neurometabolite concentration, age and the percentage correct answers in the Raven