Topiramate increases human brain GABA within thirty minutes

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Introduction

Topiramate is a broad-spectrum antiepileptic drug used as adjunctive and monotherapy [1,2]. It is one of the most powerful of the new AEDs, effective in a wide variety of seizure types. Topiramate may become useful in the management of headache, mood disorders, and pain [3]. Topiramate appears to have multiple antiepileptic actions in rodent models [4, 5]. Topiramate is associated with above normal GABA, homocarnosine, and pyrrolidinone levels in epilepsy patients [6, 7]. In humans without epilepsy, topiramate raises brain GABA within three hours of the first 200 mg dose [8]. We measured the GABA and homocarnosine response to topiramate in patients with complex partial seizures.

Methods

Studies were done with a 2.1 Tesla Oxford Magnet Technologies (OMT) 1 meter bore magnet equipped with a modified Bruker AVANCE spectrometer and OMT shielded gradients and power supplies. The back of the head rested on an 8 cm distributed capacitance radio-frequency surface coil tuned to the 1H NMR frequency of 89.43 MHz. From the scout image a 3.0x1.5x3.0 cm (14 cm3) volume in the occipital cortex was chosen for MR measurements. Homonuclear editing of the 3.0 ppm C4-GABA and the 3.4 ppm C4-pyrrolidinone resonances were performed using the J-editing pulse sequence described previously [9, 10]. Brain GABA measurements were corrected for co-edited signals from homocarnosine and macromolecules [9, 10, 11]. Homocarnosine was measured as previously described [6, 10, 11]. The median age of the fifteen patients (four men) started on topiramate was 32 years (range 19-49). Other antiepileptic drugs used included carbamazepine, phenytoin, gabapentin, valproate, lamotrigine, and phenobarbital, with eight patients on monotherapy. All subjects gave informed consent for the study approved by the Yale Human Investigations Committee.

Results

The first, 100 mg dose of topiramate increased brain GABA within 30 minutes of oral administration (Figure 1). The maximal increase was seen within two hours. Brain GABA remained elevated for over 24 hours.

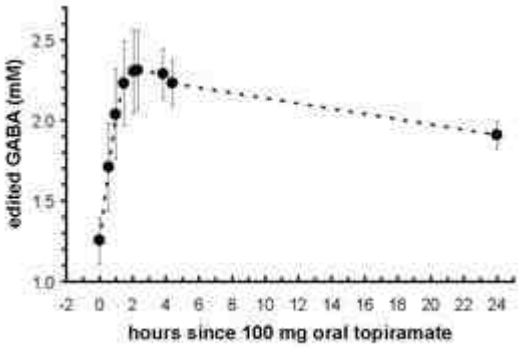

Figure 1 shows serial mean edited GABA measurements with 95% confidence interval error bars.

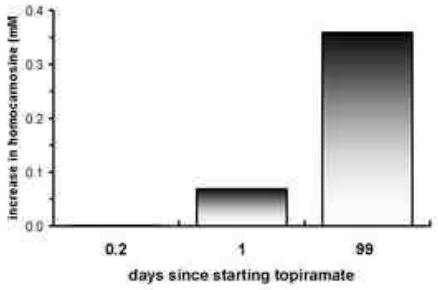

Figure 2 shows the mean increase in occipital lobe homocarnosine. Within 24 hours of the first dose, homocarnosine increased and continued to increase with daily topiramate.

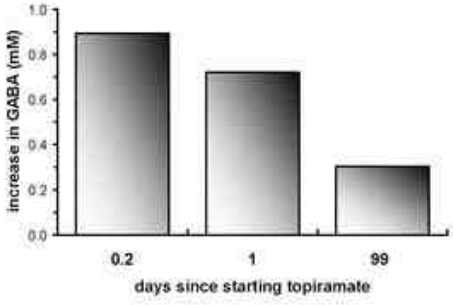

Figure 3 shows the increase in brain GABA alone (edited GABA minus homocarnosine). Within four hours, GABA increased by 0.9 mM (95% CI 0.7-1.1). By 24 hours, part of the GABA had been converted to homocarnosine by homocarnosine synthetase. This enzyme is localized to a subclass of GABAergic neurons. Substrates required for homocarnosine synthesis include ATP, histidine, and GABA [12]. Because edited GABA remained constant, GABA levels decreased are more was converted to homocarnosine with daily use of topiramate.

Discussion

The first 100 mg dose of topiramate rapidly increases human brain GABA within 30 minutes. Homocarnosine begins to increase within 24 hours. The increase in brain GABA and homocarnosine with topiramate has not been reported in animal models [4, 5]. The mechanisms that cause the increases in brain GABA remain unknown. Further studies in humans using stable-isotope and C13-spectroscopy should be helpful in defining the metabolic mechanisms that increase GABA.

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