Topiramate increased GABA, homocarnosine, and pyrrolidinone in patients with complex partial seizures.

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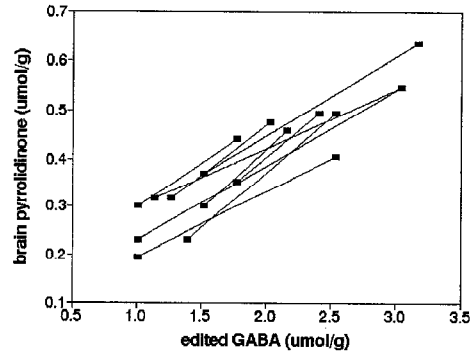
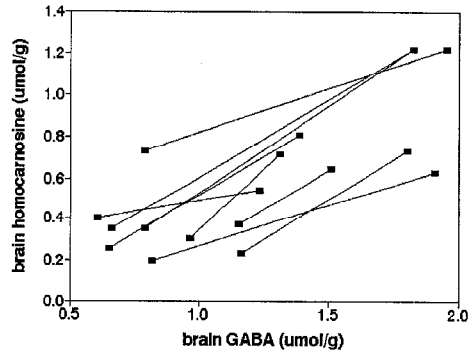
Introduction. Topiramate is a new antiepileptic drug with multiple putative mechanisms of action [1]. In rodents, it does not increase brain GABA significantly. Recently, topiramate was reported to increase spin-spin edited GABA in healthy subjects [1]. In human cerebrospinal fluid, "conjugated GABA" consist primarily of micromolar amounts of homocarnosine and pyrrolidinone, and small amounts of other GABA containing peptides [3]. Free GABA is present in nanomolar concentrations. Homocarnosine, a dipeptide of GABA and histidine, is a proposed inhibitory neuromodulator synthesized in subclasses of GABAergic neurons [4]. Regional human brain homocarnosine concentrations do not correlate with GABA. Increased brain homocarnosine is associated with improved seizure control [5]. Pyrrolidinone, the internal lactam of GABA, is an important intermediate in the metabolism of brain polyamines [6]. Chronic oral administration of pyrrolidinone raises brain GABA levels and has anticonvulsant effects [7]. We report our serial , in vivo measurements in patients with epilepsy.

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 cm^3) volume in the occipital cortex was chosen for NMR 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 [8, 9]. Homocarnosine was measured in T1 edited spectra [10].

Nine patients (three men) with complex partial seizures were enrolled to serially measure the effects of adjunctive topiramate on brain GABA metabolism. Seven patients were on monotherapy with carbamazepine (2), primidone (2), gabapentin (2), and valproate (1). One patient was taking valproate and primidone; the ninth patient carbamazepine and lamotrigine.

Results and Discussion. Mean edited GABA increased by 1.2 µmol/g (95% CI 0.8 - 1.6) with the start of daily topiramate therapy (292 mg/day, range 75 - 500). Pyrrolidinone increased in all patients on average by 0.21 µmol/g (95% CI 0.16 - 0.26). As shown in Figure 1, there was a linear relationship between edited GABA and pyrrolidinone. Homocarnosine increased in all patients, on average by 0.5 µmol/g (95% CI 0.3 - 0.7). There was a correlation between brain GABA and homocarnosine (Figure 2), but not as strong as between edited GABA and pyrrolidinone. Brain GABA (edited GABA minus homocarnosine) increased by 0.80 µmol/g (95% CI 0.5 - 01.1).





In a recent meta-analysis, topiramate was shown to be the most powerful of the newer antiepileptic drugs [11]. Our unexpected observations of a major increase in brain GABA, homocarnosine, and pyrrolidinone following the use of topiramate suggests that the response of GABA metabolism to topiramate is different in humans and rodents. Observations made in rodent models must be confirmed in patients. The increase in human brain GABA, homocarnosine, and pyrrolidinone should contribute to the seizure protection provided by topiramate.

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NIH-NINDS grants: NS06208, NS32126.
Topiramate was supplied by Ortho McNeil.