Increased GABA Concentration Correlates with Decreased fMRI Signals in Vigabatrin-Treated Anaesthetized Rat Brain

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Introduction

GABA is the major inhibitory neurotransmitter in the mammalian cortex. GABA is synthesized by glutamic acid decarboxylase (GAD) and converted to succinic semialdehyde by the action of GABA transaminase (GABA-T). When GABA-T is inhibited by its irreversible inhibitor vigabatrin (VGB), an antiepileptic drug, GABA accumulates substantially in the brain in a dose-dependent fashion [1]. Transplanted genetically engineered GABA-producing cells have also been shown to significantly raise seizure thresholds [2]. Here we report the effect of acute VGB treatment on the fMRI response to somatosensory stimulation in α-chloralose-anesthetized rats.

Methods

Male adult Sprague-Dawley rats (185±25g, n = 18) were studied on two 11.7 Tesla Bruker spectrometers. All rats were orally intubated and mechanically ventilated with a mixture of 70% N_2O/30%O_2 and 1.5% isoflurane. A femoral artery and a femoral vein were cannulated for monitoring arterial blood gases (pO_2, pCO_2), pH, MBP, and for intravenous infusion of α-chloralose. After surgery, isoflurane was discontinued and pancuronium bromide was administrated (4 mg/kg every 90 min, i.v.) to facilitate immobilization. Arterial blood pO_2 was within 120-150mmHg, pCO_2 within 25-35mmHg, MBP within 80-100mmHg, plasma pH within 7.35-7.45. The rats were divided into two groups: the VGB-treated group (VGB, 500 mg/kg, 0.6 cc, i.v., n = 10 for fMRI, n = 3 for spectroscopy) and the control group (saline, 0.6 cc, i.v., n = 5). For spectroscopy studies, an adiabatic PRESS sequence was used to measure brain GABA from a 50 µl voxel in the somatosensory cortex. For fMRI studies, both forepaws were stimulated through needles inserted in between digits 1, 2 and digits 3, 4, respectively. The needles were connected to a stimulator that generated 2 mA 0.3 ms pulses at a frequency of 3 Hz. Three-slice single-shot spin-echo EPI (2-mm thickness coronal slices with in-plane resolution of 400 µm x 400 µm) was used to measure the fMRI response. TR/TE=500/25 ms. Activation maps were generated from pixels presenting a minimum cross-correlation coefficient of 0.3. To compare relative fMRI signal changes in the somatosensory cortex, regions of interest (4x4 pixels) were chosen based on the center of the highest intensity in activation maps on both sides of the cortex.

Results

A typical set of localized ^{1}H spectra from the VGB-treated rat brain was given in Fig. 1 (4 Hz exponential line-broadening). Activation maps (overlaid on the EPI images) as a function of time from the VGB-treated group were presented in Fig, 2. Fig. 3 showed a time course of the fMRI signal intensity averaged over the duration of stimulation with VGB treatment. On acute administration of VGB, the time course of the fMRI signal (in % change of EPI signal intensity) decreases significantly accompanied by a gradual decrease in the area of activation. The effects

Fig. 1,

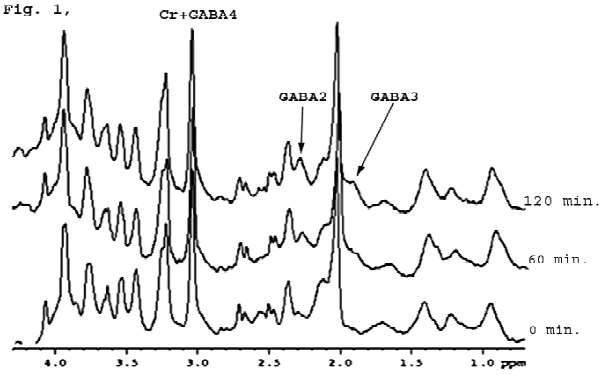
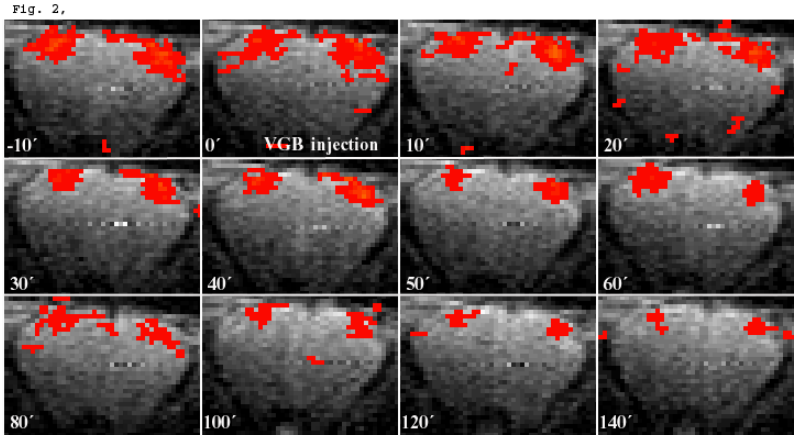


Fig. 2,



of VGB and saline administration on the relative changes in fMRI signal (in % change of fMRI signal) were shown in Fig 4. At the 30 min time point after VGB administration, the relative changes in fMRI signal between the two groups started to differ with statistical significance ($p<0.01$). Prior to this point, differences in the changes in fMRI signal between the two groups are not statistically significant (Fig. 4) ($p>0.20$).

Discussion

Brain GABA was found to increase progressively over time after VGB administration (Fig. 1). Correlating with the spectroscopic results, we found significantly depressed fMRI response to forepaw stimulation in the somatosensory cortex in the VGB-treated group while in the control group the fMRI response had no significant variations. The preliminary findings of the present study therefore suggest that the increased availability of cortical endogenous GABA caused by inhibition of GABA-T suppresses the fMRI signal intensity in α-chloralose anaesthetized rat brain. The mechanism of this suppression could be due to feedback inhibition at GABAergic synapses which would reduce neuronal firing. Our findings are also consistent with the suggestion that VGB may cause a use-dependent or frequency-dependent enhancement of GABA-mediated transmission [3]. Finally, the fMRI signals measured in this study contain both microvasculature BOLD response and the secondary signal enhancement caused by CBF in-flow effects with both decreasing with attenuated neuronal activities.

Fig. 3,

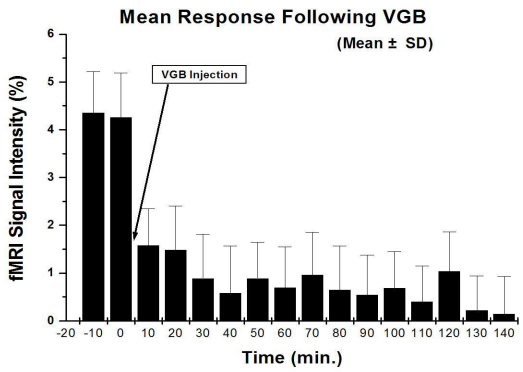
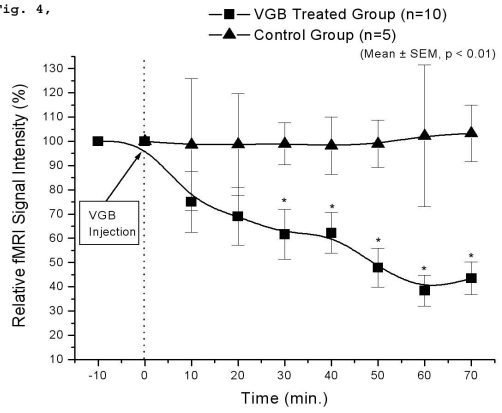


Fig. 4,



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