In Vivo Detection of Cortical [2-^{13}C]GABA Turnover from Intravenously Infused [1-^{13}C]Glucose at 11.7 Tesla

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Introduction

In GABAergic neurons, glutamic acid decarboxylase (GAD) converts [4-^{13}C]Glu directly into [2-^{13}C]GABA. The turnover of [2-^{13}C]GABA is a direct measure of the activities of GAD and the GABA shunt, which are closely related to the metabolic aspect of the primary inhibitory function in CNS. The purpose of this report is to demonstrate that, at 11.7 Tesla (vertical 89-mm bore) and using broadband adiabatic ^{13}C decoupling, [2-^{13}C]GABA can be resolved and measured in proton spectra, allowing, for the first time, direct in vivo measurement of time-resolved kinetics of cortical [2-^{13}C]GABA turnover from intravenously infused [1-^{13}C]glucose. Gabaculine was administered to assess the effects of GABA shunt blockade on [2-^{13}C]GABA turnover.

Materials and Methods

Male Sprague-Dawley rats (150-180 g, n = 8) fasted for 24 hours were studied. The spectroscopy voxels were centered in the neocortex. Gabaculine (100 mg/kg, 0.6 cc, i.v.) was injection one hour prior to the time course measurement. A new adiabatic POCE pulse sequence was designed and implemented. It consists of a 500 μs 90^o adiabatic half-passage (AHP) pulse applied for nonselective excitation followed by six 180^o adiabatic full-passage (AFP) pulses (hyperbolic secant, 1.5 ms, μ = 5, 1% truncation) for single-shot three-dimensional spatial localization via adiabatic slice selective refocusing with a pair of identical AFP pulses per dimension to localize a 4 x 2.5 x 4 mm^3 spectroscopy voxel (40 μL). Broadband adiabatic decoupling was based on the tanh/tan pulses (3 ms, ζ = 10, κ = 20, R = 150).

Results

Fig. 1 shows an in vivo short-TE PRESS proton spectrum prior to gabaculine injection (TR/TE = 2700/15 ms, 4.5 x 2.5 x 4.5 mm^3, NS = 256, AQ = 206 ms). Fig. 2 shows the edited GABA spectra before and one hour after gabaculine injection using a novel one-dimensional doubly selective homonuclear polarization transfer method (TR/TE = 2700/68 ms, 4.5 x 2.5 x 4.5 mm^3, NS = 256, LB = 5 Hz). The negative peak at 2.35 ppm was the Glu-4 signal resulted from partial polarization transfer from the Glu-3 signal at 2.11 pm. After acute administration of gabaculine the signal of the edited GABA doublet at 3.02 ppm acquired from the α-chloralose anaesthetized rat brain significantly increased from 1.1 ± 0.1 μmol/g to 2.4 ± 0.3 μmol/g (mean ± SD, n = 8). Fig. 3 shows a typical set of time-resolved POCE spectra acquired one-hour after gabaculine injection (11.5 min per spectrum with a 3.5 min interval for periodical re-shimming). Fig 4 shows the averaged simultaneously determined time courses of [4-^{13}C]Glu, [4-^{13}C]Gln and [2-^{13}C]GABA.

Discussion and Conclusion

The following relationship was maintained: f.e.([4-^{13}C]Glu) > f.e.([4-^{13}C]Gln) > f.e.([2-^{13}C]GABA). Since [4-^{13}C]Glu is the metabolic precursor of [4-^{13}C]Gln via the glutamate-glutamine cycle, the precursor-product relationship dictates that f.e.([4-^{13}C]Glu) > f.e.([4-^{13}C]Gln). Without inhibiting GABA-T the turnover time of [2-^{13}C]GABA has been found to be much shorter than that of glutamate, which has been considered as evidence of compartmentation of glutamate. With infusion of [1-^{13}C]glucose started one hour after acute gabaculine treatment, we found that f.e.([4-^{13}C]Gln) > f.e.([2-^{13}C]GABA), which is consistent with the concept that astrocytic glutamine is the primary metabolic precursor of GABA after acute GABA-T inhibition. In the intact brain, the GABA shunt activity allows rapid incorporation of ^{13}C labels from [1-^{13}C]glucose through the small GABAergic glutamate precursor pool into [2-^{13}C]GABA. During acute inhibition of the GABA shunt, endogenous repletion of the small glutamate precursor pool is inhibited as a result of the blockade of the GABA shunt. Astrocytic glutamine becomes the primary sources of carbon skeleton for the accumulating GABA pool. Following acute GABA-T inhibition using gabaculine and subsequent infusion of [1-^{13}C]glucose, the accumulation of [2-^{13}C]GABA is a measure of mainly the trafficking of ^{13}C labels from astrocytic [4-^{13}C]Gln to GABAergic neurons, which, as revealed by this study, is much slower than the rate of label incorporation via the GABA shunt in the intact brain.

Fig.1

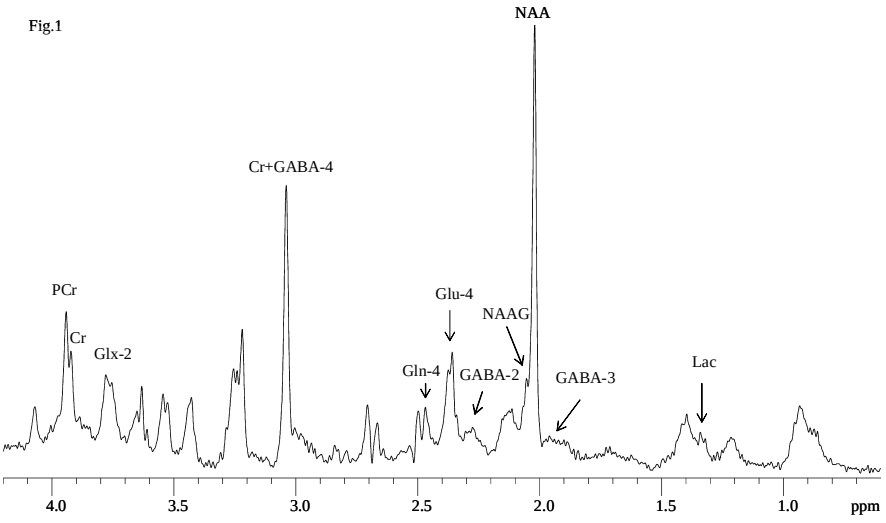

Fig.2

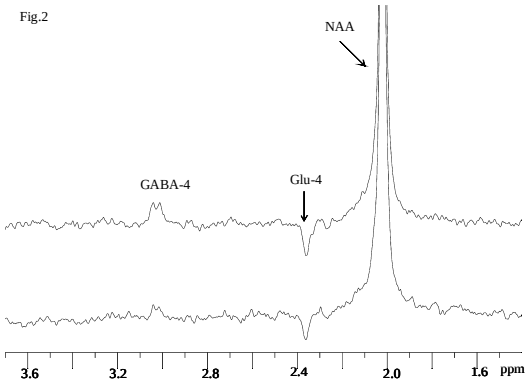

Fig.3

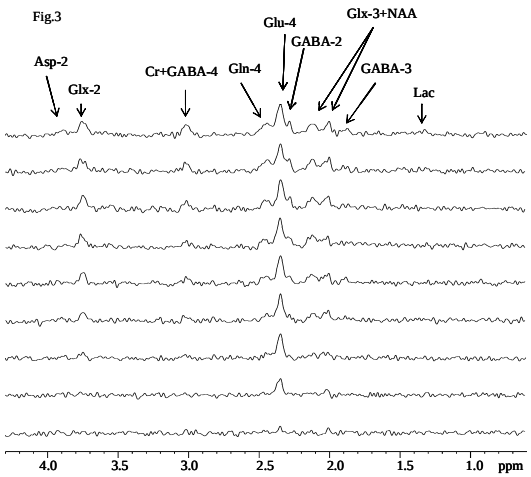

Fig. 4