GABAssale: Selective Homonuclear MQC Transfer Schemes for Unambiguous *in vivo* GABA Detection with Full Signal Recovery and Complete Water Suppression in a Single Scan

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Abstract

This study describes selective homonuclear multiple-quantum coherence (MQC) transfer schemes for achieving efficient, distortion-free and unambiguous *in vivo* detection of GABA in a single scan. GABA MQ coherences involving only the γ– and β-CH_2 of GABA are created with frequency-selective rf pulses. These MQCs are gradient-encoded, and then "read" with a β-CH_2 selective pulse and gradient-decoded for detection. Water and the strong overlapping creatine resonances are eliminated in a single scan, with full GABA signal recovery.

Introduction

γ-Aminobutyric acid (GABA; $H_2NC^{\gamma}H_2C^{\beta}H_2C^{\alpha}H_2COOH$), the major inhibitory neurotransmitter in the mammalian brain, plays a key role in normal brain function. Dysfunction of GABAergic neurotransmission has been implicated in the pathophysiology of a wide variety of neuropsychiatric and neurological disorders, including schizophrenia, depression, and epilepsy. Noninvasive measurement of GABA level changes *in vivo* would thus be of great value in the study of the etiology of these disorders. Spin echo difference spectroscopy and multiple quantum coherence (MQC)-filtered ^1H NMR spectroscopic techniques have been proposed for measuring *in vivo* brain GABA. However, these 'editing' schemes have significant limitations. The spin echo difference spectroscopy method is highly vulnerable to subtraction and motion artifacts, whereas most previously proposed MQC approaches suffer from inefficient coherence selection/suppression that leads to signal loss, and/or to inadequate supression of undesired metabolite and water coherences. Here, we describe three-spin system variants of the *selective* homonuclear MQC (sel-MQC)[(1)] transfer experiment, which overcome these limitations of the existing GABA editing methods, to achieve efficient, distortionless and unambiguous detection of GABA.

The Concept

Conceptually, our proposed GABA editing sequences (e.g., Fig.1) are three-spin extensions of our previously described

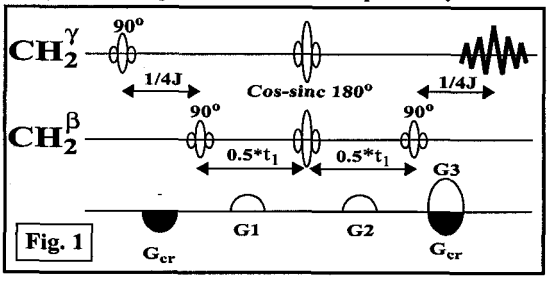

Fig. 1

sel-MQC lactate editing methods[(1)], in which MQC creation is achieved with only frequency-selective rf excitation pulses. Although the GABA spin system is slightly more complex, a significant simplification of its scalar coupling interactions can be achieved through a judicious use of frequency-selective rf excitation pulses. In the first variant shown in Fig. 1, the first and second frequency-selective 90° pulses, separated by a J-evolution delay of $1/4J_{\beta\gamma}$ and applied on the GABA γ-CH_2 and β-CH_2, respectively, create a mixture of zero (ZQC), single (SQC), double (DQC) and triple (TQC) quantum coherences involving only the β- and γ-CH_2. During the subsequent MQC evolution period, t1, a pair of symmetric gradient pulses, G1 and G2, are applied to phase-encode all coherences with order > 0. These two MQC "labeling" gradients are separated by a 180° cosine-modulated sinc pulse that is tailored to excite only the β- and γ-CH_2 resonances, with no excitation of the α-CH_2 resonance, to refocus the chemical shifts and B_0 inhomogeneity dephasing of the β- and γ-CH_2 spins. Finally, a β-CH_2-selective 90° "read" pulse converts the labeled MQ coherences to transverse magnetization that can be refocused into in-phase

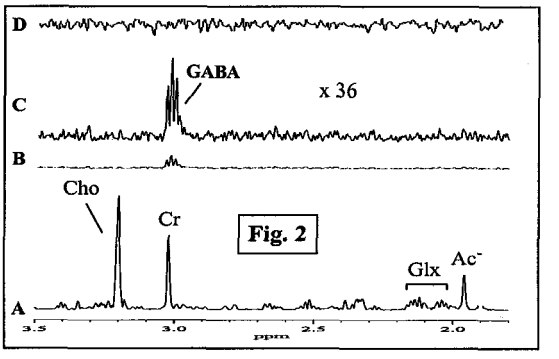

Fig. 2

SQC for detection with an appropriate choice of the decoding gradient, G3. Using G1:G2:G3 = G1:G2:2(G1+G2) selects the DQC pathway, whereas using G1:G2:G3 = G1:G2:3(G1+G2) selects the TQC pathway. Only the DQC data are shown here. **No other coherences survive this MQC filter.** The strong Cr resonance that overlaps the GABA γ-CH_2 at 3.02 ppm remains in SQ throughout and is destroyed in a single scan. Water is never directly excited and is also completely eliminated. Note that in this variant, use of only band-selective excitation pulses has effectively spin-decoupled the α-CH_2 from the β and γ protons, simplifying the spin system. Three other variants will be demonstrated in which **(a)** the 180° cos-sinc pulse is applied to the α and β-CH_2 for **full signal recovery, (b)** only a γ-CH_2-selective 180° pulse is used, and **(c)** a slice-selective, rather than a frequency-selective, 180° pulse is used. Volume localized editing is achieved by preceding all variants with 2- or 3D ISIS. Preceding variant **(c)** with outer volume suppression (OVS)[(2,3)] permits single-shot localized GABA editing.

Proof of Concept

The efficiency of detecting GABA using the proposed detection schemes was evaluated on a 11.75 T Bruker DRX-500 spectrometer. Data were recorded from a rat brain extracts. The results are shown in Fig. 2. Fig. 2A shows the 1D extracts spectrum. In Fig. 2B (blown up in 2C), a cleanly edited GABA from the extracts sample can be seen. Note the flat baseline and maintainance of the correct triplet structure. Water, Cr and all other resonances have been completely eliminated. To ascertain complete elimination of Cr, data were recorded from a 200 mM Cr solution with the editing sequence. Fig 2D shows 100% Cr suppression. A fuller theoretical and experimental verification of the proposed methods will be given.

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(2) Shungu & Glickson, *Magn. Reson. Med.* **30**, 661 (1993)
(3) Shungu & Glickson, *Magn. Reson. Med.* **32**, 277 (1994).