Brain metabolism in glutamatergic and GABAergic compartments detected by in vivo 13C NMR spectroscopy at 14.1 T

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Introduction: The combination of dynamic 13C NMR spectroscopy and the infusion of 13C-enriched substrates is a powerful method to probe metabolic fluxes in vivo. The increase in magnetic field opened the opportunity for enhanced sensitivity and spectral resolution, which has been explored to study brain metabolism [1]. We now investigated the metabolism of γ-aminobutyric acid (GABA) in the brain using localised 13C NMR spectroscopy at 14.1 T. GABA is a ubiquitous amino acid that is widely known as a major inhibitory neurotransmitter. GABA is synthesized in the cytosol from glutamate by the enzyme glutamate decarboxylase (GAD) and subsequently transported into mitochondria where it is catabolised by enzymes of the GABA shunt: in mitochondria, GABA is converted into succinic-semialdehyde (SSA) by GABA-transaminase, with simultaneous amination of 2-oxoglutarate to glutamate; SSA is further catabolized to succinate by SSA dehydrogenase, for dual use in the tricarboxylic-acid (TCA) cycle, and as an electron donor in the mitochondrial electron transport chain. This GABA shunt was included in the model within a GABAergic compartment and GABAergic neurotransmission was modelled as GABA uptake by astrocytes and its metabolism through the glial TCA cycle.

Methods: Male Sprague-Dawley rats (n=6, 271±8 g) were prepared and maintained during the NMR experiment as previously described, under α-chloralose anaesthesia [1,3]. Field homogeneity was adjusted by FASTMAP [4]. The VOI size was 5x8x8 mm3. Localized 1H and 13C NMR spectroscopy was performed on a 14.1 T, 26 cm VNMRS spectrometer (Agilent, Magnex) with a coil consisting of a 1H quadrature surface coil and a 13C linearly polarized surface coil [1,5]. 1,6-[13C]glucose was infused to induce a step function in plasma fractional enrichment (FE) [1], while 13C spectra were measured. Total metabolite concentrations were determined by 1H NMR spectroscopy using SPECIAL [6]. 13C NMR spectra were acquired using semiadiabatic distortionless enhancement by polarization transfer (DEPT) combined with 1H localization [1,5]. Both 1H and 13C spectra were quantified with LCModel [1,7]. Metabolic fluxes were determined with a newly designed mathematical model of brain metabolism that included glial, glutamatergic and GABAergic compartments.

Results: High spectral resolution at 14.1 T and spectra analysis with LCModel allowed for the first time the quantification of FE in the three alphatic carbons of GABA in vivo with a time resolution of 20 minutes. FE of glutamate (Glu C2, C3, C4), glutamine (Gln C2, C3, C4) and aspartate (Asp C2, C3) was quantified at a resolution of 5 minutes, as previously described [1]. A 3-compartment model [2] was fitted to these 13C FE curves and preliminary results show that the GABA-Gln cycle, which depicts GABAergic neurotransmission, is 21±2% of all neurotransmitter cycling (Glu+GABA) and that the GABAergic compartment is responsible by 10±2% of total glucose oxidation, against 48±3% in glutamatergic neurons. In addition, we found that 42±4% of glucose oxidation occurs in glia, from which 24±2% is accounted by anaplerotic pyruvate carboxylation [1].

Conclusion: Direct detection of 13C enrichment of cerebral metabolites was improved at 14.1 T with gain in both sensitivity and spectral resolution. Upon infusion of 1,6-[13C]glucose, time courses for numerous 13C-enriched carbon positions were quantified, namely in Glu, Gln, GABA and Asp, to which we fitted a 3-compartment model of cerebral metabolism that provides insight in GABA metabolism and GABAergic neurotransmission.


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