Dynamic proton MRS in pediatric brain tumors with prominent citrate

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Introduction:
Recently it was reported that prominent citrate identified a subgroup of pediatric grade II astrocytoma destined for aggressive behavior1. It is unclear, which mechanisms caused increased citrate in these tumors and whether citrate is metabolically active. In this study, we administered U-13C-enriched glucose to determine whether the elevated citrate in these tumors is involved in glucose metabolism.

Methods:
After a baseline MRS study, U-13C-enriched glucose (= 0.9 gr/kg, ≈4-5 hours fasting) was orally administered to three pediatric patients with brain tumors (two pontine gliomas, one bithalamic astrocytoma). Thereafter, MR spectra were acquired up to ≈90 min after glucose administration. The studies were carried-out on a 3T (Philips, Best, The Netherlands, one study) and on 1.5T scanner (GE, Milwaukee, two studies). Four healthy controls were studied for method evaluation. Single-voxel PRESS spectra (TR=2s (3T), TR=1.5s (1.5T), TE = 35ms, 128 averages were acquired. LCModel software (S. Provencher Inc.) was used for processing and quantitation.

Results:
Citrate was prominent in all three patients. In controls, 13C label replaced 12C and resulted in an apparent reduction of the 1H MRS detectable breakdown products of glucose such as glutamate and glutamine (Fig. 1). In patients, changes after 13C-Glc administration were less obvious (Fig. 2). When all measurements in the three patients were normalized relative to baseline levels, citrate did not change significantly. A small but significant reduction of lactate was observed (Fig. 3).

Discussion:
Glycolysis converts glucose to pyruvate. Pyruvate can then be decarboxylated to form acetyl-CoA (pyruvate dehydrogenase) and/or oxaloacetate (pyruvate carboxylase) or reduced to lactate (by lactate dehydrogenase). The first two reactions would result in 13C label accumulating in TCA-cycle intermediates such as citrate and α-ketoglutarate and subsequently glutamate (via glutamate dehydrogenase). Heteronuclear 13C-1H J-couplings alter the proton MR signals as readily observed in controls with normal TCA-cycle activity. The lack of a reduction of the citrate signal indicates that glucose-derived acetyl-CoA or oxaloacetate did not enter the TCA-cycle in significant amounts in the tumors studied. Citrate does not appear to be involved in glucose metabolism. The tumors may rely disproportionally on glycolysis for energy production (Warburg effect) which is consistent with the observed label accumulation in lactate.

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