

Dynamic proton MRS in pediatric brain tumors with prominent citrate

Ida Ashoori^{1,2}, Ashok Panigrahy^{1,3}, Arabhi Nagasunder^{1,4}, Girish Dhall⁵, Marvin D. Nelson¹, and Stefan Blüml^{1,2}

¹Radiology, Childrens Hospital Los Angeles, Los Angeles, CA, United States, ²Rudi Schulte Research Institute, Santa Barbara, CA, United States, ³Pediatric Radiology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, United States, ⁴Radiology, Children's Medical Center, Dallas, Texas, United States, ⁵Hematology/Oncology, Childrens Hospital Los Angeles, Los Angeles, CA, United States

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 disproportionately on glycolysis for energy production (Warburg effect) which is consistent with the observed label accumulation in lactate.

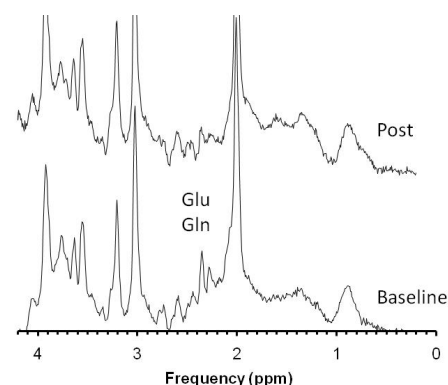


Fig. 1: In control studies, ¹³C label accumulation in breakdown products of Glc, such as glutamate (Glu) or glutamine (Gln), resulted in an apparent reduction of the proton Glu and Gln signal due to heteronuclear ¹³C-¹H J-coupling.

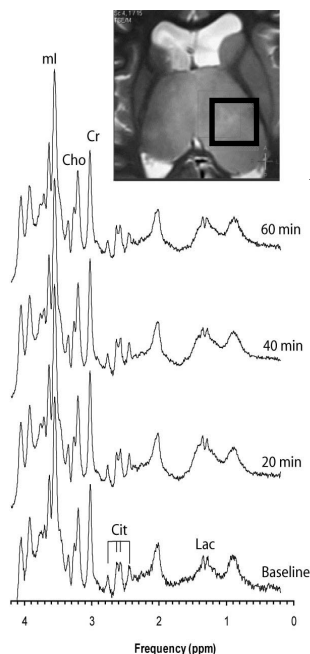
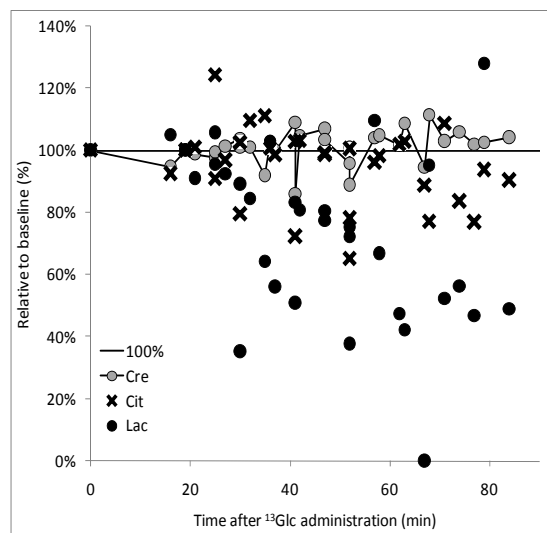


Fig. 2: Serial MRS studies of a pediatric patient with a grade II astrocytoma with prominent citrate and a small lactate peak. In this individual, only a small reduction of lactate was observed, whereas there was no change of the citrate signal.

Fig. 3: When all studies from the three patients were combined, lactate decreased significantly (mean post-Glc lactate: $75 \pm 28\%$, $p < 0.0001$ one-sample t-test), whereas citrate ($95 \pm 12\%$) was not different after U-¹³C Glc administration. Other metabolites, such as creatine (Cre), were also unchanged ($101 \pm 5\%$).



References: 1. Blüml S et al. Neuro Oncol. 2011 Oct.; 13(10) : 1107-17.

Acknowledgment: Rudi Schulte Research Institute, Ian's Friends Foundation.