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Reply:

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Is ATP Elevated in Patients With GAMT Deficiency?

We read with interest the paper by Bianchi et al., in which the authors report on the treatment monitoring of 2 patients with guanidinoacetate methyltransferase (GAMT) deficiency and 3 patients with an argininosuccinate lyase (ASL) deficiency. Repetitive MR measurements of these patients are not trivial, and some interesting observations are presented in this paper that may be very useful for their treatment.

Bianchi et al. studied the levels of brain creatine (Cr) and phosphocreatine in 1 patient with GAMT deficiency using 31P- and 1H-MR spectroscopy (phosphorous and proton MR spectroscopy) before and after therapy. The authors conclude from the 31P-MR spectra that levels of adenosine triphosphate (ATP) are elevated in the brain of this patient before therapy, and that these levels normalize with treatment. Furthermore, they speculate that this may be the result of redistribution in the creatine kinase (CK) reaction (ATP + Cr → ADP + PCr) from the reduced levels of Cr in the brains of other patients. In our opinion, this conclusion is based on increased ATP and the speculation on its origin are debatable.

Tissue levels of ATP are tightly balanced by consumption and production of ATP. Because the brain is a highly oxidative organ, most production of ATP occurs by mitochondrial oxidative phosphorylation, though other processes such as glycolysis also contribute. The primary function of the CK reaction is to dampen large fluctuations in the ratios of ATP and adenosine diphosphate (ADP) during periods of high energy demand, all in close relationship to the energy-producing and energy-consuming sites. Therefore, it is unlikely that a mere shift in the concentration of Cr will result in the drastic, global elevation of ATP as reported.

According to Bianchi et al., the supposed elevation of ATP is based on the 31P-MR spectrum of GAMT; in patient 1, in particular, the signal intensity for β-ATP (at 16.5 ppm) is increased. However, ATP has 3 phosphate groups, all giving a distinct signal intensity at different positions on the 31P-MR spectrum. If ATP were elevated, why are not all 3 signals equally elevated, since they belong to the same molecule? Although the other ATP signals (γ- and α-ATP) also represent other phosphorous compounds such as ADP, these are present at much lower concentrations (~μM range) than ATP (~mM). Therefore, changes in the levels of these compounds cannot account for an selective elevation in the signal intensity of β-ATP. We believe that the increase in the signal intensity of β-ATP may be because of experimental issues in the 31P-MR spectroscopy method. Factors such as incorrect phasing of the MR spectrum, the absence of a first-order phase correction, and insufficient bandwidth of the excitation pulse in combination with a misplaced carrier resonance could all play a role here. Unfortunately, Bianchi et al. did not provide sufficient information on data acquisition and quantification of the 31P-MR signals to resolve this issue.

Finally, the authors state that my colleagues and I, in GAMT-deficient mice, and Schulze et al., in a patient, display the same ab-...