

Cognition in Urea Cycle Defects: Role of Ammonia, Glutamine and Myoinositol

Marc Yudkoff

Dietary restriction of protein and selected amino acids usually improves clinical outcome in disorders of amino acid metabolism, but subtle defects in cognitive performance may occur even with scrupulous dietary treatment. Thus, in ostensibly asymptomatic female carriers for ornithine transcarbamylase deficiency (OTCD), an X-linked form of a urea cycle defect (see in chapter text) , significant weaknesses occur in fine motor dexterity and speed as well as nonsignificant weaknesses in nonverbal intelligence, visual memory, attention/executive skills, and math (Gyato et al., 2004). The degree of cognitive disability correlates with the rate of residual ureagenesis, as determined by measurement of $^{15}\text{NH}_4^+ \text{C}^{15}\text{N}$ conversion to ^{15}N urea. Studies with ^1H MRS (magnetic resonance spectroscopy) in female carriers suggest a diminution of the brain myoinositol concentration and an increase in the level of glutamine (Gropman et al., 2008), the latter occurring because of increased entry of NH_3 from blood into astrocytes, the site of the glutamine synthetase reaction. Accumulation of glial glutamine favors cell swelling and consequent release of myoinositol in an attempt to restore water balance. Future research may determine whether the loss of myoinositol is large enough to affect second-messenger signaling through the phosphoinositide pathway.

References

- Gropman et al., 2008 Gropman, A. L., Fricke, S. T., Seltzer, R. R., Hailu, A., Adevemo, A., Sawyer, A., et al., and Urea Cycle Disorders Consortium. (2008). ^1H MRS identifies symptomatic and asymptomatic subjects with partial ornithine transcarbamylase deficiency. *Molecular Genetics and Metabolism*, 95, 21–30.
- Gyato et al., 2004 K. Gyato, J. Wray, Z.J. Huang, M. Yudkoff, M. Batshaw, Metabolic and

Neuropsychological Phenotype in Women Heterozygous for Ornithine Transcarbamylase
Deficiency. *Annals of Neurology*. 55 (2004) 80–86.