

Title: Ornithine Transcarbamylase Deficiency *GeneReview* – Pathophysiology

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## **Pathophysiology of OTC**

The ways in which an elevated ammonia level and its secondary effects such as a high glutamine level in brain may cause brain damage have been subject of much debate [Butterworth 2002, Feldman et al 2014]; however, its most severe acute consequence is cerebral edema.

Disturbed water balance and potassium homeostasis/potassium buffering as maintained by astrocytic channels was implicated as a possible main cause of the brain damage caused by hyperammonemia [Lichter-Konecki 2008, Lichter-Konecki et al 2008, Albrecht et al 2010]. Stephan et al [2012] then showed that exposure of brain slices to high ammonia levels does lead to impaired extracellular potassium homeostasis due to the reduced capacity of astrocytes to buffer potassium. They also showed that the capacity of astrocytes to take up glutamate was impaired which could lead to disturbed glutamatergic neurotransmission. Rangroo Thrane et al [2013] were also able to demonstrate that ammonia compromises astrocytic potassium buffering resulting in an increased extracellular potassium concentration which alters neurotransmission. However they differed in their assessment of key astrocytic channels involved from Stephan et al [2012].

Prior to these findings a key role for increased glutamine synthesis in the development of the brain edema was long postulated [Tanigami et al 2005, Zwingmann & Butterworth 2005]. High brain glutamine levels associated with low levels of myoinositol (a known brain organic osmolyte [Zwingmann et al 2004]) were interpreted as evidence that the osmotic consequences of high glutamine levels result in edema and in the brain damage in hyperammonemia.

Increased extracellular potassium levels (which lower the seizure threshold) also provide a possible explanation for the increased frequency of seizures during hyperammonemic coma and during chronic mild hyperammonemia in those with a urea cycle disorder [Lichter-Konecki 2008, Lichter-Konecki et al 2008].

In persons with post-neonatal-onset OTC deficiency proton magnetic resonance spectroscopy (MRS) of the brain showed increased glutamine levels and depletion of myoinositol in an inverse relationship as well as decreased choline concentrations [Takanashi et al 2002, Gropman et al 2008]. The reduction of myoinositol also correlated with impairments in working memory (digit span backwards, and performance IQ). The glutamine/myoinositol ratio was subsequently proposed as a brain biomarker for UCD.

Diffusion tensor imaging (DTI) showed that the Fractional Anisotropy Index of the frontal white matter was lower in affected individuals than in controls, indicating changes in white matter microstructure in these regions. The degree of change seemed to correlate

with the severity of disease. These changes were not detected on T<sub>2</sub>-weighted images. DTI thus provides a means for assessing injury that may have been sustained years prior to the imaging study [Gropman et al 2010].

During a working memory task neuronal activation was increased in persons with OTC deficiency in the right dorsolateral prefrontal cortex and in the anterior cingulate cortex when compared to controls. The increased neuronal activation in these areas despite equivalent task performance was interpreted as indicating sub-optimal activation of the working memory network [Gropman et al 2013].

Additionally the brains of individuals with OTC deficiency show alterations in functional connectivity at rest. Internodal functional connectivity in the default mode network and set-maintenance network is reduced in individuals with partial OTC deficiency compared to controls [Pacheco-Colón et al 2015]. Because several of the affected areas are involved in executive functioning, it is postulated that this reduced connectivity may be an underlying cause of the executive functioning deficits of individuals with OTC deficiency.

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