Creatine Deficiency Syndromes: A Clinical, Molecular and Functional Approach

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Abstract

Creatine deficiency syndromes (CDS) are a set of inborn errors of metabolism whose biochemical hallmark is the absence of creatine/phosphocreatine in the brain. Clinical manifestations are often characterized by intellectual disability, speech and language delay, autistic-like behavior and epilepsy. It has been estimated that endogenous creatine synthesis (via argine:glycine amidinotransferase – AGAT and guanidinoacetate methyltransferase – GAMT) accounts for about half of our daily creatine requirement, while the other half is obtained from our diet by organs and tissues requiring creatine through the action of a plasmalemmal creatine transporter (CT1 – encoded by the SLC6A8 gene). Genetic defects in either AGAT, GAMT or CT1 are a predisposition to CDS. The main form of treatment is via creatine supplementation, with notable success in treating individuals with AGAT and GAMT deficiency. So far, creatine supplementation has been ineffective in treating patients with SLC6A8 deficiency.

In view of the clinical relevance of creatine, especially within the context of patients affected with cerebral creatine deficiency, the studies described in this thesis address two key issues; 1– to explore potential avenues which can be used to improve diagnosis of patients and, 2– unraveling aspects on creatine transport regulation with a view towards improved treatment outcome in patients with a defect in creatine biosynthesis.

At the level of creatine synthesis deficiency we first present a case study of an individual with AGAT deficiency, highlighting their response to creatine supplementation. Followed by functional analysis of missense variants identified in individuals with GAMT deficiency. To investigate the regulation of the creatine transporter we carried out functional gene promoter analysis, splice variant characterization, and transcriptome evaluation in response to defective SLC6A8 expression.