Effect of creatine supplementation on AGAT Expression and Metabolic Intermediates in GAMT-Deficient Mice

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Introduction

Cerebral creatine (CT) depletion is diagnostic of the two biosynthetic creatine disorders; AGAT- and GAMT-deficiency. Treatment of oral CT supplementation is used to replenish the CT levels. It is also in part successful at reducing the elevated, neurotoxic, guanidinoacetate (GAA) levels unique to GAMT deficiency. GAA reduction likely occurs through creatine-mediated AGAT suppression.

Objectives

1. Evaluate effect of 10-week CT supplementation (2% and 4%) on AGAT expression and CT metabolites in organs: kidney, heart, liver, calf, and brain of GAMT-deficient mice
2. Elucidate mechanism of creatine-mediated AGAT-suppression
3. Evaluate efficacy as therapy for metabolite normalization

Methodology

Wild type, GAMT heterozygous and GAMT-deficient mice, 10-12 weeks old, were fed with 2% or 4% CT containing mouse chow for 10 weeks. Mouse body weights and urine were recorder and collected weekly. Mouse organs were harvested after 10 weeks CT supplementation. Mouse urine CT and GAA were analyzed by HPLC. Mouse tissues CT and GAA were analyzed by LC-MSMS and RT-PCR.

Mouse Body Weights

Fig. 1: GAMT-deficient mice body mass gained after 2% CT of 4% CT treatment
Fig. 4: CT and GAA concentrations in GAMT-deficient mice tissues treated with 2% CT and 4% CT. WT-wild type, HET-heterozygous, MUT-mutant.
CT supplementation increases CT and decreases GAA concentration in wild type, GAMT heterozygous and GAMT-deficient urine, kidney, heart, and brain. Surprisingly, GAA was not reduced in the liver. Increasing the percentage of creatine-enrichment did not lead to normalization of GAA in GAMT-deficiency to be equal to those of the wild type.