Pathogenesis of creatine transporter deficiency
New insights into creatine transporter deficiency: the importance of recycling creatine in the brain

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Creatine represents a major nutritional supplement in relation to roles in ATP regeneration and potential neuroprotection in selected neuromuscular diseases. We call attention to the pivotal role of creatine in brain, derived from our studies on inherited cerebral creatine deficiency syndromes that feature intellectual disability and other neurological complications. Creatine is obtained from the diet, and via endogenous synthesis from arginine and glycine involving arginine amidinotransferase (AGAT) yielding the creatine precursor guanidinoacetate (GAA), and guanidinoacetate methyltransferase (GAMT), which generates creatine that traverses the cell membrane via the creatine transporter (CRTR). Inherited deficiencies of AGAT, GAMT or CRTR comprise the cerebral creatine deficiency syndromes which are characterized by severely reduced cerebral creatine measured by in vivo proton magnetic resonance (1H-MRS). Suboptimal clinical outcomes with arginine/glycine supplementation in CRTR deficiency (CRTR-D) highlights certain paradoxes of this disorder. The first centers on the observation that brain synthesizes creatine, and creatine uptake into brain from the periphery is limited. Accordingly, why does CRTR-D manifest cerebral creatine deficiency? It has been suggested that despite expression in all brain cell types, AGAT and GAMT rarely co-express so that intermediate GAA must be transported between AGAT- and GAMT-containing cells via CRTR to insure creatine synthesis. Support for this hypothesis includes the finding of increased cerebral and/or cerebrospinal fluid (CSF) GAA in CRTR-D. A slightly elevated cerebral GAA was reported in one patient but is usually not observed and GAA in CSF is also normal or only slightly elevated (unpublished observations in six patients). A further paradox centers on normal to slightly elevated CSF creatine in CRTR-D, whereas a reduction (as observed in other creatine deficiency syndromes) would be predicted.

These paradoxes may be clarified via examination of the neurotransmitter transporters. CRTR exhibits considerable homology to members of the SLC6 transporter family which traffic the monoamine transmitters serotonin (5-hydroxytryptamine; 5-HT), dopamine (DA), and norepinephrine (NE), and the amino acid transmitters GABA and glycine. These transporters facilitate reuptake of synaptically-released neurotransmitter from the synaptic cleft. DA, 5-HT and NE-transporter knockout mice all manifest extracellular neurotransmitter elevation coupled to severe intracellular depletion, highlighting the important role of reuptake for maintenance of neurotransmitter stores. These observations may explain the paradoxical intracellular creatine deficiency (measured by 1H-MRS) combined with normal CSF creatine seen in CRTR-D. Our prediction is
that cerebral creatine deficiency in CRTR-D derives from defective creatine recycling following release (Figure 1). In support of this, neuronal creatine is released in an action-potential dependent exocytotic manner,⁵ and CRTR activity exists in the synaptosomal membrane that could facilitate creatine reuptake,⁶ all pointing to a role for creatine as neuromodulator or even neurotransmitter. Characterization of cellular and animal deficiency models should begin to unravel these potentially novel roles for creatine.

**Figure 1.** Schematic representation of CRTR in the synaptic terminal. Creatine is synthesized in the neuron and released in the synaptic cleft. Creatine reuptake via CRTR maintains the intracellular creatine stores. Creatine recycling fails in CRTR-D, resulting in intracellular creatine depletion.
REFERENCES


