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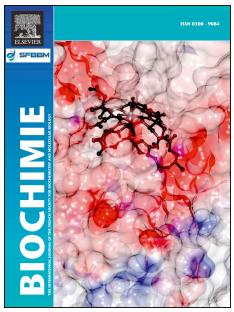

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REVIEW

Creatine biosynthesis and transport in health and disease

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ABSTRACT

Creatine is physiologically provided equally by diet and by endogenous synthesis from arginine and glycine with successive involvements of arginine glycine amidinotransferase [AGAT] and guanidinoacetate methyl transferase [GAMT]. A specific plasma membrane transporter, creatine transporter [CRTR] (SLC6A8), further enables cells to incorporate creatine and through uptake of its precursor, guanidinoacetate, also directly contributes to creatine biosynthesis. Breakthrough in the role of creatine has arisen from studies on creatine deficiency disorders. Primary creatine disorders are inherited as autosomal recessive (mutations affecting *GATM* [for *glycine-amidinotransferase, mitochondrial*]) and *GAMT* genes) or X-linked (*SLC6A8* gene) traits. They have highlighted the role of creatine in brain functions altered in patients (global developmental delay, intellectual disability, behavioral disorders). Creatine modulates GABAergic and glutamatergic cerebral pathways, presynaptic CRTR (SLC6A8) ensuring re-uptake of synaptic creatine. Secondary creatine disorders, addressing other genes, have stressed the extraordinary imbrication of creatine metabolism with many other cellular pathways. This high dependence on multiple pathways supports creatine as a cellular sensor, to cell methylation and energy status. Creatine biosynthesis consumes 40% of methyl groups produced as *S*-adenosylmethionine, and creatine uptake is controlled by AMP activated protein kinase, a ubiquitous sensor of energy depletion. Today, creatine is considered as a potential sensor of cell methylation and energy status, a neurotransmitter influencing key (GABAergic and glutamatergic) CNS neurotransmission, therapeutic agent with anaplerotic properties (towards creatine kinases [creatine-creatine phosphate cycle] and creatine neurotransmission), energetic and antioxidant compound (benefits in degenerative diseases through protection against energy depletion and oxidant species) with osmolyte behaviour (retention of water by muscle). This review encompasses all these aspects by providing an illustrated metabolic account for brain and body creatine in health and disease, an algorithm to diagnose metabolic and gene bases of primary and secondary creatine deficiencies, and a metabolic exploration by ^{1}H-MRS asssessment of cerebral creatine levels and response to therapeutic measures.