

Creatine

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Creatine is a naturally occurring compound, functioning in conjunction with creatine kinase to play a quintessential role in both cellular energy provision and intracellular energy shuttling. An extensive body of literature solidifies the ergogenic benefits gained following dietary creatine supplementation; however, recent findings have further indicated a potential therapeutic role for creatine in several pathologies such as myopathies, neurodegenerative disorders, metabolic disturbances, chronic kidney disease and inflammatory diseases. Furthermore, creatine has been found to exhibit non-energy-related properties, such as serving as a potential antioxidant and anti-inflammatory. Despite the therapeutic success of creatine supplementation in varying clinical populations, there is scarce information regarding the potential application of creatine for combatting the current leading cause of mortality, cardiovascular disease (CVD). Taking into consideration the broad ergogenic and non-energy-related actions of creatine, it could be hypothesized that creatine supplementation may be a potential therapeutic strategy for improving vascular health in at-risk populations such as older adults or those with CVD. This entry gives a short background on creatine, its cellular function and metabolism, in addition to the pleiotropic applications of creatine within just a few clinical populations. Furthermore, this entry concludes by alluding to the potential in which creatine may possess to benefit vascular health and to combat the pathology that underlies CVD.

Keywords: creatine ; vascular health ; oxidative stress ; inflammation

1. Introduction

Creatine is an organic compound that is both synthesized endogenously and found exogenously in various food sources such as meats and fish. Since creatine's isolation and extraction from animal skeletal muscle by French chemist Michel Eugène Chevreul in 1832, the function of creatine has been extensively researched. Furthermore, studies such as those by Chanutin^[1], Walker^[2], and Harris et al. in 1992^[3] have all shown that supplemental creatine can augment natural human intramuscular creatine stores. These studies, among others, pioneered the current understanding of creatine and the use of creatine supplementation to promote energy provision and to benefit skeletal muscle performance and health. Considering the undeniably important role that creatine and phosphocreatine (PCr) play in rapid energy provision, it is of no surprise that the primary focus of creatine research has centered around the ergogenic effects of creatine supplementation to improve exercise performance. The accumulation of creatine-focused research has contributed to a vast body of knowledge and has led to several authors declaring creatine as being one of the most effective and underrated nutritional supplements^{[4][5][6]}. Furthermore, with clear scientific support and expanding mainstream popularity, creatine remains one of the most dominant sports supplements on the market, accumulating more than \$400 million in annual sales^{[7][8]}.

In addition to the well-known ergogenic value of creatine^{[5][9]}, there has been an emerging interest in the clinical application of creatine. Creatine has been cited as a potential adjuvant therapy for the treatment of a variety of diseases such as myopathies, dystrophies, inflammatory diseases, neurodegenerative disorders, metabolic disturbances, and joint syndromes^[4]. With advancing understanding, it is clear that the function of creatine goes far beyond that of a primary role in metabolism and energetics. In fact, recent evidence indicates that creatine supplementation results in a multitude of non-energy-related beneficial effects on a wide range of cellular targets. Among these promising effects includes the antioxidant potential of creatine, scavenging and neutralizing the reactive oxygen species (ROS) that underly many pathologies^{[10][11]}.

2. Brief Overview of Creatine Metabolism and the Cellular Actions of Creatine

In addition to being consumed in an omnivorous diet, creatine is also synthesized endogenously. Endogenous synthesis of creatine is an interorgan process and requires the investment of three major amino acids: glycine, arginine, and methionine; together with two primary enzymes: L-arginine: glycine amidinotransferase (AGAT) and guanidinoacetate N-

methyltransferase (GAMT). The first step of creatine biosynthesis occurs in the kidneys, when AGAT catalyzes the transfer of an amidino residue from arginine to glycine, resulting in the formation of L-ornithine and guanidinoacetate (GAA). GAA then exits the kidneys and is transported to the liver where GAMT functions to transfer a methyl group from S-adenosylmethionine (SAM) to GAA, resulting in the final production of creatine. Cellular uptake of creatine is mediated by a specific creatine transporter (CRT), also known as SLC6A8. This transporter is sodium- and chloride-dependent, requiring at least two sodium ions and one chloride ion for the transport of one creatine molecule^[12]. Given its vital role in metabolism and energy provision, the largest stores of creatine are found in skeletal muscle (~95%); however, other notable stores include the brain, kidneys, and liver^[5]. Intracellularly, creatine can exist in a free form or in a phosphorylated form, PCr. Both creatine and PCr are metabolized and lost naturally throughout the day via a non-enzymatic, spontaneous reaction into creatinine, which is then excreted at a rate of ~2 g/day by the kidneys in the urine^[13] ^{[14][15]}(Figure 1).

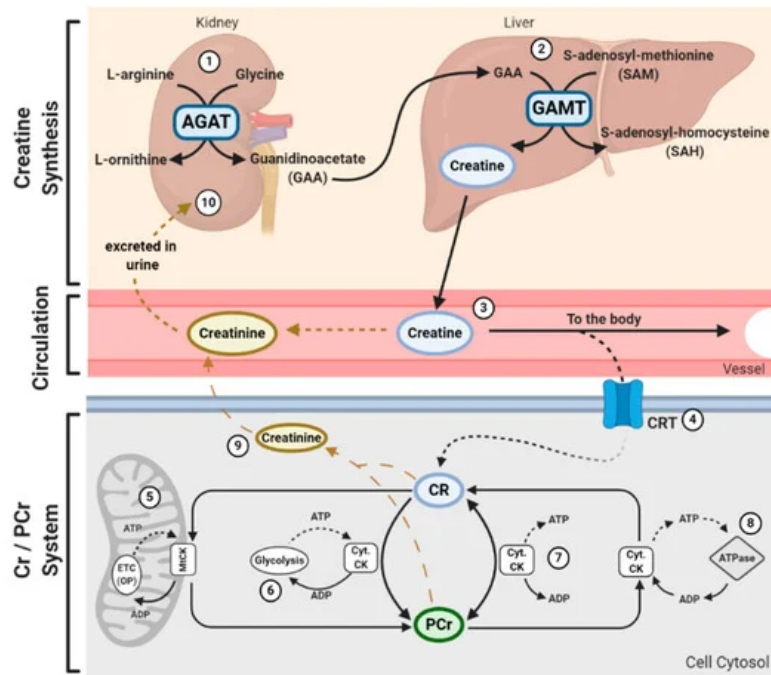


Figure 1. Physiological Journey of Creatine: Synthesis of creatine (Cr) happens at a rate of ~1 g/day^[2] via an interorgan process. (1) Within the kidneys, L-arginine: glycine amidinotransferase (AGAT) transfers an amidino group from L-arginine to glycine, resulting in the formation of L-ornithine and guanidinoacetate (GAA). (2) GAA is then transferred and processed in the liver. Guanidinoacetate N-methyltransferase (GAMT) transfers a methyl group from the methyl donor S-adenosylmethionine (SAM) to GAA, resulting in the formation of Cr and S-adenosylhomocysteine (SAH). SAH can thereon be hydrolyzed into homocysteine by S-adenosylhomocysteine hydrolase (not shown). (3) Cr is released from the liver into circulation, where Cr is transported to varying tissues such as the skeletal muscle, brain, kidney, and heart. (4) Cellular uptake of Cr is mediated by a creatine transporter (CRT), or SLC6A8. Cr carries both positive and negative charges, and is transported via secondary-active transport, driven by a sodium/chloride-ATPase generated gradient. Once in the cell, Cr has a multitude of fates. (5) Cellular Cr can be transformed into phosphocreatine (PCr) by mitochondrial creatine kinase (mtCK) which is coupled to oxidative phosphorylation (OP) via the electron transport chain (ETC). (6) Cr can be converted into PCr by cytosolic creatine kinase (Cyt. CK) coupled to glycolysis. (7) The cellular Cr/PCr pool is utilized to maintain adenosine triphosphate (ATP)/ adenosine diphosphate (ADP) ratios through ATP resynthesis or “buffering.” (8) Cyt. CKs located throughout the cytosol can utilize the high-energy PCr stores to shuttle and utilize energy at sites of ATP demand, or ATP-dependent processes, via ATPase enzymes. Such processes include ATP-gated ion channels, ATP-regulated receptors, ATP-regulated ion pumps; contractile processes, cell motility, cell signaling, or organelle transport. (9) Both Cr and PCr are naturally metabolized into creatinine via a non-enzymatic, spontaneous reaction. Creatinine diffuses freely into the circulation to be transported to the kidneys. (10) Creatinine is fully excreted in the urine.

Creatine and PCr, together with creatine kinase (CK) isoenzymes, function as quintessential high-energy compounds crucial for metabolism. In the case of low adenosine triphosphate (ATP) levels or high ATP demand, CK will catalyze the transfer of the *N*-phosphoryl group from PCr to adenosine diphosphate (ADP) to resynthesize ATP. This process quickly replenishes the ATP pool, maintaining ATP:ADP ratios and cellular homeostasis. Conversely, when ATP production from either glycolytic or oxidative pathways are greater than ATP utilization, CK can function in reverse to capture and store this cellular energy by replenishing PCr stores. There is a long-held belief that the primary function of the creatine-

phosphocreatine system (Cr-PCr system) is to serve as a temporal high-energy phosphate buffer^{[13][16]}(Figure 1). The presence of specific CKs throughout the cell are integral to the function of the Cr-PCr system. CKs exist in a variety of isoforms, which, in addition to the subcellular distribution and compartmentalization of such CKs, led to the proposal that the Cr-PCr system plays a far more complex role in energy metabolism than once believed. Cytosolic CKs (Cyt.CKs) exist as dimers, composed of either muscle (*M*) type or brain (*B*) type; therefore, three cytosolic isoenzymes exist: muscle-muscle creatine kinase (MM-CK); brain-brain creatine kinase (BB-CK); and, muscle-brain creatine kinase (MB-CK)^[17]. Specific mitochondrial CKs (MtCKs) also exist, such as sarcomeric MtCK (sMtCK) found in striated muscle and ubiquitous MtCK (uMtCK) found in other tissues such as the brain^[18]. MtCKs are found between the inner and outer mitochondrial membranes, and when in the presence of creatine, ensure the bulk of ATP from oxidative phosphorylation is converted into PCr^{[13][18]}. Cyt.CKs, on the other hand, are found within the cytoplasm and at sites of high energy consumption or demand (e.g., cellular ATPases, myofibrils, sarcoplasmic reticulum, plasma membrane)^[13]. With a sophisticated variety of CKs and their subcellular localization, the Cr-PCr system is capable of functioning as an energy shuttle of high energy phosphates, shuttling energy between sites of mitochondrial ATP production and sites of ATP utilization^[16](Figure 1).

The function of the Cr-PCr system as a temporal high-energy phosphate buffer and a spatial high-energy shuttle are not mutually exclusive and coexist in varying degrees. The masterful interplay between both shuttle and buffering abilities enables the Cr-PCr system to intricately monitor and stabilize ATP:ADP ratios within the cell, minimize adenine nucleotide loss, maintain cellular pH via hydrogen ion buffering, and to reduce free inorganic phosphates^{[19][20][21]}. Furthermore, it has been speculated that it is the interaction between MtCKs and Cyt.CKs that ensures the maintenance of ATP:ADP ratios within the mitochondrial matrix, thereby stimulating healthy respiratory chain function^[22]. This therefore leads to a reduction in electron leakage and reduced production of harmful mitochondrial-specific ROS.

From the above, it is clear that the Cr-PCr system plays a vital role in cellular function. Those readers interested in expanding their knowledge on the function, compartmentalization, and pharmacokinetics of the Cr-PCr system are directed to read reviews by Wallimann et al.^[23] and Perksy and Brazeau^[24].

3. Pleiotropic Application of Creatine

Creatine supplementation has been widely utilized by healthy individuals and athletes as an ergogenic aid to improve intermittent high-intensity exercise capacity due to the Cr-PCr system sustaining rapid ATP resynthesis. The total creatine pool (creatine + PCr) of a 70 kg individual is approximately 120 mmol/kg of dry muscle mass, or around 60–80% saturation^[5]. Pivotal research conducted by Dr. Roger Harris and colleagues demonstrated that oral creatine supplementation is capable of increasing muscle creatine and PCr stores by around 20%^[3]. Although consumed naturally in the diet (~1–2 g/day) and synthesized daily, with intramuscular creatine metabolism and excretion of around 2 g/day^[13], additional dietary supplementation with creatine analogs, such as creatine monohydrate, remains the most efficient way of increasing creatine stores. A common supplementation protocol usually involves a loading phase of 4 × 5 g of creatine for five to seven days, followed by a maintenance phase of 3 to 5 g/day^{[3][5]}. A low dose protocol of consuming 3 g/day for approximately 28 days, however, can still result in increased intramuscular creatine stores^[3]. Considering the extensive body of literature on the efficacy of creatine supplementation, there is evidence that creatine supplementation can enhance many exercise-related variables such as exercise capacity^{[25][26][27][28]}, recovery^{[5][29][30]}, resistance to fatigue^{[31][32][33]}, and lean body mass^{[5][34]}, in both young and older individuals. For in-depth reviews highlighting the ergogenic value of creatine supplementation, readers are directed to those by Kreider et al.^[5] and Butts et al.^[8].

With significant success as an ergogenic aid, the potential application of creatine supplementation in clinical populations has gained attention. Creatine supplementation has been shown to impart a variety of benefits upon skeletal muscle, such as the enhancement of force output during skeletal muscle contraction^[35], the augmentation of lean body mass^[36], fatigue resistance^{[31][32]}, and the improvement of intracellular calcium handling^[37]. Furthermore, it has been proposed that creatine supplementation may impart further favorable effects on skeletal muscle physiology and metabolism, such as enhancing growth and hypertrophy through direct modulation of components of the mammalian target of rapamycin (mTOR), secretion of myokines such as myostatin and insulin-like growth factor-1, and increasing the expression of myogenic regulatory factors which can stimulate satellite cell mitotic activity^{[38][39][40]}. Considering the beneficial impact of creatine upon muscle, several investigators have studied the effects of creatine on myopathies. Low creatine and PCr stores have been observed in those suffering from muscular disorders, contributing to poor cellular bioenergetics and muscle integrity^[41]. These findings led to the proposed hypothesis that creatine supplementation may serve as a therapeutic intervention for myopathies. Tarnopolsky and Martin supported this hypothesis, reporting substantial increases in muscle strength, exercise capacity, and body mass in patients with mitochondrial cytopathies, neuropathic disorders, dystrophies/congenital myopathies, and inflammatory myopathies^[42]. Further trials by Tarnopolsky et al.^[43], Walter et al.^[44], and Louis et al.^[45] provide additional evidence that supports the use of creatine for the therapeutic management of

various myopathies; however, the complexity and difference between myopathies has limited the ability to make an overarching conclusion. In addition, the potential therapeutic application of creatine for neurological diseases has similarly been hypothesized. The brain, despite having a relatively small mass, represents one of the largest sources of energy consumption, accounting for approximately 20% of resting metabolism^{[46][47]}. While all energy systems play a vital role in ATP provision, the presence of brain-specific CKs suggests a vital role of the Cr-PCr system within the brain^{[48][49]}. Furthermore, considering genetic creatine deficiency syndromes are often characterized by cognitive impairment, developmental delay, autistic behavior, and seizures, it is clear that creatine contributes to healthy brain function^[50]. Researchers have since tested this hypothesis and have shown that creatine supplementation can aid in the improvement of cognitive processes such as memory and attention in both young^[51] and older individuals^{[52][53]}. It has also been shown that creatine exhibits potential anti-depressant properties^[54]. Animal and in vitro models have further been used to assess the efficacy of creatine supplementation for certain neurodegenerative disorders such as Parkinson's, Huntington's, and Alzheimer's disease, some of which report promising results in regard to offering neuroprotection against oxidative stress and neurotoxicity^{[55][56][57]}. Results of clinical trials, however, remain mixed, with some trials reporting potential benefit following creatine supplementation that warrants further investigation^{[58][59][60][61]}, and others reporting minimal or no benefits^{[62][63]}.

The physiological benefits of creatine do not stop at the muscular and neurological systems. Creatine supplementation has also been found to help ameliorate hyperglycemia^[64] and improve glycemic control in those suffering from type 2 diabetes^[65], improve function in those suffering from fibromyalgia^[66], protect the integumentary system from age-related deterioration and damage^[67], increase bone mineral density and tensile strength in elderly individuals^[68], decrease triglyceride accumulation and increase liver health in models of non-alcoholic fatty liver disease^[69], and protect both mitochondrial and nuclear deoxyribonucleic acid (DNA) from markers of oxidative and inflammatory damage^{[11][70][71]}.

Despite the above described potential of creatine for the management of various metabolic, muscular, and neurological diseases, there is surprisingly very little information on the use of creatine supplementation to reduce the current leading cause of mortality in the United States (US): cardiovascular disease (CVD). Major examples of CVDs can include coronary heart disease, heart failure, stroke, atherosclerosis, hypertension, and peripheral artery disease. It has been estimated that approximately 610,000 deaths are caused by CVDs in the US every year^[72], with more than 43.7 million adults aged >60 years suffering from one or more CVDs in 2016 alone^[73]. Deteriorations in vascular integrity such as arterial thickening, stiffening, endothelial dysfunction, and inflammation are associated with most CVDs, and are all related to, or augmented by, the accumulation of ROS^{[74][75][76][77]}. Considering creatine's proposed antioxidant properties and promising application within varying clinical populations, the sparse amount of research on the effect of creatine supplementation on vascular function and health is surprising and highlights a major gap in the literature. A recently published review entitled "The Evolving Applications of Creatine Supplementation: Could Creatine Improve Vascular Health?" by Clarke *et al.* delves further into the literature surrounding the application of creatine as an antioxidant, anti-inflammatory agent, and as a substance capable of reducing homocysteine levels; all of which are proposed mechanisms in which creatine may be able to benefit vascular health. Readers are directed to this review for a deeper understanding of the relatively under researched areas in which creatine has yet to show its full pleiotropic potential.

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