Assignment3

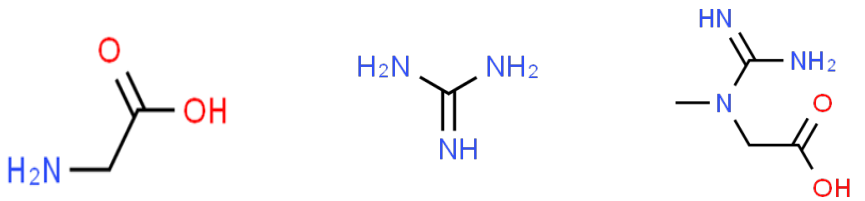
Introduction:

Creatine, with the chemical name methyl guanidine-acetic acid, is derived from methionine, glycine, and arginine and is synthesized in the pancreas, kidney and liver (Borchell 2019). According to creatine and glycine's structures, we can see that creatine is the result of glycine by adding an amidino group and a methyl group, which proves that creatine is derived from glycine.

Creatine can be produced by the body if protein and vitamin intakes are adequate. Creatine exists in muscles and can be found in foods such as milk, red meat, and seafood (Bender and Klopstock 2016). Creatine can be supplemented by eating these foods. For an extra supplement, there are many creatine products available in the market, such as liquids, powders, tablets, and so on. Almost all these products use the form of creatine monohydrate. The reason to use creatine monohydrate is that creatine monohydrate is safe to consume and is proved to have positive effects (Kreidar 2017). Gordon (1995) found that creatine supplementation can increase skeletal muscle total creatine and creatine can be converted to creatine phosphate. As a storage form of phosphates, creatine phosphate can react with ADP and convert ADP to ATP for immediate energy. Therefore, creatine provides instant and large amounts of energy in muscles. (Slide 6.2)

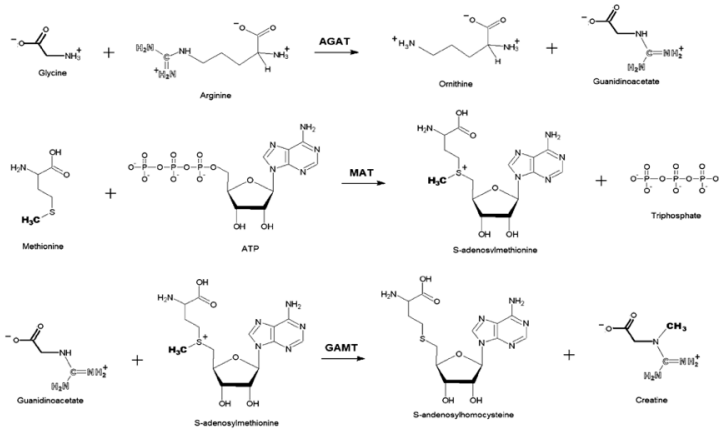
There are many claims related to creatine's benefits. The most widely validated benefit is that creatine helps muscle cells produce more energy and improves high-tensity exercise performance (Brannon, 1997). Also, Rae (2003) claimed that creatine can improve brain function. There exist some other claims. Tarnopolsky (2000) argued that creatine may help with Parkinson's disease and other neurological diseases. Also, claims exist that creatine can lower blood sugar levels and fight diabetes, and creatine can reduce fatigue and tiredness (Mawer 2019). Some of these claims are supported by some researches but have not been fully validated. Due to these benefits, creatine is used in alternative medicine as a possibly effective aid for enhancing athletic performance, increasing muscle strength, muscular dystrophy, Parkinson's disease, and so on.

Glycine contains an amine group. By adding an amidino group to the glycine, a guanidino group is formed in creatine. Creatine kinase, as a guanidinoacetate kinase, can catalyze the reaction of creatine and ATP to form creatine phosphate and ADP. The phosphate group of ATPs is transferred to creatine and binds to the guanidino group of the creatine. The produced creatine phosphate acts as a phosphate storage site. When instant energy is needed, creatine phosphate donates the phosphate group to ADP and produce ATP. Therefore, the property of the molecule is modified to have the function to provide immediate energy (Morton 2008).



Graph (left) is the structure of creatine. Graph (middle) is the structure of glycine. Graph (right) is the structure of guanidine. [cited 2020 Nov 30] Available from ChemSpider.

Metabolism



Creatine synthesis functions (Brosnan 2011)

Creatine synthesis requires three amino acids, including glycine, arginine, and methionine, and three enzymes for each step, including glycine amidinotransferase (GATM) and guanidinoacetate methyltransferase (GAMT), and methionine adenosyltransferase (MAT). The synthesis process has three steps, which are shown in the graph above. Cofactors remain unknown. Amino acid side chain' role is to promote binding and interaction of proteins.

The first and rate-limiting step is a double replacement reaction and transamination reaction. The location for this reaction is the kidneys and pancreas. An amidino group is transferred from arginine to glycine. Hydrogen is transferred from glycine to arginine. Guandinoacetate is formed from the reaction. The enzyme catalyzing this reaction is glycine amidinotransferase. The active site of the enzyme contains residues C407, H303, and D254. In the first half of the reaction, the thiol group of C407 adds to the carbon atom of the guanidino group and donates its proton to the arginine substrate, forming a reaction intermediate. After connection, electrophilicity is enhanced causing the bond between the amidino-carbon atom and the rest of the arginine to break, then ornithine is formed. In the second half of the reaction, glycine enters the active site and binds to the amidino-carbon atom of the amidino-cysteine on the reaction intermediate to complete transferring the amidino group (Humm 1997).

The second step is to form S-adenosylmethionine (SAM) with methionine. Methionine reacts with ATP to form SAM and triphosphate. The reaction is a single replacement reaction and adenosylation reaction. An adenosyl group is transferred from ATP to methionine catalyzed by methionine adenosyltransferase (MAT). The reaction mainly happens in the plasma membrane because MAT is mainly located there (Bronsnan 2011).

The third step is a double replacement reaction and methylation reaction. The reaction mainly happens in the liver. A methyl group is transferred from SAM to guanidinoacetate. Hydrogen is transferred back. Creatine is formed from the reaction. The enzyme catalyzing the reaction is GAMT. The resulting guanidinoacetic acid from the first step is methylated by SAM to form creatine. GAMT's active site is residue Asp134. Guanitinoacetate donates a proton to the oxygen of Asp134 and forms a reaction intermediate. Then, the reaction intermediate accepts the methyl group from SAM and form creatine (Zhang and Bruice 2006).

Recommendations:

The mechanism behind creatine's benefits is that creatine can provide instant and large amounts of energy. Oral supplementation of creatine is shown to increase the creatine level in the blood. Creatine is then transported by creatin-specific transporter in the blood to creatine-requiring tissues. (Gorden 1995) Creatine can react with excess ATP to form phosphocreatine catalyzed by creatine kinase in mitochondria. Phosphocreatine acts as a phosphate storage site. When the body needs large amounts of energy in a short period, phosphocreatine reacts with ADP to produce ATP at a high rate and instant energy is provided. (Slides 6.2) This reaction process is also catalyzed by creatine kinase.

The most common claim for the function of creatine is that it can improve intense exercise performance, such as sprinting and jumping. The claim has been largely investigated and is fully validated (Engelhardt 1998). 95% of creatine is found in skeletal muscle. Creatine supplementation can increase creatine in skeletal muscle. When performing high intensity activities, the rate of ATP usage is larger than the rate of ATP resynthesis, and instant energy is required and provided through the reaction of creatine phosphate and ADP. Therefore, creatine is shown to improve the performance of activities that require instant large amounts of energy. However, creating does not improve performance in endurance sports (Engelhardt, 1998), which might be because endurance sports are low in intensity and do not need rapid ATP regeneration. Creatine supplementation is validated to elevate creatine levels in the human brain (Dechent 1999). The brain constitutes only 2% of the body mass but spends 20% of energy consumption (Shulman, 2004). Creatine can also provide energy for brain activities that require instant energy. The research found that a lower level of creatine in the brain leads to a slower learning curve in the water maze (Eur 2002).

Another claim says that creatine can help with Parkinson disease and other neurological diseases. Beal (2011) argued that creatine can slow down the worsening of amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD), and extend the survival time. Also, Parkinson's disease (PD) is showed approximately a 50% improvement in a phase 2 trial. However, Bender (2016) argued that creatine does not affect ALS and PD. Therefore, the benefits of creatine in neurological diseases are not fully validated, and the mechanism is not fully understood. Besides, there are not many pieces of research to support the claim that creatine is beneficial to diabetes or reducing fatigue. Therefore, these claims are not validated.

Based on these pieces of evidence, it is proved that creatine has positive benefits for intense exercise performances and brain activities. However, creatine's benefits to help with neurological diseases, diabetes, and fatigue are not fully validated. Also, creatine can be synthesized by the body and be supplemented by eating red meat, milk, and seafood. Therefore, there is no need for extra supplements if you do not have creatine synthesis diseases or do not do intense exercises and brain activities frequently.

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