Creatine Kinase

Creatine kinase is a protein found in the eukaryotic domain of life. The basic function of creatine kinase is to catalyze the phosphorylation reaction between creatine and adenosine triphosphate (ATP) to produce adenosine diphosphate (ADP) and phosphocreatine (PCr). This result is associated with several functions in an organism. Its main function is to provide an energy reservoir. Creatine kinase can create a readily available back up of energy through the storage of PCr. This is because this reaction is easily reversible. If there is an immediate need for ATP this system provides an equilibrium buffer so ATP levels do not rapidly drop.

Although creatine kinase is found throughout the body, it is most abundant and readily used in brain cells, skeletal muscle cells, smooth muscle cells, and photoreceptors cells in the retina. This means that if there was an absence of creatine kinase it would have a large impact throughout the body. As stated before, creatine kinase gives the body the ability to store readily usable energy. This reversible storage of energy is constantly at work.

Focusing only on the effect creatine kinase has on skeletal muscle can provide a brief look into how important it is. If the body was put under stress and was pushed to perform a physical task immediately it would fatigue more quickly than usual. The ATP levels would drop without the freely useable energy provided by the reversible reaction of phosphocreatine back to creatine. This reaction provides that extra ATP when needed.

Creatine kinase (CK) is reported to be present in several places in an organism’s cells. There is CK found in the mitochondria. It can be both located in the peripheral intermembrane space and in the cristae space. There is also CK found in the cytosol of a cell. Creatine kinase is not typically a transmembrane protein because of its dominate hydrophilic residues; however, it does have sections of hydrophobic nature that gives it low solubility in water. Depending on the isoform, literature suggests that the protein may have an anchor of some sort to bind to membranes of subcellular components of the cell.

The general structure of this protein is made up of both alpha helices and beta sheets. Depending on the isoform determines the exact structure. This protein is typically an asymmetric dimer because there will be an open and closed unit for each dimer. In each unit there is usually 13-18 alpha helices consisting of 32%-38% of the overall weight and 16-19 beta sheets consisting of 15-16% by weight.

There have been a variety of isoforms identified and purified in the laboratory of creatine kinase. The following is a list of just a few of the isoforms that have been researched extensively. The main focus during the discussion is on the creatine kinase isoforms that reside in the human body. There are four main known ones. They are CK-MM (cytosolic muscle), CK-BB (cytosolic brain), CK-MB (cytosolic heart), and mtCK (mitochondrial). The cytosolic forms typically form homodimers (CK-MM,CK-BB). There is also a hybrid heterodimer between the two homodimer forms (CK-MB). In addition to the dimer form, the mitochondrial creatine kinase can be found as an octamer. The mitochondrial CK is suggested to be responsible for up to 30% of all CK enzymatic activity.
All of these isoforms have a very similar binding process. Although specific amino acids may vary between processes, the interactions are consistent. As stated before but creatine kinase provides a pathway for the reversible phosphorylation reaction between creatine + ATP to phosphocreatine + ADP. This reaction occurs through strong conformational changes in creatine kinase as the substrates bind. ATP binds as an ATP-Mg$^{2+}$ complex. This causes the majority of structure movement. Creatine alone will not induce conformation change in the active site. The ATP-Mg$^{2+}$ complex, a nitrate, and creatine binding to the active site is referred to as the transition state analogous complex (TSAC). A nitrate is included in this complex because it supposedly occupies the transferable phosphate position during transition. The presence TSAC causes two loops surrounding the active site to close on the active site. These loops are comprised of residues 59-69 and 320-330. The binding of His66 and Asp326 of these looped regions closes the active site off to any water molecules allowing the reaction to occur. There is another strong interaction between these looped regions between Ile69 and Val325. The conformational changes that occur reduced the size of the protein as well. This is seen by a studied that measure the length of the ligand free form and when TSCA was bound for rabbit CK-MM. This resulted in a reduction in size from 28 Å for the free ligand form to 25.6 Å for the ligand bound form.

Inside this binding site there is an abundance of specific interactions that give this reaction the ability to go to completion. There are a few amino acids that need to be highlighted specifically along with the ones mentioned above. Cysteine 283 is a very important amino acid regarding the speed of the reaction. From several studies it is shown that the activity will still occur without Cys283 but will be very ineffective. Essentially it anchors creatine into the binding site and then positions it for nucleophilic attack on the phosphorous from the ATP-Mg$^{2+}$ complex. This complex is located in between a group of arginines that create a positive pocket for the binding of the phosphate. These arginines are located at positions 130,132,236,292, and 320.

There is an interesting relationship between blood serum levels of creatine kinase to several health issues. When there are highly elevated levels of CK in the bloodstream, it means that there has been some type of injury or stress to tissues containing CK. This could mean tissue damage in a muscle tissue, heart, or brain. When one of these tissues is damage in some way it will leak CK into the bloodstream. Since there are a variety of isoforms, the blood can be tested to see what isoforms levels are elevated the most. This can give medical personnel a good indication what a person may be at risk for. High CK levels (depending on the isoform) have led to patients that have had or at risk for strokes, heart attacks, myocarditis, pulmonary infarction, muscular dystrophies, myopathy, and many other associated risks.

Creatine itself can also be supplemented. Many people in the fitness industry have explored this supplement extensively. Supplementing creatine has been known to increase strength and give athletes more explosiveness. By supplementing this substance the user can build up their energy reservoir as discussed earlier. Putting creatine into a person’s system will encourage the chemical equilibrium towards the phosphocreatine ADP side. This reservoir is said to benefit the user. Supplementing creatine has been tested for other people than just athletes. Parkinson’s patients have utilized this supplement because it can show signs of slowing their symptoms. Also patients that suffer from muscular dystrophy can reap the increased strength advantage that creatine supplements can provide. Although there are some benefits this supplement can be hard on the kidneys and liver. It also causes dehydration.