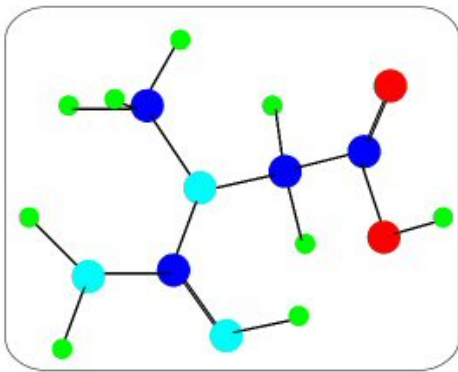


Creatine



Creatine is an amino acid that is very important for the energetic metabolism of the cell. It is reversibly transformed into phosphocreatine through the addition of a phosphoric group, the phosphoric group makes phosphocreatine a very high energy molecule. Phosphocreatine can donate its high energy phosphate group to ADP (adenosine-di-phosphate) to form ATP (adenosine-tri-phosphate). ATP is the most important source of energy for the cell, for example ATP provides the energy necessary for muscle contraction and for the maintaining of the population spike in the neurons.

Normally ATP is synthesized starting from glucose (or fatty acids in non neural tissues) and oxygen. Phosphocreatine is involved in the ATP metabolism in two ways. First of all it is needed to transport ATP from the place in the cell where it is synthesized (a little cytoplasmic component called mitochondrion) to the place where it is used (plasma cell or cytosol). To transfer ATP the cell resorts to a stratagem: ATP that is newly synthesized by the mitochondria donates its phosphate group to creatine transforming the latter into phosphocreatine. Phosphocreatine moves away from the mitochondria through the cytosol to the cell regions where ATP is used. Here phosphocreatine donates its phosphate group to ADP that is then transformed into ATP. Phosphocreatine, without its high energy group, comes back to the mitochondria as creatine and the cycle can start again. In this way ATP is “transferred” from the site of the synthesis to the site of use. This function is described in the scientific work of P.L. Greenhaff “The creatine-phosphocreatine system: there's more than one song in its repertoire. *Journal of Physiology London* 537 (3): 657, 2001”, to which we refer for further informations. This first role of phosphocreatine is what we find in the normal cell. Phosphocreatine is very important in the brain, in which the neurons continuously need a very high dose of energy and this is the reason why in case of lack of creatine the patients show a severe cerebral malfunctioning.

Normally the brain is supplied with creatine in two ways. In one way, creatine enters the brain from the blood. To enter the brain from the blood creatine, like all molecules, must cross a biological membrane called “blood brain barrier”. It is a barrier of endothelial cells and glial cells that protect the brain from undesired chemical compounds. Creatine is a very polar (hydrophilic) compound so it crosses very poorly the blood brain barrier, indeed to cross this barrier it needs a specific carrier molecule called “creatine transporter”. The creatine transporter is also necessary to cross the cell membrane of the cerebral cells (it is still debated if this is true only for neurons or for glial cells, too). If the blood brain barrier and the cell membrane don't express a functioning creatine transporter (as it happens in a rare hereditary disease) creatine can't reach the brain. The consequence is a severe cerebral malfunctioning with important neurological symptoms. In the second way, the brain has the necessary enzymes to synthesize creatine. It is not clear why in creatine transporter deficiency the brain does not synthesize its own creatine, thus replacing the missing supply from the blood. Maybe the synthesis occurs in the glial cells and lacking the transporter the neurons can not uptake it (see the scientific article of G. Lunardi, A. Parodi, L. Perasso, A.V. Pohvozcheva, S. Scarrone, E. Adriano, T. Florio, C. Gandolfo, A. Cupello, S.V. Burov, and M. Balestrino. The creatine transporter mediates the uptake of creatine by brain tissue, but not the uptake of two creatine-derived compounds. *Neuroscience* 142 (4):991-997, 2006). Certainly, in the case of a hereditary lack of one of the enzymes necessary for the synthesis of creatine the brain shows a severe malfunctioning. In this condition the clinical picture can be partially improved by high-dose oral creatine supplementation, but this therapy needs starting very early after birth to allow a normal cerebral development (see Roberta Battini, M. Grazia Alessandri, Vincenzo Leuzzi, Francesca Moro, Michela Tosetti, Maria C. Bianchi, and Giovanni Cioni.

Arginine:glycine amidinotransferase (AGAT) deficiency in a newborn: Early treatment can prevent phenotypic expression of the disease. *The Journal of Pediatrics* 148 (6): 828-830, 2006). Otherwise, the improvement is only partial.

Another role of phosphocreatine is to restore ATP levels when they are rapidly depleted. This happens for example in case of an unusually high energy expenditure by the cell, and in diseases where there is a reduced supply of blood or oxygen. In the former case there is an excessive use of ATP in comparison with the capability of the cell to synthesize it. As an example we can consider a muscle that exerts a very strong effort: this muscle quickly consumes more ATP than it can synthesize. In the latter case an organ can not synthesize enough ATP because it is deprived of blood (ischemia) or oxygen (anoxia). This is what happens in the myocardial infarction or in stroke. In both cases, phosphocreatine gives its phosphoric group to ADP providing an additional source of, or an alternative synthesis pathway for ATP. For this reason creatine is used by athletes, and it was proposed in the therapy of stroke (see Balestrino M., Lensman M., Parodi M., Perasso L., Rebaudo R., Melani R., Polenov S., and Cupello A. Role of creatine and phosphocreatine in neuronal protection from anoxic and ischemic damage. *Amino Acids* 23: 221-229, 2002). Creatine is an energetic compound, so it is very interesting in neurology because it can have a neuroprotective effect on the cells that are damaged by an ischemic event like stroke. In this case a number of neurons are quickly irreversibly damaged and die, but in the first hours from stroke other neurons are damaged only in a partial and reversible way. These neurons are the so-called ischemic "penumbra". They could be salvaged by providing them the energy that the ischemic event has prevented them from forming. Considering all the biochemical reactions that our organism uses to synthesize ATP the creatine/phosphocreatine system is the most quickly available energy supplement. This is the reason why creatine is for the researchers a very interesting compound. In the last years both creatine and creatine-derived compounds have been investigated as medicinal compounds in the therapy of stroke and of other neurological diseases.

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