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INVITED REVIEW

CREATINE KINASE: STRUCTURE AND FUNCTION

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ABSTRACT
TEIXEIRA, A. M.; BORGES, G. F. Creatine kinase: structure and function. Brazilian Journal of Biomotricity. v. 6, n. 2, p. 53-65, 2012. Found in all vertebrates, creatine kinase (CK) is a member of the phosphagen kinase family and catalyzes the reversible phosphotransfer between the ATP/ADP and Creatine/Phosphocreatine systems. CK is highly expressed in excitable tissues that require large energy fluxes and plays a significant role in the energy homeostasis of these tissue cells. The creatine kinase reaction was first identified in 1934 by K Lohman in the muscle tissue and it has undergone intensive investigation for over 80 years. The enzyme is of clinical importance and its levels are routinely used as an indicator of acute myocardial infarction. There are four major CK isoforms, which are named according to their tissue distribution or subcellular localization: two tissue (muscle or brain) cytosolic and two mitochondrial, which form dimers and octamers, respectively. In this paper we will include a brief summary of the history of the detection of creatine kinases isoforms, their main structural features, physical and catalitic properties and multiple functions such as an energy buffering function, metabolic regulatory functions and the energy transport function.

Key Words: Creatine Kinase; phosphocreatine; creatine; isoenzymes.

HISTORIC OVERVIEW

Phosphocreatine was initially indentified in muscle tissue (EGGLETON & EGGLETON, 1928), but the creatine kinase enzyme was only discovered by Lohmann in 1934 and the creatine kinase reaction in 1936 (LEHMANN, 1936). Creatine Kinase (CK) was purified and partially crystallized the first time by the group of Kuby (KUBY et al., 1954) and the

majority of the early studies on the physical properties and structure of creatine kinase were carried out on enzymes isolated from rabbit muscle. M. Eppenberger (1994) described that in 1962, Dance and Watts suggested that the active form of CK could be a dimeric molecule.

A full length cDNA for human M creatine kinase was isolated and sequenced by Perryman and colleagues in 1986 (PERRYMAN et al., 1986) and the human MCK gene isolated in laboratory in 1988 (TRASK et al., 1988) by screening ạ phage human genomic DNA library with a canine BCK probe. The human MCK gene spans 17.5 kb of the genome and contains 8 exons separated by 7 introns (QIN et al., 1998). The gene was located to human chromosome 19 and mapped to the 19q13.2-q13.3. site (NIGRO et al., 1987).

SEQUENCE HOMOLOGY AND EVOLUTION

Creatine kinase (also known as: Adenosine-5–triphosphate; creatine phosphotransferase; creatine phosphokinase; phosphocreatine phosphokinase; creatine *N*-phosphotransferase; (EC 2.7.3.2)) catalyzes the reversible transfer of a phosphoryl group from MgATP to creatine (Cr), producing phosphocreatine (PCr) and MgADP (MCLEISH & KENYON, 2005). CK is a highly conserved enzyme of 40 kDa, with its sequence being ~60% identical across all species and isoforms (MUHLEBACH et al., 1994). It is a member of the phospahgen kinase family of guanidino kinases (ATP-guanidino-phosphotransferases) (MIIHLEBACH et al., 1994). Other member of the family include glycocyamine kinase (GK), arginine kinase (AK), taurocyamine kinase (TK), hypotaurocyamine kinase (HTK), opheline kinase (OK), thalassemine kinase (TK) and lombricine kinase (LK). These enzymes have closely related primary sequences and large structural similarities but differences in guanidine specificity. The structures of the various occurring guanidino substracts are shown in figure 1. CK, AK and GK are rigidly specific for their respective substrates (VAN THOAI, 1968). CK is the only one found in in vertebrates, but is also found in many invertebrates, incluing sponges, polychaetes, and echinoderms (ELLINGTON, 2001). It is thought that AK is the most primitive phosphagen kinase and that the other members of the family arose by gene duplication followed by divergent evolution (SUZUKI et al., 1998). Since CK is present in the most primitive off all metazoans, the sponges, (ELLINGTON, 2000; ELLINGTON, 2001) it is likely that the divergence of CK from the ancestral AK occurred early in the course of metazoan evolution (SONA et al., 2004). The CK gene underwent multiple gene duplication events ultimately resulting in the production of GK and LK, as well as the multiple isoforms characteristic of CKs (flagellar, muscle, brain and mitochondrial), the mitochondrial isoform evolving very early.

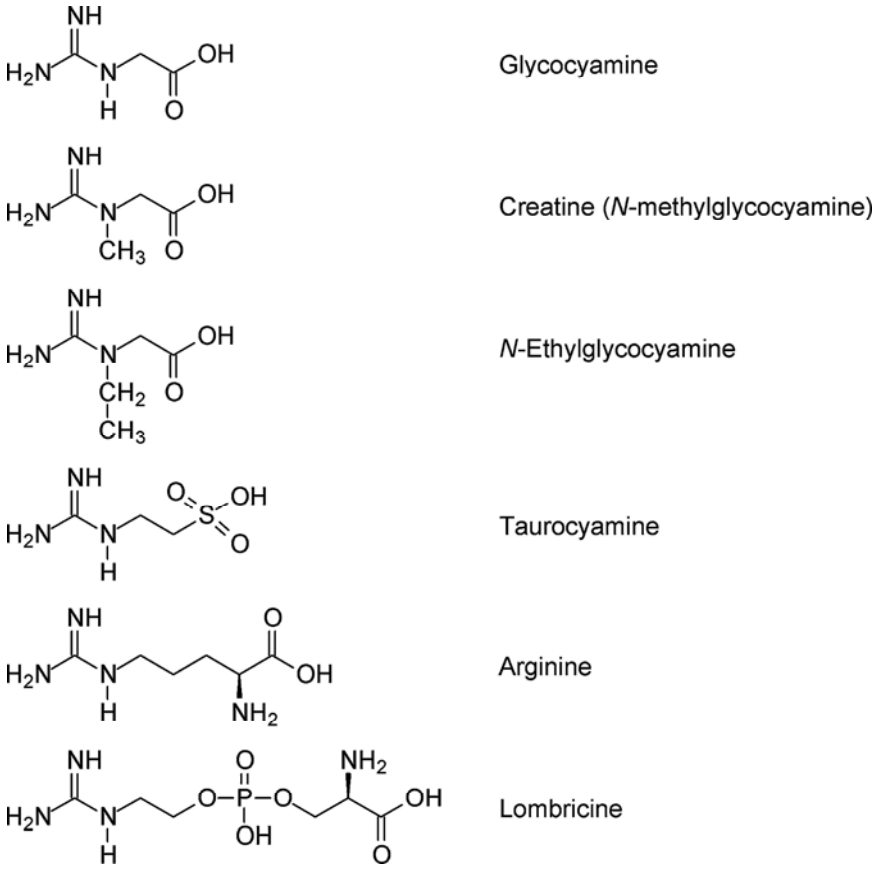

Figure 1. Structures of naturally occurring substrates for phosphagen kinases. *(Adapted from McLeish and Kenyon, 2005).*

LOCALIZATION AND ISOFORMS

There are four major CK isozymes, first separated on an agar gel plate by electrophoresis in 1963 (BURGER et al., 1963), wich have been named for the tissues from wich they were historically isolated. Two are cytosolic and two are mitochondrial. The two tissue-specific (muscle or brain) cytosolic CKs exist as homo-dimers (MM-CK and BB-CK) under physiological conditions but hetero-dimers (MB-CK) composed of muscle (M) or brain (B) monomers have also been identified (EPPENBERGER et al., 1967). The heterodimer form frequently appeared in a transitory fashion during fetal and neonatal development of skeletal muscle, but also persisted, e.g. in rat and human heart, throughout adult life (EPPENBERGER et al., 1964; DAWSON et al., 1965). The two mitochondrial isoenzymes, the ubiquitous (Mi_u-CK) and the sarcomeric (Mi_s-CK) forms usually exist as octamers but can be dissociated into dimers (BONG et al., 2008).

The ubiquitous brain-type BB-CK is widely distributed in brain, heart, smooth muscle, nervous system and other tissues, whereas the muscle-type CK (MM-CK) is the predominant isoform in highly differentiated skeletal muscle tissue (WALLIMAN & HEMMER, 1994). Only the MM-CK is able to interact with the M-band region of a myofibillar sarcomer, thus suggesting a functional importance for this specific CK-isoenzyme.

It is known that, although the overall structures of human BB-CK and MM-CK are similar, some residues move considerably as the substrates bind (LAHIRI et al., 2002). For example, there are differences between the open and closed forms of both ADP–Mg2+-bound structures. Specifically, the positions of the two loops comprised of residues 60–70 and residues 323–332 differ between the open and closed form. Also, the sequence of arginine kinase (AK) is 55% similar to the sequences of the various CKs, and the structure of the AK- TSAC structure is very similar to the structure reported for CK. In particular, the position of the two loops comprised of residues 60–70 and residues 323–332 differs between the AK-TSAC and human BB-CK-TSAC structures (PRUETT et al., 2003; ZHOU, et al., 1998).

After the discovery of Mi-CK and compartment of adenine nucleotides, it became clear that for a real understanding of the physiological role of PCr in the cells, detailed biochemical information of the behavior of CK isoenzymes in cellular structures was necessary. The structure of sarcomeric mitochondrial creatine kinase (Mi_s-CK) was reported in 1996 by Fritz-Wolf, in the presence and absence of NaATP, at 3Aº resolution. Mitochondrial Creatine Kinase is responsible for the transfer of high energy phosphate from mitochondria to the cytosolic carrier, creatine, and exists in mammals as two isoenzymes encoded by separate genes. In rats and humans, sarcomere-specific mitochondrial creatine kinase is expressd only in skeletal and heart muscle, and has 87% nucleotide indentity across the 1257 bp coding region. The ubiquitous isoenzyme of mitochondrial creatine kinase is expressed in many tissues with highest levels in brain, gut, and kidney, and has 92% nucleotide indentity between the 1254 bp coding regions of rat and humnan (PAYNE & STRAUSS, 1994).

CREATINE KINASE IN SKELETAL MUSCLE

Available data suggest that tissue levels of phosphagens are related to maximum potential rates of ATP turnover and oxidative capacity. In the case of muscle fibers, this is correlated with power output. In the case of both CP and AP, phosphagen levels in burst muscles are typically higher than corresponding levels in muscles that exhibit more sustained modes of contractile activity (ELLINGTON, 2001).

A number of researchers have hypothesized that muscle soreness is more prevalent among those individuals whith a predominance of type II muscle fibres (FRIDÉN at al., 1983; MAGAL et al., 2012). Individuals with a greater percentage of type II muscle fibres experience a greater increase in serum creatine kinase activity after muscle-damaging exercise. Creatine kinase activity is not dermined by muscle fibre types, especially when the intensity of the exercise is below a certain threshold (MAGAL et al., 2012). Currently it is clear that there are differences in the rates of phosphocreatine resynthesis between the types of muscle fibers after phosphocreatine depletion induced by exercise. In summary it appears that the rate of resynthesis is lower in type II muscle fibers during the initial minutes of recovery (possibly more lactic acidosis in this type of fiber), which can present an adverse effect on the production of energy and the performance during a subsequent exercise. However, after these initial minutes, the resynthesis of phosphocreatine in the

muscle fibers is accelerated in type II fibers, so that after 15 minutes recovery, the creatine phosphate concentration is greater than that observed before exercise. So far we do not know the mechanism responsible for this excess of phosphocreatine in type II fibers.

In human muscle creatine kinase (HMCK) residue, Cys283, forms part of a conserved cysteine-proline-serine (CPS) motif and has a pKa of about 3 pH units below that of a regular cysteine residue (WANG et al., 2006).

The MCK promoter is under the control of myogenic transcription factors, like MyoD-I, and thus parallels the upregulation of other muscle specific protein isoforms (LASSAR et al., 1989).

CREATINE KINASE IN CARDIAC MUSCLE

In cardiac muscle, the significance of the different isoforms of CK has been related to their intracelular localization rather than to kinetic diferences (SAKS et al., 1978). The heart is caracterized by having different CK isoenzymes (MMCK and MtCK) which are found specifically localized at sarcoplasmatic reticulum plasma membrane, myofilaments, mitochondria and glycolytic complexes (SAKS et al., 1978; VENTURA-CLAPIER et al., 1987).

CREATINE KINASE IN SMOOTH MUSCLE

The creatine kinase content of smooth muscle is of similar magnitude to ATP. The reported creatine kinase of various smooth muscles is small, ranging from 0.5 to 4.4mM, and is about 0.5-2 times the content of ATP (ISHIDA et al., 1994). Since the early demonstation of CK in chiken gizzard smooth muscle (GEIGER, 1956), the isoforms of BB-, MB- and MM-CK have aso been detected in smooth muscle, BB-CK being the main isoform in most smooth muscles. Another important CK isoform in terms of energetics is mitochondrial CK (Mi-CK). An appreciable amount of CK activity was detected in the enriched mitochondrial fraction of some smooth muscles (ISHIDA & PAUL, 1989; HASS & STRAUSS, 1990).

Kinetic diferences nonetheless could have some significance to subcellular isoenzyme localization in smooth muscle. The multiple isoforms of CK may be localized within the cell to perform specific functions related to other localized proteins and metabolites (CLARK, 1994).

CREATINE KINASE IN BRAIN

The brain-type cytosolic isoform of creatine kinase, BB-CK, exists primarily in the brain and retina and is associated with ion transport pumps in the brain (GROSSE et al., 1980; GUERRERO et al., 1997; KALDIS et al., 1994). Comparatively high levels of CK activity were reported in the cerebellar cortex (MAKER et al, 1973) consistent with findings which indicate that grey matter shows a higher flux through the CK reaction and higher Pcr concentrations when compared to white matter (CADOUX-HUDSON et al, 1989). The

ubiquitous form of Mt-CK is also present in contact sites of brain mitochodria (Brdiczka, 1991).

The phosphocreatine concentration in brain is approximately 4.5 mM (MICHAELIS et al., 1993), and most of this is intracellular. The PCr-dependent glutamate uptake system is present in synaptic vesicles (XU et al., 1996). Brain function appears to be linked with the creatine kinase/phosphocreatine system in several ways, which would explain the relationship between CK regulation and the development of neurodegenerative disease such as Alzheimer disease (DAVID et al., 1998).

CREATINE KINASE IN OTHER TISSUES

The CK in non-muscle cells, such as spermatozoa, electrocytes, retina photoreceptors cells, brain cells, kidney, salt glands, myometrium, placenta, pancreas, thymus, thyroid, intestinal brush-border epitelial cells, endotelial cells, cartilage and bone cells, macrophages, blood platelets, tumor and cancer cells (WALLIMAN & HEMMER, 1994), are characterized by intermittently high and fluctuating energy requirements, has attracted interest, suggesting a spatial buffering or energy transport function for the CK/PCR-system. For example the presence of large amounts of CK (B-CK and Mi-CK) and total creatine (Cr) in spermatozoa (WALLIMAN et al, 1986) and of PCr and Cr in seminal fluid (LEE et al, 1988) seem to support this idea.

CK is also present in cartilage and bone cells, PCr is present in chondrocytes as it was demonstrated by ^{31}P-NMR measurements of superfused resting zone cartilage from the growth plates of bones from young animals (KVAM et al., 1992). Bone cells in culture also show B-CK activity when stimulated with some Vitamin D metabolites, parathyroid hormone and prostaglandin E2 (SOMJEN ET AL, 1985). B-CK has also been shown to be directly and sex-specific stimulated by sex steroids in rat bone (SOMJEN ET AL, 1989) indicating that gonodal steroids may contribute to bone growth and to maintaining a balance bone-turnover, with CK being directly involved in the energetics of this process (FUNANAGE et al., 1992).

The adipose tissue contains PCr and CK with concentrations in brown fat tissue 50 times higher than in white fat (BERLET et al., 1976). In brown adipose tissue, wich is responsible for heat geration, CK activity is in the same order of magnitude as that found in cardiac or nerve tissue.

The invariable presence of sginficant amounts of CK in the thyroid of several species, incluing man, suggests that this enzyme may also have a role in thyroid tissue metabolism or hormone biosynthesis. The endotelial cells lining the inside of blood vessels, when maintaned under normoxic conditions, express various CK isoenzymes (BB-,MM- and MiC-K) and possess significant stores of PCr (LOIKE et al., 1992).

STRUCTURE AND FUNCTION

The cytosolic CKs (MMCK and BBCK) are highly conserved in their sequence and share and almost superimposable terciary structure (BONG et al, 2008). They exist as a dimer in

solution, each subunit composed of two domains: a smaller N-terminal domain containing only a-helices and a larger C-terminal domain with both b-sheets and a-helix secondary structures (Fig.2). The enzyme active site is located at the cleft of the two domains (MCLEISH & KENYON, 2005) and is thought to facilitate the entry of substrates as well as inhibitors.

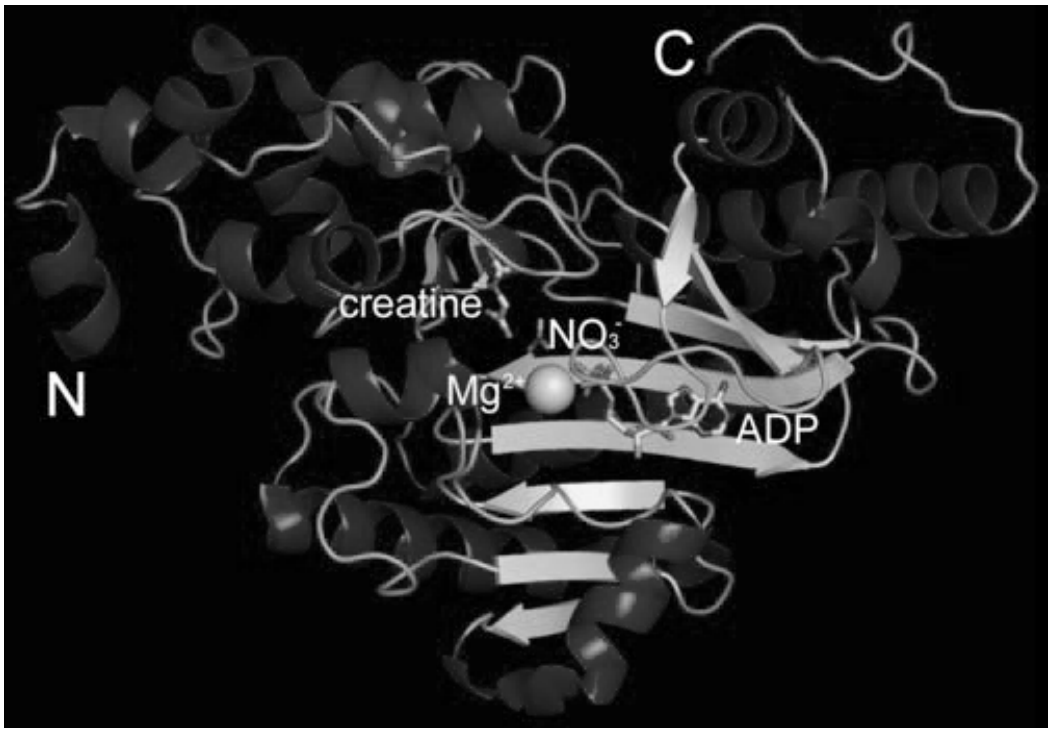

Figure 2. Structure of HBCK monomer (PDB ID: 3B6R). N and C denote the N- and C-terminus of the protein. (BONG et al., 2008; SHENG et al., 2009).

Structural and mutational studies have pointed outo that GLu232 is one of the crucial residues responsible for CK catalysis by participating in the positioning of creatine (MCLEISH & KENYON, 2005; BONG et al., 2008). The creatine kinase reaction is an equilibrium reaction (as the reaction of adenylate kinase) and therefore reversible.

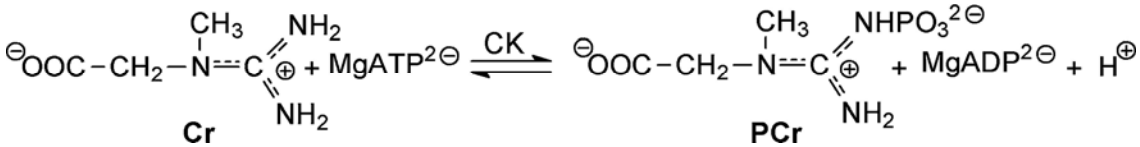

Figure 3. Reaction catalyzed by creatine kinase. (Adapted from *McLeish and Kenyon, 2005).*

For many years the main physiological role ascribed to CK was the maintenance of energy homeostasis at sites of high energy turnover such as rapidly contracting skeletal muscle cells. The discovery of the existence of creatine kinase isoenzymes in different cellular locations led to the hypothesis that fosfocreatine had several functions in skeletal muscle.

One of these functions was to mantain constant levels of ATP and ADP, buffering the cell against rapid depletion of ATP. The discovery of the mitochondrial isozymes demonstrated that CK was located in different compartments and the concept of a creatine-phosphocreatine shuttle was developed: a system power transmission between the local production of ATP (mitochondria) and the place of use (in generally, the myofibrils), where distinct isoenzymes are associated with sites of ATP production and consumption, acting as a transport mechanism for high energy phosphates.

Although guanidino kinases in general and creatine kinase in particular are present throughout the animal kingdom, functional compartmentation of CK isoenzymes has so far been mainly studied in muscles of adult mammals. Phosphagens are typically found in cells that display high and variable rates of energy turnover. Phosphagen levels can be quite high in anaerobic, phasic muscles. Furthermore, in these muscles there is a good correlation between maximum catalytic activities of the corresponding phosphagen kinases and maximum rates of ATP hydrolysis (NEWSHOLME et al., 1978; ZAMMIT et al., 1976). In phasic muscles (such as vertebrate gastrocnemius, scallop snap adductor, or lobster abdominal muscles), CK or AK activities exceed calculated maximal rates of ATP turnover by over an order of magnitude (NEWSHOLME et al., 1978). In contrast, in highly aerobic tonic muscles such as vertebrate heart and certain red muscles, as well as insect flight muscle, the ratios of phosphagen kinase activity over maximum ATP turnover rate approach or are even less than unity (NEWSHOLME et al., 1978). The above phasic versus tonic comparisons are indicative of tissue-specific differences in capacity for ATP (and ADP) buffering by phosphagen systems during short bursts of contractile activity. In spite of the long history of work on phosphagen systems, it was not until the early 1960s that Cain & Davies (1964) proved by inhibition of CK that ATP hydrolysis was the direct driving force for muscle contraction.

The significance of maintenance of high ΔG_{ATP} values has long been recognized for vertebrates. The overall capacity of phosphagens for buffering of ΔG_{ATP} is dependent on a variety of factors, including total phosphagen pool size (relative to adenine nucleotides) and the thermodynamic properties of the particular phosphagen kinase reaction. The phosphagen kinase reactions differ in terms of thermo-dynamic poise. These differences are dramatically reflected in the free energy of hydrolysis values for high-energy phosphates versus the extent of hydrolysis of the total pool (Figure 4).

If a phosphagen system is present and the phosphagen kinase reaction is near equilibrium with its substrates in vivo (KAMMERMEIER et al., 1993), the ΔG_{ATP} will be buffered at the expense of the phosphagen. This is illustrated by looking at the hydrolysis curve for CrP in relation to that of ATP; with 50% of the CrP discharged, the ΔG_{ATP} remains quite high (Figure 4). The extent of this buffering would be enhanced by increasing the total phosphagen pool size relative the adenine nucleotide pool.

The phosphagen systems differ in terms of their capacity for ΔG_{ATP} buffering. The CrP/CK system is able to buffer ΔG_{ATP} over a higher range of ΔG_{ATP} values than the AP/AK system; the other phosphagen systems show intermediate ATP-buffering properties (Figure 4). The CP/CK system might be advantageous because of its capacity for buffering of ATP at a higher range of ΔG_{ATP} values (ELLINGTON, 1989). The possession of the

other phosphagen systems, especially that of AP/AK, might be advantageous in invertebrates that live in stressful environments where hypoxia and frequent intracellular acidosis prevail (GRIESHABER et al., 1994). These conditions might lead to a rapid dissipation of the CrP pool through the high thermodynamic poise of the CK reaction, which would not be the case for the AP/AK system (ELLINGTON, 1989).

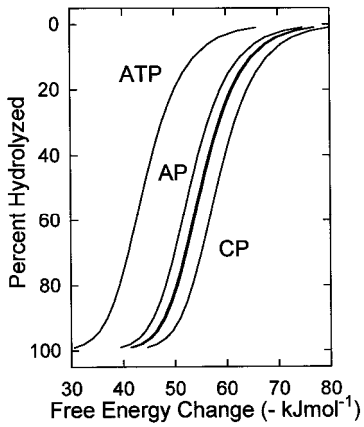

Figure 4. The relationship between the effective free energy change of hydrolysis and the extent of hydrolysis of the total pool size of ATP, AP, CP, TP, GP, and LP. Curves for TP, GP, and LP nearly superimpose on each other and fall intermediate between AP and CP. These data were recalculated and plotted for Ellington (2001) as described in Ellington (1989).

After complete degradation of phosphocreatine (the time for re-synthesizing the rest 50% stock), resynthesis is often considered to be 30s. There seems to be a wide variation in the resynthesis time depending on the type of exercise performed and the quantity and duration of exercise completed. Some factors may influence the rate of phosphocreatine resynthesis during recovery from exercise like the cellular concentrations of ATP, ADP and creatine, which is not surprising considering the equilibrium of the creatine kinase reaction. Importantly, H + is a potent inhibitor of creatine kinase. Therefore, in practice, a low pH muscle, low oxygen tension and / or a reduction in blood flow muscle severely affect the resynthesis of phosphocreatine after exercise. In fact, muscle ischemia is often used as a research tool to metabolic "stop" resynthesis of phosphocreatine and thus provide sufficient time to allow measurements of biochemical and physiological relevance to be performed.

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