

Creatine kinase in energy metabolic signaling in muscle

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ABSTRACT

There has been much debate on the mechanism of regulation of mitochondrial ATP synthesis to balance ATP consumption during changing cardiac workloads. A key role of creatine kinase (CK) isoenzymes in this regulation of oxidative phosphorylation and in intracellular energy transport had been proposed, but has in the mean time been disputed for many years. It was hypothesized that high-energy phosphoryl groups are obligatorily transferred via CK; this is termed the phosphocreatine shuttle. The other important role ascribed to the CK system is its ability to buffer ADP concentration in cytosol near sites of ATP hydrolysis.

Almost all of the experiments to determine the role of CK had been done in the steady state, but recently the dynamic response of oxidative phosphorylation to quick changes in cytosolic ATP hydrolysis has been assessed at various levels of inhibition of CK. Steady state models of CK function

in energy transfer existed but were unable to explain the dynamic response with CK inhibited.

The aim of this study was to explain the mode of functioning of the CK system in heart, and in particular the role of different CK isoenzymes in the dynamic response to workload steps. For this purpose we used a mathematical model of cardiac muscle cell energy metabolism containing the kinetics of the key processes of energy production, consumption and transfer pathways. The model underscores that CK plays indeed a dual role in the cardiac cells. The buffering role of CK system is due to the activity of myofibrillar CK (MMCK) while the energy transfer role depends on the activity of mitochondrial CK (MiCK). We propose that this may lead to the differences in regulation mechanisms and energy transfer modes in species with relatively low MiCK activity such as rabbit in comparison with species with high MiCK activity such as rat.