

***In silico* model of the mitochondrial role in the cardiac cell pathology**

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Abstract

The ability to predict clinical efficacy *in silico* could save diagnostic and pharmaceutical prescription time and resources, and might ultimately lead to more targeted, personalized therapies. This study concerns the behaviour of cardiac cell mitochondria metabolism undergoing angina pectoris and other cardiac cell pathologies using *in silico* simulations.

Introduction

A model of the mitochondria, including glycolysis/pyruvate metabolism, fatty acids β -oxidation, the Krebs cycle, the carnitine system, oxygen, CO_2 , ATP/ADP and H^+ /Pi transporters, cardiolipin synthesis, the electron transport chain (ETC), coupled to ATP production/ H^+ translocation systems and the ROS detoxification system, has been developed (Fig. 1). The model is constructed using information on the individual enzymes and transporters (Vo et al., 2004; Yugi and Tomita, 2004). Model parameters for the rate equations are estimated using experimental data from the literature. Enzyme concentrations are determined from data concerning respiration in mitochondria taken from the literature.

Results

It is shown that long-chain free fatty acids (LFA) and glucose account for the vast majority of ATP production in the heart. The results show that during ischemia LFA levels increase and, as a consequence, the palmitoyl carnitine transferase system (PCT-I and II) and pyruvate dehydrogenase (PDH) are inhibited. Low oxygen levels contribute substantially to the cumulative alteration of the Krebs cycle and the production of cellular lactate from pyruvate (Calvani et al., 2002). The uncoupling of oxidative phosphorylation has little effect on coenzyme A consumption since its level is controlled by free L-carnitine. It is also observed that the Acyl-CoA/CoA and Acyl-L-carnitine/L-carnitine ratios are altered but later recover (Fig. 2). Moreover, the rate of ATP breakdown is balanced by ATP synthesis until low oxygen levels are reached. This cycle depends on the efficiency of myocardial oxygen consumption, and may be affected during hemodynamic stress. The model predicts a pronounced decrease in β -oxidation, an increase of the Acyl-CoA/CoA and Acyl-L-carnitine/L-carnitine ratios as well as an increased lactate level. On the contrary, in healthy cardiac cells LFAs are rapidly metabolized via β -oxidation in the mitochondria and account for 60–70% of ATP production, whereas glycolysis accounts for an additional 30–40% of ATP production. The results also show how abnormalities related with the carnitine system are involved in hypoglycemia, cardiac sudden death, hypothermia, cardiac hypertrophy, arrhythmia and increased plasma carnitine. In the case of a malfunction of the PCT-I, the level of cellular carnitine increases by up to nearly 60%, while the Acyl-carnitine decreases by nearly 10% in the cytosol, generating hypothermia or lethargy. Another deficiency the model can explain is the abnormality of the PCT-II

that generates the sudden death: e.g. hypoglycemia, hypocetonemie and arrhythmia causing the sudden death. The problem is a reduction in ATP and Acyl-CoA levels while CO_2 , O_2^- and H_2O_2 increase in the mitochondria.

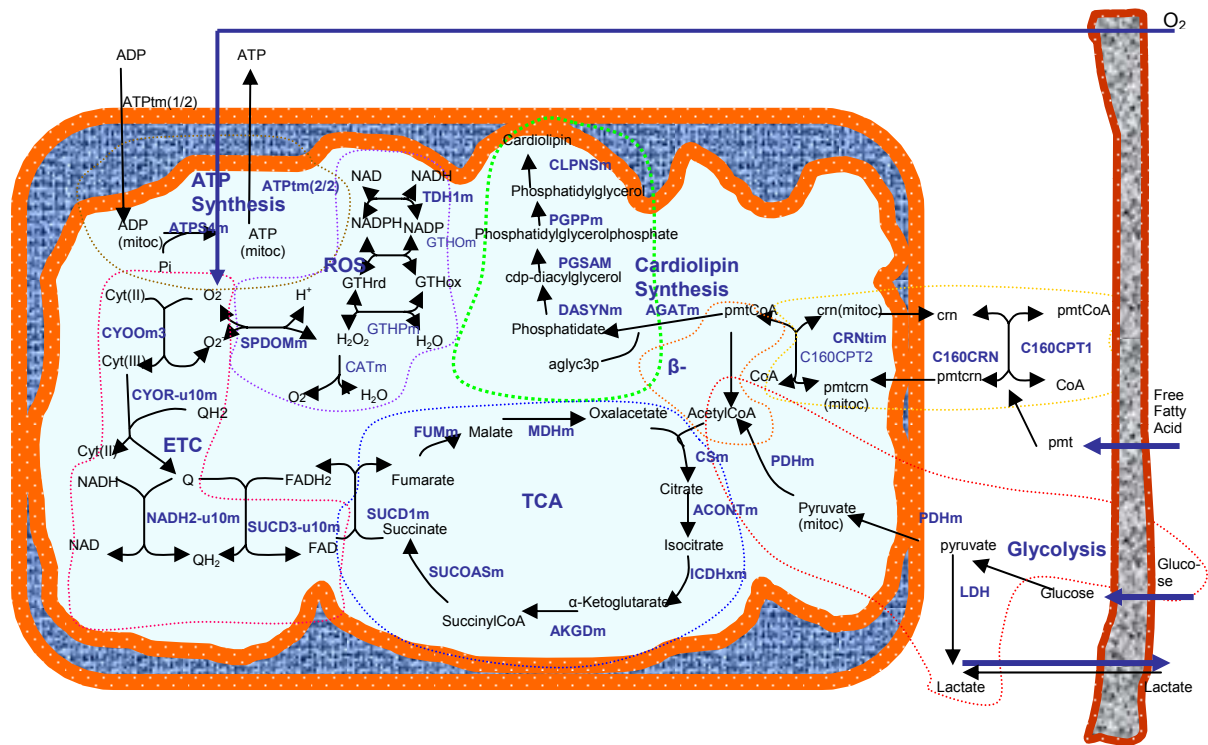


Figure 1: Mitochondrial pathways considered in the model: glycolysis/pyruvate metabolism, fatty acids β -oxidation, the Krebs cycle, the carnitine system, oxygen, CO_2 , ATP/ADP and H^+ /Pi transporters, cardiolipin synthesis, the electron transport chain, coupled to ATP production/ H^+ translocation systems and the ROS detoxification system.

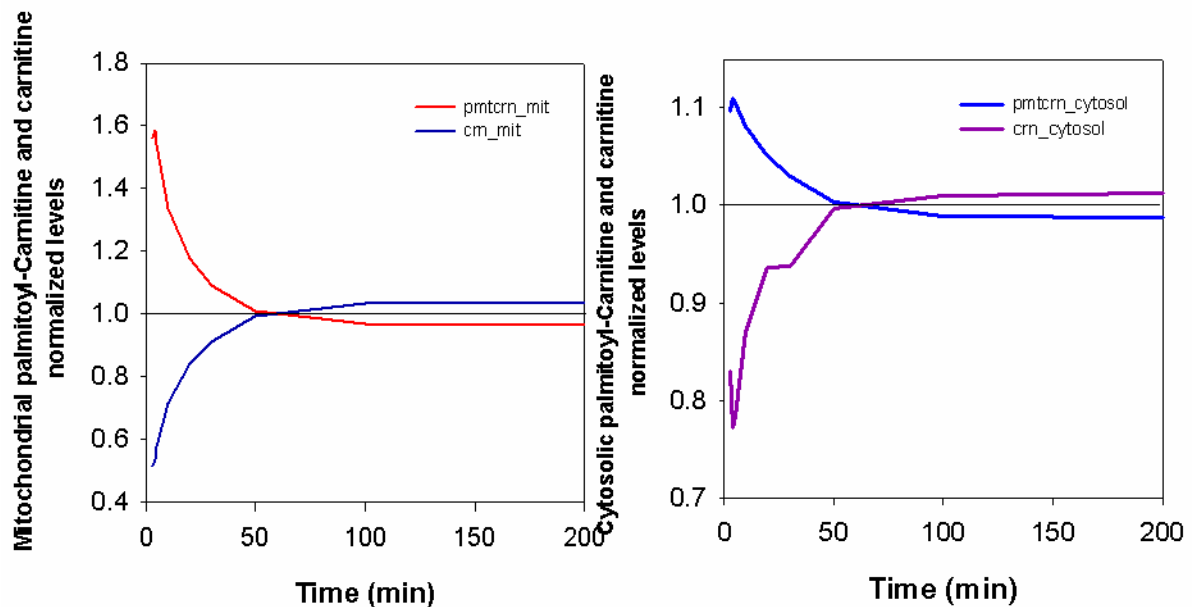


Figure 2: Mitochondrial and cytosolic Acyl-L-carnitine as palmitoyl-L-carnitine and carnitine levels during ischemia. Palmitoyl-L-carnitine and Carnitine: pmtcrn and crn.

With respect to abnormalities of the carnitine transferase system, the model simulations resulted in cardiac hypertrophy, arrhythmia and increased plasma Acyl-carnitine since in the cell, as a result, decreased the level of Acyl-L-carnitine and carnitine but keeping Acyl-L-carnitine/carnitine > 1 ratio which would affect generating even ischemia (Fig. 2). Moreover, under these abnormalities the O_2^- , H_2O_2 , and CO_2 levels accumulate in the mitochondria, affecting mitochondrial membranes. Although only 25-40% of the ATP production comes from glycolysis, under hypoglycemia both the cellular and mitochondrial carnitine increase, while cellular and mitochondrial Acyl-L-carnitine and Acyl-CoA and Acetyl-CoA decrease. The results obtained demonstrate that a Systems Biology approach can be used in the clinical diagnosis and treatment of progressive cardiovascular disorders, such as acute coronary syndrome.

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