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Abstracts

S3 Membrane Transporters

Lectures

3L.1 The ups and downs of mitochondrial calcium signalling in the heart☆

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Regulation of intramitochondrial free calcium ($[Ca^{2+}]_m$) is critical in both physiological and pathological functioning of the heart. The full extent and importance of the role of $[Ca^{2+}]_m$ is becoming apparent as evidenced by the increasing interest and work in this area of the last two decades. However, controversies remain, such as the existence of beat-to-beat mitochondrial Ca^{2+} transients; the role of $[Ca^{2+}]_m$ in modulating whole-cell Ca^{2+} signalling; whether or not an increase in $[Ca^{2+}]_m$ is essential to couple ATP supply and demand; and the role of $[Ca^{2+}]_m$ in cell death by both necrosis and apoptosis, especially in formation of the mitochondrial permeability transition pore. The role of $[Ca^{2+}]_m$ in heart failure is an area that has also recently been highlighted. $[Ca^{2+}]_m$ can now be measured reasonably specifically in intact cells and hearts thanks to developments in fluorescent indicators and targeted proteins and more sensitive imaging technology. This has revealed interactions of the mitochondrial Ca^{2+} transporters with those of the sarcolemma and sarcoplasmic reticulum, and has gone a long way to bringing the mitochondrial Ca^{2+} transporters to the forefront of cardiac research. Mitochondrial Ca^{2+} uptake occurs via the ruthenium red sensitive Ca^{2+} uniporter (mCU), and efflux via an Na^+/Ca^{2+} exchanger (mNCX). The purification and cloning of the transporters, and development of more specific inhibitors, would produce a step-change in our understanding of the role of these apparently critical but still elusive proteins. In this article I will summarise the key physiological roles of $[Ca^{2+}]_m$ in ATP production and cell Ca^{2+} signalling in both adult and neonatal hearts, as well as highlighting some of the controversies in these areas. I will also briefly discuss recent ideas on interactions of nitric oxide with $[Ca^{2+}]_m$.

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3L.2 Mitochondrial ion transport in metabolic disease

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Mitochondria are the central coordinators of energy metabolism and alterations in their function and number have long been associated with metabolic disorders such as obesity, diabetes and hyperlipidemias. Since oxidative phosphorylation requires an electrochemical gradient across the inner mitochondrial membrane, ion channels in this membrane certainly must play an important role in the regulation of energy metabolism. However, in many experimental settings, the relationship between the activity of mitochondrial ion transport and metabolic disorders is still poorly understood. We will cover aspects of mitochondrial H^+ and K^+ transport which may be determinants in metabolic disorders, including the impact of mitochondrial uncoupling on energy metabolism and aging and the role of K^+ channels in metabolic disorders.

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3L.3 The transport mechanism of mitochondrial carriers based on the analysis of pseudo-symmetry

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Mitochondrial carriers link the biochemical pathways of the cytosol and mitochondrial matrix by transporting substrates across the mitochondrial inner membrane [1]. The structures of mitochondrial carriers are three-fold pseudo-symmetrical [2,3], but their substrates and coupling ions are not. Thus, deviations from symmetry are to be expected in the substrate and ion binding sites in the central aqueous cavity [4]. By analyzing the three-fold pseudo-symmetrical repeats from which their sequences are made, conserved asymmetric residues were found to cluster in a region of the central cavity identified previously as the common substrate binding site [5,6]. Conserved symmetrical residues required for the transport mechanism were found at the water–membrane interfaces, flanking the substrate binding sites [4]. Three PX[DE]XX[RK] motifs form a salt bridge network on the matrix side of the cavity, when the carrier is in the cytoplasmic state with the substrate binding site open to the mitochondrial intermembrane space [3,7]. Three [FY][DE]XX[RK] motifs are present on the cytoplasmic side of the cavity and they could form a salt bridge network when the carrier is in the matrix state with the substrate binding site accessible from the mitochondrial matrix [4]. It is proposed that the opening and closing of the carrier could be coupled to the disruption and formation of the two salt bridge networks induced by substrate binding. The interaction energy of the cytoplasmic network allows members of the transporter family to be classified as strict exchangers or importers.

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