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Energetic depression caused by mitochondrial dysfunction



Abstract

Mitochondria not only provide most of the ATP needed for cell work and numerous specific anabolic and catabolic functions, they also contribute to Ca^{++} signalling and play a key role in the pathway to cell death. Impairment of mitochondrial functions caused by mutations of the mt-genome or by acute processes, is responsible for numerous diseases. Decreased concentrations of adenine nucleotides, leaky outer and inner mitochondrial membranes, and decreased activities of respiratory chain enzymes contribute to depression of cellular energy metabolism, one of the most important consequences of

mitochondrial impairment as characterized by decreased cytosolic phosphorylation potentials.

Full text

From ischaemic impairment

A great number of diseases are directly caused or at least accompanied by impaired mitochondria. Hereditary and acute mitochondrial diseases are known. Due to the important role of mitochondria as targets of several pathogenic mechanisms it is not surprising that the term "Mitochondrial Medicine" is increasingly used [1].

Investigation of mitochondrial function in diseased tissues

Relations between heteroplasmy and the appearance of functional deficits (thresholds) should be studied at different levels, such as DNA, enzymes, metabolites, mitochondria, tissues, or cells, and at the whole patient level (multi-level approach). A central task in this context is the characterization of mitochondrial function in human tissues and the relation to different pathological states, using both invasive and non-invasive methods. For investigation of mitochondrial function in biopsies, we and others have used the skinned fiber technique [2, 3].

Mechanisms of energetic depression

Figure 1 gives an overview of alterations at the cellular level during mitochondrial diseases. Mutations and acute disturbances cause a depression of the energy metabolism of the cell. Increased NO, oxidative stress, hypoxic or ischaemic conditions can disturb mitochondria. The same occurs during acute poisoning by inhibitors or uncouplers, and even following certain drugs. Besides energetic depression, such signals can also cause a specific release of apoptotic signal molecules, such as cytochrome c or apoptosis-inducing factor (AIF). Apoptosis occurs under conditions where the energetic state of the cell is more or less preserved. If, however, mitochondria swell and the mitochondrial outer membrane becomes leaky, the cell can become oncotic. Non-specific release of

cytochrome c should also act as an apoptotic signal, but the extent of energetic depression decides whether the cell dies from oncosis or apoptosis.

To understand the consequences of energetic depression we must consider some basic features of energy metabolism. Mitochondrial oxidative phosphorylation produces ATP in the mitochondrial matrix space. The AdN-translocator brings it into the intermembrane space (IMS). From here it has to diffuse through the porin pores of the outer membrane into the cytosol, where ATP is used for cell metabolism. ATP-dependent reactions generate ADP, and this has to be transported back into the mitochondria. To avoid inhibition of ATP-splitting reactions, cytosolic ADP concentration must be low. ATP concentration, however, must be high since it directly drives the ATP splitting reaction. For optimal cell work, the phosphorylation potential $[ATP]/[ADP]*[Pi]$ must be high in the cytosol, but low in the IMS for optimal stimulation of mitochondrial oxidative phosphorylation. All mechanisms which contribute to a decrease of cytosolic phosphorylation potentials cause energetic depression.

Decreasing concentration of adenine nucleotides

It is well known that during ischaemia and hypoxia the concentration of cytosolic adenine nucleotides decreases due to the action of AMP-desaminase. We have shown that below a threshold concentration of 2 mM extramitochondrial adenine nucleotides, the Gibb's free energy for the adenine nucleotide transport increases, but the extramitochondrial phosphorylation potential decreases. As a consequence, under these conditions, even intact mitochondria are unable to produce sufficiently high phosphorylation potentials, which are required for optimal cell work [4].

Leaky outer membranes

Mitochondrial outer membranes (OM) contain porin pores, which are open for diffusible metabolites but closed to proteins, such as cytochrome c. OM is a diffusion barrier, and rate-dependent diffusion gradients up to 23 mM have been detected [5]. These diffusion gradients cause a dynamic compartmentalisation of ADP within the IMS, since the ADP concentration is in the micromolar range. Due to its much higher concentration, ATP is not compartmentalised in the IMS. The dynamic ADP compartmentalisation is one prerequisite for the ADP shuttle systems. We know that mitochondrial and cytosolic isoenzymes of creatine

kinases as well as of adenylate kinases, can act as ADP shuttles. The biological advantage of these shuttles is the adjustment of high rates of oxidative phosphorylation at low cytosolic ADP concentrations. To achieve this, both kinase isoenzymes in the cytosol and in the IMS must work in different directions, forward in the IMS and backward in the cytosol. However, this is possible only if the metabolite concentrations are different in both compartments. The intact OM is able to create such differences, but if the OM becomes leaky, the function of the ADP shuttles is disturbed as has been demonstrated previously [6]. With reconstituted systems consisting of rat heart mitochondria and pyruvate kinase, the energetic consequences of leaky OM were investigated. ADP was regenerated by mitochondrial creatine kinase within the IMS. Both pyruvate kinase and oxidative phosphorylation competed for ADP. At intact membranes, most ADP remained within the OM, and ADP was mainly used by oxidative phosphorylation. The extramitochondrial ADP concentration remained low, and the phosphorylation potential was one order of magnitude higher than in the case of mitoplasts, where OM was partially removed by digitonin. Under this condition, mitochondrial creatine kinase also formed ADP, but this ADP was no longer dynamically separated from the extramitochondrial space. Therefore, the cytosolic ADP concentration was increased and the cytosolic phosphorylation potentials were drastically reduced [6].

Leaky outer membranes however, can cause further impairment of mitochondrial function. Cytochrome c, a component of the respiratory chain and the natural substrate for cytochrome c oxidase, is reversibly bound to the outer side of the mitochondrial inner membrane. If cytochrome c is released into the cytosol, there is a bottle-neck in the electron flow to the cytochrome oxidase, decreasing the maximal rate of respiration. The consequences of losing cytochrome c for mitochondrial function are easily detectable by means of the skinned fiber technique: an addition of cytochrome c causes an increase in the state 3 respiration rate [3, 7].

Permeability transition pore

Leaks in the mitochondrial inner membrane can be caused by opening the permeability transition pore (PTP). Permeability transition (PT) contributes to impaired mitochondrial function during ischaemia/reperfusion or sepsis. It has been speculated that a reversible opening of the PTP could have a physiological role in diminishing dangerously high oxygen concentrations [8]. In skeletal

muscle, it can happen that no ATP synthesis is required since the muscle is at rest, although the intracellular concentration of oxygen is elevated. To diminish the oxygen concentration, the PTP could be reversibly opened. Subsequently, protons can flow back into the mitochondria, and because of a decreased proton gradient, respiration increases. If however, the pore switches irreversibly to a larger opening state, this could cause energetic depression. Mitochondria swell, and because of the massive influx of protons, respiration is stimulated. Under these conditions the F_0F_1 -ATPase works in the opposite direction, splitting ATP produced by glycolysis. Such swollen mitochondria with opened PTP, are parasites of the cell and need to be destroyed. Such destruction of mitochondria is called mitoptosis [8].

Decreased capacity of the respiratory chain

Changes in the respiratory chain caused by different types of mutations

Energetic depression can also result from a decreased capacity of the respiratory chain. Mutations of the mtDNA are the most important reasons for diminished activity of respiratory chain complexes, but acute or chronic oxidative stress has also to be considered. Depending on the type of mtDNA-mutation, different functional consequences are expected. In patients with deletions, several tRNA genes and protein genes are missing. In contrast, in the case of the MELAS point mutation A4343G, only one tRNA is mutated. Our results indicate that deletions cause more severe defects than point mutations. We believe that these differences have consequences for the appearance of the functional deficit (thresholds), where the molecular defects are visible at the functional level.

Mitochondria and septic impairment

We and others have shown that impaired mitochondria play a role in endotoxaemia [2] and bacteraemia [9]. In rabbits, 100 mg endotoxin/kg significantly diminished state 3 respiration in heart mitochondria. Neither atractylate-insensitive respiration (state 4) nor intactness of outer and inner membranes were significantly altered by endotoxin. In contrast to heart mitochondria, state 3 respiration in skeletal muscle mitochondria, after application of 100 mg endotoxin/kg, did not differ from the control group. Mitochondrial parameters were altered, however, only if increased doses of

endotoxin (150 mg LPS/kg) were used. These data clearly demonstrate a dose-dependence, as well as a tissue specific action of endotoxin. The activity of complex I + III was significantly reduced in hearts of endotoxaemic animals (100 mg LPS/kg), and in skeletal muscle after administration of 150 mg LPS/kg. Both diminished enzyme activities and respiration rates caused an energetic depression, which could explain the impairment detected in perfused hearts [2]. We recently detected impaired mitochondrial function caused by significantly diminished activities of complex I + III and cytochrome c oxidase in skeletal muscle of septic patients [10]. An NO-induced oxidative stress has been suggested as a mechanism of septic impairment of mitochondria. For a recent review see [9].

Energetic depression by impaired Ca^{++} -oscillation

Cellular functions, such as muscle contractions, are triggered by oscillating Ca^{++} -concentrations in the cytosol. Cytosolic Ca^{++} oscillates due to the complex action of Ca^{++} transporters in the sarcoplasmic reticulum, the mitochondria and the cell membranes. In a cell-free model system, it has been shown that the velocity of Ca^{++} waves through a sarcoplasmic reticulum-containing agarose gel was increased by addition of intact mitochondria. This increase was reversed by antimycin A, an inhibitor of complex III of the mitochondrial respiratory chain [11]. These results show that there are important implications for Ca^{++} signalling if the mitochondrial function is disturbed.

Tissue thresholds and energetic depression

It seems that different cell functions and different tissues have unequal sensitivities for the consequences of energetic depression. For example, the visual function of the ZNS has a higher sensitivity to mitochondrial impairment than other neuronal functions, and in the hearts of patients with Kearns-Sayre syndrome, the cells responsible for electrical conduction are more affected than cardiomyocytes. An explanation could be that different cell functions require different phosphorylation potentials and that some processes can still occur even under energetic depression.

How to overcome energetic depression ?

Cells probably have different strategies to overcome energetic depression. One strategy is the increase of the number of mitochondria in the cell, for example we often find increased number of mitochondria in skeletal muscle of patients with mitochondrial defects. Furthermore, impairment at the mitochondrial level may be overcome by mitoptosis (programmed death of the mitochondrion), which can eliminate the ROS-overproducing organelles. Massive mitoptosis can result in apoptosis (programmed cell death), a mechanism to physiologically eliminate unwanted cells. Large-scale apoptosis can cause tissue decline (organoptosis), and even result in the death of the individual (phenoptosis) [8].

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Figures

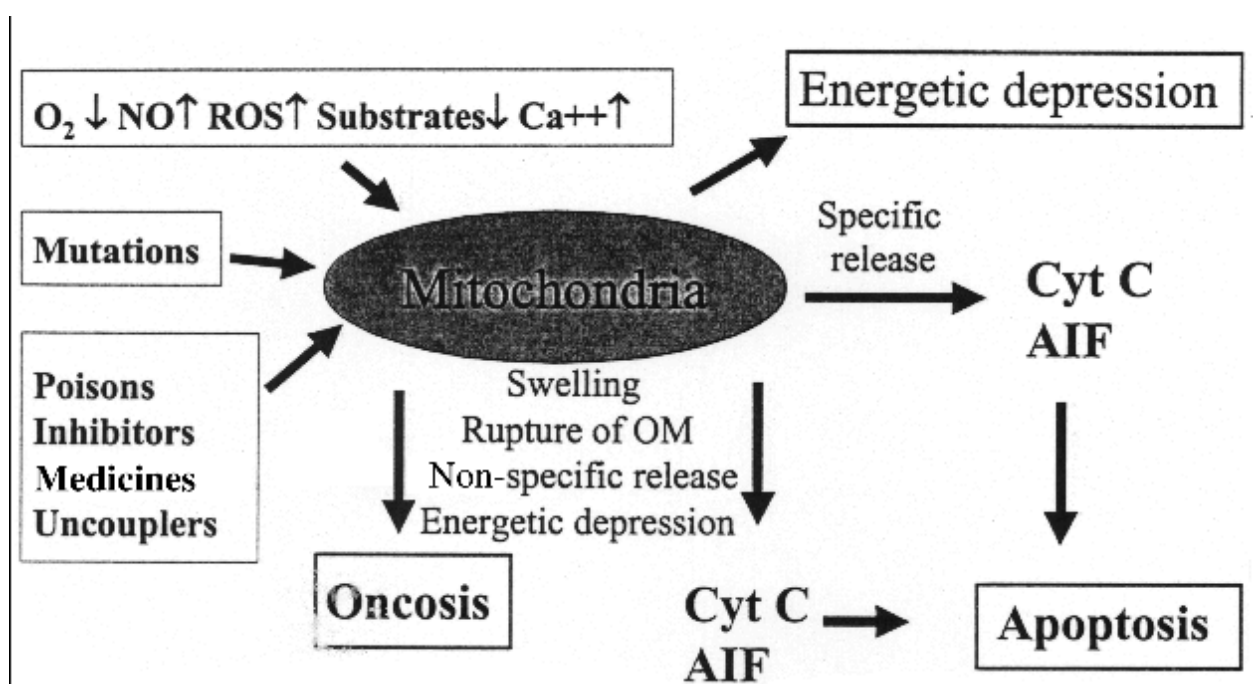


	Figure 1 : Schematic diagram showing the involvement of mitochondria in septic energetic depression and cell death. For explanations see text.

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