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Function of the outer mitochondrial compartment in regulation of energy metabolism

Dieter Brdiczka *

Faculty of Biology, University of Konstanz, P.O. Box 5560, D-78434 Konstanz, Germany

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1. Introduction

1.1. Different levels of energy metabolism and mitochondrial regulation

Excitable cells, such as nerve and muscle cells, have high ion pump activity. In addition skeletal muscle cells have a highly specialized contractile apparatus but also resemble hepatocytes as they take up glucose to form glycogen and amino acids to build protein stores. All these processes depend directly or indirectly on ATP, provided mainly by oxidative phosphorylation. Membrane depolarization and repolarization during excitation, muscle contraction and relaxation as well as Ca^{2+} release and sequestration are processes with a time-scale of milliseconds while the synthesis of glycogen and proteins goes on in seconds. The free energy of ATP hydrolysis that these processes use depends on the level of ATP, ADP and P_i according to the relation

$$\Delta G = \Delta G'_o + RT \cdot \ln[\mathrm{ADP}] \cdot [P_i]/[\mathrm{ATP}].$$

1.2. What is the signal that regulates the mitochondrial energy metabolism?

Energy-consuming processes such as ion pumps depend critically on a high phosphorylation potential. For example, the Ca^{2+} pump in the endoplasmatic reticulum works efficiently because there is not much difference between the energy consumption (590 mV) and the electrochemical work (520 mV) of the pump. This means that an ATP/ADP quotient of 10^3 is necessary to pump Ca^{2+} into the sarcoplasmic reticulum, assuming 10 mM phosphate in the calculation [1].

Indeed, ^{31}P-NMR measurements in intact heart muscle and brain tissues showed that the ATP/ADP levels did not fluctuate significantly during changes in activity. This was unexpected, because the ATP turnover increased 5- to 10-fold as well as oxygen consumption, indicating high activity of oxidative phosphorylation [2,3].

All these observations indicate that the mitochondria or the oxidative phosphorylation responds to the increased work load although the level of the main substrate ADP is not changing significantly. This leads to the question: what is the signal that stimulates mitochondrial energy metabolism?

1.3. Fast energy-consuming processes

To avoid large ATP/ADP fluctuations during fast and energy-consuming processes, creatine/phosphocreatine is used as an energy buffer and energy-transferring system. In this way, high ATP turnover during excitation increases ADP levels only locally but the creatine level (instead of ADP) globally [4]. The latter would then serve as a signal to stimulate mitochondrial metabolism in the time-scale of milliseconds (Fig 1A).

1.4. Slow energy-consuming processes

We hypothesize that metabolites other than free ADP regulate the mitochondrial activity also during slower metabolic processes in muscle at rest and in the liver. When oxidative phosphorylation generates the energy needed for building up glycogen and protein

* Corresponding author. Fax: +49 75 31882903.

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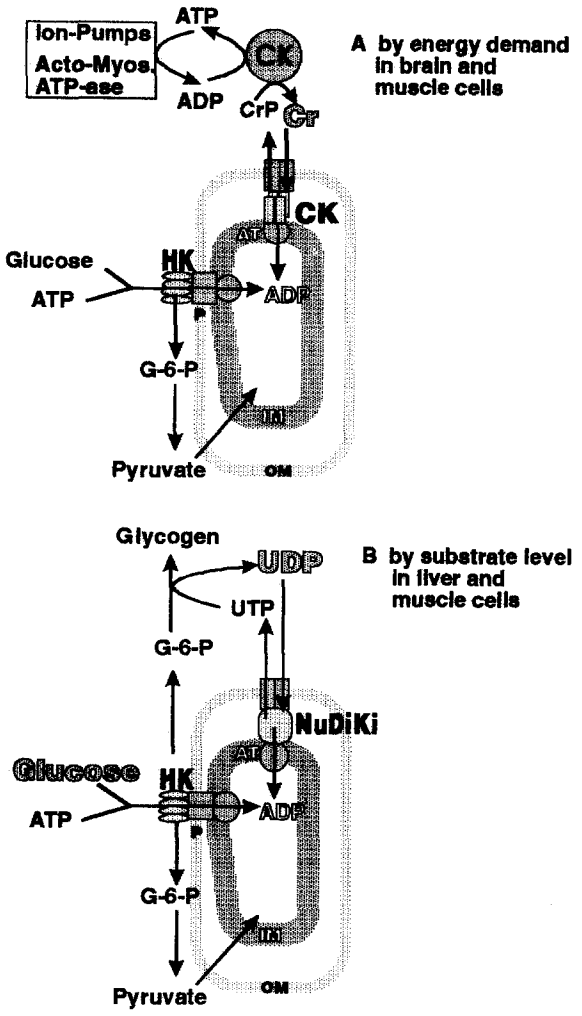

Fig. 1. Different ways of oxidative phosphorylation regulation without changing cytosolic ATP and ADP level. Activity of peripheral kinases increases the intramitochondrial ADP indirectly. (A) In the case of rapid ATP turnover upon stimulation of muscle or nerve cell activity, the level of creatine (Cr) increases. This stimulates mitochondrial creatine kinase (CK) to produce intramitochondrial ADP. The uptake of glucose increases concomitantly by activation of hexokinase (HK). (B) In the case of liver cells or muscle cells at rest, an increased level of glucose and of the UDP, produced during glycogen synthesis raises intramitochondrial ADP through bound hexokinase (HK) and nucleoside-diphosphate kinase (NuDiKi). In the contact sites, hexokinase and mitochondrial creatine kinase (which is a dimer in the active state) form tetramers and octamers, respectively. P = pore, OM = outer membrane, IM = inner membrane, AT = adenylate translocator.

stores, metabolites that are used in these pathways, such as glucose, glycerol, UDP or GDP might stimulate the mitochondrial metabolism (Fig. 1B).

1.5. Signal transmission by kinases

Specific kinases that are organized at the surface and directly communicate with the inner mitochondrial compartment activate the mitochondria. A coupling to the oxidative phosphorylation is known for hexokinase [5] and creatine kinase [6]. It may accomplish an additional function in permanently working muscles like heart or in nerve cells that both depend on blood-borne substrates. This function may be to regulate the cellular substrate (glucose) uptake according to the mitochondrial activity (Fig 1A).

In summary, the coupling of kinases to the inner compartment serves to transmit information in two directions. It tells either about increased ATP turnover and/or extramitochondrial substrate level directed towards the mitochondria or about mitochondrial activity directed towards the substrate supplying metabolic pathways.

2. Characteristics of peripheral mitochondrial kinases

One can define two groups of kinases at the mitochondrial surface according to function and location. First, energy-consuming kinases such as hexokinase and glycerol kinase generate low-energy products. They bind specifically to the outer membrane pore protein [7,8]. Second, energy-transmitting kinases such as creatine kinase, adenylate kinase and nucleoside diphosphate kinase: their products are energy-rich and able to form ATP. The latter kinases are located between the two envelope membranes [9,10].

2.1. Functional coupling to the inner compartment

Kinetically these kinases had a lower apparent K_m for ATP in the bound state, suggesting a functional coupling to the inner mitochondrial ATP. This means that they might interact directly with the adenine nucleotide translocator in the inner membrane [5,6]. It is hypothesized that the structural bases of this coupling are the contact sites between the two mitochondrial boundary membranes in which the kinases may build complexes with the adenylate translocator and the outer membrane pore.

3. Localization of kinases in the contact sites

The contact sites have been characterized by different techniques: electron microscopy, digitonin treatment and isolation. I would like to summarize briefly the results of these investigations.

3.1. Electron microscopy and treatment with digitonin

Fig. 2 schematically shows the localisation of hexokinase and creatine kinase by specific antibodies in brain mitochondria. In intact mitochondria the gold grains representing specific antibodies against hexokinase bound mainly at points of contact between the bound-

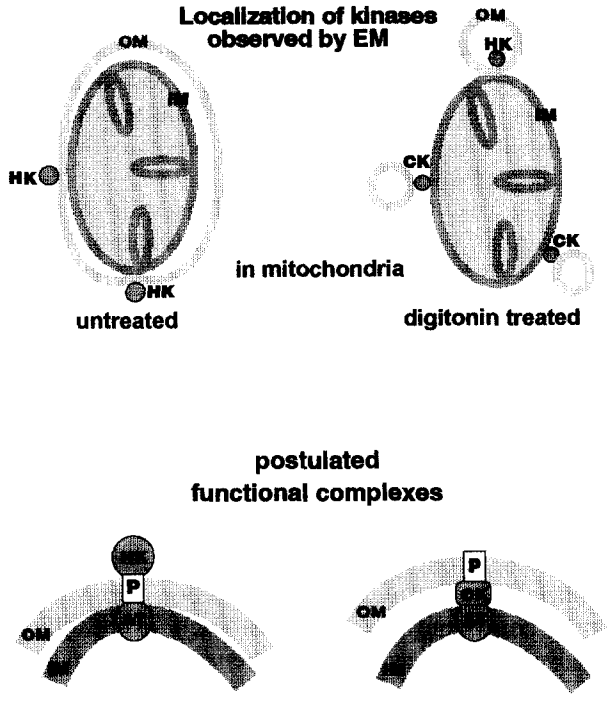

Fig. 2. The upper part of the figure schematically depicts the localization of hexokinase in intact liver and brain mitochondria as observed by electron microscopy in Refs. [11] and [12] and the localization of hexokinase in liver – and creatine kinase in brain mitochondria after digitonin treatment observed in Refs. [13] and [14]. The lower part of the figure presents the postulated functional complexes derived from the electron microscopic and kinetic analyses. HK = hexokinase, CK = creatine kinase, AT = adenylate translocator, P = porin, OM = outer membrane, IM = inner membrane.

ary membranes [11,12]. After digitonin treatment of liver mitochondria, labelled hexokinase was found in outer membrane vesicles that remained attached to the inner membrane [13]. To visualize creatine kinase in brain mitochondria by specific antibodies the outer membrane was disrupted by digitonin. In this case, more than 40% of the enzyme that was not desorbed by digitonin treatment were located between the two boundary membranes in the contact sites [14]. Considering electron microscopic results, complexes were postulated between the kinases, porin and adenylate translocator that are depicted in Fig. 2. The observation of functional coupling of the kinases to the inner compartment does not imply physical coupling, but it supports the assumption of complexes.

3.2. Isolation of contact sites

From electron microscopy and digitonin treatment, hexokinase was considered a good marker enzyme in the attempt to isolate contact points from osmotically disrupted mitochondria. The membrane fragments were separated by centrifugation on sucrose density gradients. Indeed, a fraction of intermediate density was observed in which hexokinase was enriched. The same fraction contained creatine kinase and nucleoside diphosphate kinase, while adenylate kinase was found on top of the gradients in the outer membrane fraction [12,15]. The intermediate, hexokinase rich fraction was obtained from osmotically shocked liver, kidney and brain mitochondria. The intermediate fraction was removed from the gradients and hexokinase precipitated by specific antibodies. Although the precipitate, was further purified by density gradient centrifugation the hexokinase-rich fraction was composed of inner and outer membrane markers and contained creatine kinase and nucleoside diphosphate kinase [15].

The results suggested that a complex between hexokinase and porin had been enriched with adhering outer membrane and presumably adenylate translocator with adhering inner membrane. Such a complex between porin and adenine nucleotide translocator and an additional 18 kDa protein has recently been isolated from kidney mitochondria as a benzodiazepine receptor [16].

The isolated contact site fraction was further characterized by proteolysis analysis, and the accessibility of the enzymes to specific antibodies and substrates was determined. On the whole, the results suggested that the isolated contacts were formed of a right-side-out outer membrane vesicle that enwraps an inner membrane vesicle [15,17].

4. Regulation of contact sites

We developed a method to analyse the frequency of contact sites in freeze fractured mitochondria in vitro and in situ; for details see [18,19]. By applying this method it was observed that the contacts were dynamic structures that were regulated as summarized in the Table 1. Compared to non-phosphorylating (the functional state 4) mitochondria that are set to 1 the contact frequency were about 4-times higher in phosphorylating mitochondria (functional state 3). It appeared that the formation of contacts was dependent on ligands of the adenine nucleotide translocator such as ADP and atractyloside. In contrast, the contacts decreased in the presence of uncoupler DNP, glycerol, fatty acids and glucagon [20,21] In the last column of Table 1 I list hexokinase activity that was found to correlate in hepatocytes and liver mitochondria with the contact frequency. This agrees with the observation that hexokinase had a higher affinity with the pore protein in the contact sites [17,22].

4.1. Composition and dynamics of the contact sites

The results in Table 1 suggest that contacts are labile dynamic structures, because of their regulation

Table 1
Regulation of contact sites and bound hexokinase activity in hepatocytes and isolated liver mitochondria

Effector	Relative contact site frequency	Relative bound hexokinase activity	Ref.
State 4 (O2, P_i, Substrate present)	1	1	18,19,20
State 3 (O2, P_i, Substrate, ADP present)	3.85	4–5	18,19,20
ADP (P_i lacking)	3.85	4–5	19
Atractyloside	3.85	n.d.	19
10% Dextran 70 State 4	3.70	n.d.	27
10% Dextran 70 State 3	6.15	6	27
DNP (uncoupler)	0.15	0.2	17,18
20% Glycerol	0.12	n.d.	18
Fatty acids	1.35	0.24	20
Glucagon (β-receptor)	2.23	0.64	21
Epinephrine (α_1-receptor)	6.54	n.d.	21

As a means of quantifying the difference in fracture-plane deflections, we measured the length (L) of the edge where the fracture plane deflects related to the corresponding mitochondrial area. In convex fractures, we determined the length of the edge of the exoplasmic face of the outer membrane. In concave fractures, we analyzed the deflection line on the exoplasmic face of the inner membrane. These measurements of L were expressed as length (μm) per unit of mitochondrial fractured membrane area. In every population of mitochondria, there are some which are completely void of fracture plane deflections. The number depends upon the metabolic state of the whole sample. To compensate for these differences we adjusted our calculation of fracture plane deflections as follows. We first determined on survey pictures the total area of mitochondria with no deflections, M_s, and those with deflections, M_p, and then normalized these values by the expression $M_p/(M_p + M_s)$. The final value for quantification of freeze fracture deflections L_p was then calculated from the equation: $L_p(\mu m/\mu m^2) = LM_p/(M_s + M_p)$ and the statistical differences obtained by applying the U-test.The measurements were made in the areas where the curvature was low to avoid large distortions of the measured edge lines. The data in the table are contact site frequency and bound hexokinase activity related to the values observed in mitochondria in state 4 (set to 1). They were taken from the publications listed in the last column.

and arrangement according to the metabolic function. This would support the idea shown in Fig. 2 that contact sites are arranged as functional complexes between outer (pore) and inner membrane (adenylate translocator) components and a structure (kinase) which is subjected to metabolic regulation. Such regulation of kinase structure and activity was observed to take place at the mitochondrial surface. It was reported by several laboratories that hexokinase isozymes I and II are activated by binding to the mitochondrial surface [11,23,24] and that the catalytic efficiency of the enzyme increases [5,25]. Furthermore, isozyme I forms a tetramer by binding to the membrane [26]. Mitochondrial creatine kinase in contrast to the cytosolic enzyme associates to an octamer. The octamer was concentrated in the contact sites [27] and was able to link two artificial membranes [28].

5. Influence of macromolecules on the structure of the outer mitochondrial compartment

It is known that conventional isolation methods cause extensive swelling of the outer mitochondrial compartment. Because of the assumed fragility of contacts we expected that this would interfere with the structural organization of these sites. The commonly used media adjust the physiological osmotic pressure by sugars such as mannitol or sucrose. Because exclusively the inner membrane is semipermeable for the sugar molecules, these media preserve the structure and function of the inner membrane matrix compartment, while the structure of the outer mitochondrial compartment is strongly altered. To preserve the structure of the outer mitochondrial compartment we took into account that the mitochondria are physiologically embedded in a 10–30% protein or macromolecule solution and substituted the proteins by dextran.

Conventionally isolated liver mitochondria were subjected to rapid freezing and were freeze-fractured. Pre-incubation in the presence of 10% dextran (70 kDa) led to a significant reduction of the space between the two envelope membranes and the crista membranes compared to the control. The close attachment of the envelope membranes under dextran suggested changes in protein organization in the outer compartment and raised the question whether this would also affect contact formation.

We observed that in the presence of 10% 70 kDa dextran, the frequency of fracture plane deflections was already higher in state 4 and comparable to that of control mitochondria in state 3. Full activation of dextran-treated mitochondria in state 3 led to an additional increase of contacts (Table 1) [29].

Hence, electron microscopy showed that substitution of macromolecules by dextran reduced the space between boundary and crista membranes and induced contact site formation.

6. Influence of macromolecules on the activity of peripheral kinases

We studied the effect of macromolecules on the binding of isolated hexokinase, isozyme I, to liver mitochondria. The half-maximal saturation constant was significantly lower in the presence of 10% dextran (70 kDa) than compared to the control [29]. Considering that hexokinase bound preferentially to the contact sites this suggested induction of contacts by dextran. The binding of hexokinase appeared to be a co-operative process and led to a 5- to 10-fold activation of the enzyme. This was, however, not observed when the contacts were suppressed by addition of 20% glycerol

or 50 μM dinitrophenol. In this case we found almost the same hyperbolic saturation curve that is characteristic for isolated outer membrane, and no activation of the enzyme [29].

The functional coupling of creatine kinase to the inner compartment was studied in isolated heart mitochondria in the presence and absence of dextran. Dextran improved the stimulation of the oxidative phosphorylation by creatine kinase. In addition, the ADP produced by the enzyme appeared to be separate and less accessible to simultaneously added pyruvate kinase and phospho*enol*pyruvate [30].

Compartmentation of adenine nucleotides in the mitochondrial inter-membrane space was described by several authors such as Bessman et al. [31] and Brooks et al. [32], but the reason for this was always unclear. Zimmerberg and Parsegian [33] observed that macromolecules reduced the conductance of the isolated outer membrane pore reconstituted in artificial membranes. In agreement, we observed that 10% dextran, even at as little as 10 mV transmembrane potential, led to pores in the low conductance state. This state of the pore is selective to cations, by a factor of 5–10 over anions, and significantly reduces ADP/ATP permeation [34,35]. Thus substrate exchange across the outer membrane may be physiologically limited.

7. Properties of porin kinase complexes

The cooperativity of hexokinase binding in the contact sites resulting in activation of the enzyme suggested the formation of oligomers in the complex with porin. Likewise, we observed mainly the octamer of creatine kinase in the contact sites.

7.1. Porin hexokinase complex

We were able to generate a complex between Hexokinase I and porin prepared from liver mitochondria in lauryl dimethyl amino oxide (LDAO). This complex made the enzyme 5–10-fold more active. The complex formed under conditions that favour binding of hexokinase to intact mitochondria: pH (6.5), dependence on Mg^{2+} (10 mM). Glucose-6-*P* (5 mM), that physiologically desorbs hexokinase, abolished the activation of the enzyme by porin. Analysis of the complex by column chromatography revealed a mass of 480 kDa, suggesting a composition of a porin dimer and a hexokinase tetramer [36]. This agrees with the observation made by Wilson using cross-linking that the enzyme bound to the mitochondrial membrane was a tetramer in contrast to the free enzyme that stayed dissociated as monomer [26].

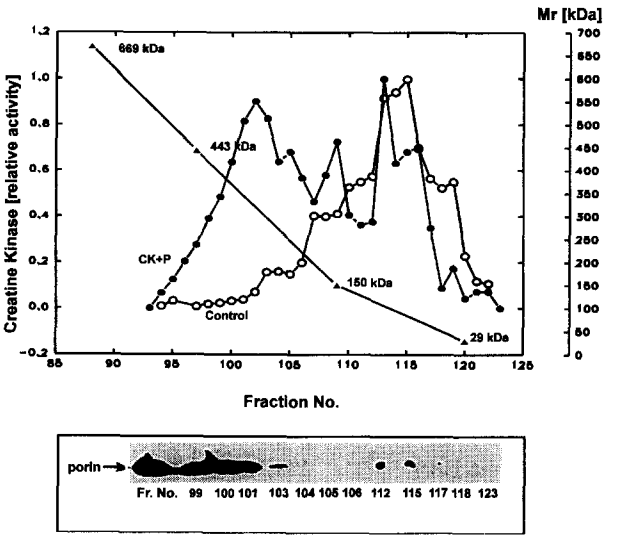

Fig. 3. Isolation and characterization of a porin/Δ5-mitochondrial creatine kinase complex by gel permeation chromatography. Upper panel: 100–200 μg of undissociated Δ5-mitochondrial creatine kinase were incubated for 1 h at room temperature with 300 μg porin in the presence of 3% Triton X-100, 1 mM EDTA and 10 mM Tris (pH 7.0) = CK + P (●). As control the enzyme was incubated without porin under identical conditions = Control (○). The samples were loaded on a 90 ml Superose 6B column and were eluted with 50 mM phosphate (pH 7.2), 0.5 mM EDTA, 2 mM mercaptoethanol. The eluate was collected in 130 fractions of 650 μl in which the activity of creatine kinase was determined by optical test. The activity profiles are presented as activity relative to the maximal activity in the eluted peak fractions. Thyroglobulin, apoferritin, alcohol dehydrogenase and carbonic anhydrase were used as molecular mass standards corresponding to 669, 443, 150 and 29 kDa, respectively. Lower panel: The presence of porin was analysed in the following way. Fractions containing creatine kinase activity, as indicated by fraction No., were concentrated by centrifugation filtration and were subjected to SDS-PAGE. The gels were blotted on nitro-cellulose sheets and decorated with specific antibodies against porin. Porin = isolated free porin.

7.2. Porin creatine kinase complex

In the experiments we used a creatine kinase that was mutated and missed the last five amino acids at the N-terminus. This deletion caused a significant reduction of the octamer formation [37]. It was thus possible to perform the experiments with completely dissociated creatine kinase. However, addition of porin resulted in formation of an oligomeric complex that was identified as the octamer (350 kDa) by column chromatography (Fig. 3) (Brdiczka, D., Kaldis, P. and Wallimann, T., personal communication). The results suggested that porin directly interacted with mitochondrial creatine kinase. In the complex the active enzyme, that is a dimer, formed a tetramer as was observed with hexokinase.

8. Summary and conclusion

Electron microscopy showed the organization of several kinases at the mitochondrial surface as complexes

between outer membrane (porin), kinase, and inner membrane (presumably adenine nucleotide translocator?). The complexes were enriched in the isolated contact site fraction. Interaction of porin with the kinases in vitro led to formation of tetramers of hexokinase and active creatine kinase. Kinetic analyses of mitochondria with intact outer compartment showed separate ATP/ADP exchange between kinases and oxidative phosphorylation.

Considering these results, we postulate that the mitochondrial metabolism in intact cells is not regulated by free ADP, but induced by substrates of kinases such as glucose or creatine (Fig 1).

Increased ATP turnover in muscle during contraction results in only a small change in the free ADP but causes a larger change of creatine because the equilibrium constant of the creatine kinase reaction at pH 7.2 favours ATP formation (ATP creatine/ADP phosphocreatine = 104.7) [38]. In addition, the level of phosphocreatine is roughly 10-times higher compared to ATP. Considering the higher concentration and the equilibrium constant, it can be calculated that a change of ADP between 40 and 70 μM results in creatine increasing from 8 to 12 mM. Thus creatine can be the signal that stimulates the mitochondrial metabolism transmitted by the mitochondrial creatine kinase [39].

Likewise, increased blood glucose in muscle at rest or in the liver stimulates the mitochondrial metabolism transmitted by the activity of bound hexokinase utilizing external ATP. The mitochondrial metabolism provides the UTP for glycogen synthesis through mitochondrial nucleoside-diphosphate kinase activity (Fig 1).

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