From mitochondrial large amplitude swelling to the permeability transition – a short historic overview

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ABSTRACT

An outline of studies on the mitochondrial large conductance permeability pore is presented starting from the early observations in the 1950s on the large amplitude mitochondrial swelling, through the concept of the permeability transition and various theories on the structure of the related permeability transition pore, up to its present identification as a part of mitochondrial (F_1F_O) ATPase/ATP synthase.

When methods for isolation of mitochondria in substantial amounts from organs such as liver [1], heart, kidneys and skeletal muscles became available in the middle of the last century, intense investigations on both their structure and metabolic functions have started. Studies in the laboratories of J. Raaflaub [2] in Zurich and Albert L. Lehninger [3,4] at the Johns Hopkins University in Baltimore have shown that liver mitochondria, the most frequently investigated intracellular organelles at that time, can take up water and increase their volume. This process could easily be followed by gravimetric or optical methods. The latter ones consisted of measuring either light transmittance (transparency) or light scattering (opacity, turbidity) of mitochondrial suspensions. It was called *swelling* and was believed to be related to mitochondrial de-energization and uncoupling of oxidative phosphorylation [3,4].

Mitochondrial swelling could be induced by a number of substances like thyroxine, inorganic phosphate, calcium ions, oleate and, importantly, a substance of lipidic nature isolated from "aged" mitochondria that also produced uncoupling of oxidative phosphorylation and therefore was called *uncoupling factor* [3]. This *factor* was soon identified as a mixture of long-chain saturated and unsaturated fatty acids [5]. A systematic study over a range of fatty acids showed that the potency to elicit swelling depended on the carbon atom chain length and the degree of unsaturation. Saturated fatty acids of 12 and 14 carbon atoms and unsaturated ones of 18 carbon atoms at *cis* configuration appeared the most active [6]. It could be therefore speculated that the potency to induce mitochondrial swelling depended on the *hydrodynamic chain length* (the distance between both ends of the molecule) that probably fitted the half thickness of the phospholipid bilayer of the mitochondrial inner membrane.

A.L. Lehninger also observed the reverse process, for which he coined the name *contraction* [7]. This effect consisted in extrusion of water, resulting in a decrease of mitochondrial volume that was manifested by increased turbidity (light scattering) of mitochondrial suspensions. In contrast to the mitochondrial swelling, their contraction was assumed to be an active process, connected with the energization of these organelles, as it was produced by addition of ATP and required the presence of Mg^{2+} [7]. While mitochondrial swelling was accompanied by liberation of non-esterified fatty acids, their contraction caused by addition of ATP was paralleled by re-incorporation of these fatty acids into mitochondrial phospholipids. This was demonstrated using isotopically labelled both [^{14}C]oleate and glycerol 3-[^{32}P]phosphate [8]. The phospholipid that was identified as the primary product was phosphatidic acid. These studies suggested that contraction was enabled not only due to the removal of free fatty acids that have accumulated but also by restoration of some lipid-like compounds indispensable for the original low permeability of the inner membrane.

A systematic study using electron microscopy revealed that the first step of the swelling was an increase of the matrix volume accompanied by the rupture of the outer mitochondrial membrane (Fig. 1) [9]. The ATP-induced contraction was reflected by matrix condensation (dehydration, Fig. 2), which, however, never led to the restoration of the original structure of intact mitochondria.

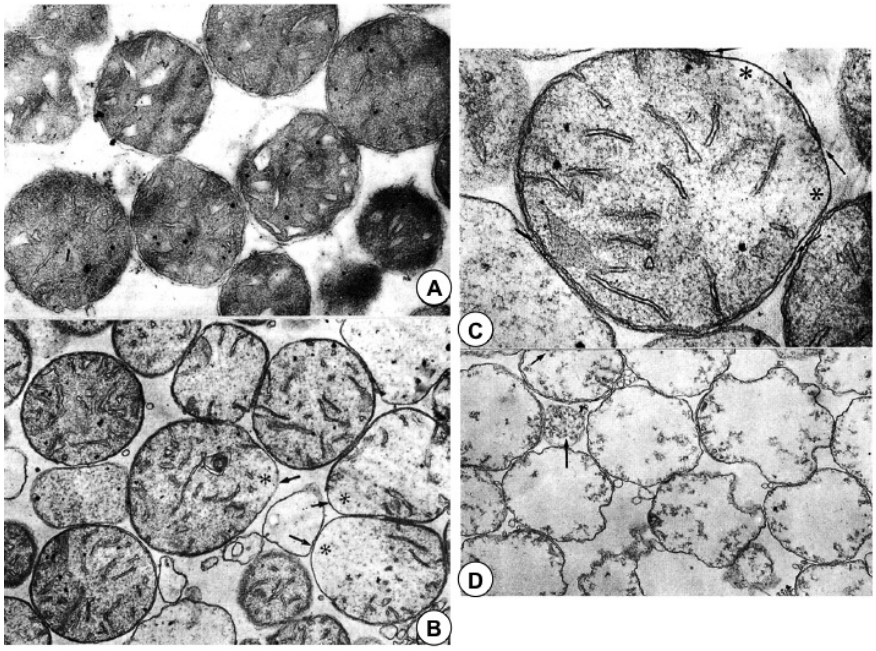

Figure 1. Electron micrographic pictures of rat liver mitochondria undergoing swelling produced by low concentrations of oleic acid. A, Freshly isolated mitochondria in isotonic sucrose (condensed conformation). B, Mitochondria after 15 min incubation in isotonic KCl at 20°C; *orthodox* conformation; slight spontaneous swelling and disruption of the outer membrane indicated by asterisks (*). C, same as B, higher magnification. D, Mitochondria swollen in the presence of 10 μM sodium oleate: complete unfolding of the cristae and removal of the outer membrane. From [9] with permission of Elsevier.

At this point it is worth mentioning that the outer mitochondrial membrane appeared to be impermeable to cytochrome *c* [10-12]. This property led us [13] to elaborate an essay for the intactness of the outer membrane in preparations of isolated mitochondria that was based on oxidation of externally added reduced cytochrome *c*. On the other hand, it is well known that programmed cell death, the apoptosis, can be induced by activation of caspases by cytochrome *c* [14]. This would require liberation of cytochrome *c* from mitochondria into the cytosol. One of the ways this process might occur would be swelling of mitochondria within the living cell accompanied by the rupture of the outer membrane, as postulated by some authors [15,16]. However, other possible ways of liberating cytochrome c from mitochondria into the cytosol, namely through contact sites between the inner and the outer mitochondrial membranes, have also been proposed (see [17] and references cited therein).

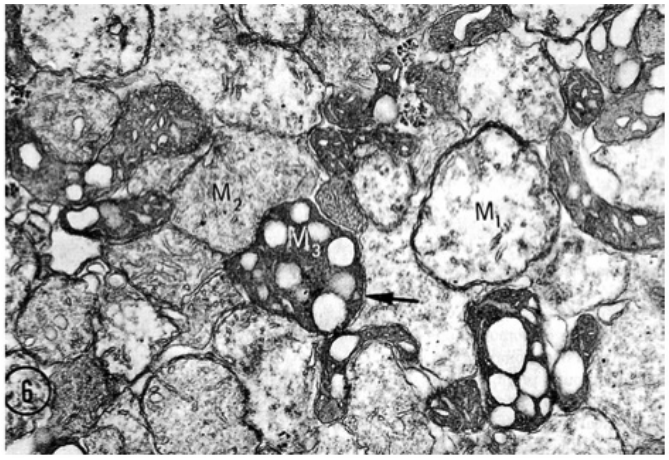

Figure 2. „Contraction" of mitochondria by ATP. Swollen mitochondria as in Fig. 1D treated with 2.5 mM ATP + 3 mM $MgCl_2$ + 0.2% serum albumin. An example of "contracted" mitochondrion is indicated by the arrow. From [9] with permission of Elsevier.

Mitochondrial swelling as described by Lehninger and co-workers and subsequently studied by Azzi and Azzone [18] could be termed *large amplitude swelling* as it eventually led to complete depletion of the outer membrane and the formation of inner membrane *ghosts* of low light absorbance (Fig. 1D). This was contrasted by *low amplitude swelling*, first observed by Chance and Packer [19] and later on studied by Azzi and Azzone [20], that was fully reversible and reflected the variation in the energy and/or metabolic state of mitochondria. These low amplitude changes in the mitochondrial volume and structure could also be observed inside living cells [21].

Both the large- and (most likely) the low-amplitude mitochondrial swelling could be interpreted as resulting from an unspecific increase of the permeability of the inner mitochondrial membrane to low molecular weight solutes. As a consequence, their concentrations inside and outside mitochondria equilibrated, whereas the concentration of high molecular weight compounds, in particular soluble intramitochondrial proteins, remained not much changed. This led to a higher osmotic pressure (the so-called colloidal, or oncotic, pressure) inside mitochondria, resulting in the influx of water. An important step in the understanding of his phenomenon was made by D.R. Hunter and co-workers [22-24] who have proposed that, under the influence of elevated external concentration of Ca^{2+} in the presence of phosphate ions, the inner mitochondrial membrane undergoes a natural transformation in which an unspecific permeability channel becomes activated. These authors concluded [22]: „The results ….. indicate that mitochondria have a built-in mechanism, which responds to low levels of calcium, phosphate, and fatty acids, resulting in simultaneous changes, including increased permeability, induction of ATPase, uncoupling of oxidative phosphorylation, and loss of respiratory control."

Understanding that the increased unspecific permeability of the inner membrane was not an artefact but reflected the natural property of mitochondria was of fundamental importance and boosted further research of this problem. The term *'permeability transition'* of the inner mitochondrial membrane was probably first used by Wingrove and Gunter [25] in 1986. The subject of utmost interest became the chemical structure and properties of the corresponding channel, the *'permeability transition pore'* (abbreviated as PTP). First studies in this area suggested that the pore may result from a kind of structural and functional 'cooperation' between the inner and the outer mitochondrial membranes [26-28]. This view represented, among others, by Dieter Brdiczka pointed

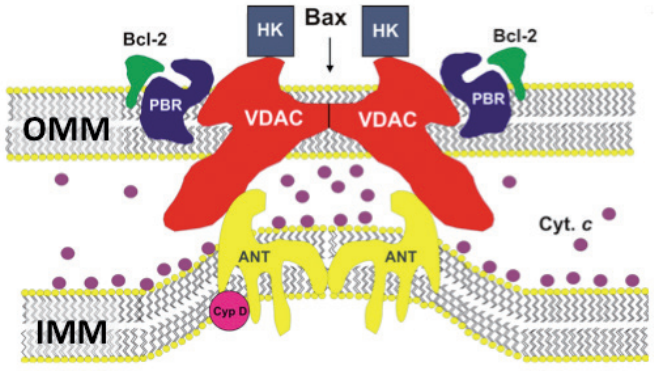

Figure 3. Schematic presentation of the contact site between the outer and the inner mitochondrial membranes according to Brdiczka. OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; VDAC, voltage-dependent anion channel (mitochondrial porin); HK, hexokinase; PBR, peripheral benzoadipine receptor; ANT, adenine nucleotide transporter; CypD, cyclophilin D; Bcl-2, antiapoptotic protein; Bax, proapoptotic protein. Model based on [17,28-31].

to the contact sites between the two membranes as possible *loci* regulating not only the permeability but also metabolic and energetic functions of mitochondria [29-31]. These sites might also be responsible for releasing cytochrome c from mitochondria to the cytoplasm as mentioned before [17], a process initiating programmed cell death (apoptosis) [14]. Arguments that PTP was located at the junction between the two membranes were essentially based on observations that proteins participating in this pore came from both the outer and the inner mitochondrial membranes. Proteins such as the adenine nucleotide transporter (ANT, an inner membrane protein), voltage-dependent anion-selective channel (VDAC, an outer membrane protein) and cyclophilin D (CypD, a mitochondrial matrix protein) appeared to be involved in the pore formation (for review see [32]). However, the list of proteins supposed to be responsible for the mitochondrial permeability was longer. Proteins such as Bak, Bax, Bcl-2, Bcl-x_L, benzodiazepine receptor, glycogen synthase kinase 3-β, hexokinase, creatine kinase, protein kinase C and several other have been considered to play regulatory roles (reviewed in [33,34]). Despite solid data supporting the contact site model of PTP, another model of PTP formation has been proposed [35,36]. This model assumed that the pore could be formed by misfolded mitochondrial proteins modified, *inter alia*, by oxidative damage and not connected with the opening of a pre-existing inner membrane pore.

Everything changed in 2004 when the group of Douglas Wallace [37] showed that mitochondria lacking ANT1 and ANT2 could still exhibit permeability transition phenomena, although the permeability was no longer regulated by ANT ligands. Shortly thereafter Baines and coworkers [38] found that mitochondria from genetically transformed mice lacking various forms of VDAC were still able to undergo PTP opening. These two groundbreaking papers have pointed out in a direct way that neither ANT nor VDACs (believed up to then to form the "core" of the pore) is an essential component of the PTP structure. Nevertheless, the effects observed for ANT and VDAC ligands suggested that these proteins could have a regulatory role. From the Brdiczka's model CypD was the only protein whose involvement in the PTP formation remained unquestioned, because experiments performed with transgenic mice lacking the peptidylprolyl isomerase f *(ppif)* gene have confirmed that this protein is the key element of PTP that is responsible for its sensitivity to cyclosporine A [39]. However, it should be pointed that cyclophilin D plays rather a regulatory role and is not involved in the pore formation.

To understand the architecture of the PTP channel, it has been proposed independently by two laboratories [40, 41] that the phosphate carrier could be a good candidate to form the "core" of PTP. However, four years later Halestrap [42] questioned this concept (in a sense his own, see [40]), showing that decreasing expression of the phosphate carrier in HeLa cells by 70% or more did not affect PTP opening. Nevertheless, the role of the phosphate carrier in PTP functioning cannot be excluded because, as observed by Kwong *et al*. [43], a complete genetic deletion of this carrier in mouse cardiac mitochondria desensitizes the PTP. These authors concluded that "although the phosphate carrier is not a direct component of the PTP, it can regulate its activity" [43].

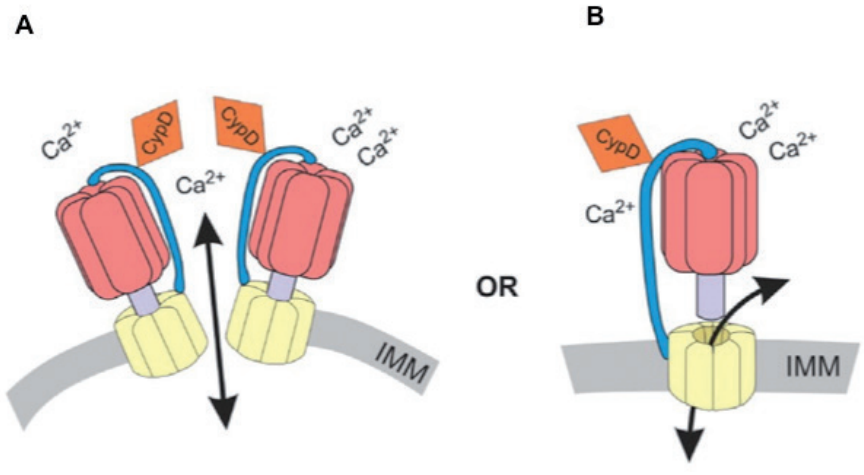

Figure 4. Proposed models of PTP composition based on the concept that its central role is played by the c-subunit ring of ATP synthase. A, Double c-subunit ring model; B, single c-subunit ring model. IMM, inner mitochondrial membrane; CypD, cyclophilin D. From [50] with permission of the authors and Elsevier.

A real breakthrough in the studies on the PTP structure came at the beginning of 2013 when Pinton and co-workers [44] have shown that subunit c of mitochondrial ATP synthase plays a critical role in PTP phenomena. These authors have shown that transient depletion of the c subunit of ATP synthase prevents PTP opening and, on the other hand, its overexpression promotes PTP opening. Shortly thereafter, the group of Jonas [45] supported this concept by proposing that the ring composed of c subunits (the so called c-ring) is the best candidate to form the PTP core. These authors demonstrated that the purified and reconstituted c-subunit ring could form a voltage-sensitive channel. However, neither cyclosporine A nor high Ca^{2+} concentration exerted any effect on channel properties of the purified c-subunit ring,

indicating that the c-subunit ring alone had no regulatory components enabling controlling PTP opening and closure. Only when the complete ATP synthase monomer was used in the presence of cyclophilin D could the typical regulation of PTP be observed. Moreover, mutation of highly conserved glycine residues responsible for the optimal packing of c-subunits within the c ring caused an increased pore conductance and decreased the sensitivity to cyclosporine A, thus suggesting that the impaired packing of c subunits may have high impact on the PTP permeability [45]. Interestingly, purified β subunit of ATP synthase added to the reconstituted c-subunit ring decreased pore conductance, indicating that β subunit could directly regulate PTP. The latter observation explains the well-known inhibitory effect of ADP on PTP opening [46].

These important findings, most of them recorded during the last decade, opened a new and fascinating view of the structure, properties and importance of PTP. Nevertheless, it was still difficult to hypothesise that the intact ATP synthase or its c-subunits ring free of the "stalk" and the "head" subunits could form the mitochondrial permeability pore. Meanwhile, Azarashvili *et al.* [47] showed that phosphorylation of subunit c by protein kinase A affected interactions between subunits in the c-subunits ring and could interfere with the interactions between subunits c and the "stalk" subunits of mitochondrial ATP synthase. Additionally, the presence of free c-subunit oligomers in calcium-induced swollen mitochondria has been found [45] suggesting that the simplest structure of PTP can be formed by partially decomposed ATP synthase (e.g. physical decoupling of F_1 from F_O). In 2014 research groups of Jonas [45] and Saris [47] have shown independently that the c-subunit rings reconstituted into liposomes exhibit channel activity, thus supporting the original hypothesis of Pinton [44] that subunit c can be a crucial element responsible for PTP formation. Similar studies leading to the conclusion that ATP synthase is involved in PTP formation has also been carried by the group of Paolo Bernardi [48]. These authors, however, propose a dimeric form of ATP synthase in their model of PTP (Fig. 4). To answer the question whether the real structure of PTP is composed of the c-subunit ring alone, of monomeric or dimeric ATP synthase, or even of ATP synthase interacting with ANT and phosphate carrier (forming together the so-called ATP synthasome) requires more studies.

The changing structure of PTP over the years and our present state of knowledge have been described comprehensively in a number of excellent recent reviews [32,48-50].

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Od pęcznienia mitochondriów po koncepcję transformacji przepuszczalnościowej – krótki zarys historyczny

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Słowa kluczowe: kanał, mitochondria, pęcznienie, syntaza ATP, transformacja przepuszczalnościowa

STRESZCZENIE

Przedstawiono krótki historyczny zarys studiów nad mitochondrialnym kanałem wysokiej przepuszczalności począwszy od badań nad pęcznieniem mitochondriów w latach 1950., poprzez koncepcję transformacji przepuszczalnościowej i różne teorie dotyczące budowy związanego z nią kanału, aż po najnowsze osiągnięcia identyfikujące ten kanał jako część mitochondrialnej (F_1F_O) syntazy ATP/ATPazy.