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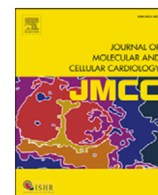

Review article

A CaPful of mechanisms regulating the mitochondrial permeability transition

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ABSTRACT

Despite the lack of its molecular identification, the mitochondrial permeability transition pore (PTP) is a fascinating subject because of its important role in cell death. This holds especially true for cardiovascular diseases and in particular for ischemia–reperfusion injury, where research on PTP inhibition has been successfully translated from bench to clinical evidence of cardioprotection. In addition, recent reports extend the relevance of PTP to heart failure and atherosclerosis. This review summarizes the major factors involved in PTP control with specific emphasis on cardiovascular pathophysiology, and highlights recent findings on the pivotal role of inorganic phosphate as a mediator of the inhibitory effects of cyclosporin A and cyclophilin D ablation.

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1. Introduction

The mitochondrial permeability transition (PT) defines a sudden increase in the permeability of the inner mitochondrial membrane to solutes with molecular masses up to 1500 Da. This process is attributed to the opening of a voltage- and Ca^{2+}-dependent, cyclosporin A (CsA)-sensitive, high-conductance channel that is termed permeability transition pore (PTP) [1,2]. In its fully open state the apparent diameter of the PTP is 3 nm, and the pore open–closed transitions are strictly regulated by a number of effectors. The analysis of the complex interplay among these various factors is the main subject of the present review.

Relevant functional features of the PTP have been elucidated by means of various techniques developed for its characterization in isolated mitochondria and cells as well as in intact organs [3–5]. However, and unfortunately, the molecular identity of this mitochondrial function is still elusive [1,6,7]. It is surprising that a "function" with little structural insights finds significant room in a scientific literature dominated by structural and molecular biology. This rather unique circumstance depends on the growing recognition of PTP involvement in numerous pathological states, and more in general in the loss of cell viability [1]. Indeed, interest in the PTP is undergoing a steady increase particularly in the neurological and cardiovascular fields, especially for common aspects related to ischemia/reperfusion (I/R) injury [1,8–11].

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The PTP can undergo transient or long lasting openings [4,12]. While short-lasting (i.e., in the millisecond range) events might be involved in physiological (and yet hypothetical, see section 3) roles of the PTP, prolonged openings of the PTP compromise energy-linked functions and jeopardize cell viability [12]. Indeed, PTP opening determines an immediate collapse of the mitochondrial membrane potential ($\Delta\Psi_m$) that is followed by ATP depletion [2,8]. The initial uncoupling-like effect is rapidly followed by respiratory inhibition caused by loss of pyridine nucleotides [5] and of cytochrome *c* [1,12]. This latter event is contributed by the rupture of the outer mitochondrial membrane that follows PTP-dependent matrix swelling. The resulting inhibition of electron flow might explain the increased ROS formation induced by PTP opening [13,14]; since the latter event is favoured by ROS [15–19], a vicious cycle of injury amplification may be established [20]. While ROS are generally reported to favor PTP opening, it should be mentioned that the highly reactive singlet oxygen instead desensitizes the PTP through selective inactivation of histidyl residues [21]. A recent report also suggests that the pore could be desensitized rather than activated by low concentrations of H_2O_2 [22] an issue that deserves further study.

Although potential consequences of PTP opening are well-established, the processes controlling the closed–open transition are still debated.

2. PTP modulation

Factors modulating the PTP have extensively been analyzed by previous reviews [2,10,23]. The following paragraphs are aimed at discussing the most relevant effectors and/or the most recent results. Besides revising aspects that have been somewhat overlooked in the cardiovascular field, major focus will be given to recent findings that point out the pivotal role of inorganic phosphate (P_i).

2.1. Dependence on matrix [Ca^{2+}]

Matrix [Ca^{2+}] is considered an essential permissive factor for PTP opening, and one that is required for the agonistic action of other inducers [2]. In this respect Ca^{2+} is unique amongst divalent metals, such as Mg^{2+}, Sr^{2+} and Mn^{2+} that instead reduce the susceptibility to PTP opening. The PTP sensitivity to Ca^{2+} is apparently increased by cyclophilin D (Cyp-D) in the sense that a larger Ca^{2+} load is required to open the PTP in the absence of Cyp-D [24]. Cyp-D, a matrix peptidyl–prolyl *cis–trans* isomerase, is the target of CsA, which inhibits the isomerase activity at the same concentrations required for reducing the probability of PTP opening [25,26]. It is still unclear whether the Cyp-D enzymatic activity is involved in PTP control. Recent work has revealed that Cyp-D actually does not affect the Ca^{2+} sensitivity of the PTP, as the Ca^{2+} load required to open the pore is identical in wild-type and Cyp-D-null mitochondria when P_i is replaced by arsenate (As_i) or vanadate (V_i) [27], a finding that revealed the key role of P_i in PTP inhibition by CsA and that will be discussed more in detail later in the review.

Although there is no doubt that rising matrix [Ca^{2+}] favors PTP opening, the actual matrix free [Ca^{2+}] required is difficult to define, since it is influenced by various factors that change together with the Ca^{2+} load (such as matrix P_i and pH). For instance, in rat brain mitochondria the sensitivity to matrix [Ca^{2+}]$_i$ has been shown to be inversely proportional to [P_i] [28]. Accordingly, the increase in [P_i] occurring under de-energizing conditions is likely to sensitize the PTP to matrix [Ca^{2+}], so that PTP opening could occur even in the absence of major [Ca^{2+}] changes. This concept fits the role of P_i as a PTP inducer that is discussed below. Notably, it appears that the PTP requirement for Ca^{2+} is very low, suggesting that PTP opening is not directly affected by mitochondrial Ca^{2+} overload as such, but requires additional factors that still need to be characterized. In addition, besides intramitochondrial events, the susceptibility to PTP opening might be increased by cellular responses triggered by intracellular [Ca^{2+}] elevation, such as ROS accumulation, generation of arachidonic acid by phospholipase A_2 and calpain activation [29–33].

The relationship between cytosolic and mitochondrial events is also relevant in analyzing the source and the pathway used for [Ca^{2+}] increase. The question is whether mitochondria are exposed to the bulk cytosolic Ca^{2+} or rather this cation is funneled into the matrix by means of specific pathways. This latter point of view is convincingly supported by the anatomical juxtaposition of mitochondria and sarcoplasmic reticulum (SR) that appears to create microdomains of localized [Ca^{2+}] increase readily available for mitochondrial uptake [34]. It has been proposed that intracellular Ca^{2+} oscillations caused by dysfunctional SR are linked to PTP opening during reperfusion [35].

This concept has been further developed by a recent study that attributed an important role to NIX in relating SR with mitochondria [36]. NIX is a BH3-only member of the BCL2 protein family that localizes to both SR and mitochondria. Notably, in cardiomyocytes the levels of NIX correlate with SR calcium stores. The genetic ablation of NIX decreased the occurrence of apoptosis in a mouse model of cardiomyopathy induced by upregulating Gq; and cell death was reestablished by specific re-expression of NIX in SR or in mitochondria [36]. However, only cardiomyocytes expressing SR-localized NIX displayed a decrease in mitochondrial membrane potential that was attributed to an increased probability of PTP opening in mitochondria exposed to SR with enriched calcium stores. Therefore, NIX might resemble the function of BAX and BAK, which in other cell types have been shown to promote apoptosis in response to agents that release Ca^{2+} from intracellular stores, such as arachidonic acid, ceramide, and oxidative stress [37].

2.2. Voltage dependence and redox modulation

PTP opening is favoured by mitochondrial depolarization. However, by modifying the threshold potential PTP inducers can increase the opening probability at physiological $\Delta\Psi_m$ values [38]. Besides being modulated by the proton electrochemical gradient created by respiration, PTP is controlled also by the inner membrane surface potential. In fact, polyanions and polycations increase and decrease the probability of PTP opening, respectively, independently of changes in $\Delta\Psi_m$ [39]. A voltage sensor has been hypothesized to explain the PTP sensitivity to both the transmembrane voltage and the surface potential [23]. This concept is supported by the role of arginyl residues in controlling both open/closed states and voltage sensitivity of the PTP [40,41].

The dependence on $\Delta\Psi_m$ is likely to be also related to redox processes, and especially to oxidative stress. Indeed, redox changes of pyridine nucleotides and glutathione appear to operate at different sites, so that PTP opening is promoted by decreasing NADPH(H^+)/$NADP^+$ and thiol/disulfide ratios [16]. Pore modulation by these redox-sensitive sites probably explains the inducing effects of ROS generated by a dysfunctional respiratory chain and/or by $p66^{Shc}$ [20,42,43].

2.3. pH dependence

The matrix pH optimum for PTP opening is about 7.3 [44]. The open probability decreases sharply below pH 7.4 through reversible protonation of critical histidyl residues that can be blocked by diethylpyrocarbonate [38,44]. Since PTP modulation by matrix pH is not affected by Cyp-D deletion, the PTP-regulatory histidyl residues are not located on this protein [24]. The pore is also inhibited above pH 7.4 through an unknown mechanism. As also discussed below, it should be stressed that these values, as well as inhibition by acidosis, are only valid in de-energized mitochondria.

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