Physiol Rev 94: 519–608, 2014
doi:10.1152/physrev.00021.2013

MITOCHONDRIAL CHANNELS: ION FLUXES AND MORE

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Szabo I, Zoratti M. Mitochondrial Channels: Ion Fluxes and More. *Physiol Rev* 94: 519–608, 2014; doi:10.1152/physrev.00021.2013.—The field of mitochondrial ion channels has recently seen substantial progress, including the molecular identification of some of the channels. An integrative approach using genetics, electrophysiology, pharmacology, and cell biology to clarify the roles of these channels has thus become possible. It is by now clear that many of these channels are important for energy supply by the mitochondria and have a major impact on the fate of the entire cell as well. The purpose of this review is to provide an up-to-date overview of the electrophysiological properties, molecular identity, and pathophysiological functions of the mitochondrial ion channels studied so far and to highlight possible therapeutic perspectives based on current information.

I. INTRODUCTION

Mitochondria, the key bioenergetic organelles, consist of an outer membrane (OMM), an inner membrane (IMM), the intermembrane space between OMM and IMM, and the IMM-enclosed matrix. The protein complexes carrying out oxidative phosphorylation reside in the IMM, while the matrix is the site of metabolic processes such as the citric acid cycle and fatty acid beta-oxidation. Passive ion movement across membranes is driven by its electrochemical gradient ($\Delta\mu_{ion}$), which has two components: *1*) the electrical one, i.e., the voltage difference between the two sides of the membrane ($\Delta\Psi m$); and *2*) the chemical one, i.e., the difference between the activities (often approximated as concentrations) of the ion on the two sides (Δp_{Ion}) (for a discussion of these principles see, e.g., Refs. 80, 912). In energized mitochondria, the membrane potential difference ($\Delta\Psi m$) created by the respiration-driven efflux of protons from the matrix is a major component of the $\Delta\mu_{ion}$ across the IMM for any ion. Under normal circumstances its value is believed to be in the 160–200 mV range (negative on the matrix side). Whether a sizeable electrical field exists across the OMM (and, in case, its modulation) remains to be clarified. It has been argued that it might exist as a Donnan potential across the semipermeable membrane, reaching a value as high as ~40 mV (1028).

In this review we discuss channel activities studied by electrophysiological techniques such as patch-clamping isolated mitochondria and mitoplasts devoid of the outer membrane or incorporating mitochondrial membrane vesicles or purified native or recombinant proteins into planar lipid bilayers. Thus the list includes not only bona fide ion channels, but also proteins with other functions (e.g., the ones involved in protein import) which conduct ions under certain conditions. Last, we briefly mention putative mitochondrial channels, i.e., proteins believed or shown to function as channels in other membranes and identified in mitochondria as well, whose channel activities have however not been proven directly in the IMM or OMM. We do not include discussion of proteins facilitating the transport of neutral species, such as aquaporin, and of carriers of the inner membrane for which no ion-conducting activity has been described.

II. ION CHANNELS AND PORES OF THE OUTER MITOCHONDRIAL MEMBRANE

A. Voltage-Dependent Anion Channel

1. Structure

FIGURE 1 illustrates the various ion channels and proteins able to conduct ions which reside in the OMM, and which include the mitochondrial porin, voltage-dependent anion channel (VDAC). VDAC1, one of the three isoforms of the most abundant protein of the OMM, was the first mitochondrial channel to be discovered (274, 1137) and has been the object of a large number of studies. Many excellent reviews are available (115, 150, 153–155, 180, 222, 272, 276–278, 313, 315–317, 544, 752, 956, 970, 1081, 1087, 1192, 1195, 1196, 1198, 1346), including comprehensive, detailed, and recent ones (273, 275, 1190, 1191, 1193) and

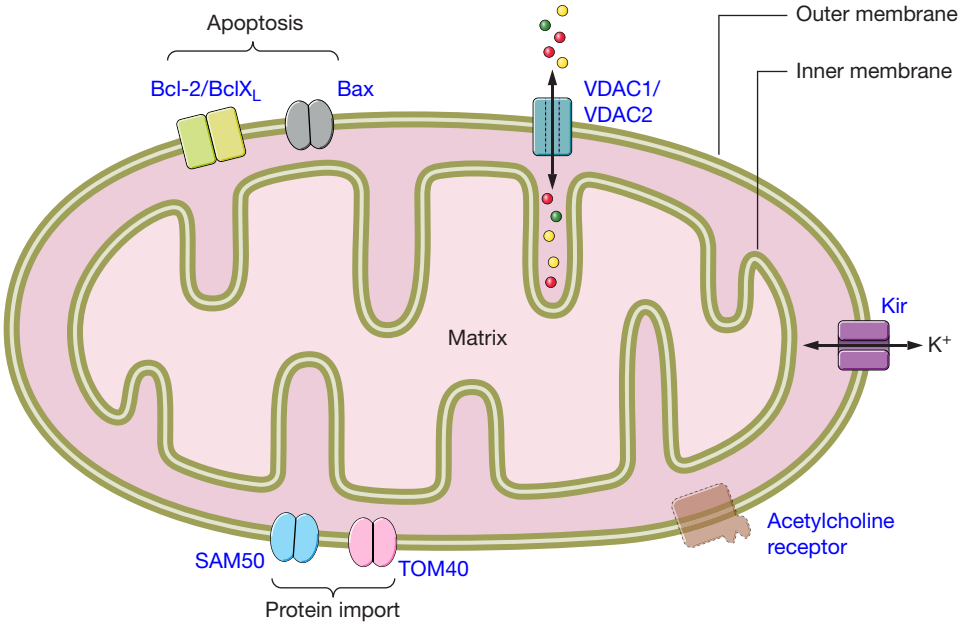

FIGURE 1. Proteins mediating ion fluxes in the outer mitochondrial membrane. Proteins working as ion channels are shown with colored filled forms. Those able to mediate the flux of ions but having principally other function are also shown (e.g, TOM40). Putative channel acetylcholine receptor is illustrated using dashed line. For further, see text.

a special issue of *Biochimica Biophysica Acta* dedicated to "VDAC structure, function and regulation of mitochondrial metabolism" [vol. 1818(6), June 2012]. We will refer to VDAC1 as "VDAC" unless we want to emphasize the isoform involved.

Some 30 years after the field was opened by the studies by Schein and Colombini, and much intervening work seeking to clarify its architecture, the structure of mammalian VDAC was reported in 2008 (122, 263, 549, 1045, 1335, 1336, 1430). The channel was confirmed to be a β-barrel, composed of 19 β-strands and an NH_2-terminal α-helix adhering to the inner wall of the pore but possessing considerable freedom of motion (1354). The NH_2-terminal segment is a crucial region, involved in many molecular interactions. The barrel measures 3.1–3.5 nm (it is slightly elliptical) in the plane of the membrane, and ~4 nm in the perpendicular dimension. The path for solute passage measures ~1.5 by 1 nm.

2. Electrophysiological properties

The channel properties of the purified and reconstituted protein have been thoroughly defined in studies using mostly the planar bilayer technique. In experiments of this type, VDAC reproducibly forms a large, voltage-dependent pore, whose characteristics, rather well conserved among species, are summarized in **TABLE 1**. A weak selectivity for anions is conferred to the fully open state by a higher density of positive versus negative charges on the inner walls (263, 1336). The channel can in any case conduct a substantial flow of cations, including Ca^{2+}, for which it also possesses binding sites (318, 447, 575, 1044, 1192). Interestingly, the fully open channel reportedly conducts Ca^{2+} rather poorly (P_{Cl}/P_{Ca} ~25 in experiments with a $CaCl_2$ gradient), while partially closed states (known to be cation selective) are much better at it (P_{Cl}/P_{Ca} ~1–4.5) with the somewhat paradoxical result that Ca^{2+} flux through a partially closed VDAC may actually be a fewfold higher than through the fully open pore (1282). Relatively small molecules such as metabolites and nucleotides can also permeate the channel. A binding site for nucleotides has been identified in the NH_2-terminal segment (1423, 1424), but NMR data have not confirmed its existence (549). NAD(P)H sensitizes the channel to voltage, stimulating its closure, and reduces the permeability of the OMM for ADP and ATP (746, 747, 1456). A binding site involving strands 17 and 18 has been identified (549). VDAC may be capable of conducting macromolecules as well, provided they are in a suitably unfolded form: in a completely in vitro system, reconstituted mammalian VDAC was found to allow the translocation of DNA sequences across a planar membrane (1261). That VDAC may be accessible to polymeric oligonucleotides is confirmed by the open-channel block produced by phosphorothioate oligonucleotides, specific VDAC inhibitors (1237, 1283, 1284). Interestingly, VDAC has been proposed to mediate entry of tRNA into mitochondria in vivo as well (1111).

The dynamics of voltage-induced gating, variously envisioned in the past, cannot be deduced from the available static structure, but much evidence points to a role of the NH_2-terminal sequence (see discussion in Ref. 1197). A recent paper reports that a double cysteine mutant VDAC in which a disulfide bond stabilizes the interaction between the NH_2-terminal helix and β-strand 11 of the barrel wall still exhibits normal gating, suggesting that any conformational changes involved may not be major ones (1292) (this paper has generated a discussion: see Refs. 1292, 1298). Another recent study based on computational modeling (1434) re-

Table 1. *Major intrinsic biochemical/biophysical characteristics of VDAC1*

Property	Reference Nos.
Structure: β-barrel, composed of 19 β-strands and an NH_2-terminal α-helix	122, 549, 1045, 1336, 1430
Conductance: ohmic with substates	153, 182, 314, 872
Highest conductance is ~4–5 nS in symmetrical 1 M KCl, ~ 0.9 nS in 0.15 M KCl	
Steep voltage dependence: the channel closes partially and occasionally completely when at voltages higher than ~20 mV of either polarity	117, 277, 1027
Slight anion selectivity for the maximal conductance state(s): P_{Cl}/P_K ~1-4.5	277, 314
Anion selectivity is determined largely by exposed charges on the inside walls of the pore	8, 181, 263, 994, 1336
Cation selectivity of the majority of substates	150, 151, 277
Occasionally also of high-conductance states	979
The channel conducts a range of ions and metabolites, including	551, 1085
Ca^{2+}	318, 447, 979, 1044
ATP	1078, 1080
Superoxide	511, 795
Variable kinetic behavior, with often "slow" gating kinetics but also fast transitions between substates	117, 872

Only exemplary references are cited.

turns to a long-standing proposal (820, 821), suggesting that gating may actually correspond to changes in the structure of the barrel (partial collapse) following removal of the stabilizing NH_2-terminal α-helix. Data have been presented supporting a model in which the NH_2-terminal can actually leave the pore lumen and participate in interactions with neighboring molecules (e.g., another copy VDAC) and the membrane (437, 489).

Curiously, a clear-cut identification of VDAC activity has not been reported in patch-clamp experiments purportedly recording from the OMM (651). While this unexpected absence is one of the elements suggesting that the seals might not have been established on that membrane, it is also compatible with the view that VDAC might actually be a strictly regulated pore, rather than a permanently open one. In line with this latter hypothesis, purified VDAC has been shown to sometimes adopt completely closed state(s) in bilayer experiments (117). In fact, VDAC, once seen as the inert hole of a sieve, have come to be considered, at the other extreme, a master gatekeeper regulating the flux of metabolites and ions between the mitochondria and the cytoplasm, with a crucial role in inter-organellar communication (cross-talk). The ruth is probably somewhere in between. Despite its abundance, VDAC may indeed pose a limit to the traffic of nutrients and metabolites across the OMM, since its downregulation by shRNA had a dramatic effect on cell growth (3, 682).

3. Regulation of VDAC

VDAC can be modulated in various ways (reviews in Refs. 305, 638). It can be phosphorylated at multiple positions (at least in vitro) by Ser-Thr kinases GSK3β (306, 828, 1180), PKA (108, 1180), PKCε; (94), Nek1 [never-in-mitosis A (Nima)-related kinase] (245, 246) and other kinases (see Refs. 305, 638), as well as by tyrosine kinases (1114). Phosphorylation is thought to regulate interaction with cytoskeletal components and is considered to be in most cases pro-apoptotic (638) except in the case of phosphorylation by Nek1 at Ser193, which has been shown to have the opposite effect (245, 246). At least four lysine residues can be *N*-acetylated as well (638), and VDAC also undergo O-linked β-*N*-acetylglucosamination (911) and *S*-nitrosylation (666, 667).

A list of factors potentially modulating VDAC (directly or indirectly) includes pyridine dinucleotides (549, 746, 747, 1456), glutamate (445, 446), ATP and ADP (1084, 1085, 1424), lipids including cholesterol, phosphatidylethanolamine, and cardiolipin (169, 369, 1081, 1083), possibly Ca^{2+} (114, contra: Ref. 1282). Proteins like VDAC itself, creatine kinase (4, 36, 76, 171, 195, 396, 768, 839, 906, 907, 909, 970, 1003, 1077, 1144, 1254, 1359), the ANT (24, 171, 1349), c-Raf kinase (739), endothelial nitric oxide synthase (eNOS; Ref. 30), tubulin (229, 490, 493, 1081, 1082, 1086), G-actin (1073, 1409), gelsolin (722), dynein light chain (1159), mitoHSP70 (1159), the TSPO (formerly mitoBzR) (849, 850, 1159), glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (1196, 1290), aldolase (1196), mutant (G37R) SOD1 (576), Bcl-xL (54, 549, 814), Bax (562), possibly t-Bid (1079, but see Ref. 1081), and COX-I (1074) are part of its interactome. These interactions constitute the basis of the involvement of VDAC in cell death and in cancer.

Tubulin has emerged as a modulator of possible physiological significance: its action as inducer of a reversible partial

block, which limits ATP permeation, depends on the phosphorylation state of VDAC (1180) and may be relevant for a complete understanding of the action of microtubule-targeting chemotherapeutics (380, 1091). Block is strongly voltage dependent, requiring a polarity negative on the side of tubulin addition in BLM experiments. This poses again the question of whether a significant $\Delta\psi$ exists across the OMM. It has been proposed that interaction with tubulin may result in an increased sensitivity of the channel to $\Delta\psi$, resulting in significant closure at potentials as low as 10 mV (1081, 1082). Microtubule-associated protein 2 (MAP-2) binds to VDAC (actually the dimer) in affinity chromatography experiments (770). Gelsolin, a Ca^{2+}-dependent acting-regulating protein, has also been reported to be able to close VDAC, thereby exerting an anti-apoptotic effect (722).

4. VDAC and hexokinase

Overexpression of hexokinase-1 and -2 (HK1, HK2) and its association with VDAC are key features of glycolytic cancers (e.g., Ref. 1391). Hexokinase binding (for structural details on binding, see Refs. 4, 1191, 1077, 1199, 1401) to the conduit channeling ATP out of mitochondria provides a metabolic benefit to glycolytic cancer cells (Warburg effect; for reviews focussed on the Warburg effect, see Refs. 227, 839, 840, 841, 842, 976, 986–988; more general, see Refs. 324, 343) and it antagonizes cell death (76, 462, 809, 810, 1199, 1254) via inhibition of Bax-induced cytochrome *c* release (420, 971, 1360) and/or inhibition of the mitochondrial permeability transition (MPT) (256). Elimination of the NH_2-terminal peptide of VDAC1, or introduction of a single mutation (K20S or G21A) antagonized both HK binding and HK-mediated protection against cell death (2, 63, 1199). Phosphorylation (on Thr51) by GSK3β prevents binding of hexokinase to VDAC (969; reviewed in Ref. 970). One of the ways the master pro-life kinase Akt is understood to produce its effects is by migrating to mitochondria, phosphorylating GSK3β (on Ser9), thereby inhibiting it and thus promoting HK-VDAC interaction (177, 969). This pro-life association of VDAC and HK appears furthermore to be dependent on cyclophilin D (801) and its acetylation status which is in turn modulated by Sirt3 (1203, 1348). Akt can also phosphorylate HK2 (on Thr473) and is thought to act as a regulator of metabolic fluxes (e.g., Ref. 1069). HK can be detached from mitochondria by G6P (76), by HK-dissociating peptides modeled on either HK (256, 435, 809, 876, 971, 1202) or VDAC1 (63) sequences and by small molecules such as clotrimazole (809, 971), bifonazole (998) (both fungicides, in the 10^{-5} M range), and methyl jasmonate (455). A soluble variant of the pilus protein FimA of pathogens such as *E. coli* K1, *Salmonella*, and *Shigella* can instead strengthen HK-VDAC interaction, antagonizing host cell apoptosis (1250). The mechanism by which HK detachment favors cell death is not yet clear and may comprise more than one factor. Proposals include disruption of aerobic glycolysis and of the energy balance of the cell, regulation of ROS production, altered interaction of Bcl-2 family proteins with mitochondria, facilitation of VDAC oligomer formation (reviewed in Refs. 1191, 1193), and MPTP opening (since death is influenced by expression of Cyp D and by cyclosporin A; Ref. 256) (see sect. III*F*). Regardless, the interaction of HK and VDAC may well represent an Achilles' heel of cancer (e.g., Ref. 421).

5. VDAC2 and VDAC3

VDAC2 and VDAC3 (858, 1040) are much less abundant than VDAC1, and less studied. Despite its comparatively low abundance, VDAC2 is the major isoform in bovine testis and spermatozoa, where it is located in part in the cellular membrane of the head and it undergoes tyrosine phosphorylation during capacitation (in human spermatozoa). The porin has been shown to be associated with the outer dense fiber of the sperm flagellum, a nonmembranous compartment (550). The axoneme and mitochondria of VDAC-less mice are altered (1116), and VDACs 2 and 3 are very important for male fertility (728). This suggests a function other than pore formation. VDAC3, purified and reconstituted after expression in yeast (it has never been obtained as a reasonably pure preparation from native mammalian tissue), gave rise to channel activity only with difficulty (1408), and whether this scant activity was really due to VDAC3 is doubtful (858). All three isoforms reportedly permeabilized liposomes with similar solute size exclusion thresholds (1408). VDAC2 forms pores resembling those of VDAC1 (854, 1408). VDAC2 has been reported to associate with ryanodine receptor 2 at SR/mitochondria junctions in the heart, and to be of major importance for the direct transfer of Ca^{2+} from the SR to mitochondria (865). VDAC1 has in turn been reported to interact with the inositol trisphosphate (IP3) receptor and to channel Ca^{2+} from the ER to mitochondria selectively, transferring an apoptotic signal (318, 495). The fact that VDAC2 deletion is embryonically lethal (while deletion of VDAC1 or VDAC3 is not, and does not seem to induce alterations of apoptosis) and its interaction with Bak (see sect. II*A6*) single out VDAC2 for special consideration as a target for anti-cancer agents acting at the mitochondrial level, also called "mitocans" (1040, 1219).

6. VDAC, apoptosis, and cancer

The role of VDAC in cell death is multifaceted and complex (e.g., Refs. 847, 1193, 1190). Several proteins of the Bcl-2 family have been reported to interact with VDAC1 and/or VDAC2. Tsujimoto's group (reviewed in Ref. 1330) first reported that pro-apoptotic Bax and Bak could stimulate the efflux of cytochrome *c* from VDAC-containing liposomes via formation of a large pore comprising VDAC and Bax/Bak (1184, 1186; see also Refs. 6, 107, 1182). Pro-apoptotic BH3-only Bid (and t-Bid) and Bik were found not

to interact with VDAC1, and did not affect its activity in liposomes (1187), whereas Bim, another BH3-only family member, was reported to activate VDAC directly (1248). The effective existence of a cooperative interaction between Bax and VDAC1 is, however, controversial. Studies in yeast used as a model system led to the conclusion that VDAC was not involved in cytochrome *c* release (1030), while Madesh and Hajnóczky (805) found evidence that VDAC alone was sufficient to allow cytochrome *c* efflux through membranes. Rostovtseva et al. (1079) could not detect any electrophysiological indication of an interaction between reconstituted mammalian VDAC and Bax, while t-Bid was observed to induce channel closure. VDAC1 and VDAC3 were found to be dispensable for the formation of the mitochondrial apoptosis-induced channel (MAC), proposed to correspond to the conduit for cytochrome *c* release (832), which requires instead the presence of Bax and/or Bak.

Tsujimoto's group was also the first to report that Bcl-2 and BclxL inhibited VDAC via their BH4 domain, and ascribed to this inhibition the protection from apoptotic death afforded by BclxL (1185). BclxL binding has been confirmed by structural studies, and localized to strands 17 and 18 of VDAC1 for BclxL (549, 814). The interaction results in a shift from the oligomeric towards a monomeric state of VDAC in micelles. Shoshan-Barmatz's group has defined domains involved in interaction with Bcl-2, which include the NH_2-terminal segment, by mutagenesis studies (2, 56). Vander Heiden et al. (1343) found that BclxL favored the open conformation of the pore, but a recent study (54) has confirmed that Bcl-2 and BclxL cause a reduction of pore conductance in vitro. In any case, all authors concur in attributing an anti-apoptotic significance to this interaction. In fact, a peptide derived from the BH4 domain of BclxL was found to have anti-apoptotic action, reducing ischemia/reperfusion (I/R) injury in isolated rat hearts (944, 1247) and apoptosis in isolated human islets (659), while, conversely, expression of peptides copying VDAC1 sequences antagonized the protection offered by Bcl-2 (55) or BclxL (54) against staurosporine-induced apoptosis. The potential biomedical relevance of these studies is evident.

The formation of dimers and higher oligomers of VDAC1 has been reported 30 years ago (769, 819) and confirmed by several studies (2, 347, 438, 555, 702, 1013, 1197, 1335, 1435). These oligomers have been proposed to form the conduit for the efflux of cytochrome *c* from the mitochondrial intermembrane space of preapoptotic cells (2, 4, 1195, 1191, 1198, 1435). A relationship appears to exist between VDAC1 oligomerization and apoptosis (2, 637, 879, 1198): oligomerization is highly enhanced upon apoptosis induction as recently observed in living mammalian cells using bioluminescence resonance energy transfer (637). Lack of VDAC1 prevented *cis*platin activation of Bax (1280) or selenite-induced cytochrome *c* release (1308). The formation of heterooligomeric complexes involving Bcl-2 family proteins has also been proposed (BclxL: 814) **(FIGURE 2)**. Overexpression of VDAC1 has been found to be conducive to cell death (804, 1044, 1179). This may be rationalized in terms of an increased formation of pro-apoptotic oligomers, or of an increase in the fraction of channels not bound to HK, equivalent to a partial detachment of HK from its VDAC binding sites. In contrast with the view that BclxL inhibits VDAC thereby antagonizing apoptosis (see above), block of VDAC by the phosphorothioate oligonucleotide G3139 (1285) or by avicins (plant saponins with anticancer activity) (517) has been observed to be pro-apoptotic. VDAC2 has been heavily implicated in the regulation of Bak activity. Korsmeyer's group reported (250) that this isoform (but not VDAC1) inhibits Bak activation and apoptosis, as later confirmed by other groups (237, 318, 737, 1058). In lymphocytes, VDAC2 deletion is fatal, but the

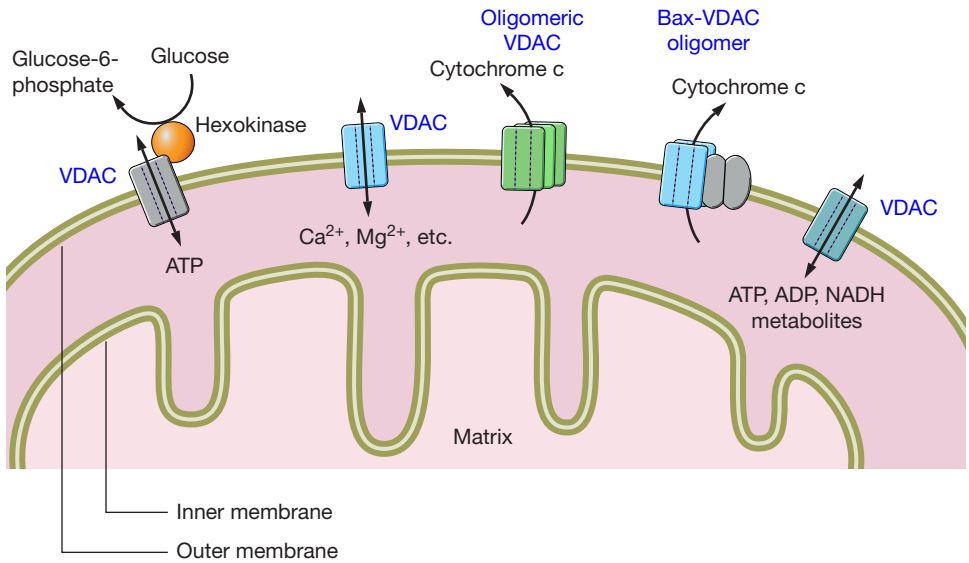

FIGURE 2. Possible forms of mitochondrial porin voltage-dependent anion channels in the outer mitochondrial membrane. Monomeric or oligomeric forms fulfill different tasks. See text for description.

cells can be rescued by the simultaneous deletion of Bak (1058). In cells lacking VDAC2, Bak relocates from the OMM to the ER (1040). According to Hajnóczky and colleagues (1091) VDAC2 can however also have a pro-apoptotic role, mediating sensitivity to t-Bid. Tsujimoto's group (1412) has reported that VDAC2 was necessary for death induction by Bax in Bak-deficient cells.

Along with the evidence in favor of the participation of VDACs in the processes of cell death, results have been presented which argue against the whole notion. In their paper reporting the irrelevance of VDAC isoforms for the MPT (see below), Baines et al. (93) also reported that Bax-induced cytochrome *c* release from mitochondria isolated from WT or VDAC1-, VDAC3-, and VDAC1/VDAC3-null cells was the same. MEFs lacking either one or both of these isoforms showed no difference in their apoptotic response to Bax overexpression, staurosporine, or tumor necrosis factor (TNF)-α. However, cytochrome *c* release can be induced via different mechanisms (even in the absence of Bax and Bak), depending on the cell type, its apoptotic protein expression profile, and the stimuli used. Lack of VDAC2 is fatal (250), suggesting that this particular isoform is the one with the most important role in apoptosis, while VDAC3 seems to have no role in cell death (318). The involvement of VDAC (93, 669) and the ANT (669) in the MPTP has similarly been nearly ruled out on the basis of genetic deletion experiments. We may remark however that compensating changes tending to reestablish physiological homeostasis are notoriously difficult to assess.

One possibly confounding factor in evaluating the role of VDAC1 in cell life or death is its localization in cell compartments other than the OMM. VDAC (called porin 31HL) was discovered in the plasma membrane of human B lymphocytes (636, 1296, 1431). This surprising observation was confirmed by a series of careful studies employing a variety of techniques, including the development of monoclonal antibodies and electrophysiological recordings (81, 116, 152, 231, 270, 327, 582, 623, 674, 1033, 1160, 1235; reviews in Refs. 316, 1068, 1297), also in plants (1068).

VDAC1 was found to localize to subdomains: caveolae (90, 116, 544, 826, 1042) and postsynaptic density fraction (884). Expression in the PM appears to depend on the presence of a PM-targeting sequence introduced by alternative splicing in the NH_2-terminal region, which directs it to the secretory pathway through the Golgi apparatus (89, 214). Alternative splicing of VDAC gene products is known, but its significance is, in general, obscure (858). PM VDAC1 may function in volume regulation and ATP release (938), and it has been reported to act as a redox enzyme (100, 736), although this activity is rather difficult to rationalize and could not be demonstrated for VDAC isolated from mitochondria (1197). It has been found to act as the receptor for plasminogen Kringle 5 (457, 458) and tissue-type plasminogen activator (459). Interestingly, the latter appears to be a substrate for VDAC's NADH-dependent reductase activity (459). VDAC1 has also been observed in the endo/sarcoplasmic reticulum (624, 758, 836, 1178, 1194, 1195, 1196, 1200).

B. Inward Rectifying Potassium Channel

An inwardly rectifying voltage-dependent potassium selective ion channel (Kir) has been observed in the outer mitochondrial membrane by patch-clamp experiments (398). The activity was regulated by cAMP and by osmolarity and blocked by cesium cations. However, inhibition by other classical potassium channel inhibitors, TEA^+ and 4-aminopyridine, was not achieved. The lack of molecular identity and of a more detailed biophysical/pharmacological characterization of this channel prevents up to now the elucidation of its physiological role, if any. Furthermore, further studies will need to exclude that this activity is related to a cationic subconductance state of VDAC or is the result of contamination by ER via the so-called mitochondria-associated endoplasmatic reticulum membranes (MAMs) (532). It is of note in this respect that Kaasik and colleagues (726) have reported the functional expression in the ER of the small-conductance calcium-activated potassium channel (SKCa), required for calcium uptake into ER.

C. Protein Import Pores TOM40 and Sam50

The transport of proteins and genetic material across membranes is now known to involve "threading" of the polymeric chain through an at least partly proteinaceous pore in a number of systems. Examples include bacterial Sec (297, 798); type II (686), type III (217, 688), and type IV (1439) machineries; and the intracellular systems of the ER (1455), peroxisomes (852), and chloroplasts (34, 695, 1243). The complex major mitochondrial systems have been extensively studied and are now known in considerable biochemical detail (e.g., Refs. 133, 134, 234, 363, 373, 519, 520, 880, 881, 910, 1147). Whether the pores formed by this apparatus qualify as "channels" might be questioned, since their physiological function is not passive ion transport. We briefly cover the topic in this review because a considerable amount of excellent electrophysiological work has been carried out to characterize the protein-conducting pores, and because they might account for some of the "orphan" activities that are not ascribable at the moment to a given protein.

The mitochondrial protein import system relies on five pore-forming complexes. The electrophysiological description of mitochondrial import systems (520, 521) developed briskly in the 1990s. The earliest relevant work was done by the group of M. Thieffry and J.-P. Henry (540), who in 1988 reported a high-conductance activity of mitochon-

drial origin studied by the "tip-dip" technique (1294) and later also in planar bilayer experiments and by patch-clamping proteoliposomes (1295). Trypsin digestion, membrane fractionation, and selective digitonin solubilization were used to establish that the channel belonged to the outer membrane (259), but was not related to VDAC1, since it was present also in porin-less yeast mitochondria (394), and had different properties (717). The channel was observed to undergo fast open-channel block by peptides copying or resembling the addressing sequence of mitochondria-targeted proteins (395, 539, 540, 1295). This led to the nickname "peptide-sensitive channel," or PSC. The behavior strongly suggested that the peptides were translocating through the channel, i.e., that this was a component of the protein import system (618, 1340). This was later confirmed by experiments with a chimeric fusion protein comprising parts of cytochrome *b*2 and dihydrofolate reductase, which blocked the channel when added on the cytoplasmic (NH_2-terminal) side (548). The channel seemingly corresponds to TOM40, involved in translocation across and insertion into (518) the outer membrane. Isolated TOM40 and TOM40 complex reconstituted into planar bilayer membranes after solubilization or by fusion of proteoliposomes from membrane preparations exhibited channel activity very similar to that of the PSC (132, 521, 548, 718). Anti-TOM40 antibodies coimmunoprecipitated PSC activity. TOM40 is a rather well-behaved channel, as perhaps expected of a protein with a significant amount of β structure, often appearing in doublets or triplets exhibiting a degree of cooperativity (e.g., Ref. 132). This is coherent with the view that TOM40 exists as an oligomeric complex, and that two to three copies are likely to be present even in the isolated complex (14, 15, 132, 717, 1043). We note that an analogous activity has not been reported to have been observed in patch-clamp experiments considered to involve seals on the outer mitochondrial membrane of intact mitochondria. Single-channel conductance varies to some extent depending on the species of origin, and also exhibits intrinsic variability. Thus, for example, the yeast complex in tip-dip and patch-clamp (on proteoliposomes) experiments characteristically showed conductance steps of 320–330 pS (619, 1295) in 150 mM NaCl (550 pS in 150 mM KCl in planar bilayer experiments with recombinant TOM40; see Ref. 14), similarly to the *Neurospora crassa* pore (~300 pS; Ref. 717), while the most prominent current variations observed with the mammalian counterpart corresponded to a conductance of ~200–220 pS (1295). The single-channel current-voltage relationship is ohmic or slightly rectifying. In planar bilayer experiments with *S. cerevisiae* and *N. crassa* channels application of potentials higher than ~70 mV of either polarity decreased the open probability (548, 718). This latter behavior resembles that described for VDAC and also for the mammalian MMC (e.g., Refs. 1267, 1273), although in both cases lower voltages are involved. The channel exhibits a spontaneous flickering that is eliminated by trypsinization of the cytoplasmic side (259), and possibly is due to the elimination of a 2.5-kDa NH_2-terminal fragment (548). Fast "closures" are furthermore produced, both with the native and the trypsin-treated channel, by cationic peptides applied to the extramitochondrial (trypsin-sensitive) side, and this may be considered one of the defining features of the channel. Selectivity also varies somewhat depending on the species, but is always cationic [e.g., P_K/P_{Cl} ~8 for the *S. cerevisiae* channel (545); ~3 for the *N. crassa* channel (717)]. The permeabilities of the various cations follow the order of their mobility in water, suggesting that the pore may indeed provide a wide permeation pathway. The diameter of the roughly cylindrical structure has been estimated at 2.0–2.2 nm by the polymer-exclusion method (548) and by EM imaging (14, 15, 717). Whether this diameter may be sufficient to admit a polypeptide is not certain, and there has been some speculation that the polypeptide permeation pathway may actually be formed by the assembly of a few monomers plus cofactors (14). The characteristics of mammalian TOM40, which have been much less studied, appear to be similar to those of the yeast counterpart (807, 1255).

The "sorting and assembly machinery" (SAM) and the TOB/SAM complex (363, 1364), centered on Tob55, are devoted to the incorporation of β-barrels (which transit first in the intermembrane space) into the OMM and participate in determining mitochondrial morphology (186, 685, 1440). While different supramolecular complexes involving also TOM components can assemble and operate (1300), the core SAM complex consists of a membrane-embedded component, SAM50, homologous to bacterial Omp85, and two smaller subunits, SAM35 and SAM37, the latter one not essential for cell viability (135, 374). SAM50 have conserved roles in VDAC biogenesis from yeast to mammalian systems (701). The SAM pore from yeast has been characterized after reconstitution in the planar bilayer, both as the recombinant purified SAM50 protein and as the purified complex (725). It is slightly cation-selective (P_K/P_{Cl} ~4). With the reconstituted complex the channel is observed as a flickering activity with a major conductance of 160 pS in symmetrical 250 mM KCl. Addition of the β-signal peptide (identified in the same piece of work) in this case reduced the gating frequency and induced a shift of the most prominent gating transitions to 320 pS, with occasional 640 pS (i.e., 4X) events. The effect of the targeting peptide was found to depend on the presence of SAM35, which appears to "present" the incoming protein to the pore-forming subunit inducing it to assume an active, dynamic state. The pore may actually be formed by an oligomeric assembly of SAM50 (itself a β-barrel) monomers, a model which can better account than a monomer-based one for the postulated sidewise release of the transiting protein into the membrane and for the flexibility required to accomodate partially folded substrates.

D. Pores Formed by Bcl-2 Family Members

1. Electrophysiology of Bcl-2 family proteins

A key step in apoptosis is the release of cytochrome *c* and other pro-apoptotic proteins from the intermembrane space of mitochondria. Various mechanistic models have been proposed for this process. One that enjoys considerable popularity envisions the formation of macropores in the OMM by oligomers or aggregates of the Bcl-2 family proteins Bax and/or Bak. Mitochondrial pro-apoptotic factors (cytochrome *c*, AIF, Smac/Diablo, some procaspases) would permeate the OMM via these pores. The origins of this model go back to the structural resemblance between the anti-apoptotic Bcl-2 family member BclxL and the membrane translocation (and pore-forming) domain of diphteria toxin and bacterial colicins (892, 1140). An analogous similarity was then noticed for Bax (1259) and various other family members (1010). The three-dimensional structures comprise two central hydrophobic alpha-helices surrounded by six or seven amphipathic alpha-helices. Accordingly, at least BclxL (110, 866), Bcl-2 (1141, 1145), Bax (43, 321 687, 767, 1145, 980, 1139, 1187, 1269), t-Bid (1139), and Bad (1024, 1025) have been observed to form channels in experimental membrane systems (planar bilayer or vesicles). In general, these are not well-behaved channels, and their properties are variable. Even within the same experiment, they can display a range of conductances. Bax channels can be voltage-dependent or not (767; Tombola, Zoratti, and Szabò, unpublished observations) and can be weakly or moderately selective either for cations or anions, at times switching selectivity during the recording (767; Tombola, Zoratti, and Szabò, unpublished observations). Schlesinger et al. (1145) found Bax channels to be slightly anion-selective, while Antonsson et al. (43), Pavlov et al. (980), and Dejean et al. (321) reported a weak preference for cations. Bcl-2 and BclxL appear to produce unselective or cation-selective pores, depending on pH. BclxL, Bcl-2, Bax, and Bid have been reported to be pH-sensitive, with acidic pH values favoring activity, although channels can often be observed also near neutrality (43, 866, 1139). The composition of the artificial membrane can also influence the channels' behavior (e.g., Ref. 1139).

2. Channel formation and apoptosis

The physiological relevance of the results obtained with purified proteins in reconstituted systems is uncertain. In many studies the proteins used were actually constructs with partial deletions. For example, Basañez et al. (110) reported that anti-apoptotic full-length BclxL did produce pores upon reconstitution into lipid vesicles, but their size was insufficient to allow permeation by cytochrome *c*. Pores with a larger diameter, possibly involving lipidic components and capable of allowing cytochrome *c* release, were formed by the product of caspase-3 cleavage, or by the pro-apoptotic cleaved forms ΔN61-BclxL and ΔN76-Bclxl. Considering the variability displayed in each case, the channel activities of pro- and anti-apoptotic proteins in vitro are rather similar. Monomeric Bax or Bak are generally considered not to form pores, which require instead oligomerization induced by treatment of isolated recombinant Bax with detergents (but see Ref. 577) or the interaction with caspase 8-activated Bid (t-Bid) (44, 45, 329, 687, 860, 861, 1376), Bim (e.g., Ref. 432) or other BH3 domains (358). Saito et al. (1106) have concluded that while a Bax dimer can form a pore, a tetramer is needed for cytochrome *c* release (687). Prokaryotes provide many examples of aggregation of monomers to form a large pore, e.g., pneumolysin (444, 1303).

It may be surmised from all this that oligomerization most likely underlies pore formation by Bcl-2 and BclxL as well. The possible functions of pores formed by anti-apoptotic proteins have not been identified, insinuating the doubt that an ion channel-forming capacity of pro- and anti-apoptotic Bcl-2 family proteins may actually not be relevant for cytochrome *c* release (39, 738). In fact, we have found that a single-point mutated Bax form (BaxK128E) which has lost its pro-apoptotic character when expressed in cells is still capable of forming pores upon reconstitution in planar bilayers (1269). Overexpression of Bcl-2 did not lead to the detection of activity attributable to this protein in a patch-clamp investigation of isolated mitochondria (898). On the other hand, the direct addition of Bax, Bak, or Bid to isolated mitochondria has been reported to result in OMM permeabilization, while the mitochondria maintain transmembrane potential, oxidative function, and the ability to import proteins (328, 1187, 1357, 1376). Toroid-shaped structures formed by Bax in artificial membranes have been visualized directly (376). Membrane-inserting alpha helices 5 and 6 of Bax are necessary for the protein to have its pro-apoptotic function (535, 844), and peptides corresponding to this segment are sufficient to permeabilize membranes (423, 424), although whether they give rise to channel activity was not investigated.

In experiments by Martinou's group (1089), the pores formed by full-length Bax in the presence of t-Bid were deemed not large enough to allow the passage of cytochrome *c*, and interactions with other components of the OMM were proposed to be required. Among the proteins proposed to control OMM permeabilization by Bax and/or Bak are VDAC-2 and VDAC-1 (2, 93, 250, 562, 737, 1058, 1092, 1136, 1190, 1412). However, Baines et al. (93) have shown that all three mammalian VDAC isoforms are dispensable for cell death.

a) MAC MITOCHONDRIAL APOPTOTIC CHANNEL. The groups of K. W. Kinnally and of E. A. Jonas have reported electrophysiological studies showing the formation of large pores

presumably in the outer membrane of mitochondria of apoptotic cells (reviews in Refs. 322, 323, 611, 651, 830, 1103). Kinnally's group had previously studied a high-conductance, multilevel mitochondrial pore, but their first publication describing what was considered to be an OMM pore involved in cytochrome *c* release (dubbed "Mitochondrial Apoptotic Channel", MAC) appeared in 2001 (980). The study utilized mitochondria isolated from hematopoietic FL5.12 cells. With these cells apoptosis can be induced by IL-3 depletion and involves Bax migration to mitochondria. Recordings from "intact" (unswollen) mitochondria, assumed to be from the OMM, did not reveal single-channel transitions, but the average patch conductance was reportedly higher in the case of organelles isolated from apoptotic cells (~13 versus ~6 nS). Single transitions of various sizes up to ~2.5 nS could instead be observed in proteoliposomes formed with OMM preparations from apoptotic cells (which contained more Bax than nonapoptotic controls). The authors reported that the frequency of detection of MAC (in proteoliposomes) was about fourfold higher when the preparation came from cells deprived of IL-3. It could not be detected if the cells overexpressed Bcl-2 (interestingly, no novel channels attributable to Bcl-2 could be detected either), but it was found with normal frequency if the Bcl-2 expressed was a mutant, functionless Bcl-2 variant. MAC was characterized in this system as being voltage-independent, slightly cation-selective, and easily distinguishable from activity attributed to TOM40 or VDAC. Important similarities between the activity produced by reconstituted Bax and MAC were noted, the difference consisting in practice in the size of the most common events. In fact, an analogous activity could be observed in proteoliposomes obtained from a VDAC-less yeast strain expressing human Bax, strongly suggesting that Bax, but not VDAC, was present in MAC. Subsequent studies in the same proteoliposome system revised upward the upper limit of MAC conductance, produced evidence for an effect of cytochrome *c* and other bulky molecules compatible with permeation through the channel (488), and found an inhibitory effect of the amphiphilic cationic peptides propranolol, trifluoperazine, and dibucaine, while cyclosporin A had no effect (831). MAC was also characterized in some more detail by F. Vallette's group, who used a rat model of liver apoptosis and patch-clamping of proteoliposomes containing membrane fractions isolated from mitochondria having different properties reflecting the progress of the apoptotic process (484). MAC was found to be clearly distinguishable from VDAC and the MMC/MPTP (both also observed) on the basis of its biophysical properties and pharmacology. Its conductance was often close to 3 nS (150 mM KCl) with occasional higher values. Practically nonselective, it was found to close in response to low-to-moderate voltages of either polarity. Cytochrome *c* reduced its conductance to a low level in ~50% of trials. In these experiments, MAC was found to appear late in the apoptotic process, in a mitochondrial fraction (LAM2) which had already lost 90% of its cytochrome *c* and contained Bax predominantly as an ~80 kDa oligomeric complex (while Bax was present as lower oligomers or monomers at earlier stages of apoptosis). Kinnally's group also presented further immunological and pharmacological data confirming that Bax (and/or Bak) was at least a component of MAC (321) and in favor of its role in cytochrome *c* release from the intermembrane space and hence in apoptosis (992). The model arrived at envisions t-Bid-induced progressive MAC formation from Bax/Bak. While the involvement of other proteins is not ruled out, MAC forms independently of VDAC1 or VDAC3 (832). No conclusion has been reached concerning VDAC2 (see above for references) or the adenine nucleotide translocase(s), an IMM protein which has also been proposed as a partner of Bax (147, 197, 1446). Overall, these findings are in excellent agreement with the model, based on biochemical studies by several laboratories, envisioning the formation by Bax of wide cytochrome *c*-permeable openings in the OMM.

B) IN-CELL RECORDINGS OF BCL-2 FAMILY PORES. Jonas and coworkers were the first, and so far to our knowledge the only, researchers to achieve gigaohm seals and single-channel recording from intracellular membranes reached by perforating the outer membrane with a two-concentric-electrodes device (610) and used it to, record activity of both low- and high-conductance channels from squid presynapse intracellular membranes reputed to belong to mitochondria (605, 609). High-conductance activity was reportedly potentiated by electrical stimulation of the synapse; it was dependent on elevation of Ca^{2+} levels and was eliminated by pretreatment with FCCP, a $\Delta\Psi m$ dissipator (605, 612). Unitary conductance steps observed ranged up to 2.5 nS (605). Large channel activity was also potentiated by the presence of BclxL in the patch pipette (607, 609). In this case conductances mostly fell in the 100- to 760-pS interval (609). In the same experimental system, large multi-conductance (0.3–2.0 nS) pore activity was also readily observed by intracellular (mitochondrial) patch-clamp recording under hypoxia (608, 612). This development was inhibited by the cysteine protease inhibitor Z-VAD-fmk. Similar activity (0.3–3.8 nS) was elicited by a pro-apoptotic form of BclxL produced by deletion of NH_2-terminal residues 2–76 (607, 612), and it was observed in mitochondria isolated from ischemic rat brain (187). Ischemic preconditioning was found to block index ischemia-induced BclxL cleavage (yielding ΔN61-BclxL) and large channel activity. The effect was mediated by Akt and Bad, and resulted in block of casp-3 activitation and prevention of apoptosis (877). These observations led to the conclusion that NH_2-terminal-truncated form(s) of BclxL may, together with other proteins, generate large pores in the OMM of ischemic cells, accounting for the release of pro-apoptotic factors (187, 934). Note that this model envisions the involvement of the cleaved BclxL forms. Assuming cleavage by casp-3, which is known to occur (e.g., Ref. 415), runs into an apparent

catch-22 difficulty: cleavage would be needed for the formation of a cytochrome *c* efflux pathway, necessary for caspase activation. Nonetheless, mice expressing a knocked-in caspase-resistant form of BclxL exhibited a reduction in the relevant mitochondrial activity and in the susceptibility to ischemic neuronal death (934). Thus the mechanism may serve in the acceleration/amplification relatively late phase of the apoptotic process (934) (delayed cell death; compare with the late appearence of MAC observed by Guihard, Ref. 484), or some other protease(s), possibly a zinc metalloprotease or a calpain, might intervene to generate pro-apoptotic forms as well.

Remarkably, in similar experiments application of Bax resulted in the observation of relatively small channels, similar to those observed with full-length BclxL, and only occasionally of giant conductances comparable to those elicited by ΔN-BclxL (606, 611). Expression of ΔN-BclxL was sufficient to induce death of neurons and of Bax- and Bak-less MEFs (934). Indeed, the authors point out that the process they investigated may not coincide with apoptosis as narrowly defined (934), making the point that in neurons, the cells they studied, Bax is downregulated, while BclxL is abundant (611).

Patch conductance in seals on isolated mitochondria was observed to be increased by Zn^{2+} (100 μM in bath). Of note, Zn^{2+} is an activator of the MMC/MPTP (593, 775, 1397; contra Ref. 330). Large-conductance channel activity was inhibited by the permeant Zn^{2+} chelator TPEN, but not by impermeant EDTA (187). This points to a process taking place in the matrix. The authors recognized this, but still assigned the activity to the OMM, hypothesizing that matrix Zn^{2+} might indeed activate the MPTP, resulting in the release of a messenger which in turn would activate the conductances they recorded in the OMM (187, 611). Mitochondria from ischemized brain had a higher content of chelatable Zn^{2+} and of ΔN-BclxL. Zn^{2+} is known to be involved in ischemic neuronal death (e.g., Ref. 219).

The same group also discovered an interaction of BclxL with the β subunit of the mitochondrial F_0F_1 ATPase, an interaction which appears to reduce proton leakage across the IMM (19, 249). This obviously demands that BclxL is present in the mitochondrial matrix, as indeed found by the authors. If BclxL is present at the level of both the OMM and matrix, it is reasonable to assume that it is also there at the IMM. These considerations, plus the characteristics of the pores observed (high-conductance, multi-level) the role of matrix Zn (see above), and the common involvement of the conductances under discussion and of the MMC/MPTP (e.g., Ref. 95) in ischemic death raise the question of the relationship between these two entities. May they coincide? Since the MPT involves the inner membrane, an obviously important point here is the identity of the membrane the seals were established on in Jonas' experiments. The authors adopted early on the view that it was the OMM, but the direct evidence provided is limited. The first argument, the effects of BclxL, a protein thought to be located exclusively at the OMM, was invalidated by the later report, by the same group, showing that BclxL was present also in other mitochondrial districts. A second criterion used was that the probability of observing ΔN-BclxL-elicited large channels was reduced when the intracellular patch pipette contained NADH (607). Millimolar NADH has been reported to reduce the permeability of the OMM to ADP (747) and the conductance of VDAC (1456). Jonas et al. (607) therefore surmised that VDAC may participate in the formation of the megachannels they observed, and performed a few experiments on mitochondria isolated from wild-type as well as from VDAC1-less yeast (607). With wild-type yeast mitochondria, an activity with conductances in the 200–400 pS range was attributed to VDAC (implying that the seal had been established on the OMM). Whether this activity was influenced by NADH was not reported. The presence of ΔN-BclxL (lacking amino acids 2–76) in the pipette resulted in a different pattern of activity, with larger (500–1,000 pS) and NADH-attenuated conductances. This behavior is in keeping with the already mentioned conclusion that *N*-cleaved pro-apoptotic forms of BclxL form large channels. VDAC1-less yeast mitochondria exhibited larger conductances (700–800 pS) that were unaffected by either NADH or ΔN-BclxL. We may note that NADH (used in the millimolar range) is a reducing agent which might, in general, counteract oxidative stress-induced phenomena. Another relevant point may be that in the 1997 methodological paper (610) the fluorescent dye present in the intracellular pipette appears to label entire, discrete subcellular compartments, suggesting a whole-organelle rather than an organelle-attached configuration. It thus seems to us that the identity of the patched membrane is a matter deserving further attention. In particular, nobody has tried yet to simulate the electrical properties of the electrical circuit representing a seal on the OMM in the presence of an intact IMM separated by only several nanometers of a conductive medium and joined to the OMM at contact sites. Be this as it may, the observations summarized above led Jonas (611) to propose that ischemic conditions lead to the appearence in the OMM of a pore composed by ΔN-BclxL, dephosphorylated Bad and VDAC.

III. ION CHANNELS OF THE INNER MITOCHONDRIAL MEMBRANE

A. Potassium-Selective Channels

FIGURE 3 gives an overview of all electrophysiological activities in the IMM.

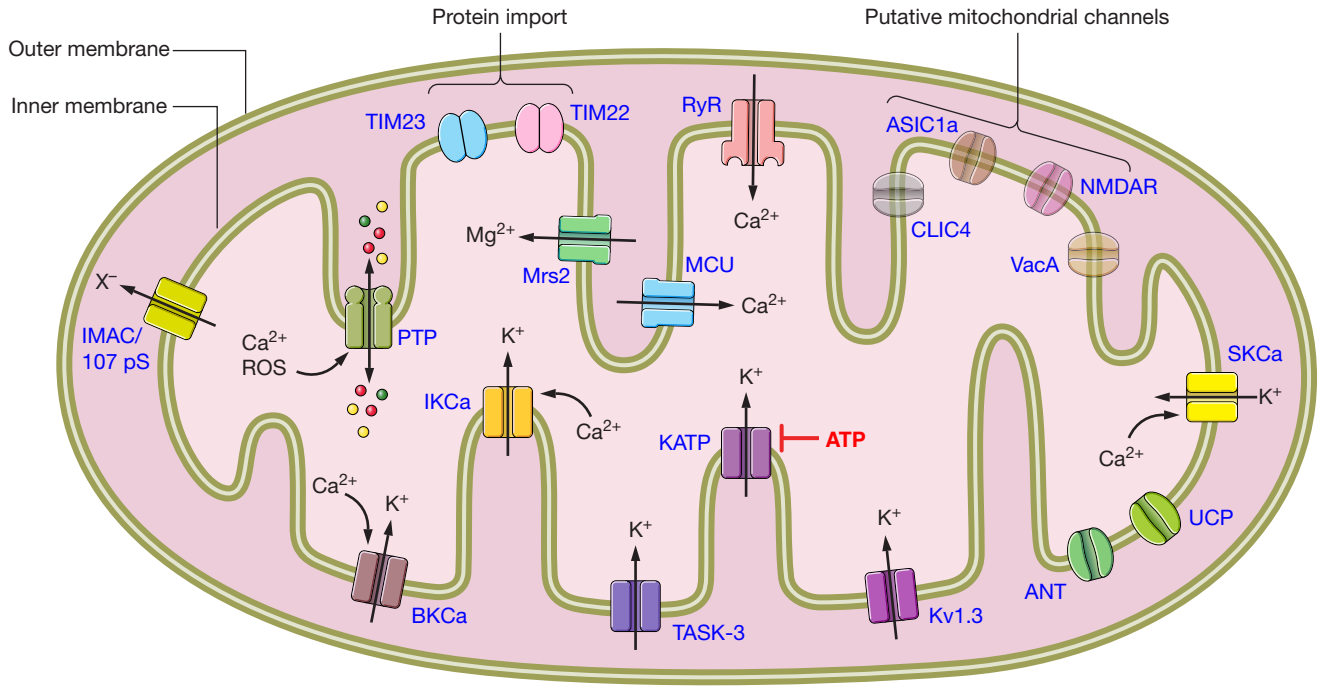

FIGURE 3. Proteins mediating ion fluxes in the inner mitochondrial membrane (IMM). Bona fide ion channels are shown with colored filled forms. Proteins giving rise to channel activities under certain circumstances [ANT, UCP, Tim22, Tim23] are also shown. Putative channels whose channel function has not been proved in IMM are listed as well. Main factors activating (red arrow) or inhibiting (violet arrows) channel activities are shown. For further details, see text.

1. ATP-dependent potassium channels

A) THE PLASMA MEMBRANE K_{ATP} CHANNEL. The mitochondrial K_{ATP} (mito K_{ATP}) channels, namely its very existence, its composition, properties, regulation, function(s) and physiological and medical relevance, constitute the most controversial topic in the field of mitochondrial channels. Part of the uncertainties fueling the debate derive from the complexities characterizing the much-studied plasma membrane (PM) counterpart, which it is therefore worthwhile to briefly recapitulate. Via binding of nucleotides at different sites, and other forms of regulation, PM K_{ATP} channels act as an important sensor of the cellular metabolic/energetic state, closing when energy (ATP) is abundant, and opening when the cell is "starved." Given the nature of this review, we do not discuss here the varied functions of these channels. For more detailed information on all aspects of PM K_{ATP} lore, the reader is referred to the several reviews on the topic (11, 16, 66, 67, 212, 213, 403, 750, 889, 914, 1031, 1181, 1304, 1444).

I) Composition. The proteins giving rise to the ATP-sensitive channel activity observed in patch-clamp experiments (see below) were identified in the mid-1990s (12, 31, 32, 569, 570, 1109). K_{ATP} channels are heterooligomers composed by a tetramer of ~40 kDa Kir potassium channel-forming monomers associated with four regulatory sulfonylurea receptor (SUR) ~160 kDa subunits in an octameric complex (1204; reviews in Refs. 11, 84, 1173).

"Kir" stands for "K^+-selective inward rectifier," a family which differs from the general template of K^+ channels in that each monomeric polypeptide comprises only two membrane-spanning α-helices (1, 46, 545, 913, 1098, 1366). The namesake inward rectification is due to voltage-dependent block by cytoplasmic Mg^{2+} or polyamines. These channels are classified into seven subfamilies: ATP-sensitive channels are formed by the members of the Kir6 group, which comprises Kir6.1 and Kir6.2. These "core" channels have an inhibitory ATP binding site (403), which can be modulated by phospholipids (1331, 1402).

Sulfonylurea receptors (SURs) (16, 211, 403, 750, 889, 1181) are members of the family of ATP binding cassette (ABC) transporters (552). ABC transporters have also been classified into seven subfamilies. The ones involved in the formation of K_{ATP} channels belong to the ABCC/MRP subfamily, which includes also, e.g., the cystic fibrosis transmembrane conductance regulator (CFTR). As far as is known, SURs do not act as "pumps," and their function seems to be essentially that of regulating K_{ATP} channel activity.

Each SUR monomer has three transmembrane domains (TMD0–2) and two cytoplasmic nucleotide binding folds (NBFs) that come together to generate two interacting sites that can bind MgATP/MgADP. Engagement of these sites promotes activity of the channel. The major SUR forms, produced from two genes with nearly 40 exons each

(1181), are SUR1 (high affinity for sulfonylurea) and a couple of splicing isoforms, SUR2A and SUR2B (lower affinity). These are the proteins generally considered to partner with Kir6.x in the formation of PM K_{ATP} channels. However, several other "short" splice variants of SUR2, some with a compromised or missing COOH-terminal NBF, have been reported in the heart (403, 1181) and can form "unconventional" K_{ATP} channels with Kirs (1032). Several alternative splicing forms of SUR1, lacking transmembrane helices or an NBF domain, or even most of the protein (470, 510, 1110, 1146), have also been detected. While some are unproductive (470, 510), others can form channels by pairing up with Kirs (510, 1110, 1146, 1181). A further recent study provides evidence that these short forms are present in mitochondria and, therefore, may actually be a component of "mito K_{ATP}" (1421). Not much is currently known about the overall functional significance of these forms, but they may well contribute to the complexities of K_{ATP} regulation and pharmacology.

Even considering only the major forms of SURs, it is obvious that in principle a variety of complexes can assemble. At least in most cases, mercifully, octamers appear to comprise only one type of Kir and only one type of SUR (443) (but see below). This restriction leads to the expectation that six major types of Kir/SUR complexes may form, which have all been reported (see **TABLE 2**). For both Kir6.x and SURs, the expression of one or the other form is organ- and cell-type specific, but this segregation is not absolute, and the formation of heterocomplexes has been demonstrated in several studies (review in Ref. 1444). Different forms may coexist in the same cell (271). Molecular biology studies have provided convincing evidence that heteromers comprising combinations of different Kir6.x (e.g., Refs. 82, 85) or SURs (e.g., Refs. 251, 777, 1378) can form functional channels.

II) Biophysical properties of plasma membrane K_{ATP} channels. The biophysical properties of the native PM K_{ATP} channels need to be kept in mind when considering the questions associated with mito K_{ATP}. Given our purposes here, we will focus on the conductance, which obviously depends on ionic conditions.

Kir6.2-based channels are more commonly expressed, and the cardiac type (Kir6.2-SUR2A) is often referred to as representative of K_{ATP} channels. They are most readily observed in the absence or at lowered levels of ATP, e.g., in ex*ci*sed membrane patches or in the membrane of cells treated with mitochondrial poisons (e.g., KCN). However, Kir6.1-based (KNDP) channels need Mg^{2+} and nucleotides for activity. K_{ATP} channels are strongly K^+-selective channels (current reversal potential close to theoretical). For the cardiac type (less so for the Kir6.1-based channels), the single-channel current-voltage relationship shows inward rectification, pronounced in cell-attached experiments or when activity is recorded in the presence of low-millimolar range Mg^{2+} on the cytoplasmic side. This is an example of "unidirectional" fast channel block, which results in the reduction of the average amplitude of the current conducted by the open channel. Physiological blockers, acting from the cytoplasmic side, have little effect on the conductance in the voltage range negative to the K^+ reversal potential. The slope of the current-voltage relationship in this latter

Table 2. *Tissue-dependent molecular composition of plasmamembrane K_{ATP} channels*

Tissue	Composition	Reference Nos.
Pancreatic β-cell	Kir6.2-SUR1	12, 568
Most, but not all, central neurons		771, 1233, 1438
Mouse dentate gyrus granule cells		1288
Heart (ventricular)	Kir6.2-SUR2A	23, 84, 931, 1444
(Other heart tissues express also Kir6.1 and SUR1)		403
Skeletal muscle	Kir6.2-SUR2A (but also other SURs, depending on muscle type/age)	403, 1256, 1324, 1325
Nonvascular smooth muscle and portal vein (portal vein also has Kir6.1/SUR2B)	Kir6.2-SUR2B	403, 460, 574
Vascular smooth muscle (KNDP)	Kir6.1-SUR2B (KNDP)	403, 1369, 1411
Mouse colon smooth muscle		601
Guinea pig stomach smooth muscle cells	(Kir6.2 mRNA also found)	1208
Hippocampus neurons	Kir6.1-SUR1	1229
Frog retinal Mueller glial cells		1216
Neonatal heart (atrial)	Possibly heteromeric (all subunits found by PCR)	109

range is referred to here as the conductance of the channel. Discrete subconductance levels can be observed (86, 628), and cooperativity upon clusterization has been proposed (86).

The expression of components in suitable model cells has allowed researchers to precisely define a set of intrinsic properties of the various K_{ATP} channels. Conductance values of defined-composition (cloned) channels are as summarized in **TABLE 3**.

In these heterologous expression systems, the values depend essentially on the Kir isoform expressed: in symmetrical 140 mM KCl Kir6.1 complexes exhibit a conductance of ~33–35 pS, versus 67–80 pS for Kir6.2. The conductance of Kir6.1/6.2 concatemers depends not only on the proportions of the two monomers within the tetramer, but also on their relative position (86). In native cells, the picture is less well defined. In some cases also smaller conductances than those reported in **TABLE 3** can be observed (1037). Considering the values recorded in at least approximately symmetrical high K^+, in ventricular cardiomyocytes and skeletal muscle myocytes the channels do exhibit the conductance expected of Kir6.2-SUR2A complexes (with values reaching however up to ~100 pS). In pancreatic cells or insulin-producing cultured cells, thought to express Kir6.2-SUR1 channels, conductances seem to cluster around 50–65 pS, and even lower values are observed in some cases in recordings from neuronal membranes (e.g., Ref. 993). Smooth muscle cells, believed to express predominantly SUR2B, present a range of conductance values, including conductances close to the values expected for Kir6.1-based channels as well as for Kir6.2-based ones (see **TABLE 3** and Ref. 1037). This is in agreement with expression studies. Some of the lowest conductances reported in the literature were obtained with cells of this type (e.g., ~13 pS in symmetrical 140 mM KCl in rat mesenteric artery vascular smooth muscle cells; Ref. 1286). Overall, conductances ranging roughly

Table 3. *Conductances of cloned plasmamembrane K_{ATP} channels*

Cloned K_{ATP}	Recording Conditions	Conductance, pS	Reference Nos.
mKir6.2-haSUR1 in Cos1 cells	Exc i.o. patch in symm 140 mM KCl	76.4 ± 1.0	568
mKir6.2-haSUR1 dimeric constructs in Cos1 cells	Exc i.o. patch in symm 140 mM KCl	79.2 ± 1.3	588
Dimeric mKir6.2-haSUR1 constructs in Cosm6 cells	Exc i.o. patch in symm 140 mM KCl	75	1204
mKir6.2 and haSUR1 in HEK293 and SH-SY5Y	I.o. patch. Symm 140 mM KCl	~70	235
Dimeric hKir6.2-hSUR1 constructs in Cosm6 cells	Exc i.o. patch in symm 140 mM KCl	69 ± 3	266
hKir6.2 and hSUR2A in CHO and human ventricular cells	Excised i.o. patch. ~150 mM KCl symm	~80	84
mKir6.2 and mSUR2A in HEK293 cells	Excised i.o. patch. ~150 mM KCl symm	80.2 ± 0.7	940
Kir6.1/SUR2A in COS7	Excised i.o. patch (140 mM KCl symm)	33.6 ± 4.2	675
Kir6.2/SUR2A in COS7 (cardiac type)	Excised i.o. patch (symm 140 mM KCl)	67.1 ± 1.6	675
Kir6.1–6.2 tandem constructs (2+2; aabb)/SUR2A in COS7	Excised i.o. patch (symm 140 mM KCl)	58.9 ± 1.5	675
Kir6.2-SUR1 in COS-1 cells	Excised i.o. patch (symm 140 mM KCl)	74.3 ± 0.7 (no PKA) 72.1 ± 2.9 (+PKA)	143
Kir6.2-SUR1 in HEK293	Excised i.o. patch (symm 140 mM KCl)	~70	824
Kir6.1-SUR2B in HEK293	Cell attached (~145 mM KCl in pip) and i.o. excised patch (symm 145 mM KCl)	~33	1411
Kir6.1-SUR2B in HEK293	I.o. excised patch (symm 145 mM KCl)	~35	1131
Kir6.1-SUR2B in HEK293	I.o. excised patch (symm 145 mM KCl)	35.7 ± 0.3	1369
Kir6.2-SUR2B in HEK293	Cell attached (pip: ~145 mM KCl)	80.3	574
Kir6.2-SUR2B in HEK293	I.o. excised patch (symm 145 mM KCl)	~80	1131
Concatemers hKir6.1/6.2-hSUR1 in Cosm6 cells	Kir6.1(4)-SUR1(4) in exc i.o. patch in 150 mM KCl (symm)	34.2 ± 0.1	85
	Kir6.2(4)-SUR1(4) (idem)	68.1 ± 0.1	
	$Kir6.1_X/6.2_Y$ (X+Y=4)-$SUR1_4$; X,Y>0;	48.8–62.0 (concatemers: conductance depends on stoichometry and position)	

Exc, excised; i.o., inside out; symm, symmetrical; pip, pipette.

from 10 to 100 pS have been attributed to PM K_{ATP} channels.

In several cases, mitochondrial K_{ATP} channels have been studied after reconstitution in planar lipid bilayers. The technique has also been used in a few studies of the plasma membrane channel. Parent and Coronado (967) recorded it upon fusion of vesicles of rabbit skeletal muscle t-tubule membrane. In 260/60 mM KCl (*cis*/*trans*; vesicles added in *cis*) they observed a conductance of 67 ± 2 pS in the absence of Mg^{2+}. The channels apparently tended to associate in pairs. Kovacs and Nelson (694) incorporated ATP-sensitive channels from canine aorta smooth muscle. The paper does not report a conductance value, which can be estimated from the linear portion (at *cis*-positive potentials) of the rectifying plot at ~80 pS with 120/5 mM (*cis*/*trans*) KCl. With similar ionic conditions, Mayorga-Wark et al. (845) measured a conductance of 180 ± 6 pS (no Mg^{2+}) for ATP-modulated K^+ channels from basolateral membranes of mudpuppy (a salamander) enterocytes. Oosawa (945) used a preparation of membranes from insulin-secreting HIT T15 cells. In this study an ohmic conductance of ~53 pS was measured in symmetrical 140 mM KCl.

In single-channel recordings, the K_{ATP} channels exhibit typical "bursting" behavior, with at least two time constants needed to describe the distribution of both open and closed times (e.g., Refs. 628, 1231, 1232, 1326).

III) Regulation of PM K_{ATP} channels. The defining features of the K_{ATP} channels are generally considered to be their regulatory and pharmacological properties, preminently regulation by ATP (and also by GTP, UTP; e.g., Refs. 121, 400, 628, 914, 1031, 1332). The "core" Kir channels have an inhibitory ATP binding site (e.g., Ref. 82), which in the case of Kir6.2 accounts for inhibition in the 10–100 μM range. In experiments with excised membrane patches, ATP concentrations in the double- or triple-digit micromolar range are often enough to cause a drastic decrease of the channel open probability (P_o) (while there is no effect on its conductance; e.g., Refs. 628, 918). Free ADP is also inhibitory, although with a ~10-fold lower K_i than ATP (627, 1231). From the point of view of channel behavior, the effect of ATP is to reduce the burst duration and the number of openings per burst and to increase the frequency and duration of interburst closures (e.g., Refs. 628, 1231), as well as to stabilize a long-lived closed state (1231, 1232). High Hill coefficients for inhibition point to cooperativity by multiple receptor sites (628). In fact, all four Kirs need to be in the ATP-free permissive state for the channel to be open. Inhibition does not involve phosphorylation, since it is brought about also by nonhydrolyzable analogs (401, 628, 1231). The effect is very rapid and reversible so that K_{ATP} may be regarded as a ligand-gated channel (121). Importantly, the Kir subunit also binds to phosphatidylinositol 4,5-bisphosphate (PIP_2) (and other lipids, such as PIP_1 and, importantly, long-chain acyl CoAs; e.g., Ref. 734). This interaction is activating, i.e., in the absence of ATP PIP_2-Kir interactions tend to keep the channel open (e.g., Ref. 602). These features account for the increased activity of Kir6.2-based channels when membrane patches are excised and ATP is washed away, and also for the subsequent channel rundown as PIP_2 is lost (403). This interaction obviously implies regulation of K_{ATP} activity by the cellular signaling pathways which use phosphatidylinositolphosphates as messengers.

While binding of ATP to the Kir subunit inhibits, binding of Mg-adenine nucleotides to the SUR subunits activates the channel, contrasting the inhibitory effect on Kir (e.g., Ref. 627). MgADP can also reverse channel rundown, at least partially. Affinities differ among the various subunits. In the case of the Kir6.1-SUR2B subtype, the dependence of the open probability on ATP is bell-shaped. The channels strictly require nucleoside di- or triphosphate binding to SUR to open, and will become inhibited at higher concentrations via the Kir6.1 site. Contrary to the "cardiac type," these channels (the "K_{NDP}-type") do not therefore appear upon membrane patch excision, and need the presence of, typically, MgADP to be observed. ATP/ADP levels probably contribute, along with PIPs, to setting the levels of K_{ATP} activity, even though ATP is not expected to fall below millimolar levels in living cells. There is, however, no scarcity of other regulatory biochemistry and interactions.

The modulation of PM K_{ATP} by pH is complex, with early studies leading to seemingly contradictory conclusions. In studies involving expression of recombinant rodent Kir6.x and hamster SUR1 in *Xenopus* oocytes, Xu and colleagues established that high levels of CO_2 (hypercapnia) and, equivalently, intracellular acidification to pH 6.8–6.6 activates the channels via a conserved histidine of the Kir subunit (1369, 1395, 1396, 1404, 1405). Extracellular acidification had only a modest effect. The Kir6.2-SUR2A channel of ventricular heart cells was found to exhibit a bell-shaped pH dependence, with acidification increasing its P_o in the 7.6–6.0 range and decreasing it below pH 6. Recombinant Kir6.2-SUR1 expressed in HEK cells has furthermore been reported to be directly activated (P_o increase) by alkaline intracellular pH, with a peak at pH 8.0 (822).

A further layer of complexity is provided by phosphorylations. The channels are in fact targets for a number kinases, including PKC, PKA, and metabolism-sensing AMPK. The resulting effects depend on channel composition and on the site of phosphorylation (403; see also Ref. 75). Thus phosphorylation by PKC can be inhibitory in smooth muscle and insulin-secreting cells and activating in cardiomyocytes. PKA activates K_{ATP} in vascular smooth muscle cells. At least both Kirs, hSUR1 and SUR2B, can be phosphorylated by this kinase (403). AMPK activates cardiac-type channels (1249) but inhibits those of insulin-secreting cells (238).

Activation of K_{ATP} may also take place downstream of PKG (and thus downstream of NO) (e.g., Refs. 635, 1104): it involves phosphorylation (not necessarily of the K_{ATP} itself) and it may also involve ROS, specifically H_2O_2 (235, 236). H_2O_2 is in fact believed to act as an activator of K_{ATP} (72). NO can also act by direct nitrosylation (635).

IV) Pharmacology of PM K_{ATP} channels. Given the complexities of their biophysical properties and modulation, researchers have resorted to pharmacological tools in their efforts to characterize and distinguish K_{ATP} channels and their effects, in particular as pertains to the mitochondrial one(s). Needless to say, this approach is not without its own difficulties. Like most ABC "pumps," SURs can interact with a number of exogenous ligands, and this results in a rich pharmacology (889, 1031, 1174). Some of these ligands can interact also with other cousin ABC transporters (e.g., glibenclamide with CFTR, MRP1, MDR1) as well as other proteins. This promiscuity is a pharmacological headache and contributes to the disputes surrounding mito K_{ATP}.

Sulfonylureas (e.g., tolbutamide, glibenclamide) and meglitinides (e.g., repaglinide, nateglinide), used to manage diabetes mellitus, inhibit β-cell K_{ATP} by binding to SUR with affinities in the micromolar range. A binding site on Kir6.2 has a much lower affinity. Currently binding to SURs is envisioned as involving two sites: one (A) which is specific of SUR1, and one which is common to all three major SURs (B) (1174). A first subset of drugs (including tolbutamide, nateglinide) binds specifically to site A, a second (including glibenclamide/glyburide) to both sites. Full inhibition can only be obtained in the presence of nucleotides interacting with the Kir site. Sulfonylureas thus seem to act essentially by preventing the stimulatory effect of MgADP at SURs. For our purposes it is important to mention 5-hydroxydecanoate, often considered to be a specific inhibitor of mito K_{ATP} (see below). Li et al. (763) have recently reported that this compound can inhibit cardiac PM K_{ATP} activated by oleoyl-CoA in excised membrane patches (provided some ATP is present). In intact myocytes however, it failed to reverse K_{ATP} activation induced by metabolic inhibition or by rilmakalim, a K_{ATP} opener.

Mirror-like, K_{ATP} channel openers, a group of chemically diverse molecules (e.g., cromakalim, nicorandil, pinacidil), act similarly to MgADP, antagonizing inhibition by MgATP at Kir (64, 121, 888, 889). A common activating site is involved, comprising amino acids in the last transmembrane helix of SUR (888). Only one activator of SUR1-containing channels is known, namely, diazoxide (and its derivatives). Although known to activate also SUR2B-made K_{ATP}, this compound was initially thought not to activate SUR2A-comprising channels. This notion led researchers to attribute its cardioprotective effect in ischemia to mito K_{ATP}. However, D'hahan et al. (332) have reported that it can actually activate also cardiac-type (Kir6.2-SUR2A) channels, provided intracellular ADP is present at concentrations >10 μM. Diazoxide and ADP were in fact found to act cooperatively in inducing channel opening (843). Diazoxide can therefore activate all known types of K_{ATP} channels, while the other activators act on SUR2-based ones. Generalizing, SUR2B has an approximately fourfold higher affinity for openers than SUR2A (888). Thus pharmacological tools are in principle available to distinguish between SUR1- and SUR2-containing channels. Opener binding is greatly facilitated by the presence of Mg^{2+} and hydrolyzable ATP (889).

B) MITOCHONDRIAL ATP-DEPENDENT POTASSIUM CHANNELS. An IMM ATP-sensitive K^+ conductance has been the object of much interest and of ongoing debate due to its putative involvement in "ischemic preconditioning." More than 20 years have elapsed since the first reports of an ATP-sensitive mitochondrial inner membrane K^+ channel (571, 976), but its very existence, let alone its molecular composition and its functions, are a matter of dispute (e.g., Refs. 58, 59, 138, 167, 210, 304, 428, 498, 514, 928–930, 1275–1277). The majority of investigators are convinced that such a conductance is present (while some still maintain it does not), but its identity remains a question mark. Pharmacological data are inconclusive, and the presence in mitochondria of proteins corresponding to PM K_{ATP} components has not been unequivocally established by biochemical or immunological methods.

I) Electrophysiology: not quite enough? The logically foremost hypothesis is that the mito K_{ATP} channel(s) may represent a mitochondrial population of whatever K_{ATP} is present in the plasma membrane, e.g., Kir6.2-SUR2A in the case of ventricular myocytes. Electrophysiology in general is a convenient fingerprinting tool which ought to allow a definite answer and provide hints as to the possible alternative identiti(es) of the channels. Surprisingly few patch-clamp studies have been devoted to the study of mito K_{ATP} **(TABLE 4)**. The first was the seminal study by Inoue et al. (571). This work used rat liver mitoplasts obtained by digitonin treatment followed by hypotonic swelling and Ca^{2+}-induced fusion. Mitochondrial preparations normally contain ER and PM contaminants, and thus the mitochondrial origin of the channels cannot be taken for granted. In excised inside-out patches the ATP-inhibited K^+-selective channel had a conductance of ~10 pS in 100 (pipette) vs. 33 (bath) mM KCl, lower than the conductances reported for PM K_{ATP} variants under comparable ionic conditions (see above). Patching in the mitoplast-attached mode mitoplasts obtained from human Jurkat lymphocytes, Dahlem et al. (296) observed an outwardly rectifying ATP-modulated channel with a conductance of 15 pS at matrix-negative and of 82 pS at matrix-positive potentials in 150 mM KCl (bath and

Table 4. *Conductances of mitochondrial K_{ATP} channels*

System	Patch and Ionic Conditions	Reported Conductance (Max)	Reference Nos.
Patch clamp			
Human Jurkat lymphocytes	Mitoplast-attached or i.o. patch; 150 mM KCl	82 pS outward rectifying	296
RLM	Fused mitoplasts. Excised i.o. patch. 100 (pip) vs. 33 (bath) mM KCl	~10 pS (slightly outwardly rectifying; possibly coordinated pairs) (no Mg)	571
Bilayer			
BHM	Partially purified protein fraction; symm 1 M KCl	30 pS chord at +85 mV	976
Reconstituted proteoliposomes from RLM	Symm 150 mM KCl	16 pS chord at +100 mV	1420
BHM (Bovine ventricular myocardium SMPs)	50 (*cis*) vs. 150 (*trans*) mM KCl (SMPs in trans)	103 pS (slightly rectifying) >60 pS by 1 mM Mg in *trans* (matrix) (not if in *cis*)	137 139
BHM (Bovine ventricular myocardium SMPs in *trans*)	50/150 (*cis/trans*) KCl	110 ± 8 pS (pH 7.2) 145 ± 5 pS (pH 8.2)	138
Purified 55 kDa prot from RLM, RHM, RBM	Symm 100 mM KCl	10 pS and higher (up to 100; cooperating clusters invoked). Rectifying	870
Purified 55 kDa prot from RLM	Symm 100 mM KCl	Cluster-like cooperative behavior	871
Human ventricular IMM preparation	Symm 150 mM KCl	Cluster-like cooperative behavior (or substates) in ~20 pS steps (up to 120)	594, 595
BHM (bovine ventricular myocardium SMPs)	Symm 150 mM KCl	56 pS (and others from 10 to 100 pS)	1443
SMPs from *A. castellanii* (in *trans*)	50/450 (*cis/trans*) mM KCl	166 ± 10 pS (90 pS in pos. range)	640
RHM (rat ventricular myocardium SMPs)	Symm 150 mM KCl	Several from 26 to 105 pS (26, 47, 58, 66, 83, 105)	903

Symm, symmetrical; i.o., inside out.

pipette). The conductance of this channel may be considered to be in line with expectations based on PM K_{ATP} studies, although the voltage dependence is inverse.

We note that small-conductance Ca^{2+}-activated K^+ channels [SK1–3; K(Ca)2.1–3; many variants reported, heterocomplexes can be formed] (reviewed in Refs. 7, 985, 1239), have conductances compatible with the lower values reported in these studies, are not voltage-dependent but exhibit inward rectification due to open channel block, and are activated by Ca^{2+} in the submicromolar range, i.e., at contamination levels. They are furthermore activated by some compounds having a distinct, although partial, resemblance to diazoxide, pinacidil and other activators of K_{ATP}, suggesting the possibility of a pharmacological crossover (see **FIGURE 4**). Sensitivity to apamin is characteristic. SK1–3 are strongly expressed in the nervous system, but they are present in many other cell types, including atrial and ventricular cardiomyocytes (e.g., Ref. 1333), smooth muscle (e.g., Ref. 1067) and liver (e.g., Ref. 279).

Electrophysiological data concerning mito K_{ATP} are provided by a number of papers using the BLM technique with purified proteins or membrane fractions (99, 136, 137, 139, 594, 870, 871, 903, 976, 1443). The first reconstitution of a mitochondrial protein increasing the K^+ conductivity of a bilayer may have been the one by Mironova et al. (869), published in Russian. Subsequent developments of the research by this group are summarized below (see sect. III*A1*B*III*) in the context of the discussion on the molecular identity of mito K_{ATP}.

Another set of studies employing BLM was carried out by the group of Adam Szewczyk. These authors fused BH submitochondrial particles to study a well-behaved slightly rectifying cation-selective channel with a conductance of ~100 pS (*cis*-negative range) in 150/150 or 50/150 (*cis/trans*) mM KCl (136, 137, 139). The activity could be inhibited by ATP/Mg^{2+} (0.5 mM) added on the side (*cis*) of the membrane opposite to that of SMP addition (*trans*). ATP or Mg^{2+} alone in *cis* did not have this effect. Neither did ATP/Mg^{2+} added in *trans*, or the nonhydrolyzable ATP analog AMP-PNP/Mg^{2+} added on either side. Inhibition by *cis* ATP/Mg^{2+} was reversed by diazoxide and BMS-191095 (see below) as well as by *cis*-side addition of GDP. Mito K_{ATP} had been previously found to be activated by guanine nucleotides in experiments monitoring K^+ transport-induced swelling (977). 5-Hydroxydecanoate (5-HD), gliben-

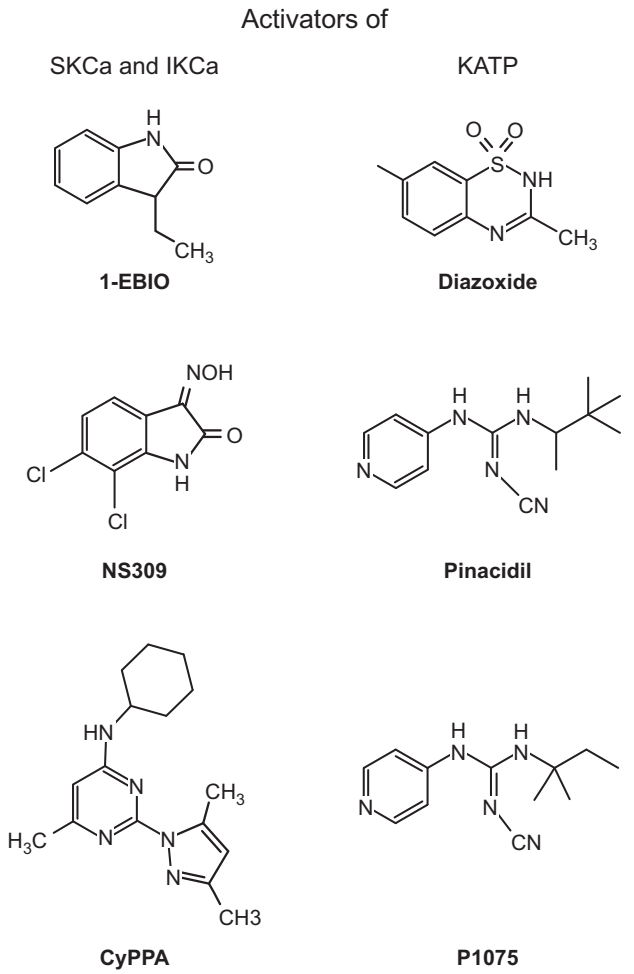

FIGURE 4. Small molecule activators of SK_{Ca}/IK_{Ca} and K_{ATP} have structural similarities.

clamide, and quinine also inhibited, while HMR-1098, considered to be a specific PM K_{ATP} inhibitor (see below), did not. Mg^{2+} (1 mM) added in *trans* caused a marked decrease of the single-channel conductance measured in the *cis*-negative voltage range, coherent with an open channel block. The channel was modulated by *trans* (i.e., presumably matrix-side) pH, with a transition to basic conditions (pH 7.2 to >8.2) increasing both the mean P_o and the single-channel conductance. Decreasing the *trans* ("matrix") pH to 6.2 apparently reduced the P_o, but unfortunately this effect was not studied in detail (pH 6.2 may or may not fall in the acidic inhibitory range of PM K_{ATP} values; a pH-dependence curve may contribute to establishing the identity of mito K_{ATP}). A shift of the *cis*-side pH to 8.2 had little effect, while a decrease from 7.2 to 6.2 resulted in a significant decrease of the P_o.

Jiang and colleagues (594, 903) incorporated an IMM fraction from human ventricular myocytes into BLMs and observed activity with stepwise conductance variations up to ~ 120 pS in symmetrical ~ 150 mM KCl. The different conductance levels were attributed to cooperative behavior or subconductance states. This activity was inhibited by ATP and 5-HD, and activated by GTP and diazoxide and by PMA, a PKC activator [all added to the same (*cis*) chamber as the SMPs]. It was furthermore activated by isofluorane, putatively accounting for the preconditioning effect of this anesthetic (595, 903). Western blotting indicated the presence of PKC-δ (but not -ε) in the preparation. An anti-Kir6.2 antibody detected a 56-kDa protein in mitochondria. The apparent size reminds one of the analogous observation by Mironova et al. (871).

K^+-selective conductances of various sizes (predominantly 56 pS in 150 mM KCl) were also observed by Zhang et al. (1443) upon reconstitution of SMPs obtained from beef heart (BH). In this work MgATP had no significant effect when added on the same side of the BLM as the SMPs (*cis*, in this case), but inhibition was observed upon addition to the opposite side. The effect was reversed by GTP (*trans*). This behavior is analogous to that observed by Bednarczyk and colleagues (137) and by Mironova et al. (871). 5-HD on the same side of SMPs and glibenclamide inhibited (while HMR-1098 did not), and diazoxide reactivated the activity. Superoxide provided by the xanthine/xanthine oxidase system (in *cis*) produced a rapid activation of the channels attributable to the oxidation of thiol groups.

Despite differences and uncertainties, the channels described by these groups may be considered to resemble each other and to probably correspond to the same molecular species.

II) Pharmacology and pathophysiological role. An important role has been assigned to mito K_{ATP}, especially in the heart, in protection from I/R injury, preconditioning (384, 895), and postconditioning (634). In ischemic preconditioning (IP) (900, 663, 664), the application of brief period(s) of reversible ischemia results in myocardial "stunning" (i.e., the temporary loss of the ability to contract) and "adaptive" biochemical changes, including increased phosphocreatine content. Upon subsequent prolonged ischemia, ATP decline and lactate production occur at a slower rate than in untreated tissue so that myocyte death and irreversible damage take longer to develop (e.g., Refs. 588, 589, 641, 900, 901). Elaborate signaling pathways have been identified as mediating acute ischemic preconditioning (for reviews on signaling, see Refs. 216, 527, 528, 664, 781, 1416). The belief that a mito K_{ATP} acts as a crucial element has probably influenced their tracing and the interpretation of some of the observations. One can distinguish between a so-called "trigger phase," in which cells are primed for resistance to the final, severe (referred to as "index") ischemic episode, and a "mediator phase," i.e., the actual deployment of protective biochemical instruments when damage is being wrought, i.e., at reperfusion after index ischemia. Cell death associated with I/R damage is thought to be due largely to the onset of the mitochondrial permeability transition, and protective action is widely thought to consist in

repressive measures preventing or limiting this phenomenon (e.g., Refs. 526, 766). This latter stage is discussed in section III*F*, but we may anticipate here that a major end-effector may be inhibition (by phosphorylation) of GSK-3β, whose activity is understood to facilitate onset of the MPT.

The biochemistry of ischemic preconditioning has been intensively studied. A sequence of brief ischemic episodes has been reported to result in changes in the antioxidant enzyme system (303) and cell membrane phospholipids (613). Ischemia causes the release of G protein-coupled receptor (GPCR)-coupled effectors like adenosine (269, 481, 1341), bradykinin (which induces production of NO and ROS; e.g., Ref. 941), and opioids (1153; see also Refs. 982, 983). Activation of kinases, including PKCε, p38 MAPK, PKG, and tyrosine kinase(s) (91), is part of downstream signaling. As already mentioned, K_{ATP} channels are targets for various kinases, including PKC, PKA, and PKG, and are activated by reactive oxygen species (ROS) (H_2O_2) (1268). ROS generation is widely considered to be a sine-qua-non of preconditioning (e.g., Refs. 996, 997, 996). K_{ATP} channels, and specifically mito K_{ATP} channels, along with mitoBKCa, have been assigned a central role in their generation (339).

Indeed, pharmacological evidence soon identified K_{ATP} activation as a major element in the mechanism of preconditioning, since inhibitors abolished the effect (471, 477, 478, 479, 481, 776, 791, 1299, 1307). Conversely, K_{ATP} openers mimicked preconditioning, reducing the size of the infarcted area, and K_{ATP} inhibitors again abolished this effect (e.g., Refs. 478, 480, 848, 1122). Logically, sarcolemmal K_{ATP} was initially considered to be involved (e.g., Refs. 974, 1321). However, chemical preconditioning was induced, among other K_{ATP} openers, by diazoxide, which appeared not to be able to activate cardiac-type (SUR2A-containing) channels (386, 569, 574, 940, 1176). Mito K_{ATP} had meanwhile been discovered, and in 1996 Garlid and co-workers (429, 430) reported, on the basis of swelling experiments with isolated mitochondria and reconstituted proteoliposomes, that it was vastly more sensitive to diazoxide than the sarcolemmal channel (implying, incidentally, that they cannot be the same complex, or at least that they partecipate in different regulatory interactions). Diazoxide, considered as a specific mito K_{ATP} opener, was reported to protect mitochondrial functionality during ischemia (e.g., Ref. 578). Like nicorandil (1128), another K_{ATP} activator, it induced the oxidation of mitochondrial ETC flavoproteins while leaving sarcoplasmic K_{ATP} unaffected (778, 779). Mitochondrial flavoproteins are components of the respiratory chain which become more oxidized when the mitochondrial $\Delta\mu_H$ decreases and respiration is therefore stimulated, which is what is expected to happen if the K^+ conductance of the IMM increases, but also upon protonophoric "uncoupling." In several subsequent papers flavoprotein oxidation was used as a gauge of mito K_{ATP} opening (e.g., Refs. 668, 1437). Garlid's group (579) also showed that ATP-sensitive K^+ flux in mitochondria could be inhibited ($K_{1/2}$ ~50 μM) by 5-HD, a known inhibitor of ventricular myocyte sarcolemma K_{ATP} (~10–100 μM; Ref. 922) also known to counteract the protective effects of ischemic preconditioning (e.g., Refs. 70, 848). Following a later report that 500 μM 5-HD did not inhibit Kir6.2-SUR2A channels expressed in HEK293 (559), the drug came to be considered and used as a selective inhibitor of mito K_{ATP} (e.g., Refs. 668, 1129). Inhibition of sarcoplasmic K_{ATP} by 5-HD has recently been reported to take place in membrane patches, requiring the presence of some ATP, but not in whole myocytes (763). In fact, 5-HD is but one member of the family of fatty acids, which generally inhibit K_{ATP} (368, 428, 642). On the contrary, acyl-CoA esters are activating (467, 734, 823). Adding to the complexity, 5-HD can be converted to its acyl-CoA derivative (and further metabolized) (515).

Other purportedly selective agents have been reported. The effects of the most commonly used ones on PM K_{ATP}, mito K_{ATP}, and preconditioning are summarized in **TABLE 5**.

If a compound, say diazoxide, is considered a specific modulator of mito K_{ATP}, its effectiveness in cardioprotection supports a role of mitochondrial channels in the phenomenon, and, by implication, their existence. The bulk of the evidence supporting the involvement of mito K_{ATP} in protection against I/R damage is pharmacological. Unfortunately, the lack of activity of the drugs on sarcoplasmic K_{ATP} cannot always be taken for granted, and other cellular targets possibly accounting for their effects have been identified. This is particularly true of the most important of these agents, diazoxide (268). For example, the report that PKC is needed for diazoxide to activate mito K_{ATP} (1371) suggests that the effect of the drug may involve more than a one-to-one interaction with a single protein. Most, if not all, of the pharmacological agents reportedly activating mito K_{ATP} can behave as membrane-permeable weak acid/base pairs, and thus as uncoupling, $\Delta\mu_H$-dissipating agents (see **FIGURE 4**) (553) (including glibenclamide: Ref. 1274; diazoxide: Refs. 469, 697; contra for diazoxide: Ref. 196). As mentioned, an uncoupling effect is expected to lead to an increase of the respiratory rate and to the oxidation of flavin-based prostetic groups in the enzymes of the respiratory chain, as verified (e.g., Ref. 1124).

To assign a change of flavin fluorescence observed upon addition of a mito K_{ATP} activator to channel opening one needs therefore to show its reversibility by mito K_{ATP} inhibitors, and/or its modulation by signaling pathways expected to impact on K_{ATP}, as indeed has been done in many studies (e.g., Refs. 646, 668, 778, 968).

These controls weaken the contention that preconditioning by diazoxide and other agents may derive from an unspecific uncoupling resulting in the production of ROS. ROS

Table 5. *Modulators of PM K_{ATP} and mito K_{ATP}*

Modulator	Effect on PM K_{ATP}	Effect on Mito K_{ATP}	Physiopathological Effects
Amiodarone	Inhibits (1130)	None (1130)	Antagonizes preconditioning (676)
HMR-1098 (also indicated as HMR-1883)	Inhibits (452, 1098)	None 137, (1129)	Does not antagonize preconditioning (333, 441, 621)
P-1075	Activates (1129, 1410)	None (1129, 1410) Activates (599, 600, 942)	Reduces skeletal muscle infarction (891)
BMS-191095	None (474, 476)	Activates (474, 476)	Cardioprotection (475, 476)
Levosimendan	Opener	Opener (678)	Protective effect against ischemic damage (301, 361, 472, 473, 554, 827, 859, 1023, 1220, 1334, 1419)
Diazoxide	None (386, 560, 569, 574, 940, 1176) Activates in pancreatic β cells (364, 522)	Activates (429, 430)	Protective effect (578)
5-Hydroxydecanoate (5-HD)	Inhibits (920-922)	Inhibitor (579)	Counteracts protective effect during preconditioning (70, 546, 547, 848, 1417)
Bepridil	Inhibits (1127)	Opener (1127)	Not tested
MCC-134	Activates (1123, 1433)	Inhibits (1123)	Antagonizes preconditioning (670, 1123)
Quinine	Inhibits (1109)	Inhibits (139)	Not tested

Only exemplary references are provided. Reference numbers are given in parentheses.

can indeed be produced by protonophore-treated cells (e.g., Ref. 1125). ROS production upon treatment with mito K_{ATP} openers such as diazoxide (e.g., Refs. 365, 538, 708) and P-1075 (942) has also been reported, and it has been described to be inhibited by K_{ATP} blockers such as glibenclamide and 5-HD (e.g., Refs. 230, 815, 942, 996, 997, 1007). 5-HD has also been found to block ROS production induced by agents presumably acting only indirectly on mito K_{ATP}, such as 6-hydroxydopamine (1071), NMDA (409), acetylcholine (1418). These and other observations have led to a model in which ROS are considered to be the effectors of protection downstream of mito K_{ATP} (see below; e.g., Refs. 230, 302, 705, 950), although the matter is somewhat controversial (699, 815).

On the opposite front, at least one group has reported that in experiments with permeabilized cells diazoxide induced an increase in the rate of oxygen consumption which was not antagonized by 5-HD and did not depend on the concentration of K^+ in the perfusion medium (677). The same group reported on the other hand that the effects of levosimendan were potassium dependent (678, 679). Others have reported that diazoxide does not induce an increase in mitochondrial ROS production (356, 384) or that it antagonizes generation of superoxide (356, 382, 1268), or that it may have either a pro-oxidant or an anti-oxidant effect, depending on the metabolic state and the transmembrane potential of the mitochondria (357, 1062). Superoxide production by the respiratory chain can take place mainly at two sites, namely, complexes I and III (e.g., Refs. 699, 896) but complex II also contributes (for references see, e.g., Ref. 745). In the case of the former, superoxide formation depends on the redox state of a flavine mononucleotide, linked in turn to the poise of the NAD/NADH couple: an increased supply of reducing equivalents (e.g., because of reverse electron flow from site II, or increased $\Delta\mu_H$) is expected to increase superoxide formation, while uncoupling (depolarization) is expected to decrease ROS production at this (matrix-facing) site (e.g., Ref. 1175). Thus activation of mito K_{ATP} would be expected to reduce superoxide production by this source (e.g., Ref. 392). At coenzyme Q:cytochrome *c* oxidoreductase (the bc1 complex, i.e., complex III of the respiratory chain), superoxide formation is believed to be accounted for by single-electron reduction of oxygen by semiubiquinone in the "o" center. This is likely to be the process involved in ROS production by uncoupler-treated mitochondria, and it would be expected to be stimulated by opening of mito K_{ATP} and consequent depolarization. Several studies have reached the conclusion that activation of mitochondrial K^+ channels reduces or prevents the generation of ROS (for references, see Ref. 1268). Garlid's group also identified complex I as the source of superoxide (35).

"Mild uncoupling" with protonophores has in any case been proposed to result in ROS-mediated cardioprotection by itself (196, 293, 878). Uncoupling by the classical protonophore dinitrophenol (DNP) results in depletion of ATP and, in the presence of K_{ATP} activators which modify the nucleotide dependence of the channels, may cause activa-

tion of PM K_{ATP} (1124). The effect may however be due instead to a direct interaction of DNP with the channels (22).

Why would an increase of the IMM permeability to K^+ cause ROS generation? One answer is formulated in terms of variation of $\Delta\psi m$ (see above). Another invokes matrix alkalinization due to increased proton pumping to compensate K^+ entry (35, 281, 295). One reason this conclusion was reached was that H_2O_2 production (followed using fluorescent probes) correlated with matrix pH (also monitored with a probe), but not with loss of $\Delta\Psi m$ induced by CCCP, a classical protonophore and uncoupler. Other groups (including ourselves: Ref. 1125) have however reported that ROS production is indeed stimulated by protonophores (such as FCCP or DNP), which are not suspected to induce matrix alkalinization.

An important role in signal transduction to mitochondria in the context of preconditioning is assigned also to the mitochondrial (183, 185, 868) population of gap-junction protein connexin 43 (reviews in Refs. 1096, 1154, 1156, 1157). IPC did not result in cardioprotection in connexin (Cx) 43-deficient mice (538) or in knock-in mice in which Cx43 had been substituted by Cx32 (1072). Cardioprotection is associated with increased phosphorylation of Cx43 at S262 and S368 by PKC (PKCε; Refs. 345, 346, 1155, 1234). The GSK3β signal (phosphorylation/inhibition of GSK3β is protective, because it leads to upregulation of mito K_{ATP}) has also been proposed to involve Cx43 (1293). On the other hand, a recent study has placed Cx43 upstream, as a cofactor in signal transduction from the δ opioid receptor, and more precisely in the activation of I_B PI3K (573). Nicorandil may actually exert its mito K_{ATP}-opening effect at least partly via the NO-PKG pathway (719). ROS proceed to activate PKC (e.g., Ref. 684).

Finally, pharmacological evidence has also been mustered in support of the view that plasma membrane, not mitochondrial, ATP-sensitive channels are responsible for preconditioning. Suzuki and co-workers (1257, 1258) came to this conclusion in the case of diazoxide-induced preconditioning, considering HMR1098 to be a sarc K_{ATP} channel blocker, and 5-hydroxydecanoate a mito K_{ATP} channel blocker (see also Ref. 1249).

In summary, in our opinion the exact physiological role of mito K_{ATP} and the mechanism of its involvement in cardioprotection will be proven only following its definitive molecular identification.

III) Molecular identity based on biochemical/genetic evidence. All considered, the biophysical characteristics of at least part of the conductances observed in BLM and patch-clamp studies are in fair agreement with what may be expected of a Kir6.2-based channel. However, other hypotheses concerning the molecular identity of mito K_{ATP} have been put forward. In experiments employing purified proteins, Mironova and co-workers (869, 871) described a channel with a conductance in the order of 24 pS in 0.1 M KCl, formed by a protein with an apparent mass of ~55 kDa obtained via a detergent-free ethanol/water extraction procedure from beef heart mitochondria. In 1999 this protein was reported to produce activity compatible with the presence of clusters of interacting K^+-selective and redox-sensitive channels which were inhibited by millimolar ATP added on the opposite side of that of protein addition (871). A preparation based on Triton X-100 solubilization of rat liver and beef heart mitochondria and containing essentially a protein migrating in gels with an apparent molecular mass of 54 kDa, produced, upon incorporation into BLM, channels with a chord conductance of ~30 pS at 85 mV in 1 M KCl (976). When reconstituted into liposomes, this preparation allowed transmembrane K^+ fluxes to take place. This activity was inhibited by the combination of Mg^{2+} and ATP (neither of the two alone had a detectable effect). While the reported affinities for inhibiting nucleotides are in the range required for inhibition of K_{ATP} channels in the absence of Mg^{2+} (see above), the requirement for both ATP and a divalent cation seems to be at variance from that reported for classical PM K_{ATP} channels. K^+ transport in the liposome assay was, remarkably, inhibited by glibenclamide with K_i ~50–70 nM, even though only one band was seen in the preparation. In 2004 Mironova et al. (870) tentatively identified the ~55 kDa protein band (which in 2D gel electrophoresis split into at least five bands; apparently the same band obtained with the Triton-based procedure, see below) as corresponding to the mitoKir component of the putative mitoKir-SUR complex, despite the difference in the apparent molecular mass (Kirs have molecular mass of ~40 kDa). The current-voltage curve showed rectification (although divalent cations were not present). Single-channel chord conductance values in symmetrical 100 mM KCl ranged from 10 to 100 pS, a variability interpreted as evidence of cluster behavior. According to this report the K^+ transport activity conferred by the protein was insensitive to 5-HD, glibenclamide, cromakalim and diazoxide, but it was inhibited by TPP^+ with $K_{1/2}$ ~50 nM. ATP inhibited with a $K_{1/2}$ of 500–900 μM (depending on the type of assay and on $[Mg^{2+}]$). The gel electrophoretic analysis of the ethanol-extracted preparations used in the 1992 and 2004 papers shows only one band, but Triton solubilization-based preparations from rat brain and liver mitochondria were shown to contain also another protein with an apparent molecular mass of 63 kDa (99, 870). This was proposed to correspond to a SUR subunit, accounting for the properties of the reconstituted channel. In studies of K^+ flux upon reconstitution in liposomes the transport mediated by this preparation was inhibited by ATP, 5-HD, and glyburide, and stimulated by diazoxide and cromakalim in the concentration range expected for a Kir-SUR channel.

The 63-kDa protein, whose sequence was not determined, may correspond to a "short" SUR splicing isoform (see sect. III*A1*A*I*). The idea that alternative forms may be involved in the formation of mito K_{ATP} has experimental support. Kir6.2 and SUR2A or short forms of the latter have been identified in ventricular myocyte (1211; Kir6.1 as well) and brain (729) mitochondria by immunofluorescence, immunogold labeling, and Western blotting. In an informative study, Ye et al. (1421) identified 28-, 55- and 68-kDa splicing short forms of SUR2A (in addition to the long form) and a 55-kDa form of SUR2B in gradient-purified mitochondria from mouse heart. Mitochondria from mouse brain contained the same species except for the 68-kDa form. Coexpression of the 55-kDa form of SUR2B and Kir6.2 in an heterologous system produced an ATP-sensitive channel with an ~50% lower conductance than that of the Kir6.2-SUR2A cardiac-type K_{ATP} channel. This activity was glibenclamide-insensitive and could not be reinstated by diazoxide or pinacidil after inhibition by ATP, suggesting that at least this particular SUR short form may be pharmacologically inert. Interestingly, a 28-kDa protein binding glibenclamide with low affinity has been found in beef heart mitochondria (BHM) (1274, 1278). Short forms of SUR have been found in mitochondria also by other studies (729, 1032, 1211, 1279).

O'Rourke, Marbàn and collaborators have compared the pharmacological profiles of cardiac mito K_{ATP} and of molecularly defined PM K_{ATP} expressed in HEK cells, using patch-clamp to assess PM K_{ATP} activity and flavoprotein oxidation as an index of mito K_{ATP} (559, 777). The uncoupling effect of glibenclamide was taken into consideration. These investigators concluded (at the time): "Our results demonstrate that mito K_{ATP} channels closely resemble Kir6.1/SUR1s K_{ATP} channels in their pharmacological profiles." A different nature of the SUR unit might explain some of the peculiarities of mito K_{ATP} modulation by ATP (see above). A recent study reports detecting Kir6.1 and SUR1 in hepatic mitochondria (905). It is however difficult to be sure that the activities and/or immunoresponsive material described do not originate from contaminating PM proteins or mitochondria-associated membranes (MAMs). Ardehali et al. (57), for example, did not detect Kir6.1 in their preparations of rat liver mitochondria (RLM). Concerns about the specificity of antibodies also linger. This objection has been forcefully made by Marbàn's group, who found that two commercial antibodies thought to be specific for Kir6.1 recognized instead completely unrelated mitochondrial proteins (413). In addition to the studies already mentioned (597, 729, 1211), immunoanalytical approaches have been used by Kuniyasu et al. (715), who found no evidence of Kir or SUR subunits in the mitochondrial fraction obtained from rat hearts (despite the fact that all were apparently present in the microsomal fraction). The adenoviral vector-mediated expression of Kir6.1 or Kir6.2 or dominant-negative constructs derived from them in rabbit ventricular myocytes did not affect mito K_{ATP} activity as assayed by flavoprotein fluorescence; immunohistochemistry versus Kir6.1 did not provide evidence for a localization of this subunit in mitochondria (1169).

Kir6.2 has been targeted to the mitochondria of HEK293 and HL-1 cells (780). Its expression in the organelles conferred resistance to hypoxic stress, a cell culture-level counterpart of ischemia-reperfusion. Mice KO for either Kir6.1 (863) or Kir6.2 (862, 1172, 1258), as well as mice overexpressing Kir6.2 in part of the brain (543) have been generated and used in a number of studies (supporting, inter alia, the involvement of Kir6.2 in protection from I/R damage: Refs. 543, 1107, 1252, 1253), but surprisingly so far to our knowledge they have not been exploited to investigate the nature of mito K_{ATP}.

SUR1- (1189) and SUR2-deleted (264) mice are also available. Mito K_{ATP} studies have apparently not been performed with the SUR1 KO mouse. Despite resulting in various cardiovascular problems (9), SUR2 disruption turned out to protect the heart against I/R damage compared with WT controls (1240), and ischemic preconditioning did not provide further protection (1421). As mentioned above, in these animals short-form variants of SUR2 continue to be expressed and were localized in mitochondria (1032, 1421). The short (55 kDa) form can cooperate with Kir6.x subunits to produce a K_{ATP} channel with somewhat altered properties, e.g., insensitivity to glibenclamide (1032). Protection has been associated with a "bioenergetic phenotype" comprising increased IMM permeability to K^+, reduced $\Delta\Psi m$, increased resistance to Ca^{2+} overload, increased basal rate of ROS generation (9). $\Delta\Psi m$ and K^+ uptake (swelling) were not altered by diazoxide, suggesting that sensitivity to the opener may indeed be associated with the long form of SUR2. This is relevant because of the possibility that the effects of diazoxide may be unrelated to the presence of a K_{ATP} in mitochondria. Besides the possibility that they may "simply" derive from uncoupling (see above; Ref. 553), it has been suggested that they may have to do with inhibition of the succinate dehydrogenase complex (516, 867, 1135) (pinacidil, on the other hand, inhibits NADH oxidation; Ref. 516).

Recent studies in *C. elegans* have cast further doubts on the existence of Kir-SUR mito K_{ATP}. *C. elegans* exhibits "ischemic preconditioning," and swelling assays on purified mitochondria show a behavior compatible with the presence of mito K_{ATP} channels with a pharmacological profile analogous to that of mammalian mito K_{ATP} (1386). Deletion of any or all three Kir-encoding genes in *C. elegans* did not grossly affect the preconditioning protection phenotype. Furthermore, mutant mitochondria (including triple-KO) exhibited near-normal mito K_{ATP} channel activity, as assayed by the Tl^+ transport technique (1390). Tl^+ transport was activated by diazoxide and atpenin A5, and activation could be reversed by 5-HD and glyburide (1387). These results obviously suggest that Kir subunits may actually not be involved in forming mito K_{ATP}.

Finally, a complex comprising SDH, the ANT, mitochondrial ATPase and mitochondrial ATP-binding cassette protein 1 (mABC1) was found to exhibit mito K_{ATP}-like properties upon reconstitution into proteoliposomes and planar lipid bilayers (57, 58; see also Ref. 485). K^+ transport in proteoliposomes was enhanced by diazoxide, pinacidil, 3-nitropropionic acid (3-NPA), and malonate (see also Ref. 1385) (inhibitors of SDH) and antagonized by 5-HD, glibenclamide, and ATP. The channels observed displayed a predominant conductance of "< 100 pS in 100 mM K^+." Selectivity for K^+ was however low. The data presented do not allow a meaningful comparison with the properties of the mito K_{ATP} channels observed in other planar bilayer experiments. P_o was increased by diazoxide and 3-NPA. ATP, 5-HD, and glybenclamide decreased it, while atractyloside and HMR-1098 did not have a significant effect. Those who refute the identification of mito K_{ATP} with this complex point out that the concentrations required to activate mito K_{ATP} are much lower than those required to inhibit SDH and suggest that SDH may act as a regulator of mito K_{ATP} and as a mediator of mito K_{ATP} opening (428, 1384, 1388). The proposal has been made that mito K_{ATP} opener-induced ion fluxes may be mediated by the ANT (680). The existence of a supramolecular protein complex sensitive to mito K_{ATP}-targeting pharmacological agents is supported by results obtained with a mouse expressing a mutated mitofusin-2 (MFN2) gene (MFN2 is an OMM protein involved in mitochondrial fusion). In this animal complexes II and V are functionally impaired, but the defect can be rescued by 5-HD, while diazoxide-induced symptoms in controls resembled those associated with mutant MFN2 (485).

In constrast to all above hypotheses, impressive evidence has been presented that the ion-conducting portion of mito K_{ATP} may actually be formed by a mitochondrial population of the inward-rectifying K^+ channel ROMK2 (Kir1.1b), a short form of ROMK (412). ROMK is ATP-sensitive and shares other characteristics with K_{ATP} channels, including Mg^{2+} block and the ability to associate with ABC proteins like the CFTR and SUR2B (see Ref. 412 for references). Its single-channel conductance at negative voltages is ~32–43 pS (cell attached; 110 mM KCl in pipette) (e.g., Refs. 261, 1060). Conductance values reported for mito K_{ATP} tend to be either above or below this range, and as stated also by Foster and coworkers (412), more work is required to confirm the identification. ROMK-KO mice (790, 792) and rats (1451) have been obtained, although they are short-lived, and fairly selective inhibitors of the channel are being developed (174, 1287).

2. Big-conductance calcium-activated potassium channel

The large-conductance calcium- and voltage-activated K^+ channel BKCa (also named MaxiK, Slo1, KCa1.1, and KCNMA1) is ubiquitously expressed at the plasma membrane of excitable and nonexcitable cells including sensory and epithelial cells and smooth muscle. BKCa is important in smooth muscle contraction but also for cytoprotection during I/R, hypertension, and cancer cell metastasis (292, 371, 388, 1105, 1222). The predicted molecular mass for a single subunit is 125 kDa; however, the channel has different forms due to alternative splicing. The single-channel conductance of BKCa ranges from 100 to 300 pS in 150 mM KCl (735). Either Ca^{2+} binding to its cytoplasmic (or matrix, for mitochondrial channels) domain or membrane depolarization induces its opening (598, 908, 1432), thereby coupling membrane potential and intracellular calcium concentration (557, 735). Calcium decreases the energy required to open the channel, causing a leftward shift in the P_o/voltage relationship. Voltage dependence is conferred by the four TM segments (VSD: voltage sensor domain) preceding the pore-forming TM segments, as in the case of Kv channels. Activity is further regulated by beta subunits (β1-β4) having two transmembrane domains and a molecular mass around 26 kDa (1088). Importantly, leucine reach repeat-containing LRRC-subunits with a single transmembrane domain also regulate activity and have been shown to shift the voltage required for channel activation by −140 mV in case of the PM BKCa (1414). Both native and cloned BKCa channels are activated in electrophysiological experiments by calcium in the micromolar range and are stimulated by 12,14-dichlorodehydroabietic acid (diCl-DHAA) (1108); the benzimidazolones NS004, NS1619, and NS11021 (54, 149); and by the indole carboxylate compound CGS7181 (560). Only the last compound shows however high potency and selectivity towards BKCa, acting below 0.1 μM concentration when applied to inside-out patches (560). BKCa α-knockout mice are viable and are characterized by a phenotype of bladder hyperactivity, urinary incontinence, cerebellar ataxia and Purkinje cell malfunction, and a shortened lifespan (855, 1132).

A) MITOCHONDRIAL BKCA ACTIVITY AND PHARMACOLOGY. The presence and activity of BKCa has been revealed also in intracellular membranes, including nuclear membrane, ER, Golgi, and mitochondria (1212). MitoBKCa (929, 1276) has been observed by direct patch-clamping of mitoplasts of mammalian cells as well as in planar lipid bilayer experiments. The channel has been identified in mitochondria of two glioma cell lines, in astrocytes as well as in ventricular cells, skeletal muscle and brain and in endothelial cells, with conductance values ranging from 276 to 307 pS in 150 mM symmetrical potassium solution (see **TABLE 6**). MitoBKCa was shown to be activated by calcium, diCl-DHAA (1108), NS1619 (1214), 17β-estradiol (937), and hypoxia (252) and was found to be blocked by specific inhibitors charybdotoxin (483, 1215), iberiotoxin (252, 253), and paxillin (536, 537). **TABLE 6** reports the main properties of the mitoBKCa observed in different systems. In summary, modulators of PM BKCa act also on the mitochondrial form of this channel, but no drug acting exclusively on the mitochondrial channel is available.

Table 6. *Electrophysiological and pharmacological properties of mitoBK$_{Ca}$ channels*

Cell Type and Method	Conductance	Pharmacology	Reference Nos.
Human glioma cell line/patch clamp	276/295 pS in 150 mM K^+	Ca^{2+} as activator: EC_{50} 0.9 μM at +60 mV, 6.9 μM at −20 mV; charybdotoxin as inhibitor: EC_{50} 1.4 nM at −40 mV	483, 1205,
Guinea pig ventricular myocyte/patch clamp	307 pS in 150 mM K^+	Ca^{2+} as activator: activity observed at 512 nM Ca^{2+} applied; charybdotoxin as inhibitor: 200 nM charybdotoxin blocked activity after 30 min	1407
Rat ventricular myocyte/patch clamp	270/260 pS in 140 mM K^+	17 β-Estradiol (30 μM) increased P_o; activation by diCl-DHAA; paxillin as inhibitor	937, 1108
Rat astrocytes/patch clamp	295 pS in 150 mM K^+	Activity in the presence of 1 μM calcium; hypoxia increased channel activity; 100 nM iberiotoxin and 1 nM Bax decreased activity	252, 253
Endothelial cell/patch clamp	270 pS in 150/150 KCl	Activated by Ca^{2+} and NS1619, inhibited by paxillin and iberiotoxin	141
Skeletal muscle/BLM	300 pS in 50/450 mM (*cis*/*trans*) K^+	Activity in presence of 300 μM Ca^{2+}, 200 nM iberiotoxin blocked activity	1215
Rat brain/BLM	265 pS in 50/450 mM (*cis*/*trans*) K^+	Increased activity in presence of 300 μM calcium or with 30 μM NS1619 Activity inhibited by 1 μM charybdotoxin	1214
Rat brain/BLM	211 pS in 200/50 mM (*cis*/*trans*) K^+	Activity observed in absence of added calcium; complete block by 10 mM TEA^+ at +20 mV; and by 100 nM iberiotoxin; no sensitivity to charybdotoxin	385

Evidence for the presence of BKCa channel protein in mitochondria has also been provided by Western blotting, electron microscopy, and immunofluorescence microscopy (353, 633, 1020, 1215). Douglas and colleagues (353) provided biochemical evidence for the presence of a 125-kDa protein recognized by anti-BKCa antibody in mitochondria of several brain regions including Purkinje cells and cerebellum granule cell neurons. O'Rourke's group (1407) has reported the recognition of a 55 kDa protein in cardiac mitochondria and of an 80 kDa protein in liver mitochondria. The reason for the detection of proteins with lower than the predicted molecular was not clarified in this latter work. A 120-kDa band reacting with an anti-BKCa antibody was present in mitochondria from cardiomyocytes, while it was absent in liver organelles (1183). Finally, a protein with the expected molecular of 110 kDa was immunoprecipitated using an anti-BKCa antibody from mitochondrial preparations made from cochlea and brain (633). In summary, both electrophysiological and biochemical evidence locate a population of BKCa channels to mitochondria. It is not known whether the regulatory mechanisms mentioned in the case of PM-located BKCa operate also in mitochondria, where the channel is thought to be activated primarily by calcium, but the mitoBKCa channel β4 subunit protein (26 kDa) was found in mitochondria, e.g., in brain (1020). Src kinase as well as LRR proteins are also present in this organelle (565, 1113) and might a priori modulate the gating properties of the mitochondrial channel. Interestingly, a charybdotoxin-insensitive BKCa channel activity has recently been described in a whole brain preparation by using the basolateral membrane technique (385). The authors hypothesized that lack of charybdotoxin block might be due to regulation by β4 subunits. Alternatively, this behavior might be expected assuming, e.g., that the observed

activity was due to heterooligomers between KCa1.1 and other BKCa family α subunits (e.g., Slo2, see below), given that heterooligomerization might lead to channel activity with intermediate pharmacological properties (604).

B) MOLECULAR IDENTITY. Mito BKCa has been proposed to be the same species as PM-located BKCa, and indeed pharmacological evidence currently favors KCa1.1/Slo1 as the mitochondrial channel. The molecular mass of the bands detected on Western blots by anti-BKCa antibodies suggests that the mitochondrial form is the same as the PM-located form or possibly corresponds to alternatively spliced BKCa. Interestingly, a BKCa isoform called glioma BKCa (gBKCa) was found to be expressed in different types of human cancer cells, including glioma, breast, colon, pancreas, stomach, duodenum, lung, and liver cancer. gBKCa is characterized by a 63-amino acid-long insert, against which a specific antibody was recently generated which is not able to recognize the unmodified BKCa channel protein. Both anti-BKCa and anti-gBKCa revealed localization of the respective isoforms in the PM, mitochondria, Golgi, and ER, indicating that distribution of gBKCa and BKCa within the cells is identical (434). This finding suggests that BKCa and gBKCa undergo the same modifications leading to organellar targeting within the cell. A splice variant, BKCa-DEC harboring a specific amino acid sequence at the COOH terminus of the protein (VEDEC) (643), was identified as a mitochondrial candidate (633). In another study BKCa located to the plasmamembrane while a splice variant (different from BKCa-DEC) was clearly targeted to mitochondria (1317). Both studies however addressed the question of targeting using a heterologous system where possible mistargeting due to overexpression was not ruled out. A recent study highlighted that ~20% of the proteins that interact with BKCa, as identified by proteomics, are mitochondria related (633), including cytochrome *c*, ATP synthase, and chaperon HSP60. Whether these interactions regulate channel activity is still an open question. Recently the participation of the Slo1 (KCa1.1) channel in the formation of mitoBKCa has been questioned by using a genetic mouse model lacking the Slo1 gene: an identical mitoBKCa activity and pharmacological profile was found in both $Slo1^{-/-}$ and wild-type mice, suggesting that Slo1 does not give origin to mitoBKCa (1389). It is to mention that calcium did not activate mitoBKCa in wild-type mouse mitochondria in these experiments based on the use of Tl^+-sensitive fluorophore loaded into the mitochondrial matrix, raising the question of whether mitoBKCa activity was measured. The authors proposed that the widely expressed Slo2 genes are crucial for the formation of mitoBKCa. The large-conductance K^+ channel gene family indeed includes Slo2, encoded by two genes in mice [Kcnt1 (Slo2.2/Slack) and Kcnt2 (Slo2.1/Slick)]. In *C. elegans*, both Slo1 and a single gene coding for Slo2 exist; therefore, the authors used knockout worms to rule out a role for Slo1 and to propose instead that Slo2 contributes to the calcium-sensitive, charybdotoxin- and iberiotoxin-insensitive mitoBKCa in *C. elegans*. Given that Slo2, in contrast to Slo1, does not harbor the S0 segment (i.e., it has only 6 TM segments), application of a specific antibody against the S0 segment might a priori discriminate between Slo1 and Slo2 as mitoBKCa forming components in mammalian mitoBKCa.

C) PHYSIOLOGICAL FUNCTION. Information on the physiological role of mitoBKCa has been obtained prevalently by pharmacological means and only recently using a knockout mice model. MitoBKCa has been proposed to be activated under pathophysiological conditions that increase mitochondrial Ca^{2+} uptake. Opening of mitoBKCa protects against damage to the heart and other organs caused by ischemia and reperfusion (for reviews, see e.g., Refs. 928, 929, 930). Preconditioning hearts with small molecule BKCa openers or β-estradiol resulted in decreased cardiomyocyte death due to ischemic insult and in reduced myocardial infarction (148, 149, 189, 937, 1241, 1370, 1407). For example, activation of the mitoBKCa channel by NS1619 (1183) or by NS11021 has been shown to be effective in protecting the normoxic hearts against ischemia (53). Hypoxia-activated mitoBKCa channels also protect cardiomyocytes isolated from chronically hypoxic rats (252), which are resistant to injury induced by acute oxygen deprivation (189). The involvement of mitoBKCa was further indicated by the finding that cardioprotective effects could be antagonized by paxillin, a BKCa inhibitor acting also on mitoBKCa.

The protective effect of BKCa openers has been attributed to a partial depolarization of the IMM reducing the driving force for calcium influx and thus preventing excessive calcium accumulation in the matrix (631, 1108). Opening of the calcium-inducible MPTP can thus be prevented (253). In isolated mitochondria from heart and brain, as well as in isolated heart, activation of mitoBKCa with NS1619 and CGS7184 was shown to reduce ROS production (537, 712, 1231). MitoBKCa may also fine-tune mitochondrial volume: its activation by application of NS11021 leads to charybdotoxin-sensitive K^+ influx and swelling in the presence of permeable anions. Improved mitochondrial respiratory control might also explain the cardioprotective effect of mitoBKCa (53). Importantly, a functional coupling has been recently described between mitoBKCa and the respiratory chain complexes (142).

Small molecule mitoBKCa inhibitors used in the above studies to define the physiological role of mitoBKCa might however have also additional, mitoBKCa-unrelated effects. For example, NS1619 at high concentrations induces matrix K^+ and H^+ influx through leak, a nonspecific transport mechanism (20). Another study reported that NS1619 is an effective inducer of immediate neuronal preconditioning in cultured cortical neurons, but its neuroprotective effect is independent of the activation of BKCa channels (431).

BKCa channel opener CGS7184 affects intracellular calcium homeostasis by interacting with the sarcoplasmic reticulum RYR2 channels (1394). BMS-204352, another BKCa channel activator, inhibits L-type calcium channels in ventricular myocytes with a K_D of 6 μM (1223), while paxillin inhibits BKCa and various isoforms of SERCA, with IC_{50} values of 5–50 μM (178). Furthermore, NS11021, at concentrations that confer cardioprotective effects (149), induces a charybdotoxin-insensitive respiratory control decrease and a drop in membrane potential of nearly 30 mV even in the absence of K^+ (53). Thus accumulating evidence suggests that depending on the concentrations used drugs acting on BKCa might have off-target effects, suggesting caution when interpreting results obtained using these drugs. In fact, for example, a recent study showed that isoflurane-mediated cardioprotection was abolished by paxillin in both wild-type and $Slo1^{-/-}$ hearts lacking the KCa1.1 α subunit (1389), suggesting a BKCa-independent and thus nonspecific action of paxillin. The same study also challenged the notion of a role of KCa1.1 in protection against ischemia/reperfusion injury, proposing instead an involvement of Slo2 (see above).

With regard to a possible role of mitoBKCa in the regulation of apoptosis, patch-clamp experiments using recombinant Bax showed an inhibition of mitoBKCa, which might contribute to opening of the MPTP which takes place during cell death (253). Opening of BKCa in isolated brain mitochondria was shown to inhibit ROS production by respiratory chain complex I and was hypothesized to be beneficial for neuronal survival (712). Paxillin but not iberiotoxin accentuated TRAIL-induced apoptosis in glioma cells, but the effect of paxillin was not due to its action on BKCa channels (632).

3. Intermediate-conductance calcium-activated potassium channel (IKCa): electrophysiology and pharmacology

KCa3.1, also called IK1 or SK4 or Gardos channel, is an intermediate-conductance potassium channel expressed in various tissues (epithelial and endothelial tissues, immune system, sensory neurons and microglia but not in excitable tissues), is composed of six transmembrane domains (S1-S6), with the pore loop located between S5 and S6, as well as cytoplasmic NH_2 and COOH termini. It displays a non-ohmic conductance ranging between 10 and 80 pS in 150 mM potassium (105). Its activation by intracellular calcium has been reported to occur at EC_{50} values in the range of 95 to 350 nM (depending on experimental conditions) and depends on the constitutive binding of calmodulin to the calmodulin binding domain (CMBD) region at the COOH terminus of the channel. PM-located IKCa (KCa3.1) has been implicated in numerous physiological processes, including cell proliferation and differentiation by regulation of membrane potential and calcium signaling in erythrocytes, activated T and B lymphocytes, macrophages, microglia, vascular endothelium, epithelia, and fibroblasts. Despite the wide expression and important physiological functions of IKCa, the absence of this channel protein in transgenic knockout mice does not result in severe physiological changes, possibly because of developmental compensation (1399). Nevertheless, IKCa is currently being proposed as a target in autoimmune diseases (730), cardiovascular diseases (1400), treatment of hypertension (665), cancer therapeutics (e.g., Refs. 451, 864), and Alzheimer's disease (806). TRAM-34 (1-[(2-chlorophenyl) diphenylmethyl]-1H-pyrazole) (IC_{50} 20 nM), cyclohexadiene 4 (IC_{50} 1.5 nM) and clotrimazole are among the most potent and used inhibitors of IKCa, while DCEBIO (EC_{50} 1 μM) and NS309 (EC_{50} 30 nM) are known activators (1399).

Recently, this channel has been recorded from the inner mitochondrial membrane of human colon carcinoma cells (311), of HeLa cells (human cervix adenocarcinoma cells), and of mouse embryonic fibroblasts (1126). The channel protein was detected in purified mitochondrial fractions also by Western blot, revealing that the molecular weights of the IKs in the PM and IMM are the same (311, 1126). Mito IKCa was inhibited by clotrimazole and TRAM-34. The biophysical and pharmacological properties of the mito IKCa and of the PM IKCa channels of the same cells were indistinguishable, with mito IKCa showing conductance ranging from 10 to 90 pS in 150 mM KCl, activation by submicromolar Ca^{2+} and inhibition by TRAM-34 in the 10^{-8} M range (1126). The physiological role of mito IKCa has not been studied in detail so far, but a role similar to that of other mitochondrial potassium channels may be envisioned, i.e., a contribution to the regulation of membrane potential, volume, and ROS production. TRAM-34 induced a hyperpolarization of the mitochondrial membrane (as expected if a positive charge-carrying influx is inhibited), confirming that functional IKCa is expressed in the IMM. Given the proposed role for other mitochondrial K^+ channels in cell death (see below), the membrane-permeant TRAM-34 was used in an attempt to induce cell death, and the effect of recombinant Bax on channel activity was studied. In contrast to BKCa (KCa1.1) and Kv1.3, IKCa was not inhibited by Bax (1126). Interestingly, while TRAM-34 used alone at 2–80 μM concentration did not induce apoptosis (1036, 1126), in combination with the death receptor ligand TRAIL it synergistically increased the sensitivity to TRAIL of melanoma cells (1036). Whether this effect is to be ascribed to the PM or the mitochondrial population of IKCa (or both) is unclear. Given that both TRAM-34 and TRAIL are characterized by relatively good safety profiles, coadministration of the two drugs might be exploited for melanoma treatment. TRAM-34 and clotrimazole have also been shown to decrease the viability of epidermoid cancer cells when applied together with cisplatin, apparently via an action on the PM-located IKCa, involved in the apoptotic volume decrease (748).

4. Small-conductance calcium-activated potassium channel (SKCa)

A recent report presents biochemical, microscopic, functional, and electrophysiological evidence of their presence in the IMM of guinea pig heart cells (1242). When the authors incorporated a purified mitochondrial membrane fraction into planar lipid bilayers, they observed Ca^{2+}-modulated, apamin-inhibited activity. The conductance steps observed with symmetrical 200 mM KCl ranged from 180 pS at 1 μM Ca^{2+} ($P_o = 0.5$) up to 730 pS with 100 μM Ca^{2+} ($P_o = 1$). These values are unexpectedly high for SKCa, as the authors recognize. Dolga et al. (348) studied by patch clamp of HT-22 neuronal mitoplasts an activity ascribed to SKCa on the basis of its pharmacological properties. The study highlighted a role of the channel activity in protection against glutamate-induced oxytosis (348). These papers support the notion that a mitochondrial population of these channels may exist and might account for some of the electrophysiological observations ascribed to mito K_{ATP}.

5. Voltage-gated mitochondrial potassium channel Kv1.3

A) PM Kv1.3. Voltage-gated potassium channels (Kv) comprise a large family of channels that are expressed in both excitable and nonexcitable cells (reviews in Refs. 60, 492, 590, 803, 935, 1428). They control the resting plasma membrane potential and the frequency of action potentials in excitable cells, while in nonexcitable tissues, such as pancreatic islets, the immune system, and epithelial cells, they are involved in feedback regulation of the plasma membrane potential, and thus in processes ranging from secretion to cell proliferation. Downstream events are the result of a signaling cascade that most often involves modulation of voltage-dependent Ca^{2+} channels and variations of cellular Ca^{2+} levels. Each Kv gene encodes a protein subunit, four of which may form either homotetramers or heterotetramers within the same family (Kv1-Kv12) (492). Functional diversity of Kv activities is enhanced by factors including heterotetramerization and the association of accessory proteins, such as the β-subunits which can modulate gating properties and assist multimerization (1026, 1318). Alternative splicing and posttranslational modifications also contribute to variety of activity, and various mechanisms have been proposed to regulate protein expression itself.

Kv channels share with other potassium channels the general structure of the selectivity filter, in which coordination of a transiting K^+ by four carbonyl groups belonging to the four polypeptide chains stabilizes the ion, allowing it to shed solvation water and to overcome the membrane lipophilicity barrier (354, 597, 598, 782, 788, 803, 886, 1339, 1422, 1450). Voltage dependence is mediated by a voltage-sensing region bearing a net positive charge (597, 1289, 1314). A characteristic of Kv channels is the presence of a vestibule which helps to gather and concentrate cations for eventual transport through the pore, due to the presence of a set of acidic amino acids which impart an overall negative charge to the vestibule walls. These conserved residues can interact with a strategic basic (positive) amino acid present in the peptide toxins of some venoms, such as ChTx, MgTx, IbTx, ShK, which can therefore "plug" and block the channel (1051, 1429). Other toxins approach instead the channel via the membrane lipid bilayer and interact with the voltage sensor (e.g., Ref. 803).

Kv members are known to be located in the plasmamembrane, but Kv1.3 has been localized to mitochondria as well (see below). This channel, first discovered in lymphocytes (216), is expressed also at least in the CNS, macrophages, kidney, testis, adipose tissue, osteoclasts, liver, and skeletal muscle (492). PM Kv1.3 has been implicated in the regulation of cell proliferation (218), apoptosis (for review, see Refs. 1260, 1270) and volume (731, 732), and in neurotransmitter release by excitable cells (e.g., Ref. 1201). Furthermore, Kv1.3 seems to participate in the pathways regulating energy homeostasis and body weight by a still poorly clarified mechanism (1406). One intriguing possibility, still to be explored, is that the mitochondrial Kv1.3 rather than the PM-located channel may be involved in energy homeostasis.

The PM-located Kv1.3 channel displays an activation threshold between -50 mV and -60 mV, a single-channel conductance of 24 pS in T lymphocytes (955) and is activated by depolarization (962). The discovery of the physiological roles of K^+ channels first in T-cell activation and later in other cell types was made possible mainly by the use of specific scorpion (ChTx, MgTx) and sea anemone (Shk) toxins (see above). In addition, potent small molecule inhibitors of Kv1.3 have been identified, including Psora-4 (IC_{50} 3 nM) (1347), PAP-1 (IC_{50} 2 nM) (1148) and clofazimine (IC_{50} 300 nM) (1059). The clarification of its pathophysiological roles and the availability of potent inhibitors have made this channel a promising pharmacological target (157) for various diseases, including several autoimmune diseases (255, 1398), diabetes (262), and cancer (e.g., Refs. 56, 300, 389, 1244).

B) MITOCHONDRIAL LOCALIZATION OF Kv1.3. Interestingly and unexpectedly, functionally active Kv channels have been identified in the IMM. The first was Kv1.3, the main voltage-gated homotetrameric channel expressed in lymphocytes. Localization of Kv1.3 to the IMM in lymphocytes and subsequently in other cell types has been demonstrated by multiple techniques: patch clamp (see below), immunogold transmission electron microscopy in lymphocytes (1265), macrophages (1352) and postsynaptic medial nucleus of the trapezoid body (MNTB) neurons (433), immunofluorescence in gerbil hippocampus (140) and Western

blot in the above cells as well as in PC-3 prostate cancer, MCF-7 breast adenocarcinoma (487), SAOS-2 osteosarcoma, B16F10 melanoma cell lines (741) and in J774 macrophages (744). In all these cases the channel protein was revealed in genetically nonmanipulated cell lines or tissues, either healthy or cancerous. The mitochondrial localization was further proven by biochemistry using purified mitochondria and different markers to assess contamination by ER and/or PM. Given that Kv1.3 as well as mitochondrial markers become enriched in the purified organellar fraction while the intensity of ER/PM markers decreases (487), it can be concluded that the protein is indeed present in the IMM. Different antibodies raised against distinct regions of Kv1.3 were used in the above studies revealing a 65-kDa band, suggesting that the primary sequence of the mito Kv1.3 is highly homologous (if not the same) to that of the PM Kv1.3. However, the targeting mechanism is still unclear: mitochondria-specific targeting due to possible alternative splicing or, more likely, posttranslational modifications are possibilities for consideration. It is interesting to note that Kv1.5 also has a dual localization to PM and mitochondria at least in macrophages (744) and another Kv channel, Kv10.1, has recently been described as functional channel in the nuclear membrane beside being active in the PM (247).

c) BIOPHYSICAL AND PHARMACOLOGICAL PROPERTIES OF MITO Kv1.3. Functional expression of Kv1.3 in mitochondria even at the highly negative resting potential (approximately −180 mV) is indicated by hyperpolarization upon incubation of isolated organelles with specific Kv1.3 inhibitors, namely, margatoxin and ShK. Under physiological conditions, Kv channels are expected to allow an electrophoretic inward flux according to the electrochemical gradient for K^+ (e.g., Ref. 167). Entry of potassium is compensated by the respiratory chain-driven efflux of protons and by activity of the electroneutral K^+/H^+ antiporter, to avoid volume changes and depolarization. Patch clamping of the IMM of lymphocyte mitochondria (1265) and of gerbil hippocampal cells (140) confirmed that active Kv1.3 channels are present in the IMM of various cells. Stable transfection of CTLL-2 lymphocytes with the Kv1.3-coding gene gave rise to electrophysiological activity in both the PM and the IMM, with characteristics of the PM Kv1.3 channel (1265). This finding further suggests that the mitochondria-located channel is a product of the Kv1.3 gene. In fact, channel activity recorded in the range between −60 to +60 mV displayed some of the known characteristics of Kv1.3 in lymphocytes: a slope conductance of 25 pS in 150 mM KCl, potassium selectivity, a slight rectification, and inhibition by specific inhibitors margatoxin and Psora-4 (1264, 1265). The activity attributed to mito Kv1.3 in gerbil hippocampal mitochondria was sensitive to 10 nM MgTx but was not inhibited by agitoxin, a blocker of Kv1.x channels (140). The channel was voltage dependent in the −50/+50 mV voltage range and showed a conductance of 109 pS in 150 mM KCl medium. Heterotetramerization of Kv1.3 with other Kv1.x channels in hippocampal mitochondria and/or possible association with regulatory β subunit might account for the biophysical/pharmacological properties of this channel being different from those found for Kv1.3; however, further work is required to identify subunits contributing to the observed activity.

d) MITO KV1.3 AND APOPTOSIS. Mito Kv1.3 is expected to participate in regulation of mitochondrial membrane potential, volume, and ROS production, similarly to other K^+ channels found in the IMM. The role of mito Kv1.3 under physiological conditions has not been elucidated in detail; however, a crucial role for this channel in apoptosis became evident first in lymphocytes and later in other systems as well. The mechanistic features of apoptosis are broadly understood, and it is widely accepted that mitochondria have a central role since the release of cytochrome *c* (and other proteins) contributes in a fundamental way to the activation of caspases, which marks the point of no return. Expression of a mitochondria-targeted Kv1.3 construct was sufficient to sensitize apoptosis-resistant CTLL-2 T lymphocytes, which lack Kv channels, to several pro-apoptotic stimuli. Mito Kv1.3 has been identified as a target of Bax, a pro-apoptotic Bcl-2 family protein, and physical interaction between the two proteins in apoptotic cells has been demonstrated (1264, 1269). Incubating Kv1.3-positive isolated mitochondria with Bax triggered apoptotic events including membrane potential changes (hyperpolarization followed by depolarization due to the opening of MPTP), ROS production, and cytochrome *c* release, whereas Kv1.3-deficient mitochondria were resistant. Highly conserved Bax lysine 128 protrudes into the intermembrane space (38) and mimics the already-mentioned crucial lysine in Kv1.3-blocking peptide toxins. Mutation of Bax at K128 (BaxK128E) abrogated its effects on Kv1.3 and mitochondria, indicating a toxinlike action of Bax on Kv1.3 to trigger at least some of the mitochondrial changes typical of apoptosis. It should be noted that inhibition of the channel is not equivalent, either logically or experimentally, to its absence. Evidence for the physiological relevance of the interaction of mito Kv1.3 with Bax via lysine 128 has been obtained also in a cellular context, using Bax/Bak less double knockout mouse embryonic fibroblasts (1269). Mutant BaxK128E was unable to mediate cell death in DKO MEFs challenged with various apoptotic stimuli. These findings are not in contradiction with the view that Bax contributes to cytochrome *c* release, but indicate that a K^+ channel-dependent event is important for the release of cytochrome *c* and that expression of mito Kv1.3 sensitizes cells to apoptosis. As mentioned, TRAM-34, a blocker of mito IKCa has also been shown to induce an early mitochondrial hyperpolarization (1036). Blocking the IMM channel(s) would not per se be expected to result in permea-

bilization of the OMM to proteins. This might however be obtained with the intermediacy of ROS, which may prompt Bax migration to mitochondria (13, 298, 916, 1004) and/or the onset of the MPTP, which provides a mechanism alternative to Bax oligomerization for cytochrome *c* efflux (464, 948, 949, 1047). In accordance with our findings, platelets, where Kv1.3 is the exclusive Kv channel expressed, were resistant to apoptosis in Kv1.3 knockout mice (846).

Recently we reported that Psora-4, PAP-1, and clofazimine, three distinct membrane-permeant inhibitors of Kv1.3, induce death by directly targeting the mitochondrial channel in multiple human and mouse cancer cell lines, while membrane-impermeant, selective, and high-affinity Kv1.3 inhibitors ShK or margatoxin did not induce apoptosis, further proving the crucial role of mito Kv1.3 for this process (741). Importantly, the membrane-permeant drugs killed cells also in the absence of Bax and Bak, a result in agreement with the current mechanistic model for mitoKv1.3 action **(FIGURE 5)**. Genetic deficiency or siRNA-mediated downregulation of Kv1.3 abrogated the effects of the drugs, proving specificity of their action via Kv1.3. The importance of our findings was validated in vivo: intraperitoneal injection of clofazimine reduced tumor size by 90% in an orthotopic melanoma B16F10 mouse model, while no adverse effects were observed in several healthy tissues. Similar results were obtained for primary human cancer cells from patients with chronic lymphocytic leukemia (B-CLL) which express higher level of functional Kv1.3 than B cells from healthy subjects (743). Importantly, only pathological ex vivo cells of patients underwent apoptosis when treated with any one of the three drugs, while residual healthy T cells were resistant. Such selective action of these drugs on tumor cells might be ascribed to a higher expression of Kv1.3 in cancer lines/tissues with respect to healthy ones; however, other factors are also expected to contribute. In fact, we observed that a synergistic action of channel expression and of an altered redox state accounts for apoptotic sensitivity of the pathological cells (743). The fact that clofazimine is already used in the clinic for the treatment of, e.g., leprosis (1059) and shows an excellent safety profile highlights the chance of exploiting mito Kv1.3 targeting for therapy. A positive correlation between expression of Kv1.3 in different cancer cell lines and the sensitivity of these cells to clofazimine as death-inducing agent has been observed (742).

In summary, inhibition of mito Kv1.3 results in the generation of ROS and facilitation of cytochrome c release. It may therefore be expected that inhibition of other Kv family

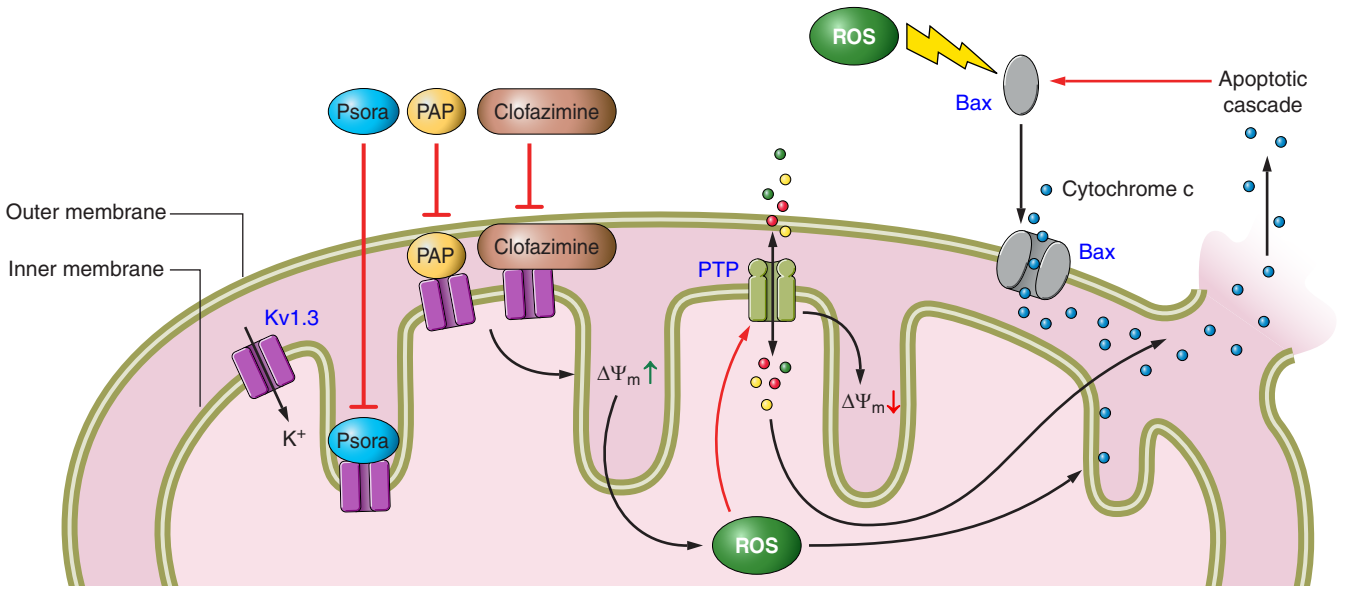

FIGURE 5. Mechanistic model for the action of mitochondrial Kv1.3. MitoKv1.3 is a component of the machinery controlling mitochondrial volume, ion homeostasis, and transmembrane potential. In cells challenged by a pro-apoptotic stimulus, Bax begins to migrate to the mitochondria, undergoing a conformational change and inserting into the outer mitochondrial membrane (OMM). There, it can interact via a protruding lysine residue with Kv1.3 and other Kv-family channels in the inner mitochondrial membrane, blocking K^+ flux (see text and Ref. 1264). This causes a transient hyperpolarization and hence enhanced production of reactive oxygen species (ROS) by the respiratory chain. These ROS can further stimulate Bax recruitment and/or induce the mitochondrial permeability transition (red arrow). The consequence is loss of cytochrome *c* (blue circle) via Bax oligomers or OMM rupture caused by swelling of the matrix compartment following MPTP induction. The latter event also results in the collapse of the potential and in the dispersion of small molecules (multicolored) such as NADH and tricarboxylic acid cycle intermediates into the cytoplasm. Pharmacological inhibition (red arrows) of mitoKv1.3 with membrane-permeant small molecules Psora-4, PAP-1, and clofazimine is sufficient to induce the same phenomena and thus cell death in cancerous cells, which are already subjected to a higher-than-normal redox stress.

channels present in the IMM of other cell types would promote apoptosis in a similar manner. It is to note that indeed the action of Bax is not restricted to Kv1.3: Kv1.1, mito Kv1.5, and mito KCa1.1 can also interact with Bax (253, 744). Indeed, in macrophages, which express both Kv1.3 and Kv1.5 in their mitochondria, downregulation of both channels is required to prevent staurosporine-induced apoptosis (741). Thus mitochondrial voltage-gated K^+ channels beside those of the plasmamembrane are emerging as therapeutic targets for oncological diseases (740).

6. TASK-3 two-pore potassium channel: role in apoptosis

Recently TASK-3 (TWIK-related Acid-Sensitive K^+ channel-3; KCNK9), a two-pore potassium channel known to reside in the plasma membrane, was identified in mitochondria of melanoma and keratinocyte cells by immunochemical and molecular biology methods (1099). A strong intracellular TASK-3 positivity was found also in healthy intestinal epithelial cells (693). PM TASK-3 is characterized by a small, 18-pS conductance in 140 mM symmetrical potassium at hyperpolarizing voltages, by an inward rectification at single-channel level, by high open-channel noise, and by burst-like behavior with the open probability increasing at depolarizing potential (68). In another study, in the presence of 2 mM Mg^{2+} on the extracellular side, the single-channel unitary conductances were 27 and 17 pS at −60 and +60 mV, respectively (648). The channel is maximally active at pH 7.4 and is inhibited with a p*K* value of 6.7 (375). Zinc at 100 μM concentration selectively blocks TASK-3 over TASK-1 in physiological conditions but is less effective at acidic pH and high extracellular potassium (265). Furthermore, TASK-3 is sensitive to other divalent cations (902) and to ruthenium red with an IC_{50} of 0.7 μM (294). PM-located TASK-3 has an important role in the regulation of apoptosis and in tumorigenesis (973, 990). A TASK-3 knockdown melanoma cell line displayed altered size, DNA content, and morphology. Furthermore, reduced expression of TASK-3 resulted in compromised mitochondrial function, suggesting that this two-pore potassium channel is functionally present in the mitochondria of the WM35 melanoma cells, and its function is essential for the survival of these cells (692). Interestingly, external ROS-induced mitochondrial ROS production was significantly lower in the knock-down cells with respect to control ones. Whether this alteration of ROS production is linked to resistance to apoptosis of cancer cells, as well as the contribution of the putative mitochondrial TASK-3 versus the PM-located channel in determinaing resistance to apoptosis still remains to be understood.

The mitochondrial localization of functional TASK-3 has been recently demonstrated by the group of Adam Szewczyk, using immunofluorescence and patch clamp on mitoplasts obtained from a human keratinocyte HaCaT cell line (1306). The channel conductance was 83 pS at positive voltages and 12 pS at negative voltages in symmetric 150 mM KCl and activity was voltage-dependent with the probability of channel opening (P_o) increasing at positive potentials. Lidocaine (1 mM) and acidic pH (6.2), known to modulate PM TASK-3, completely blocked channel activity. These characteristics of mitoTASK-3 are compatible with those of PM TASK-3.

7. pH-sensitive potassium channel

Recent single-channel studies (626) on the IMM of mitochondria from embryonic rat hippocampus revealed the presence of a previously undescribed outwardly rectifying, voltage-dependent potassium channel displaying a conductance of 68 pS at positive voltages and of 10 pS at negative voltages in symmetric 150 mM KCl. The channel was insensitive to activators and inhibitors of other known mitochondrial potassium channels, including paxillin and those affecting two-pore channels and inward rectifying channels (lidocaine and tertiapin, respectively), but was regulated by pH: a decrease of the bath solution pH from 7.2 to 6.2 resulted in complete block of the channel. The lack of sensitivity to known potassium channel blockers did not allow to hypothesize a molecular candidate. The physiological function and tissue distribution of this channel are also unclear at the moment.

B. Calcium Channels

1. Mitochondrial calcium uniporter: molecular identity, electrophysiology, and physiology

Matrix-negative voltage-driven Ca^{2+} uptake across the IMM is carried by the mitochondrial Ca^{2+} uniporter (MCU). Furthermore, a non-MCU Ca^{2+} channel and a mitochondrial ryanodine receptors (mito RyR) have been also proposed to contribute to this process (for recent reviews, see Refs. 1021, 1066). As to calcium efflux, Na^+-dependent (mito NCX) and Na^+-independent Ca^{2+} efflux systems have been identified along with the mitochondrial permeability transition pore, which allows exit of various ions and metabolites (see sect. III*F*) (e.g., Refs. 290, 355). The long-studied calcium uniporter characterized in bioenergetic studies (1021, 1038) was shown to correspond to a highly calcium-selective ion channel by the seminal work of Kirichok et al. (658). Mitoplasts from COS-7 cells, obtained by osmotic swelling, were patch-clamped in the whole-mitoplast configuration, revealing an inwardly rectifying current (I_{MiCa}) with an amplitude depending on Ca^{2+} concentration and a density of 55 ± 19 pA/pF at −160 mV with 100 μM $[Ca^{2+}]_c$. The current exhibited a high half-saturation at 20 mM Ca^{2+} and lacked typical Ca^{2+}-dependent inactivation. The authors determined also the single-channel conductance, ~6.5 pS in 105 mM Ca^{2+}, leading to an estimate of 10–40 MCU/μm^2. Interestingly, the open probability declined rapidly with depolarization, suggesting a feedback

control on calcium uptake into mitochondria. Proof in favor of the identification of I_{MiCa} being transported by the MCU was obtained by its inhibition with 200 nM ruthenium red or even lower concentrations of ruthenium 360, two classical blockers of the MCU. Furthermore, I_{MiCa} displayed a selectivity for divalent cations similar to that of the uniporter and was sensitive to cytoplasmic Mg^{2+} (658). In a recent study the whole-mitoplast MiCa current was found to be different in mitochondria isolated from different types of tissues, but the mechanism underlying these differences was not investigated (397). A priori, posttranslational modifications and/or association with regulatory subunits might account for differences in activity (changes in protein expression level, which was not determined, cannot be excluded either).

In another study, three distinct activities with different conductances (11, 23, and 80 pS in 105 mM Ca^{2+}) and different sensitivity to ruthenium red have been recorded in mitoplasts from endothelial and HeLa cells (587, 188). Recording of the mitochondrial megachannel, expected to be activated at the high calcium concentrations used (see below), was avoided in these studies either by the use of MMC inhibitor cyclosporin A (Bodnarenko; Ref. 188), or, apparently, by preparation of mitoplasts with the French press instead of hypoosmotic shock (397). Co-existence of multiple pathways for mitochondrial calcium uptake and/or the presence of tissue-specific channel activities is suggested by these results (see also Ref. 556). The characterization of MCU as a calcium-selective channel as well as the elaboration of MitoCarta, a compendium of mitochondrial proteins (953), allowed the long-sought molecular identification of the mitochondrial Ca^{2+} "uniporter" (120, 319). In this case the protein seems to be a specifically mitochondrial one with no predicted localization elsewhere within the cell. Silencing of the gene encoding for a coiled-coiled protein Ccdc109a resulted in a reduced calcium uptake, while its overexpression enhanced calcium entry into the matrix. Importantly, recombinant proteins obtained either by expression and purification from *E. coli* or by an in vitro transcription/translation system gave rise in both cases to the activity of a small, 6–7 pS (in 105 mM calcium) calcium-permeable channel when studied in BLM experiments (allowing a lower signal to noise resolution with respect to path clamp) (319), with characteristics compatible with those described for MCU activity studied in mitoplasts by direct patch clamping (658). Application of the in vitro expression system allowed us to avoid even trace contamination by other membrane proteins, which might have eventually led to MCU-independent channel activity. Further proof in favor of the identification of Ccdc109a as MCU was obtained by inhibition of the current with ruthenium red and gadolinium and by loss of channel activity and reduced calcium uptake upon mutation of two negative charges (D260 and E263) in the putative, highly conserved pore loop region (120, 319). Mutation of S259 to alanine resulted in loss of sensitivity to ruthenium red in calcium uptake assays (120). Nonetheless, it must be mentioned that the behavior of the channel observed with the recombinant proteins was somewhat different from that observed for I_{MiCa} in the paper by Kirichok and co-workers. Recent optimization of the MCU expression in our group yielded MCU activity with similar kinetics to that of I_{MiCa} (**FIGURE 6** and Ref. 1039). The finding that Ccdc109a is responsible for the pore formation and for the production of I_{MiCa} has been later on confirmed by the Clapham group, using RNAi-mediated knockdown of Ccdc109a (240). They observed that under these conditions, the mitochondrial Ca^{2+} current was almost completely abolished and concluded that the functional uniporter pore at the mitochondrial inner membrane is formed by Ccdc109a multimers. Oligomerization of MCU was proven experimentally using immunoprecipitation and Förster resonance energy transfer (FRET) (1039). Furthermore, native gel electrophoresis of recombinant MCU suggested tetramerization (1039). Nonetheless, beside Ccdc109a, several proteins have been proposed to be required for channel activity. MCU-dependent calcium uptake has been recently shown to be regulated in intact cell by another two-transmembrane-segment protein, Ccdc90a (816) **(FIGURE 6)**. This protein acted as a positive modulator of calcium uptake, prompting the authors to suggest that it is required for channel activity, although a direct effect on the channel activity has not been proven. Instead, in the case of the recently identified one-transmembrane segment EMRE protein, whole-mitoplast patch-clamp experiments were performed showing that mitoplasts obtained from cells lacking EMRE had significantly reduced I_{MiCa}, whereas the current was recovered upon EMRE reexpression (1119). This finding adds further complexity to the current view, especially considering that EMRE is not expressed in all types of organisms where uniporter activity has been observed by the experimental approaches of classical bioenergetics. Thus EMRE might represent an accessory subunit [e.g., similar to the one-transmembrane KCNE1 (minK)] or might form the channel pore together with Ccdc109a depending on the type of organism and/or tissue. Indeed, MCU is also able to heterooligomerize: a protein (MCUb) with two predicted transmembrane domains, displaying high sequence similarity to MCU (50%) but with an altered pore region has been shown to oligomerize with MCU and act as a dominant-negative subunit (1039).

Further regulators of MCU have been identified during the last few years. The EF-hand protein MICU1 located in the intermembrane space was first proposed to act as positive regulator (1006) and later as a gate-keeping negative regulator, essential to avoid calcium overload (817). Finally, MICU1 was identified as a sensor of cytosolic calcium concentration, able to regulate uptake through MCU depending on $[Ca^{2+}]_c$. Indeed, loss of MICU1 caused mitochondrial Ca^{2+} accumulation during small $[Ca^{2+}]_c$ elevations

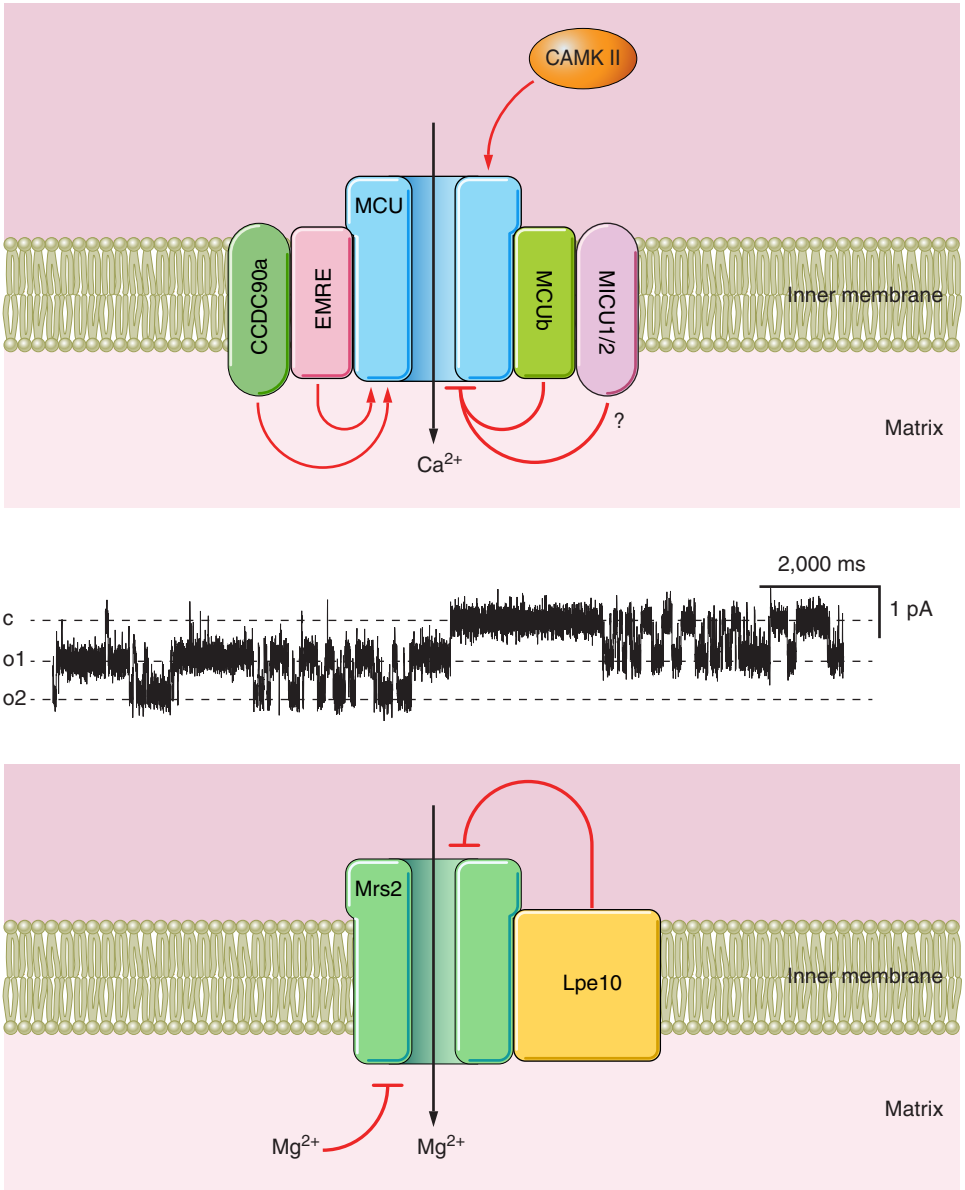

FIGURE 6. Regulation of the mitochondrial calcium uniporter mitochondrial Ca^{2+} uniporter (MCU) and of the magnesium transporter Mrs2. CCDC90a, EMRE, and CaMKII have been reported to activate, while MCUb to inhibit MCU activity. Inhibitory effects of MICU1/MICU2 are still debated. In the middle panel, activity of in vitro expressed MCU recorded at −100 mV in 100 mM calcium gluconate is shown. See text for further details.

but attenuated the response to $[Ca^{2+}]_c$ transients induced by IP_3 receptor activation (289). A further regulator with a still undefined role is a paralog of MICU1, MICU2 (1022). The interpretation of these findings in terms of regulation of MCU activity in intact cells is complicated by the fact that overexpression of MCU leads to elevated levels of MICU1 and MICU2 as well, while silencing of MICU1 and MICU2, either alone or in combination, alters MCU protein levels (1022). In addition, whole-mitoplast current carried by MCU has been shown to be increased by a constitutively activated calmodulin-dependent kinase II (CaMKII) mutant, identifying CaMKII activity as a central mechanism for the regulation of mitochondrial Ca^{2+} entry during myocardial cell death (603) **(FIGURE. 6)**. In summary, the mitochondrial uniporter that is responsible for the calcium uptake into the matrix is a multiprotein complex including the pore-forming protein and several regulatory subunits.

Much attention is being dedicated to MCU, because it participates in the control of Ca^{2+} signaling, and may thus be a very useful tool to influence the myriad cellular calcium-dependent processes, ranging from proliferation to exocytosis to cell death (1066). Subthreshold apoptotic signals were shown to synergize with cytosolic Ca^{2+} waves (1017), evoked by a physiological stimulation, in opening the permeability transition pore which ultimately leads to release of proapoptotic factors and cell death. Prolonged MPTP opening leads to complete collapse of the membrane potential and thus to passive release of calcium through MPTP itself. In accordance, the genetic ablation of the MPTP regulator cyclophilin D impaired Ca^{2+} overload and necrotic cell death upon oxidative stress (92). Cells overexpressing MCU underwent more pronounced apoptosis upon challenging with H_2O_2 and C2-ceramide (319). On the other hand, observations in a MCU knockout mice which became

available very recently (960) cast doubts on the crucial role of MCU for the regulation of basal metabolism, since the mice exhibit no dramatic phenotype. This surprising result is possibly due to compensating mechanisms. Furthermore, the absence of MCU expression did not confer protection from cell death upon ischemic insult, although MCU knockout mitochondria did not show Ca^{2+}-induced MPTP opening, suggesting that other death-mediating events come into play in the knockout animals. While the animal model is therefore not fully conclusive regarding the physiopathological importance of MCU for calcium signaling, mutations of MICU1 observed in humans were associated with proximal myopathy, learning difficulties, and a progressive extrapyramidal movement disorder (783). The phenotype was proven to be caused by a primary defect in mitochondrial Ca^{2+} signaling, demonstrating the crucial role of mitochondrial Ca^{2+} uptake in humans. Finally, an MCU-targeting microRNA, miR-25, whose overexpression in colon cancer cells resulted in MCU downregulation, impaired calcium uptake, and increased resistance to apoptosis (825). Thus MCU might play a role in tumorigenesis.

2. Ryanodine receptor

Western blot analysis, immunogold electron microscopy, as well as high-affinity binding of [^{3}H]ryanodine indicate that a low level of ryanodine receptors (mRyR) is localized within the inner membrane of heart mitochondria (172). Ryanodine receptors (RyRs) are the major ion channels responsible for Ca^{2+} release from the sarcoplasmic reticulum in muscle cells. Binding of specific antibodies against type 1 RyR to mRyR and the absence of mRyR in hearts from RyR1 knockout mice are consistent with the identification of mRyR as RyR1, and not the cardiac sarcoplasmic reticulum type 2 RyR isoform (RyR2) (173). On the other hand, IMM localization of RyRs by immunogold labeling was not confirmed by another group (1112).

Ryanodine receptor purified from the SR membrane of skeletal and cardiac muscle is characterized by a large single-channel conductance ranging from 400 to 750 pS in 250 mM K^+ or Cs^+ (399). Similar activity was observed in single-channel recordings using IMM vesicles enriched in mRyR in bilayer experiments (28). Addition of 50 μM Ca^{2+} increased the channel's open probability, while both ryanodine (at 10 μM) and imperatoxin A induced the appearance of long-lasting subconductance states of both mRyR and SR RyR isoforms RyR1 and RyR2. mRyR, similarly to MCU, is inhibited by low concentrations of ruthenium red (1–5 μM) and by Mg^{2+} (172). On the other hand, cyclosporin A and bongkrekic acid did not exert an effect on mRyR current, indicating that mRyR activity is not related to either the MPTP or adenine nucleotide translocator (ANT). A recent study described a 225 pS (in 150 mM CsCl) cation-selective channel by directly patch-clamping mitoplasts of heart, which displayed multiple subconductance states and was completely inhibited by addition of 100 μM ryanodine. Interestingly, this channel was observed only in 1% of successful experiments, indicating a very low density of this protein (1102).

From a physiological point of view, it has been proposed that mRyR might represent an efficient mechanism for fast and transient uptake of calcium during excitation-contraction coupling into mitochondria to stimulate ATP production needed for metabolic demands (177). It is of note in this respect that mitochondria in RyR1-overexpressing cells undergo fragmentation and have a higher ATP concentration under basal conditions compared with mitochondria from nontransfected cardiac H9c2 myoblasts (931). On the other hand, the group of Sheu (1101) hypothesized that upon calcium overload in the matrix, mRyR might be responsible for calcium efflux, preventing thus activation of the MPTP (see below).

C. Magnesium-Permeable Channel Mrs2

Mg^{2+} is the most abundant divalent cation in both prokaryotic and mammalian cells (808). The majority of Mg^{2+} is not free in the cytosol, but is bound to enzymes, ATP, and other nucleotides, where it acts as cofactor. Furthermore, Mg^{2+} serves as an essential structural element for ribosomes. In mammalian cells cytosolic $[Mg^{2+}]_c$ is usually maintained in the range of 0.5–0.7 mM, thanks to several Mg^{2+} transport systems across the cell membrane (including SLC41A1, SLC41A2, TRPM6, and TRPM7) (883). Furthermore, intracellular buffering and compartmentalization into organelles also contribute to maintenance of an optimal Mg^{2+} concentration, and mitochondria have been shown to act not only as pools of calcium, but also as storage site for magnesium (e.g., Ref. 710). Mitochondria accumulate Mg^{2+}, using their inner membrane potential, via Mrs2, which is a Mg^{2+}-selective channel expressed in the mitochondrial inner membrane (671).

Mrs2, a member of the ubiquitously expressed CorA-Mrs2-Alr1 superfamily of Mg^{2+} transporters (1035), was the first metal ion channel protein to be identified in the inner mitochondrial membrane from the molecular point of view. CorA, the first prokaryotic Mg^{2+} transport system to be identified, is an ion channel, capable of transporting Mg^{2+}, Co^{2+}, and Ni^{2+}. It was discovered by a Co^{2+} resistance screen in *Escherichia coli* and *Salmonella enterica* (883). The crystal structure of a bacterial CorA protein has been solved (379, 793), suggesting that a negatively charged loop between the two transmembrane segments of the protein accounts for selectivity and provides a gating mechanism (981, 1015). The eukaryotic homologs of CorA are ALr1, whose overexpression in yeast leads to aluminium resistance (800), and Mrs2, the Mg^{2+} channel of the inner mitochondrial membrane, in humans encoded by a gene located on chromosome 6 (6p22.1-p22.3). Interestingly, Mrs2 regulates RNA splicing (of group II introns) (466,

1381), most probably indirectly, given that the ribozyme involved needs an optimal Mg^{2+} concentration for function. The role of Mrs2 as a Mg^{2+} transporter was hypothesized following discovery of its homology to CorA (215) and was proven by the partial complementation of Mrs2-deficient yeasts, which are defective in mitochondrial function but are viable if supplied with fermentable substrates, by a CorA homolog as well as by human Mrs2 (1467). The existence of a Mg^{2+} specific mitochondrial transporter was a topic of discussion but Schweyer and colleagues proved that Mrs2 is indeed deputed to Mg^{2+} transport in the IMM by using mitochondria isolated from wild-type and Mrs2-deficient yeasts, and measuring high capacity, rapid Mg^{2+} influx into the matrix with the fluorescent indicator dye Mag-fura (671). Mitochondrial magnesium uptake, induced by an increase of external Mg^{2+} levels, was abolished in Mrs2-deficient yeast, while it increased upon Mrs2p overexpression (671). The driving force for Mg^{2+} influx into the matrix is the mitochondrial membrane potential (671). Mg^{2+} efflux from isolated mitochondria with low membrane potential also depended on Mrs2. Mg^{2+} uptake was inhibited by 1 mM Cobalt(III)hexaammine [Co(III)Hex], an analog of the hydrated Mg^{2+} cation, previously shown to inhibit CorA-mediated Mg^{2+} influx into bacteria (711). Very recently, a novel Mg^{2+}-selective fluorescent probe based on the rhodamine skeleton (KMG-301) was developed (1188). KMG-301 was shown to respond to Mg^{2+} concentration changes in mitochondria in intact cells and may be useful when studying pathologies linked to altered magnesium concentration, like those related to hypomagnesemia (1149).

1. Channel activity of Mrs2

In addition to biochemical evidence using HA-tagged Mrs2 (671), electrophysiological single-channel patch-clamp analysis, performed on inner membrane vesicles from Mrs2p-overexpressing yeast mitochondria fused with giant liposomes, also provided information on the mitochondrial localization of this protein as well as on its function as a Mg^{2+}-permeable channel (1142). Mrs2 was shown to form a Mg^{2+}-selective, cobalt-sensitive (1 mM inhibited activity) channel of high conductance (155 pS when working with 105 mM $MgCl_2$ in the pipette and 150 Na gluconate in the bath) in right-side-out proteoliposomes. A channel of unknown molecular identity with lower conductance (65 pS) was also observed under these conditions, also in preparations from Mrs2-deficient cells. Similarly to the mammalian TRPM7, Ca^{2+}, Mn^{2+}, or Co^{2+} were not permeating through Mrs2, while a conductance of 45 pS was observed with Ni^{2+} in the solution (1142). The presence of Mg^{2+} on the matrix side significantly decreased the open probability of the channel, suggesting that influx of Mg^{2+} into the matrix via Mrs2 is controlled by an intrinsic negative feedback (639). Further proof in favor of Mrs2 as a magnesium transporting channel was obtained via mutation of negatively charged residues that might be relevant for the attraction of Mg^{2+} to the pore: E341K, E342K substitutions in the loop region of Mrs2p abolished conductance, Mg^{2+} influx as analyzed by mag-fura2 and complementation of growth defect of the Mrs2-deficient yeast strain (1375). Mutations in coiled-coil domains of Mrs2p also altered single-channel conductance. α-Helices in the coiled-coiled region of CorA have been proposed to undergo conformational changes during transition between open and closed states of the CorA pore (793). Modification of the corresponding helices in Mrs2 significantly change the characteristics of the channel, suggesting that this region of the protein contributes to gating. Recently, a modulating factor of the Mrs complex has been identified: a corA-related protein present in yeast, Lpe10, upon coexpression with Mrs2 decreased the channel conductance of this latter protein from 155 to 103 pS. Weghuber and colleagues (1230) also showed occurrence of heterooligomerization between Mrs2 and Lpe10 and speculated that Mg^{2+} influx at negative mitochondrial potentials might be limited by this reduced conductance. **FIGURE 6** highlights some similarities between MCU and Mrs2.

2. Pathophysiological roles

Magnesium transport across the IMM has been assessed by bioenergetics studies (for reviews, see Refs. 344, 622). However, the requirement for the presence of a high-conductance Mg^{2+} channel in mitochondria is not self-explanatory, given that the steady-state Mg^{2+} concentrations in mitochondria (in the range between 0.2 and 0.8 mM) (620) and cytoplasm (1.5 mM) (1100) are in the same range. However, physiological conditions might exist under which a high-conductance channel can come into play. For example, mitochondrial matrix ATP concentrations may vary considerably depending on the physiological state of cells. A burst in ATP synthesis is expected to result in binding of a considerable part of free Mg^{2+}, given that the binding constant of Mg^{2+} to ATP is much higher than to ADP: such an event may a priori trigger a rapid influx of Mg^{2+}. $[Mg^{2+}]$ of mammalian mitochondria has been shown to increase by ~30% upon stimulation of respiration by addition of ADP (620). Vice versa, ATP synthesis in mitochondria was proposed to be regulated by the Mg^{2+} concentration in mitochondria (961). As mentioned above, Mrs2 is involved also in Mg^{2+} release from mitochondria. A cAMP-dependent pathway for fast release of mitochondrial Mg^{2+} under hormonal control has been found (1075, 1076), although this finding was challenged by another group (29). It is currently accepted that remarkable alterations in intracellular $[Mg^{2+}]$ are observed in several diseases like hypertension (1224) and type II diabetes (241), and a contribution by mitochondrial Mg^{2+} buffering is likely. In addition, recent data indicate that in dopaminergic cells challenged with 1-methyl-4-phenylpyridinium ion (MPP^+), a model for Parkinson's disease, magnesium was released from mitochondria, and altered magnesium homeostasis was proposed to be related in a still not fully clarified way to Parkinson's

condition (1188). Interestingly, during both extrinsic and intrinsic apoptosis an early increase in cytosolic Mg^{2+} occurs (260, 975), and this ion seems to be required for cytochrome *c* release (647), a crucial event during cell death. Furthermore, long-lasting knockdown of Mrs2 by shRNA in HEK 293 cells caused cell death by inducing loss of respiratory complex I and mitochondrial membrane depolarization (1018), in accordance with previous observation showing that mutation in Mrs2 is linked to OXPHOS deficiency (267). Importantly, genetic evidence points to a crucial role of Mrs2 in demyelinating syndrome in a rat model: a mutation leading to progressive disruption of myelin was shown to result in complete functional inactivation of Mrs2 (721, 727). Finally, a subtractive hybridization method applied on vincristine- or adriamycin-resistant and parental human gastric adenocarcinoma cell lines highlighted upregulation of Mrs2 (248), raising the possibility that high expression of Mrs2 protects against death (1392).

D. Nonselective Cation Channels: Electrophysiology of Protein Import Channels

Two protein import/incorporation systems have been characterized in the IMM. The Tim23-based one is dedicated to the import of proteins endowed with a "traditional," NH_2-terminal positively charged mitochondria-targeting sequence of amino acids. It handles proteins destined to the matrix and can also open laterally to allow insertion into the IMM. Tim22 and cofactors specialize in proteins which do not have a cleavable terminal sequence and rely instead on internal, less easily defined addressing signals, such as the IMM carriers (1213), and catalyze their insertion into the membrane (e.g., Refs. 133, 881). Both proteins are believed to occur, within their respective complexes, as dimers (like TOM40), in the inactive state in the absence of preproteins. The arrival of a presequence induces activation of the pores and membrane potential-requiring engagement by the presequence (119).

1. TIM23

Beginning in the early 1990s, K. W. Kinnally's group published a series of papers (40, 224, 650, 655, 656, 1465, 1466) describing a "multiple conductance channel" (MCC). The major features of this entity included a peak conductance of up to ~1.5 nS (150 mM KCl) with prominent 0.5 nS gating and numerous other substates, suggesting a close relationship, or identity, with the "mitochondrial megachannel" (MMC) characterized in the same period by our group and identified as the electrophysiological counterpart of the permeability transition pore (see below). The substate structure suggested for both channels a binary structure, confirmed by polymer exclusion experiments on the yeast MCC (833). Other relevant characteristics of the MCC were a slight cationic selectivity and a voltage dependence favoring opening at negative potential. MCC detection was reported to be favored by Ca^{2+} (655), and sensitivity to CSA was noted (1466). Furthermore, the MCC was inhibited by low concentrations of Ro5–4864 (4′-chlorodiazepam) and protoporphyrin IX (PPIX), two ligands of the mitochondrial benzodiazepine receptor (now called TSPO), thought to be a modulator of the permeability transition pore (656). These pharmacological features supported the notion that the MCC might coincide with the MMC/MPTP described by Zoratti and Szabò (1272). The MCC was also observed by the Albany group in yeast mitochondria, which undergo the PT with difficulty (see Ref. 79).

In 1995 Lohret and Kinnally (786) discovered that the MCC could be transiently blocked by leader peptides in a voltage polarity-dependent manner (positive voltage on the side of peptide addition required). The "flicker" rate of the channel increased in a dose-dependent manner, saturating at ~25 μM, and the occupancy of the reduced (approximately one-half of maximal) conductance state was correspondingly much increased. This suggested an involvement in protein transport across the IMM (652, 784, 786). Several alternative possible identities for the MCC were experimentally ruled out. VDAC and the ANT were excluded by experiments with yeast strains (785, 787), proteins encoded by the mitochondrial genome were excluded by studies employing a Rho0 cell line (897), and unpublished work mentioned by Kinnally et al. (653) discounted Tom20, Tom70, the phosphate carrier, and the "mitochondrial ABC transporter" (765). Indeed, MCC activity was found to be depleted by preincubation of yeast IMM-containing proteoliposomes with anti-Tim23p antibodies which blocked protein import into mitoplasts (784). No such depletion was observed when the proteoliposomes were prepared with an OMM fraction, in which an activity attributed to the PSC/TOM40, practically undistinguishable from that of the MCC (653, 784, 893), was observed. MCC activity in mitoplasts from yeast carrying the G186D mutation in the *tim23* gene, which prevents import of several precursor proteins, was identical to that observed in the wild-type, but was no longer affected by leader peptides. The mutant Tim23 protein was found to be rapidly degraded, with an at least 10-fold reduction of its content in proteoliposomes compared with wild-type. MCC activity (although altered as mentioned) was however observed with the same frequency in the two cases. Tim23 was therefore considered to be more likely to be a modulator of MCC activity than a component of the channel, but this view was abandoned after the work by Truscott et al. (1327) discussed below, and Tim23 came to be considered as a constituent of the MCC ion conduit (e.g., Ref. 893). A subsequent study confirmed this view by highlighting the role of another key component (e.g., Ref. 21) of the Tim23 translocation pore, Tim23 homolog Tim17, which is present in a 1:1 ratio with Tim23 and is closely associated to it. In a yeast strain conditionally depleted of Tim17, the MCC had a lower maxi-

mal conductance (~700 pS), did not show a flickering behavior, and was not voltage dependent. Signal peptides did not induce the fast flickering "closures" observed with the wild-type, but rather an irreversible closure of the channel. Since in the mutant there was no evidence of a binary structure, and the pore appeared to be larger than in the wild-type (by polymer exclusion experiments), the authors concluded that the structure had been drastically altered, with the formation of a single, wider pore which was however incapable of translocating peptides (833). Deletion of 11 NH_2-terminal amino acids of Tim17 resulted in MCC channels with the properties of the Tim17-less complex, pointing to a lack of incorporation of ΔNTim17 in the assembly, or in fairly normal channels lacking however voltage dependence. The voltage gate was shown to be formed, at least in part, by two aspartates at positions 4 and 8 of Tim17. Deletion of only the 24 COOH-terminal amino acids of Tim17 allowed the normal twin-pore structure and behavior to be retained, but still caused the channel to display transitions of unusual sizes.

Considering the role of Tim17 and possibly of other factors of the native membrane it may not be surprising that the pore activity of recombinant *S. cerevisae* Tim23 expressed in *E. coli* and reconstituted into planar lipid bilayers (1327) did not exactly match that observed by patch-clamp. While the lack of Tim17 led to a higher-conductance, stand-alone pore in the experiments just mentioned, the main conductance of renatured and reconstituted Tim23 was lower than what would have been predicted on the basis of MCC properties, namely, ~450 pS in 250 mM KCl. A range of other conductance states was observed, up to 1.35 nS. Cationic selectivity was more pronounced (P_K/P_{Cl} = 16.1). The channels responded to a rapid transmembrane voltage (of either polarity) increase above 50 mV by opening, but closed, in a slower process, upon prolonged application of a steady potential. The CoxIV leader peptide caused current decrease and rapid flickering at the single-channel level in an asymmetrical fashion: nM concentrations were sufficient for a clear effect when added on one side (the same the NH_2-terminal was exposed to, presumably corresponding to the cytoplasm), while micromolar concentrations were needed when added on the opposite one. The G186D mutant was not affected by leader peptides, in agreement with the results of Lohret et al. (784). Truscott et al. (1327) also fused wild-type IMM vesicles with the planar membrane. This led to the observation of MCC-like activity which could be inhibited by antibodies versus the NH_2-terminal added on one side (but not if added on the other side). The authors also addressed the possibility that Tim17 might contribute to pore formation. The G112E mutant of Tim23, which forms a relatively unstable core complex, produced activity similar to the wild-type protein when reconstituted by fusion of membrane vesicles or incorporated after heterologous expression and reconstitution, suggesting to the authors that Tim23 forms the protein translocation pore by itself. As mentioned above, six years later Martinez-Caballero and co-workers (833) came to a somewhat different conclusion. Truscott et al. (1327) also observed formation of channels with characteristics similar to those produced by the full-length protein upon reconstitution of a COOH-terminal portion. These channels were however sensitive to leader peptides only at high concentrations of the latter, confirming that the NH_2-terminal domain is instrumental for binding and delivering presequences to the pore.

The role of Tim50, the third component of the key complex, was addressed in another planar bilayer study (853): this protein turned out to be responsible for holding the dimer together and the pores closed in the absence of translocation substrates, acting as a gate that opens when presented with the appropriate signal. Its addition to a bilayer containing open Tim23 channels induced their closure in a stepwise fashion, resembling the transitions to substates. The pores could be reactivated by the addition of leader sequence peptides, and displayed upon reactivation the typical flickery activity associated with the presence of the peptides. The study thus clarified important mechanistic aspects, explaining how, in this case, membrane "tightness" is maintained despite the presence of potential huge pores.

2. TIM22

The Tim22 complex, also a "twin pore" translocase, whose task is the insertion into the IMM of multitopic membrane proteins, forms a similar pore (e.g., Ref. 1055). In this case reconstitution/planar bilayer studies came first (696, 1056). In the work by Kovermann et al. (696), *S. cerevisiae* Tim22 was expressed in *E. coli*, purified, reconstituted in liposomes, and observed after fusion of the latter into planar bilayers. The activity was consistent with a large channel (conductance ~540 pS at in symmetrical 250 mM KCl) with multiple subconductance states, roughly positioned at 67-pS intervals. A range of pore costriction sizes between ~11 and 18 nm was deduced from the conductances recorded and considered to be wide enough to contain two polypeptide strands. The channel was permeable to cations, with the lower sublevels displaying higher P_K/P_{Cl} ratios, in a range from ~4 to ~15. The channel exhibited an intrinsically moderately rectifying current-voltage relationship, while linear plots were obtained when plotting the size of the gating transitions versus voltage. In experiments with planar bilayers containing multiple copies, the channels were activated at increasing potentials of either sign. An uncharged peptide (P2, added at submicromolar concentrations) copying a sequence of the phosphate carrier believed to act as an internal mitochondria-targeting signal induced flickering and, at higher concentrations, closure at voltages negative on the side of liposome addition. The effect took place only at voltages near the mitochondrial physiological voltage range, even though the P2 peptide is uncharged, suggesting that the voltage may "prime" the channel pro-

tein for interaction with the peptide. The latter only acted when added on the *trans* side of the bilayer, indicating incorporation with an asymmetrical orientation. The positively charged leader peptide of an IMM protein (CoxIV) only affected the channel activity at micromolar concentrations, indicating specificity.

Rehling et al. (1056) purified the whole TIM22 complex from yeast. Upon incorporation in liposomes and fusion into BLMs this preparate produced channel activity resembling that of the recombinant protein, but gave clear evidence of a coordinated behavior between two channels, with also a decrease of the occurrence of subconductances. The P2 peptide induced flickering of one pore, while driving the other into a closed state. This effect did not require as elevated a voltage as in the case of recombinant Tim22, with ~75 mV being sufficient. Furthermore, in these experiments, in the absence of peptides, high voltages were found to induce closure of the pores. X-ray crystallography confirmed the twin structure and estimated pore size.

A few years later Campo's group reported a patch-clamp study of an activity assigned to the Tim22 complex in giant proteoliposomes containing IMM or directly in the inner membrane of *S. cerevisiae* mitochondria (991). Yeast strains expressing Tim23 or Tim22 under the control of a galactosidase promoter were used. Membranes with a low content of Tim23 (but a normal content of Tim22) showed no electrical activity unless the P2 peptide was present in the pipette (i.e., on the intermembrane side of the IMM). In this latter case (but not with the CoxIV leader peptide) a binary channel "awakened," with properties similar, but not identical, to those described in the study by Rehling et al. (1056). A binary structure was indicated by a prominent half-conductance substate, and other substates were also present. The full conductance was pegged at about 1.1 nS in 150 mM KCl (versus a similar value measured in the bilayer studies, but in 250 mM KCl). A slight cationic selectivity (P_K/P_{Cl} = ~8) and voltage dependence were two further characteristics. The channel functioned at low voltages, provided activating peptide was present (submicromolar to micromolar range). The effect of P2 was evident also at low (~75 mV) voltages. Increasing voltages, especially if the sign was positive on the matrix side of the membrane, induced increased occupancy of substates and closures. This latter behavior is in line with that observed upon reconstitution of the isolated Tim22 complex (1056), and resembles that of Tim23 as well. The Tim22-deficient (but Tim23-expressing) strain showed instead the already-described activity assigned to this latter complex, which is very similar, to the point that the most reliable criterion to distinguish between the two appears to be the difference in the effects of positively charged (NH_2-terminal) versus neutral (internal) addressing peptides in the two cases (991). The requirement for P2 for activation of the Tim22 channel suggests that internal signals like the P2 sequence must be presented to the pore-forming portion of the complex for it admit the protein to be transported.

3. OXA1

The other known protein-insertion machine of mitochondria is Oxa1, homologous to bacterial YidC, which facilitates outward protein transport across and insertion into the IMM (reviews in Refs. 951, 1368). A recent paper (709) reports that this protein, either isolated from *S. cerevisiae* or produced in *E. coli*, also form channels upon reconstitution into planar bilayers having a lipid composition close to that of the IMM. As might have been expected at this point, the channels are similar to those formed under analogous experimental conditions by the Tim/Tom components: gating events measuring ~500 pS in 250 mM KCl, with several subconductance states down to ~75 pS, cationic selectivity (P_K/P_{Cl} ~10), a voltage dependence ensuring that the pore remains closed at physiological transmembrane potentials. Incorporation events always resulted in the appearence of channel quadruplets, coherent with the occurrence of Oxa1 as a tetramer. The gating characteristics indicated pairwise cooperativity between the four subunits, which seem therefore to form a dimer of dimers. A peptide corresponding to the targeting sequence of Cox2, a known substrate of Oxa1, induced flickering transitions between subconductance states, while the leader peptide of Cox4 (which uses Tim23) had no such effect.

A matter of relevance is the relationship between the IMM protein transport systems and the MMC/MPTP. It has been proposed that they might coincide (1458). For one thing, positively charged peptides have been reported to induce mitochondrial swelling in a manner reminiscent of the classical PT-induced phenomenon (723, 724, 1221). The conductance values and their multiplicity, voltage dependence, binary structure, and gating behavior (although signal peptides have not been used in studies on the MMC/MPTP) are all similar. The major difference appears to be selectivity, which for the MMC is mainly anionic, with cationic selectivity associated with "unruly" activity (308). No report has been published, to our knowledge, of the effect of pharmacological agents impacting on the MPTP (Ca^{2+}, CSA, ATP, divalent cations, thiol reagents, etc.) on the channels of the protein import systems. Any differences might conceivably be related to the diversity of the species used: the MMC/MPTP has been studied in mitoplasts from mammalian organs and cells (indeed, as mentioned, yeast mitochondria do not readily undergo the permeability transition) while Tim23 and Tim22 channels have been studied mostly in yeast.

E. Anion-Selective Ion Channels

1. Inner membrane anion channel

A) ELECTROPHYSIOLOGY. The "107 pS" anion-selective channel of the IMM, also called "mitochondrial Centum picoSi-

emens" (mCS) channel in some papers and later equated with the "Inner Membrane Anion Channel" (IMAC) described in bioenergetics studies (see below), was characterized in the first, ground-breaking patch-clamp investigation of a mitochondrial membrane (1225). After its first identification in the IMM of giant mitoplasts obtained from the liver of cuprizone-fed mice, the channel has been observed in mitoplasts from rat liver, heart, brain and brown adipocytes, and from beef heart (662, 887, 1226, 1227) as well as in mitoplasts from mouse liver and from various cultured cell lines (De Marchi, Szabo, and Zoratti, unpublished observations). This is a well-behaved, reproducible activity displaying bursting kinetics. Fitting the distribution of the open and closed times requires at least one and two exponentials, respectively (101, 662, 1225, 1228). Single-channel conductance, 107–110 pS in symmetrical 150 mM KCl, is ohmic. The conductance displays a relatively high temperature coefficient of 1.2 pS K^{-1} (190). The open probability depends sharply on voltage: the channel becomes more active at matrix-positive (unphysiological) potentials. The parameter most strongly affected is the long component of the distribution of closed times (1228). The channel infrequently enters subconductance states, the major one with a conductance about one-half of the full one (190, 662, 1227). Anion selectivity is modest (P_{Cl}/P_K ~4.5), and the channel was found to conduct also sulfate and phosphate (190, 662). pH was initially reported to have no effect (1225), but Borecký et al. (190), working with brown fat mitochondria, concluded that the open probability was sharply pH dependent, going from a very low to a high value in the interval 6.0–8.5. An anion permeation pathway activated by alkaline pH was also observed by Antonenko et al. (41) in RL mitoplasts. Regulation by membrane stretch was discounted (1227). The Ca^{2+} (and even more so the Mg^{2+}) dependence of the channel has not been thoroughly investigated. However, the significance of regulation by Mg^{2+} is attracting attention (720). According to Kinnally et al. (655), washing mitoplasts with EGTA strongly increased the portion of patches showing 107-pS channel activity. On the other hand, the experiments leading to the discovery of the channel were routinely performed in the presence of 100 μM Ca^{2+}, and omission of this ion did not result in alterations of the activity (1225). Other laboratories have also reported observing the channel irrespective of the presence of Ca^{2+} (for a discussion see 1228).

B) PHARMACOLOGY. In the original investigations the 107-pS activity was found to be insensitive to alkalinization, quinine, and DCCD (1227). This argued against an identification with the anion uniporter previously described by Beavis and co-workers (124, 127, 129, 130, 131, 426). Various other mitochondrial drugs, including atractylate, bongkrekate, oligomycin, ruthenium red (1227), and cyclosporin A (1271), were also found to be ineffective. On the other hand, Klitsch and Siemen (662) found that the channel they observed in brown adipose tissue mitoplasts, most likely the same observed in other tissues, was inhibited by purine nucleotides. Jezek et al. (592) had found that BATM (only) had a GDP-sensitive Cl permeation pathway which was not inhibited by DCCD or amphiphilic amines, suggestive of UCP-mediated phenomena. Importantly, the concentrations required to inhibit the 107-pS channel did not match those needed to inhibit UCPs (662). The amphipatic compounds amiodarone (an antiarrythmic drug) and propranolol (a β-blocker) (41, 190), the triazine dye Cibacron blue 3GA and nifedipine (190) also inhibited the channel. Antimycin A (224), as well as protoporphyrin IX (PPIX) and the drugs PK1195 and Ro5–4864 (4′-chlorodiazepam) (these last three high-affinity ligands of the TSPO/mitoBzR) (656), reportedly decreased the P_o of the channel, apparently by causing a shift of the correlation between P_o and voltage towards more positive voltages. High (μM) levels of the phenylhydrazone protonophoric uncouplers FCCP and CCCP also inhibited the 107-pS channel (225). This effect was reverted by dithiothreitol, strongly suggesting that it was mediated by redox effects involving thiol groups. Redox sensitivity is another inadequately explored property of the 107-pS channel. IMAC, with which it has been equated (see below), is activated by oxidative stress (48) due to the presence of thiol groups (130, 131, 1029). The channel has also been reported to be activated by fatty acids (1150, 1151).

C) IDENTIFICATION OF THE 107-PS CHANNEL AS THE IMAC. The story of anion transport across the IMM may be reconduced to studies carried out in the 1960s showing that in the presence of a K^+ ionophore passive swelling of mitochondria could be supported by the K^+ salts of various anions, such as chloride, sulfate, and nitrate. This salt inflow was favored by alkaline pH values (77, 200, 201). Selwyn and Walker (1177) may have been the first to propose the presence in the IMM of a proteinaceous anion permeation pathway. The idea was reformulated and a detailed model based on the available data was presented by Garlid and Beavis (426). These authors pointed out the already-known basic properties of the anion "uniporter" mediating passive, electrophoretic anion transport: low discrimination among anions, pH dependence, inhibition by divalent cations (Mg^{2+}; anion transport is typically induced with the divalent cation ionophore A23187), quinine, propranolol, and DCCD. Beavis and co-workers then characterized this channel, the IMAC, in detail, relying on measurements of mitochondrial swelling under the various conditions of interest (123–131). Although the initial assessment of the properties of the 107-pS channel had suggested otherwise (see above and discussion in Refs. 190 and 1460), the characterization by Borecký and colleagues (190), in brown fat mitochondria, convincingly showed that the properties of IMAC deduced from swelling experiments largely overlapped those of the

107-pS channel deduced from patch-clamp experiments, thus underpinning the reciprocal identification of the two entities. A comparison of the properties of IMAC and the 107-pS channels is shown in **TABLE 7**. Antonenko and coworkers have reported that alkalinization of membrane patches appears to reversibly activate weakly anion-selective channels (alkaline-induced anion-selective activity; AAA) with a conductance of 45–50 pS (150 mM KCl) and substates, which are inhibited by Mg^{2+}, amiodarone, propranolol, quinine and tributyltin, and have proposed that this channel may correspond to the IMAC (41, 42, 650).

D) FUNCTION. The function(s) of IMAC have not been satisfactorily elucidated. Given its voltage dependence and its modulation by Mg^{2+} and matrix pH, it would be expected to become activated only under stressful circumstances. A role in mitochondrial volume control has been envisioned from the outset of research on this topic, as was logical given that it was studied indirectly in swelling experiments.

O'Rourke's group has focused on mitochondrial cooperative phenomena taking place in the heart. These researchers have shown that mitochondrial depolarization following an ischemic insult can propagate as a wave across tissue during global ischemia (e.g., Refs. 799, 1449). Furthermore, mitochondria can behave as a coupled oscillatory network: the depolarization of a few mitochondria can cause oscillations of $\Delta\Psi m$ throughout the cell (49, 50, 52, 280). Depolarization and oscillations, which contribute to postischemic arrhythmias, involve both IMAC and the MPTP, are propagated through ROS-mediated ROS release, and set in when ROS production exceeds a threshold level (e.g., Refs. 47, 175, 193, 194, 1218, 1415, 1455, 1448, 1462, 1463). IMAC inhibitors, such as PK11195, 4-chlorodiazepam, or DIDS, prevent the reversible collapse of $\Delta\Psi m$ and protect the ischemized heart from arrhythmias. IMAC is proposed to be activated by ROS and to function in propagation by facilitating superoxide release from the mitochondrial matrix (reviews in Refs. 17, 18, 51, 205).

E) IDENTITY. What molecule(s) are responsible for IMAC activity is an essentially unexplored issue. Its sensitivity to ligands of the TSPO have led to the suggestion that it may be regulated by this outer membrane protein (e.g., Refs. 47, 49). The means for a two-way clarification may become available once a TSPO KO mouse will be developed. It could provide the material to investigate *1*) its relationship to the IMAC and to the 107-pS channel; 2) its contribution to the PT (1207); and *3*) the role of this protein in the development of ischemic damage (including arrhythmias). IMAC might be formed by a still-to-be-discovered CLC-family mitochondrial component. The possibility always remains that it might correspond instead to an "altered" mode of functioning of a carrier devoted to the transport of anions, e.g., the phosphate carrier (see Ref. 190).

2. Other inner membrane chloride channels: electrophysiology and pharmacology

Several papers have reported anion-selective conductances in the IMM in addition to the IMAC/107 pS and the putative CLIC channel (see sect. IV*B*). In general, they have not been studied intensively, their observation may depend

Table 7. *A comparison between IMAC and the 107-pS channel*

Property	Reference Nos.	
	IMAC	107-pS channel
Permeability to several anions	77, 426, 130	190, 662
Block by Mg^{2+}	426, 127	190 (refer to unpublished data by Borecký and Siemen)
Activation by alkaline pH	426, 125, 127, 130	190
Steep T dependence	774, 126	190
Thiol groups present (inhibition by mercurials, etc.)	131, 128, 130	?
Inhibition by quinine	129	Negative according to 1227
Inhibition by amiodarone, propranolol	129	40, 190
Inhibition by DCCD	124	
Inhibition by tributyltin	130, 1029	41
Activation by fatty acids	1150, 1151	1150
Inhibition by CCCP, FCCP	?	225
Antimycin A	?	224
Inhibition by TSPO ligands	129, 130	656
Inhibition by purine nucleotides	?	662
Inhibition by Cibacron Blue	130	190
Inhibition by dihydropyridines	1441	190

strongly on experimental conditions, and their biochemical identity remains largely mysterious. Given the physiologically matrix-negative transmembrane potential maintained by mitochondria, they are likely to be a manifestation of transport systems having to do with the export of metabolites/small molecules from the matrix. For a recent review on intracellular chloride channels, see Reference 370.

Kinnally's group (41, 42, 650) found that the selectivity of mouse liver mitoplast patches, cationic at pH 6.8, became less marked at pH 8.3. This was attributed to the reversible activation of ~45 pS (150 mM KCl) anionic channels which could be inhibited by Mg^{2+}, amiodarone, propranolol, quinine, and tributyltin, suggesting they might correspond to the IMAC (see sect. III*E1*). Alkalinization also activated a slightly cation-selective 15-pS channel.

Patch-clamping yeast mitoplasts, Ballarin and Sorgato (102, 103) observed two ATP-sensitive slightly anion-selective channels. The smaller one displayed an outwardly rectifying current-voltage relationship, with values in the ~44–51 pS range (depending on yeast strain; 150 mM KCl) at matrix-positive voltages. The P_o instead mildly decreased in the positive range. Selectivity was modest, with a P_{Cl}/P_K ratio of only 2–3. The activity was completely blocked by ~1 mM ATP or UTP added to the matrix face of excised patches. The channel was insensitive to Mg^{2+}, glibenclamide, 4-aminopyridine, and bongkrekate. The current conducted by the larger channel also rectified slightly in the outward direction (i.e., influx of anions into the matrix was more facile than efflux), with values of ~800 pS at a matrix voltage of +40 mV and of 400 pS at −40 mV (150 mM KCl). The voltage dependence was sharper in this case, with matrix-negative potentials favoring closure and positive ones favoring opening. ATP (submillimolar range) in this case seemingly blocked the channel in a permanently open state. This channel was slightly anion-selective as well (P_{Cl}/P_K ~4). Mg^{2+} and bongkrekate did not change its behavior. As part of the same study, yeast mitochondrial membranes were incorporated into proteoliposomes, which were patch-clamped. The smaller of the two channels could be identified in the records obtained with this experimental system, and exhibited properties similar to those observed in the work on the native mitoplast membrane. However, a larger conductance (~500 pS) behaved differently, showing no rectification of voltage dependence, and cationic selectivity.

The larger of the two yeast channels just mentioned bears a partial resemblance to the one studied by our group by patch-clamping rat and mouse liver, HCT116 and MEF mitoplasts (312). This is an ~400 pS (300–500 pS range) channel whose observation was inversely correlated to that of the MMC/MPTP. This circumstance, a conductance close to that of the major half-conductance substate of the MMC, and the similarity of the other biophysical properties led to the proposal that it might coincide with one of the two "halves" believed to form the binary MMC, and to its nickname half "MPTP" (HP). Its presence in patches was not strongly influenced by $[Ca^{2+}]$, but the persistence of the activity was. In all systems investigated, the channels showed an analogous set of properties. Selectivity was anionic, with P_{Cl}/P_K in the 7–18 range. Modest (20–40 mV) applied voltages of either sign were most often sufficient to induce channel closure, with a higher effectiveness of pipette-negative potentials. The sensitivity to voltage and the kinetics of closure induced by a voltage step differed however widely depending on the individual channel, suggesting a modulation by posttranslational modifications. The channel could be inhibited by the combination of acidic pH and Mg^{2+}, by BHT, ATP, DIDS, and SITS, but not by several other potential inhibitors, including CSA, 4′-Cl-diazepam (Ro5–4864), clonazepam, carbenoxolone (a connexon blocker), NPPB, IAA-94, as well as niflumic and flufenamic acids (typical chloride channel inhibitors). An identification with VDAC was ruled out by its observation in the mitoplasts of cells lacking one or the other (or combinations) of the three VDAC isoforms. The properties of the HP were similar to those characterizing the often-observed but still mysterious "maxi chloride channel" of the PM, and the proposal was put forward that it might be a mitochondrial version of the latter. This will only help in establishing its biochemical nature if that of the maxi-chloride channel is clarified. The proposal was made that it might coincide with the TSPO (formerly the peripheral or mitochondrial benzodiazepine receptor) (312), but the pharmacology is not coherent with this idea, the TSPO is an outer membrane protein, and furthermore it has been shown not to be the pore-forming component of the MMC/MPTP (1207).

Other studies of mitochondrial anion-selective channels have used reconstitution-based approaches. Ashley and coworkers (533, 534) reconstituted IMM membranes from sheep cardiac mitoplasts into bilayers. They observed two channels, INMAC and SMAC, with conductances of ~100 pS and 50 pS, respectively (symmetrical 100 mM KCl), various substates, a P_{Cl}/P_K of ~8 with, at least in the case of SMAC, poor discrimination among various anions. SMAC seemed to derive from INMAC upon more vigorous sonication of the membranes. The channels were not affected by SITS, H_2O_2, propranolol, quinine, ATP, or pH (5.5–8.8), thus seemingly discounting an identification with IMAC. INMAC was voltage insensitive, while *cis*-positive voltages drove SMAC into its lower conductance substates (~25 and 50% of maximal conductance). The substate behavior of SMAC was consistent with a tetrameric structure modeled as a dimer of (functionally somewhat different) dimers. SMAC (but not INMAC) also displayed Ca^{2+}- and Mg^{2+}-sensitive rectification considered to be related to the membrane surface charge. These interesting activities have not, to our knowledge, been studied further.

K. Ondrias' group has been studying anion-selective mitochondrial channels in planar lipid membranes (review in Ref. 1310). The preparation used contained contaminations by ER and PM membranes, estimated, in the case of rat heart, at ~1% each on the basis of marker ATPase activities (811). Significant contamination by lysosomal, Golgi nuclear, and possibly also peroxisomal membranes was also present if the SMPs had not been purified by centrifugation on a Percoll gradient (672, 1310), and the authors themselves consider that some of the activities observed might be of nonmitochondrial origin. These authors observed 100–170 pS (811, 813) or 70–130 pS (691) or 117 ± 31 pS (62–220 range) (672) (250: 50 mM KCl) [~155 pS in symmetrical 450 mM KCl (691); ~100 pS in symmetrical 150 mM KCl (1309)] chloride-selective channels from rat heart SMPs. Analogous channels from rat brain showed a lower conductance of 120 pS in 450 mM KCl (691). The properties of the channels were evidently rather variable, as emphasized in particular by Kominkova et al. (672) and discussed by Tomaskova and Ondrias (1310). No substates were observed. Kominkova et al. (672) classified the activities they observed into two groups: the well-behaved and the "ragged" channels. This latter categories refers to "noisy," fast activity characterized on average by a lower conductance, P_o, and selectivity. Selectivity was in general rather variable (672, 811), with no correlation between reversal potential and channel conductance. P_{Cl}/P_K values of ~4–6 were reported in two publications (813, 1309), while the summary of the work published in 2010 mentions a range of calculated values from 1.8 to 17. Interestingly, Ondrias et al. (943) and Tomaskova and Ondrias (1310) have reported that rat heart mitochondrial channels of various conductances (including high ones: 712 and 430 pS in 250/50 KCl) can exhibit sudden switches from cationic (K^+) to anionic (Cl^-) selectivity. Anion selectivity appeared to predominate at voltages close to zero, while the channel favored K^+ passage at more positive or negative potentials. An analogous diversity of behavior, with periods of more regular and periods of "wilder" activity, and transitions between anionic and cationic selectivity, was observed by us when studying the MMC pore, which is also, most of the time, an anion-selective channel (308).

The P_o of the channels studied by Ondrias' group showed a bell-shaped voltage dependence, declining on both sides of zero voltage in the range from −60 to +100 mV (1309). P_o was reduced dose-dependently by tributyltin (low micromolar) as well as by BGK and, less potently, by atractyloside (ATR) and CATR (high micromolar range). Bongkrekate (BGK), ATR, and CATR inhibited only from the *trans* side, i.e., opposite to the side of addition of the SMPs (811, 813). NPPB, phloretin, H_2S-donor NaHS, acidic pH, DIDS, and SITS inhibited, on the contrary, only from the *cis* side (672, 691, 812, 813, 1309, 1310). ADP and ATP in the millimolar range were reported not to inhibit (811), but later were found to have complex and variable effects, ranging from none to reduction of the apparent single-channel conductance and to irreversible block (672). Inhibition was found to be time-dependent and to take place (in a minority of attempts) only from the *cis* side (672). Conductance and selectivity tended to be higher for the channels that were influenced by ATP. The nonhydrolyzable ATP analog AMP-PNP reversibly blocked the channels in some experiments, suggesting that ATP hydrolysis was not involved in the process.

These channels were considered to be probably different from those observed by Ashley's group, given their higher conductance (although in different media) and a *cis*-side-specific pH sensitivity which caused the well-behaved channels (only) to close upon shifting the pH from 7.4 to 5.8. Furthermore, different conductances and different sensitivities to the isothiocyanate stilbene derivatives suggested that channels in heart and skeletal muscle and channels from brain might be distinct entities. The concentrations of stilbenoids needed for inhibition were in any case higher than those found to inhibit IMAC (123) and UCP channels (561).

The biochemical nature of these channels and their possible relationship to activities observed by other laboratories remain to be clarified. They are unlikely to correspond to CLIC channels for reasons of conductance (much lower for the latter). The authors suggest that more than one species may be present, and that most of their observations might be reconducible to the 107-pS/IMAC channel, but while this remains a possibility, the reported voltage dependence matches poorly and pharmacology only partially. Given the variability, the channels may be formed by IMM carriers. As mentioned in section III*G*, at least PiC forms anion-selective channels upon reconstitution, and one may expect other members of the family to behave analogously. Yet another possibility is that the activity may arise from a CLC protein, given the reports of a CLC family member in plant mitochondria (794, 1281). CLC family members form both channels and H^+/Cl^- exchangers, (reviews in Refs. 591, 1454). The distinction between transporters and channels is not always straightforward (see references in sect. III*G* and, e.g., Ref. 5), and indeed, it may be that intracellular CLCs normally function as exchangers rather than channels (370). The conductances of the family members that have been studied at the single channel level (e.g., Ref. 1034) are however small compared with the activities being discussed, are poorly selective, and channel gating properties quite different (see sect. IV*B*). A 64-kDa protein has been proposed to form intracellular Cl channels (1054).

With the assumption that at least part of the conductances described do not represent an altered state of membrane components whose physiological function is not ion conduction, the question of what "purpose" mitochondrial an-

ion-selective channels serve remains. In organellar membranes such as endosomes or thylakoids, the main function of chloride channels is thought to be that of short-circuiting voltage differences, so as to allow the establishment of pH gradients or the accumulation of cations. In mitochondria, the pH is moderately alkaline and the $\Delta\Psi m$ strongly negative on the matrix side. An electrophoretic anion transport would drive anions outwards, and tend to collapse the voltage gradient which the proton pumps have labored to create. In fact, this is thought to be the function of UCP in brown fat tissue (see sect. IV*A*). In other tissues, nonshivering thermogenesis may also be a function of these channels, or otherwise the problem of the expected uncoupling can be liquidated by considering that the channels are presumably kept mostly closed under physiological conditions. This however does not help much to clarify their function. As mentioned in connection with IMAC, it might be that of allowing the efflux of superoxide, or of anionic metabolites and intermediates. Unless some special feature, e.g., a proximity effect, is at work in the native membrane, it is difficult however to imagine that poorly selective channels such as these would be employed for such purposes: they would have to remain open for a considerable fraction of time to transport a significant flow of solutes for which they do not have any special affinity. Mitochondrial carriers, a large and efficient array of syn- and antiporters, have evolved to take care of such tasks. We are therefore left with the traditional job to be performed by ionic fluxes, i.e., volume regulation. Given the characteristics of the system, anion channels would be expected to be important in the process of regaining normal volume after an episode of passive swelling.

F. Nonselective Mitochondrial Megachannel/Permeability Transition Pore

The properties of the mitochondrial permeability transition pore (MPTP) are deduced from those of the phenomenon it causes, the permeability transition (MPT), and from electrophysiological observations. The MPT is defined as the nonselective permeabilization of the inner mitochondrial membrane to solutes of molecular mass up to 1.5 kDa, due to opening of a large pore. As a consequence, the transmembrane electrochemical proton gradient is dissipated, ATP synthesis stops, and substrates and nucleotides are lost from the mitochondrial matrix. If MPTP opening is widespread and sustained, it causes cell death, classified as a type of necrosis. Various insults and stresses can cause this "dysfunction," which is becoming a pharmacological target in major pathologies like infarct, stroke, and neurodegeneration.

The MPT has been most often studied by following the swelling of isolated mitochondria caused by influx of water and solutes through the open pore(s), driven by the osmotic gradient due to the presence of indiffusible matrix proteins (i.e., a colloidosmotic process). Swelling of the matrix compartment, along with electrophysiological recordings from mitoplasts, shows that the MPT is a phenomenon of the inner membrane. More recently, research has increasingly utilized more physiological and complex systems such as cultured cells, organs, and laboratory animals, and assessment of the MPT has become even more indirect (and sophisticated), relying increasingly on the evaluation of parameters such as the transmembrane potential, the rate of oxygen consumption by cells, and the Ca^{2+} retention capacity in permeabilized cells. Such a state of affairs poses some complications: IMM permeabilization may conceivably result from the activation or formation of more than one kind of channel, that is, the possible existence of more than one MPTP must be kept in mind.

In the absence of definitive genetic evidence on its molecular composition, the MPTP must be defined operationally on the basis of its pharmaceutical and biophysical properties. This is no easy task, because the MPT is a many-faceted, multi-factor phenomenon with no absolute dependence on any one parameter. A minimum set of properties may nonetheless be subjectively chosen, such that any phenomenon attributed to the MPTP ought to display them. This list might include *1*) a requirement for the presence of Ca^{2+} in the matrix; *2*) dependence on matrix pH: acidification inhibits; *3*) voltage dependence: the MPTP will open upon depolarization if the mitochondria have been suitably primed by Ca^{2+} loading or other treatments; and *4*) redox sensitivity: oxidative stress favors the MPT.

Many reviews covering the various aspects of MPTP physiology and pharmacology, the various hypotheses about its composition, its role in cell death, autophagy, and assorted pathologies have been published, and most are tabulated in **TABLE 8**. We provide here a brief overview. The MPT has been clearly recognized as one of the mitochondrial processes one can hope to exploit for cancer therapy, while inhibition of its onset is being considered instead as a way to protect from ischemic damage, neurodegeneration, and other pathologies, e.g., some forms of dystrophy.

1. Classical hallmarks of the MPTP

Information on the properties of the open MPTP has been obtained from biochemical experiments following swelling of isolated mitochondria (water follows the suspension medium osmolite into the matrix, once the IMM has become permeable to the osmolite itself) and the permeation of tracers as well as from electrophysiological studies. Most characteristics have been established by Hunter and Haworth's fundamental work (529–531, 563, 564). Solute exclusion studies suggested a diameter of 2–3 nm and indicated that the pore is nonselective, or only poorly selective. A high-conductance channel (dubbed MMC) has been identified as the MPTP on the basis of its pharmacological pro-

Table 8. *A tabulation of reviews on the MPTP*

Focused On	Reviews
General properties and possible functions	79, 160–162, 166, 924, 1061, 1337, 1351, 1461
Electrophysiology	1457, 1458, 1460
Molecular composition	99, 199, 410, 468, 496, 502, 508, 756, 1459
Regulation	144, 163, 168, 334, 406, 873–875, 964, 1049, 1464
Involvement in cell death	97, 350–352, 449, 468, 500, 654, 753, 754, 875, 1046, 1328, 1329
Involvement in autophagy	71, 461, 644
Involvement in dystrophy	158
Involvement in I/R injury	95, 335, 338, 423, 463, 497, 499, 505–507, 645,873, 874, 933, 1094, 1095, 1374
Involvement in cardioprotection (conditioning)	184, 286, 337, 340, 498, 503, 894, 895, 954, 995, 997, 1118
Targeting the MPTP for ischemic damage and cardiac disease	33, 96, 340, 524, 583–585, 764, 890, 933
Involvement in neurodegeneration	287, 359, 360, 414, 829, 1019, 1246
Targeting the MPTP for neurodegeneration	74, 829, 1291
Targeting the MPTP for cancer	61, 416, 454, 494, 581, 1041

Most reviews cover various aspects and provide at least some general information on the MPT. I/R, ischemia/reperfusion.

file (309, 834, 1457, 1460, 1461) and proposed to consist of a dimer of cooperating, mildly anion-selective pores which can occasionally turn into an irregular, cation-selective channels. Full MPTP conductance in patch-clamp experiments with 150 mM KCl is in the range 0.9–1.5 nS, with a preferred value of ~1.3 nS. A characteristic of this activity is the abundance of substates, including a preminent half-size one which is often entered as a "way station" during closures or openings of the full conductance and is favored by high-salt media (Szabo and Zoratti, unpublished observations). The presence of this half-MPTP (HP; see above) underlies the proposal of a dimeric structure of the MPTP.

In some experiments, the full-size pore appears to develop gradually from smaller pores. Thus electrophysiological evidence indicates that the MPTP can actually adopt a variety of states. A similar conclusion is also suggested by other experimental approaches, and in fact, the idea that MPTPs of different sizes may exist in different mitochondria and that the size of the pore may depend on the MPT-inducing conditions has been around for a long time (e.g., Refs. 203, 1014). A major line of evidence consists in the observation that the time course of mitochondrial swelling does not always coincide with that of other phenomena thought to be associated with the MPT. Work performed up to the early 1990s, pointing to a "first stage" of the MPT involving an MPTP conformation selectively permeable to H^+ and possibly K^+ has been reviewed (923, 1461). In the investigations by Gogvadze et al. (453), a selective Ca^{2+} efflux from Ca^{2+}-loaded, prooxidant-treated mitochondria took place before swelling. This efflux was sensitive to a battery of MPTP inhibitors, including cyclosporin A, the paramount one, so the authors considered it to represent a first stage of a process leading eventually to a "classical" MPTP. The group has proposed that the mechanism involves NADP hydrolysis and ADP-ribosylation of IMM proteins. There is also evidence that membrane-modifying agents such as gliotoxin or phenylarsine oxide (PhAsO) induce CSA-sensitive Ca^{2+} release unaccompanied by swelling (1161–1163). Control of this phenomenon by redox events resembles that of the MPTP. Glutathione is lost by mitochondria upon induction of the MPT (1133), but the efflux can be partially uncoupled from MPT-dependent swelling: various MPT inhibitors, including CSA, polyamines, and polycations, inhibit Ca/P_i-induced swelling at concentrations that do not effectively block either glutathione loss or transmembrane potential decrease (1063, 1064, 1134). Higher concentrations of spermine or CSA do block GSH release and depolarization, suggesting that the same machinery responsible for the MPT may be involved. Broekemeier and Pfeiffer (204) obtained evidence suggesting the gradual development of the MPTP, from a K^+-permeable to a Mg^{2+}-permeable to a sucrose-permeable pore. The same group reported the indirect observation of a $\Delta\Psi m$-dissipating, sucrose-impermeable pore that remained active when MPTP closure was induced by Ca^{2+} chelation (203). This pathway, putatively an MPT substate, was inhibitable only in the presence of Mg^{2+} and under conditions (hypoxia) leading to a reduced state of the respiratory chain. This suggested an association of the pore, and by inference of the MPTP, with a complex of the respiratory chain. As mentioned below, the full-size MPTP is regulated by electron flow through complex I. Evidence has been presented by Ichas and coworkers for the formation of a Ca^{2+}- and K^+-permeable, sucrose-impermeable, Mg^{2+}-, ADP-, CSA-inhibitable, matrix pH-regulated "narrow MPTP" (566, 567 and references therein). This form of the channel,

for some reason best observed in hypotonically swollen mitochondria, was desumed to be activated not by Ca^{2+} but by matrix alkalinization following Ca^{2+} or Sr^{2+} uptake. Massari (837) analyzed the kinetics of swelling by isolated RLM in sucrose medium and concluded that sucrose influx follows different kinetics in subpopulations of isolated mitochondria, implying the existence of pores with different permeabilities, i.e., dimensions. A limited-permeability form of the MPTP has been deduced to mediate the thermogenic effects of T3 hormone (1425, 1426) and to result from cross-linking of thiols (689) and from the application of low levels of long-chain fatty acids (690) in permeabilized pancreatic β cells.

This vision of the MPTP as a "variable pore" is consistent with its putatively "accidental" nature, i.e., with the concept that it is formed by membrane components whose main task is something else. What these components may be is still, after 40 years of work, an unsolved riddle, but the solution may have just been found.

2. Molecular composition

The idea that the ANT may be the centerpiece of the MPT is old (563, 1461). Because ATR favors, and BGK inhibits, MPT development, the idea arose, supported by use of other ANT ligands, that the MPTP would be formed by the exchanger in its C conformation (ATR-induced; BGK stabilizes the M conformation) (on the ANT see, e.g., Refs. 326, 661, 926, 984). Indications emerged however in the 1990s that other proteins may be involved, i.e., that the MPTP might be formed by a supramolecular complex. Submitochondrial particles (formed by the IMM with an inside-out orientation) were not permeabilized by Ca^{2+} even in the presence of cyclosporin (501), suggesting the participation of outer membrane proteins. The ANT was found to be one component of a complex that contained also VDAC, the mitochondrial benzodiazepine receptor (now known as TSPO), creatine kinase or HK and cyclophilin D (CypD) (170, 171, 288, 835, 850), which, when reconstituted in membranes, gave rise to a large pore (170, 171, 835). TSPO ligands affected MPTP activity (e.g., Refs. 656, 706, 1273). The electrophysiological properties of the MMC/MPTP were found to be compatible with a participation of VDAC (1267, 1273), and the idea took hold (e.g., Ref. 1350), and still perdures despite the evidence to the contrary mentioned below, that the MPTP was formed by the complex mentioned. The participation of the ANT found support in work performed largely by Halestrap and co-workers (496, 501, 508), who rationalized the MPT-favoring effects of oxidative stress, thiol reagents and NADH oxidation, besides pharmacological aspects, in terms of their effects on the binding of CypD and ADP (both considered to modulate Ca^{2+} sensitivity) to different sites of the ANT. The MPTP's voltage dependence was explained as an effect of voltage on carrier conformation and ADP binding. The idea was also seemingly confirmed by studies showing that isolated ANT can form a high-conductance pore at high (1 mM) Ca^{2+} levels (207, 208, 1093).

The model however did not stand the test of genetic experiments. It was much weakened when it was shown that the MPT took place also in mouse liver mitochondria in which the expression of both ANT-1 and ANT-2 isoforms had been eliminated (669). To accomodate the undeniable effects of ANT ligands (ATR favors, and BGK inhibits, MPT development) the carrier is now considered by many to be one of the regulatory components of the pore (see discussion in Refs. 98, 176, 1446). Another, definitive blow came from the observation that the MPTP was still present, with much the usual characteristics, in cells in which the three VDAC isoforms had been eliminated by pairwise gene knockout (and siRNA silencing of the third) (93, 312, 703). CypD was confirmed to be a component of the MPTP by studies showing that its deletion decreased MPT-related damage in ischemia (92, 904, 1143). Subsequent studies confirmed this and the regulatory role of the isomerase: the MPT can still be elicited in the absence of CypD, although it requires more drastic conditions (111, 308). CypD has recently been found to act by masking an inhibitory P_i binding site (112, 759). Thus Pi would appear to be the real MPTP inhibitor in the presence of the CypD ligand cyclosporin A (CSA); the role of the latter would be to unmask the regulatory site by causing CypD detachment. Finally, the TSPO has also been found to be disposable for the MPT (1207), although it retains the role of a regulatory component.

The collapse of the ANT-VDAC model has opened the way to other more or less speculative models. The phosphate carrier (PiC) and at least two other members of the "tripartite" carrier family, the aspartate-glutamate exchanger and the ornithine-citrulline exchanger, have been proposed as candidates (see discussion in Ref. 98). The similarity between the pore activity observed upon reconstitution of components of the mitochondrial protein import system and the MPTP channel points to a possible identification of the former with the latter (see above and discussion in Ref. 1457). Other candidates include inorganic polyphosphate (e.g., Ref. 979) and unspecific aggregates of membrane proteins caused by oxidative stress (e.g., Ref. 697).

Recently, CypD has been found to interact with the lateral stalk of the F_0F_1 ATP synthase (448, 449). Azarashvili's group, on the other hand, has reported that ligands of the TSPO (see above) promote both opening of the MPTP and dephosphorylation of subunit c of the ATP synthase in rat brain mitochondria (706). These findings pointed to the possibility that the ATP synthase itself might form the MPTP, previously neglected essentially on the weak grounds that oligomycin does not affect the pore. Indeed, a recent study by Bernardi's group and ourselves has shown that the subunit binding CypD is OSCP, and that the binding site is the same used by Bz423, which facilitates MPT

onset, just like CypD. Furthermore, dimers of the ATP synthase isolated by BNE, when added to planar bilayer membranes, induced ion channel activity with characteristics compatible with those of the MMC as defined in patch-clamp experiments (450) **(FIGURE 7)**. While more work is clearly needed, these findings allow one to hope that the long search for the identity of this extraordinary channel is finally at an end.

3. Regulation of activity

The MPT in isolated mitochondria is favored by Ca^{2+} loading in conjunction with inducers such as P_i, sources of ROS, thiol cross-linkers and acylating agents, $\Delta\Psi$m-reducing and surface potential-modifying agents, fatty acids, ligands stabilizing the C conformation of the ANT (ATR, CATR, acyl-CoA's, pyridoxal-5-phosphate), and compounds that can deplete the mitochondria of protective molecules (e.g., ADP depletion by PP_i). Pore opening can be inhibited, or open pores closed, by agents that counteract the action of inducers. For example, radical scavengers will protect against oxidation of thiol groups, dithiothreitol will reverse it. In addition, as already mentioned above, the MPT is classically inhibited by CSA (although many papers describe or refer to CSA-insensitive forms of the MPTP), matrix acidification, adenine nucleotides, divalent cations other than Ca^{2+}, and compounds that stabilize the M conformation of the ANT (BGK, matrix ADP). Which parts of the electron transport chain are used may also have important consequences on MPT induction (see below). It is worth emphasizing that since the MPT is influenced by many factors, the effects described in the literature are rarely all-or-nothing; their magnitude depends on conditions.

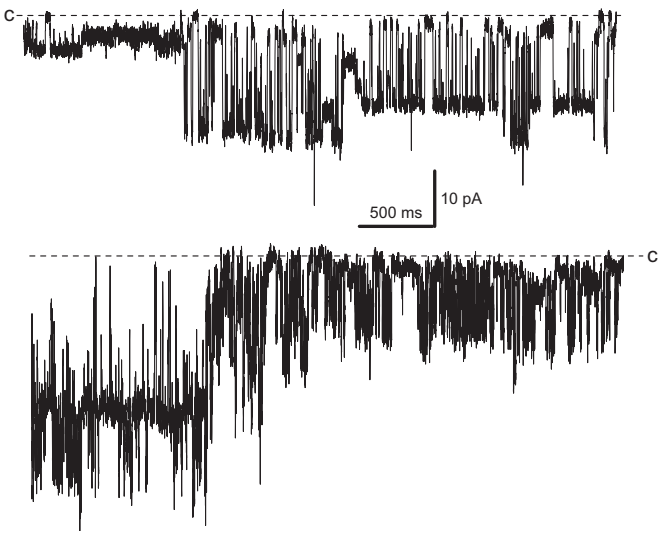

FIGURE 7. ATP synthase dimer and the mitochondrial megachannel MMC corresponding to MPTP. *Top current trace*: activity observed in 150 mM KCl at −40 mV in lipid bilayer experiment following incorporation of purified dimers of ATP synthase. *Bottom trace*: MMC recorded at −40 mV in mouse liver mitoplast.

Unless inhibitors are administered or Ca^{2+} is sequestered, prolonged closure after prolonged opening of the full-size MPTP does not occur readily in vitro. Endogenous protective factors such as NAD(P)H and ADP are rapidly lost through the open pores, along with tricarboxylic acid cycle intermediates. Swelling may result in the loss of cytochrome *c* upon rupture of the OMM, and respiration may be permanently impaired. This scenario may not apply to brief openings.

Matrix Ca^{2+} is required for MPT occurrence, although high accumulation levels are not strictly necessary. The amount of Ca^{2+} needed for induction depends on the coadjuvating agent used and on the content of MPT-antagonizing compounds such as ADP, which may vary in each mitochondrion. In experiments with previously permeabilized, A23187-treated, and completely uncoupled mitochondria, depleted of endogenous protectants, Chernyak and Bernardi (254) found that 1 μM Ca^{2+} was sufficient to induce measurable permeabilization; a maximal effect was obtained with 10–30 μM Ca^{2+} (with 1 mM P_i). In electrophysiological experiments, at contaminating Ca^{2+} levels the probability of observing MPTP activity in a membrane patch is low, and when such activity is observed it often disappears (inactivation) in a short time (312). Thus Ca^{2+} seems to be necessary not only for activation or assembly of the pore, but also to keep it open, as confirmed by the immediate disappearance of the activity if Ca^{2+} is chelated. Ca^{2+}/P_i has long been the classical inducer cocktail. Why P_i is special is still unclear. It is thought to help Ca^{2+} accumulation by indirectly buffering the matrix pH, but if this were the whole story other permeable weak acids (e.g., acetate) ought to have the same effect.

At any rate, pore opening by Ca^{2+} does not strictly require P_i or other coadjuvants, as shown by electrophysiological experiments. Haworth and Hunter (531) pointed to the presence of two Ca^{2+} binding sites, displaying cooperative effects, on the matrix side. Ca^{2+} appears to act competitively against a variety of inhibitors, including ADP, CSA, divalent cations, protons, local anesthetics, and $\Delta\Psi$m (in the sense that at higher Ca^{2+} loads lower extents of depolarization are needed to produce the MPT) (see Ref. 1461). This is clearly observed in patch-clamp experiments: sequential additions of ever-increasing concentrations of Ca^{2+} and divalent cations (Sr^{2+}, Mn^{2+}, Ba^{2+}, Mg^{2+}), ADP, protons, or CSA result in the correlated activation/inhibition of the MPTP (1263). Inhibitory binding sites for divalent cations (including Ca^{2+}), with IC_{50} in the 0.2–0.3 mM range, have been identified on the cytoplasmic side of the mitochondrial membrane (165). Ca^{2+} and other divalent cations may compete for the same binding sites (possibly on cardiolipin, see discussion in Ref. 1457), but it seems unlikely that the same sites are involved in the case of the other agents mentioned. The most convenient way to represent such a system may be in terms of a chemical equilibrium:

Activator(s) + closed state(s) = inhibitor(s) + open state(s), which can be pushed toward one state or the other by altering the concentration (activity) of activators or inhibitors. Another representation is to consider that the effect of CSA, ADP, divalent cations, and protons consists in shifting toward higher Ca^{2+} the relationship between probability of MPT opening and Ca^{2+} load. Adenine nucleotides inhibit the MPTP with their effectiveness following the order ADP > ATP > AMP. The protective effect of ADP can be modeled as a decrease in affinity of the activating sites for Ca^{2+}, induced by a mechanism other than direct competition, and was classified by Haworth and Hunter (529) as mixed-type inhibition, decreasing the V_{max} of MPT propagation in a mitochondrial suspension and increasing the apparent K_m for Ca^{2+}. Haworth and Hunter (529) concluded that two cooperative binding sites per pore are present. Binding of either two Ca^{2+} ions or two ADP molecules would substantially inhibit binding of other species. The MPTP would open only if two Ca^{2+} ions, and no ADP, are bound. Note that this model is in agreement with a dimeric composition of the MPTP, also indicated by completely unrelated observations (see above).

Matrix protons inhibit MPT onset and induce MPTP closure in a Ca^{2+}-competitive manner (164, 529, 531, 1263) probably through protonation of histidine. It has been proposed that the interaction of CypD with the MPTP precursor may become disrupted (915; contra: Ref. 501), but the mechanism remains in doubt.

While Ca^{2+} is a key effector at least in vitro, MPT induction by oxidizing conditions has long been known, and indeed, it is considered by some to be an essential feature of the MPT (617, 700). Ca^{2+}-treated mitochondria produce more ROS (e.g., Ref. 802), and this enhanced ROS production may well contribute to MPTP opening. Thus antioxidants antagonize the MPT, and pro-oxidants promote it (e.g., Ref. 309).

The redox state of some thiol groups is understood to account for redox sensitivity. Pore formation via the DTT-reversible (1008) formation of disulfide bridges may not require Ca^{2+} accumulation (although it is favored by it), and whether the pore thus formed has or not exactly the same properties as the one induced by Ca^{2+}/P_i is still an open question. The defining characteristics of the pore in patch-clamp experiments (conductance, kinetics, selectivity, voltage dependence) appear to be the same when the activity is induced by Ca^{2+} plus P_i or the thiol reagents MitoTracker Orange (MTO) or phenylarsine oxide (De Marchi, Szabo, and Zoratti, unpublished observations). The redox regulation of the MPTP has been the subject of thorough studies by Bernardi's group (254, 283, 285, 1008, 1009; see also Ref. 203). Two sites (S and P) formed by vicinal, cross-linkable cysteines were identified on pharmacological grounds. The S site reflects the redox state of the glutathione pool, while the P site is influenced by the state of the mitochondrial pyridine nucleotide pool. In this latter case, the effects observed might actually arise via a direct interaction mechanism, as originally proposed by Haworth and Hunter (529, 563). In any case, it appears that both glutathione and pyridine nucleotides modulate the MPT in an additive fashion. Under normal circumstances these pools are in redox equilibrium. In in vitro experiments, their redox poise depends on conditions such as the respiratory substrates used (179, 406, 407) or the presence of rotenone, an often-used inhibitor the first site of the respiratory chain.

Nitric oxide can also affect the MPT. Low concentrations of NO have little effect or inhibit MPT onset via *S*-nitrosylation of protein thiols, while higher ones facilitate it by causing formation of disulfide bonds and via the oxidizing effects of $ONOO^-$ (104, 206, 751, 1016). Interestingly, at low NO donor concentrations, a facilitating effect was exhibited by ATP, which normally is an MPTP inhibitor. This facilitation was sensitive to ATR (936, 1016). Another, potentially important anti-MPT mechanism of NO is mediated by activation of PKG, one of the RIS kinases (191).

Work performed mainly by E. Fontaine, P. Bernardi, and co-workers has implicated complex I of the respiratory chain as a major regulator of MPTP activity (242, 406, 407, 759). At least in muscle mitochondria, a lower Ca^{2+} load is required to induce the MPT when reducing equivalents are provided to the respiratory chain through complex I than when energization is through the other sites. Ubiquinone analogs affect MPTP opening in manners depending on their structure and on the origin of mitochondria (331, 407, 440, 834, 1363). Complex I and CypD seem to share a common MPTP-regulatory pathway: in cells expressing high levels of CypD, inhibition of complex I by rotenone has little effect, while in cells expressing low levels of, or no, CypD inhibiting complex I also inhibits the MPTP with a similar dose dependence (759). It should be mentioned that in various studies inhibition of complex I has been found to go hand-in-hand with MPT induction and cell death, likely because of enhanced ROS production (402, 1166–1168).

Voltage dependence can be summarized by stating that the pore tends to open upon depolarization. Electrophysiological observations at the single-channel level on isolated, washed-out membranes indicate that this is an intrinsic property of the pore, independent of binding or blocking events or of secondary phenomena such as ROS production by uncoupler-treated mitochondria (698, 1165). In patch-clamp experiments, the application of moderate (30–60 mV) potentials with the physiological polarity to an MMC/MPTP observed at low voltage is sufficient to induce long-lasting (but reversible) closure within seconds. The effectiveness of the voltage pulse apparently increases with its absolute value: when the voltage is applied to an open channel, the average lag time before closure becomes shorter, and the open probability in the subsequent period lower, as

the potential increases (Szabo and Zoratti, unpublished observations). When open at potentials of physiological polarity, the RLM MPTP tends to reside in the maximal conductance state, with relatively infrequent transitions to various substates, and occasional full closures. At potentials of the opposite polarity, substate visits are more frequent, and the current record is more likely to assume a "noisy" appearance, but the probability of prolonged sojourns in fully closed state(s) does not increase markedly with voltage. The probability of the channel residing in the full-conductance state thus decreases with increasing potentials of either sign, but with different modalities.

Membrane surface potential is an integral component of the $\Delta\Psi m$ acting on the pore; thus agents modifying the surface potential may exert their action indirectly via changes of this parameter. This has been proposed as a possible or partial explanation for the effects of acyl-CoAs (159), of fatty acids, of long-chain acyl cations such as sphingosine and analogous compounds, of trifluoperazine and other local anesthetics capable of forming amphipatic cations, of external divalent or trivalent cations (204), of polyamines (204, 1064), and of compounds shifting the conformation of the ANT between the C and M states (159), such as ATR and BGK. Bernardi's group (167) has presented evidence that many important MPTP modulators (Ca^{2+}, Mg^{2+}, ADP, fatty acids, thiol oxidation, and cross-linking) act by modifying the pore's sensitivity to $\Delta\Psi m$ decrease. The MPT-inducing agents act to increase (i.e., shift towards physiological values) the threshold potential for MPTP opening, with the opposite being true for negative modulators. Eriksson et al. (377, 378) used chemical modification experiments to conclude that Arg or possibly Lys residues, probably located on the matrix side of the IMM, play an important role in voltage sensing. Since modification did not alter the rate of ATP/ADP exchange, the data suggested that the ANT was not the protein forming the MPTP, as widely believed at the time.

The origins of the current perduring interest in the MPT can be traced to the discovery that cyclosporin A is a powerful inhibitor (204, 288). This cyclic endecapeptide, an inhibitor of calcineurin and widely used immunosuppressant, is effective on the MPT induced by a variety of agents, although the inhibitory effect may be partial, transient, or both, and its characteristics may depend on experimental details (1459). The favored mechanistic model for the effect on the MPT is formulated in terms of MPT-permissive binding of CypD to the MPTP precursor. CSA is thought to inhibit by competing for CypD, with which it forms a complex no longer able to bind to the MPTP precursor. This model has been a key element for the candidacy of two proteins of the IMM, the ANT and, very recently, the F_0F_1 ATP synthase, as MPTP precursors (see above). While CypD is universally recognized to play a role in the MPT, this role is now recognized to be "merely" that of enhancing the sensitivity of the process to Ca^{2+}, as proposed early on (498). Definitive evidence came from the demonstration that CypD-null mitochondria could still undergo the MPT at higher Ca^{2+} loads (111, 1206). The pore responsible for permeabilization was shown to have essentially the same properties as the one observed in wild-type mitochondria, implying that CypD has a permissive role, but does not intervene to determine the properties of the pore once it has been activated (308).

For several years in the 1980s, the MPTP was thought to be due to membrane "defects" caused by the accumulation of lysophospholipids and free long-chain fatty acids in the IMM upon activation of Ca^{2+}-sensitive mitochondrial phospholipase A_2 (1461). While this model has been largely abandoned, it remains true that the MPT is facilitated by fatty acids, preminently by arachidonic acid (999, 1164, 1380), and fatty acid acyl-CoAs (418, 952). More recent work has furthermore pointed to an important role of calcium-independent phospholipase $A_{2\gamma}$ ($iPLA_{2\gamma}$) in promoting MPTP opening induced by Ca^{2+} and oxidative stress (202, 419, 657, 885). LCFAs have been proposed to act indirectly, via kinases and Bax, to promote low-conductance MPT gating and heat production in vivo (1115). Snake phospholipase A_2 neurotoxins can enter neurons and cause activation of the MPTP in their mitochondria (1065). The mitochondrial effects of LCFA, which are not limited to MPT induction (e.g., Ref. 1251), appear to depend on tissue type, resulting in induction of the "classical" MPT in liver mitochondria, while a CSA-insensitive permeabilization is induced in heart mitochondria (341, 342). Another physiological effector proposed to produce low-conductance MPTP gating by an indirect action mediated by mitochondrial Bax (1425, 1426) is thyroid hormone (T_3), long known to modulate metabolic efficiency and thermogenesis by controlling the degree of coupling of oxidative phosphorylation (e.g., Ref. 797).

The permeability transition is furthermore promoted by alterations of the cardiolipin pool. Since cardiolipin is of fundamental importance for the function of the ANT (660), this observation was taken to support the candidacy of the ANT as the MPTP-embodying IMM component (243, 966, 1011, 1012, 1457), but is compatible with alternative hypotheses. Important endogenous inhibitors of the MPT are also natural polyamines (reviewed in Refs. 10, 1315). Conversely, it has been proposed that polyphosphate, a natural polyanion with a significant presence in cardiac mitochondria, may be the species forming the MPTP upon complexation with Ca^{2+} (1170, 1171).

A cross-talk between apoptosis effectors, in particular Bax, and the MPTP has been proposed in several studies (e.g., Refs. 209, 253, 714, 761, 762, 1091, 1305, 1379), but our group did not find evidence for a direct interaction in studies with isolated mitochondria (223, 310). Anti-apoptotic

BclxL has been reported to antagonize opening of the MPTP as observed indirectly as a collapse of the mitochondrial potential and directly as channel activity in patch-clamp experiments (615, 1316). The MPTP is reportedly activated, under conditions of oxidative stress and I/R injury, by p53, which accumulates in mitochondria and induces necrosis by interacting with CypD (1345).

In a physiological context, the MPT is subject to regulation by cellular phosphorylation pathways. The processes taking place during postischemic reperfusion and pre- and postconditioning, and the modulation (repression) of the MPTP in cancerous cells have been investigated in some detail (for references, see **TABLE 8**). Hypoxic preconditioning (HPC) apparently increases a basal rate of opening of the MPTP in cardiac myocytes (523, 528). The model is coherent with current paradigms: a major signal emanating from hypoxic mitochondria is increased ROS generation, due to the respiratory chain being in a highly reduced state and enhanced mono-electronic "leakage" to residual oxygen. ROS promote MPTP opening, and MPTP opening may itself contribute to oxidative stress: ROS increased under HPC conditions in wild-type myocytes, but not in CypD$^{-/-}$ cells, pointing to a positive-feedback on ROS production (indeed, death by sustained simulated hypoxia/reperfusion was reduced by HPC in the case of wild-type cells, but not for CypD$^{-/-}$ cells).

This somewhat paradoxical increase of ROS in hypoxia determines a negative feedback response by the cell, which antagonizes the MPT and thus affords protection from reperfusion damage or, in preconditioning, in subsequent ischemic episodes. ROS contribute, by direct action or by inhibiting redox-sensitive phosphatases, to the activation of the so-called RIS reperfusion injury salvage (RIS) kinases, a group including Akt, Erk1/2, PKC-ε;, PKG, and P70s6K (which can also be activated downstream of surface receptors). These kinases in turn phosphorylate and inactivate glycogen synthase kinase-3β (GSK3β; also involved in the canonical Wnt signaling pathway). GSK3β is constitutively active, and its inactivation results in desensitization of the mitochondria to MPT induction (reviews on this pathway: Refs. 526–528, 873, 874, 954, 1049). Importantly, CypD is phosphorylated by GSK3β (1048). This model is still somewhat controversial (e.g., Ref. 498), since some studies have found no correlation between limitation of infarct size and activation of RIS kinases (e.g., Refs. 917, 1217). Nishino et al. (917) reported that the heart of a double knock-in mouse expressing costitutively active forms of GSK3α and -β which could not be phosphorylated and thereby inhibited still benefitted from pre- or postconditioning, and that pharmacological inhibitors of GSK3β failed to mimick conditioning (while CSA, the MPTP inhibitor, protected) (for an in-depth discussion please see Ref. 1049). A recent study however confirms that inhibition of GSK3 results in reduced cerebral infarct size in vivo (1338). Other kinases, including PKC-ε; (427), Akt (1049), and PKA (989), may act directly on mitochondria protecting from the MPT. During severe hypoxia or ischemia, oxidative phosphorylation is obviously reduced or blocked, and cellular ATP levels are reduced. This is expected to stimulate AMPK activity, but this kinase seems to have been less studied, in this context, than the (other) RISKs, although it has been identified as a target of efforts to improve the functionality and preservation of organs destined for transplantation (192). Various studies (e.g., Refs. 790, 1048) have demonstrated an inhibitory effect of AMPK activation on GSK3β. CaMKII on the other hand facilitates MPT onset in ischemized cardiac myocytes, reportedly by increasing Ca^{2+} influx mediated by the mitochondrial Ca^{2+} uniporter (MCU) into the mitochondria (603, 932).

Much the same signaling pathways may be involved in desensitizing cancer cells to MPT induction (reviewed in Refs. 258, 1049). In cancer models containing constitutively active ERK, this kinase acts through the GSK3β-CypD axis to repress cell death by MPTP inducers such as arachidonic acid or BH3 mimetic EM20–25 (1048). MPTP desensitization in cancer cells seems to be also mediated by tumor necrosis factor receptor-associated protein-1 (TRAP-1), a chaperone homologous to Hsp90, which is localized in mitochondria in tumoural but not in healthy cells (25–27, 838). This protein and mitochondrial Hsp90 and Hsp60 interact with CypD and antagonize its MPT-facilitating action. TRAP-1 and the Hsps are therefore new targets for "mitocan" development (26, 27, 630). TRAP-1 is a substrate of mitochondrial PTEN-induced kinase-1 (PINK1), and its phosphorylation by PINK1 protects against apoptosis induction by oxidative stress.

4. Physiopathological relevance

Ca^{2+}-induced IMM permeabilization has been observed in yeast, fungi, plant, fly, amphibian, fish, and, obviously, mammalian mitochondria (reviewed in Refs. 79, 166, 1238, 1337, 1351, 1358). While the characteristics of the phenomenon vary depending on the system, its conservation suggests a physiological role for a controlled IMM permeabilization. What this role may be remains an open question. A long-standing proposal is that the MPTP may act as a Ca^{2+} release channel whose brief openings would allow the mitochondria to get rid of excess Ca^{2+} accumulated because of thermodynamics (162, 166). In support, Molkentin's group (372) has reported that CypD$^{-/-}$ mice suffer from cardiac defects associated with alteration of MPTP-mediated Ca^{2+} efflux and consequent overload of the mitochondrial matrix.

The MPT is a signal for autophagic elimination (mitophagy) (71, 461, 644, 1427). Its occurrence leads to mitochondrial recruitment of Parkin, a key ubiquitin ligase whose loss-of-function mutations causes Parkinson's disease. Surprisingly, collagen VI deficiency-linked Ullrich

congenital muscle dystrophy turned out to be associated with increased cell death caused by abnormal occurrence of the MPT (158, 572) and, in fact, can be contrasted by administration of CSA (37, 856, 857). In this pathology autophagy is defective, preventing the elimination of dysfunctional mitochondria, and its reactivation ameliorated the dystrophic phenotype (482).

Autophagy is involved in development, in caloric limitation-induced lifespan extension, in opposing aging, obesity, neurodegeneration, and in a number of other major conditions and diseases (for comprehensive recent reviews, see Refs. 69, 465, 899, 946, 947, 1052, 1120). Autophagy seems to intervene to protect cells during I/R (1367), and also to be key process in the phenomenon of ischemic preconditioning (e.g., Refs. 228, 491). It is altered in cancer (581, 673) and neurodegeneration (749, 1356). Although its function in these major pathologies is still debated, it may mainly represent a prosurvival/proliferation strategy. Defects in autophagy are associated with inflammation, an oncogenic factor. On the other hand, direct or indirect induction of the MPT is a pharmacological strategy against cancer (see sect. III*F5*).

The MPT is most notorious for its key role in the mechanism of I/R damage (see **TABLE 8**). During reperfusion, the conditions in the cell cytoplasm are nearly ideal for the onset of the MPT. Indeed, ablation of CypD or treatment with MPTP inhibitors produces clear protective effects (see **TABLE 8** and Refs. 92, 439, 525, 586, 603, 645, 939, 1095, 1143). Transient opening of the MPTP is also believed to be one of the factors accounting for ischemic preconditioning (see **TABLE 8** and Refs. 523, 683, 939, 1121). Thus the occurrence, in a relatively mild form, of the MPT appears to be a protective factor antagonizing more severe later occurrences.

In general, the MPT may be suspected to play a role in all degenerative, necrotic diseases. One example is pancreatitis (reviewed in Ref. 486). It is important for neurodegeneration in pathologies such as Alzheimer's disease, Parkinson's disease and ALS, acute consequences of stroke, cardiac arrest, brain trauma, insulin-induced hypoglycemia and epileptic crises, and ethanol-induced death of neurons in mouse pups. In mice, lack of CypD protected neurons in experimental autoimmune encephalomyelitis (a model of multiple sclerosis) (411), and muscle cells from atrophy following denervation (291, 307), but caused behavioral disturbances (796). The MPT may contribute to aging (336), and the MPT may occur more easily in aged tissues and animals (336, 1452, 1453; reviewed in Ref. 965) because of changes in the modulatory pathways.

In cancer, signaling pathways are activated which desensitize the mitochondria to MPT induction (1048, 1319) (see above, also for the connection with autophagy and a protective mitochondrial chaperone network in cancer), while chemotherapeutic agents causing oxidative stress may activate signals causing cancer cell death via the MPT (257, 284). Transplant patients, treated with CSA to prevent transplant rejection, have a high incidence of cancer not only because of the drug's immunosuppressive action, but also because CSA inhibits the MPTP (919).

5. Pharmacology

MPT inhibitors are of great interest because of the role of the MPT in cardiac damage and other pathological situations. Recently, a powerful derivative of CSA has been obtained by conjugation of a triphenylphosphonium group (362, 818). Nonimmunosupressive but still MPT-inhibiting analogs of CSA are available: NIM811 (1362) and Debio-025 (Alisporivir) (456, 1301). They, and Sanglifehrin A, another cyclophilin-binding compound which however is immunosuppressive, have been tested as cardiac protectors (933). Antamanide, produced by *Amanita phalloides*, likewise inhibits the MPT by binding to CypD (78). In this context, it is interesting that specific inhibition of MPTP-associated "necroptosis" can result in cell death by "classical" apoptotic OMM permeabilization (513), highlighting the concept that necrosis and apoptosis may function as reciprocal back-up mechanisms.

For oncological applications MPT inducers are relevant (e.g., Refs. 416, 745), although other mechanisms may account for chemotherapeutic action at least in part and in some cases, and the likelihood of noxious side effects, for example, on the nervous system, must be kept in mind. A large number of compounds, many of which are natural products, have been shown to induce the MPT in cultured cells, often as a consequence of oxidative stress and/or disruption of Ca^{2+} homeostasis. The effect is often observed at relatively high concentrations. One class of such compounds is that of mitochondria-penetrating peptides, such as mastoparan-like sequences, peptides of the innate immunity systems or the molecules developed by Kelley's group (see, e.g., Refs. 558, 614). Prominent among these candidate drugs are peptides and small molecules disrupting the interaction of HK with the mitochondrial membrane system (see above): jasmonates (e.g., Refs. 404, 405, 1053); arsenite (733); TNF or TRAIL and actinomycin D (649, 972); lonidamine, betulinic acid, the synthetic retinoid CD437 (282, 583, 755); further natural compounds like berberine (1000–1002), chelerythrine (417, 1365), stevioside (978), cinnamaldehyde (625), andrographolide (244), neosergeolide (232), 7-xylosyl-10-deacetylpaclitaxel (596), honokiol (760), α-bisabolol (233), shikonin (512, 513). The MPT can be activated (or inhibited) indirectly, by acting on the signaling pathways which modulate its occurrence. For example, induction of oxidative stress by gold complex AUL12, which inhibits respiratory complex I, can lead to activation of GSK3α/β, favoring MPT opening (257, 258).

G. Channel Activity by Carriers of the Inner Mitochondrial Membrane: Electrophysiology of the Adenine Nucleotide Translocator and of the Phosphate Carrier

The dozens of mitochondrial "tripartite" solute/metabolite carriers have been the object of much productive research over the past few decades, and their structure, mechanism, regulation, and pathophysiological relevance are either fairly well known or at least much discussed (reviews in Refs. 661, 926, 957–959, 1320, 1323, 1383, 1138, 509). The most closely scrutinized one is the abundant and paradigmatic ATP/ADP exchanger. The structure of two of its conformations, in both cases with bound carboxyatractyloside, have been resolved (925, 984) and together with much biochemical data form the basis for mechanistic models. The protein has long been considerd to function as a homomeric dimer, although data and arguments in favor of a monomeric structure have been presented (106, 716, 927). In either case, the most popular proposed mechanisms are of the sequential type: binding of the nucleotide to be transported takes place in a cavity which can be accessed alternatively from one side or the other of the membrane through the operation of "gates" (716, 926, 984, 1070, 1323). Thus normal carrier operation does not compromise membrane "tightness": when one of the gates is open, the other is closed, preventing permeation by ions or solutes. However, one can easily imagine that under some conditions (e.g., oxidative stress, specific drugs or alterations of cardiolipin, known to be an essential component) both gates may happen to be open simultaneously, transforming the carrier into a channel. Several examples are known of carrier proteins exhibiting channel-like as well as transporter-like behavior (e.g., Refs. 221, 1158, 320, 542, 1342). The idea that IMM transporters might turn into pores was promoted by the indications that the ANT (or other carriers, in particular the phosphate carrier: Refs. 508, 756, 757, 1344), might be a core component of the MPTP (e.g., Refs. 197, 283, 288, 496, 502, 504, 851, 1393, 1461).

The first electrophysiological evidence that the ANT could indeed form an ion-conducting pore was published by Skulachev's group in 1994 (1302). BHM ANT was incorporated into liposomes and hence, by fusion, into BLMs. Multiple transitions in the hundreds of picoSiemens range and up to 2.2 nS (180 mM Na_2SO_4) were observed and considered to be similar to MMC/MPTP activity.

In 1996 Brustovetsky and Klingenberg (207) reported patch-clamping giant proteoliposomes containing purified ANT from BHM. The activity they observed had $P_K/P_{Cl} \sim 4$ and exhibited multiple conductance levels, including between 300 (i.e., one-half) and 600 pS (100 mM KCl). As the transmembrane voltage was increased to values above 150 mV (either polarity), the open channel entered a fast-gating mode and closed transiting through the half-size and lower-conductance states. This behavior resembles that observed with the MMC/MPTP (see sect. III*F*). Another major characteristic linking this pore to the MPTP was the dependence on Ca^{2+}: the channel was commonly observed with Ca^{2+} in the millimolar range, but not at $[Ca^{2+}] = 0.1$ μM or with Ca^{2+}-free solutions. Activity was furthermore inhibited at acidic pH values. BGK and CAT affected the activity, coherently with an involvement of the ANT, but CSA did not, coherently with the lack of CypD in the preparation. The conclusion that the ANT could form channels, and these channels were those of the MPTP was reinforced by the similar results of a subsequent study employing recombinant *N. crassa* ANT purified after expression in *E. coli* (208). A possibly similar activity, anion selective, with conductance levels of 200 and 600 pS in 250 mM KCl and responding to inhibitors of the ANT, was observed (but not shown in a publication) by Wagner's group in experiments in which IMM vesicles from yeast were incorporated into BLMs (1327).

At about the same time as Brustovetsky and Klingenberg's experiments, Brdiczka's group isolated a complex containing at least VDAC, ANT, and hexokinase or creatine kinase from rat brain, incorporated it into planar bilayers and observed pores with a conductance of up to 6 nS in 1 M KCl and a bell-shaped voltage dependence (169, 171). Proteoliposomes reconstituted with this complex in the membrane could be loaded with ATP or malate, which were released by external application of Ca^{2+}, in a cooperative manner with ATR or with long-chain fatty acids (1380). This latter process was inhibited by *N*-methylVal-4-cyclosporin, suggesting that the reconstituted material was the MPTP complex. A similar behavior was observed with liposomes containing highly purified ANT, which became permeable to metabolites if treated with Ca^{2+}, ATR, or $HgCl_2$, while ADP inhibited the efflux of liposome contents. However, in this case *N*-methylVal-4-cyclosporin had no effect (1093), suggesting that the ANT alone was not sufficient for MPTP formation.

Kroemer and co-workers (198, 1353) purified instead ANT from rat heart mitochodnria (RHM) and studied this preparate by the tip-dip technique. Incorporation of the purified ANT in BLM did not result in currents being recorded unless Ca^{2+} (mM) or atractyloside (40 μM) were present. With these activating agents channels were observed with considerably lower conductance than those reported by Brustovetsky and Klingenberg: chord conductance levels of 70 and 250 pS were observed in experiments with Ca^{2+}, and of 30 pS in those with ATR (100 mM symmetrical KCl). This latter conductance had a permeability coefficient ratio P_K/P_{Cl} of ~3. Bax at low concentrations did not produce channel activity, but when a 1:4 mix of Bax and ATR-treated ANT was studied, channels were observed, with conductances of 30 and 80 pS (150 mV),

considered to be different from those observed by the same authors with higher concentrations of just Bax (200 pS) or just ANT plus activator (see above). No such cooperative effect was observed with Bax mutant forms lacking apoptogenic activity. Preincubation of the ANT with ATP abolished pore formation, so did the presence of Bcl-2. Bcl-2 by itself was found to form pores under the same circumstances so that the inhibitory effect was apparently reciprocal. Bcl-2 was furthermore able to neutralize the effect of Bax.

A similar behavior was observed using the COOH-terminal half of viral protein R (Vpr), an apoptosis-inducing accessory protein of HIV shown to interact with the ANT with nanomolar range affinity. Vpr52–96 induced permeabilization of ANT-containing proteoliposomes and at high doses (80 nM) formed 55 pS (100 mM KCl) channels in BLMs, but was without effect at concentrations below 1 nM. When the bilayer contained ANT, however, these low concentrations of Vrp52–96 induced the appearence of 190-pS channels, suggesting interaction with the ANT to form a wide pore. The copresence of Bax increased the conductance of these channels to 245 pS, while Bcl-2 (but not an incompetent partially deleted form) abolished them (393, 580). Observations with isolated mitochondria were coherent with the idea that the interaction of the peptide with the ANT induced the PT. Analogous interactions were also proposed for Bid (1436). In tip-dip experiments, 0.1 nM full-length Bid did not produce observable channel activity by itself, but elicited ~60 and 150 pS (100 mM KCl) BGK-sensitive channels when 1 nM isolated ANT was also present. In the case of untreated 1 nM ANT and also 0.3 nM Bax (a concentration too low to elicit activity by itself according to Brenner et al., Ref. 197), the copresence of 0.1 nM Bid resulted in the appearence of 340- and 450-pS channels with 240-pS flickering transitions, which were inibited by 10 μM BKCAG. When t-Bid was used, 0.1 nM by itself produced ~50-pS channels, whose conductance increased to ~100 and 270 pS when 1 nM ANT was also present. With t-Bid, the copresence of 0.3 nM Bax did not have any significant effect.

In further work by the same group, three experimental chemotherapeutic agents proposed to induce cell death via the mitochondrial permeability transition, namely, lonidamine, arsenite, and CD437 (6[3-adamantyl-4-hydroxyphenyl]-2-naphthalene carboxylic acid), were tested in a liposome system and in planar bilayer experiments. They permeabilized liposomes to a probe molecule if the liposomes contained ANT, but not otherwise. The effect was counteracted by ADP, ATP, and Bcl-2. These compounds were also found to elicit, ATR-like, channel activity from purified/reconstituted ANT. The conductances reported were of ~20 (lonidamine), 100 (arsenite), and 47 (CD437) pS (145). On the opposite side, nelfinavir, an inhibitor of HIV protease which rescues cells from apoptosis also in nonviral disease model, was found to inhibit the release of tracers from ANT-containing proteoliposomes, and interaction with ANT was proposed to underlie the redeeming effect of the drug (1373).

The overall conclusion drawn was that the ANT can form an ion-conducting pore that is regulated by members of the Bcl-2 family and other agents as expected if it had a major role in apoptosis, an idea promoted by the Villejuif group at the time. However, the idea of an involvement of the ANT in MPTP formation, or, for that matter, of the MPTP in apoptotic death has fallen out of favor after data were reported that were taken to indicate that the ANT was not a required component of the MPTP (98, 468, 669) and that the MPTP was involved in necrosis but not in apoptosis involving Bcl-2-family proteins (92) (see sect. II*D1*).

A well-behaved chloride-selective channel studied in BLM upon fusion of IMM SMPs from rat heart turned out to be inhibited by both BGK and ATR and CATR applied in the tens of micromolar range, much higher than what required to block the ANT (811). Inhibition was voltage and side of addition dependent, which nonetheless may suggest a relationship to the ANT, although the authors preferred to hypothesize an identification with IMAC. In 250:50 mM KCl, the channel's conductance determined from the current-voltage relationship in the 30/−30 mV range varied between 104 and 172 pS from experiment to experiment, with an apparently unrelated analogous variability of the reversal potential between −14 and −30 mV (low-salt side). Part of this variability might be due to an occasionally incomplete perfusion of the *cis*-side chamber, which was brought first up to 600–800 mM KCl to favor incorporation, then back to 250 by perfusing with 10 volumes.

Finally, the phosphate carrier (PiC) was studied following up on the observation that it could be converted into a unidirectional transporter upon modification with mercurials (1152, 1236). Ion conduction was studied by patch-clamping giant liposomes containing the *S. cerevisiae* protein expressed in *E. coli* (541). A relatively small, strictly anion-selective, slightly inward-rectifying channel was observed, showing a variety of chord conductances between ~4 and 40 pS (symmetrical 100 mM KCl). This activity was blocked by 10 mM P_i in a protein orientation-dependent manner, whereas lower concentrations (0.1 or 1 mM) resulted in the appearence of larger current fluctuations, corresponding to chord conductances of up to 85 pS. Sulfate, vanadate, and ADP did not block. Divalent cations were found to enhance the inhibitory effect of phosphate, and to induce a conductance decrease and a prolongation of mean open and closed times. To our knowledge, no attempt has been made to verify whether MPTP reagents have an effect on the activity associated with reconstituted PiC, which has been proposed as a component of the MPTP (756, 757, 508). The conductances reported, like those observed with

the ANT, are in any case too small for a direct correlation between the activities observed in these experiments and the MPTP.

Our group, in collaboration with D. Wolff of the Catholic University of Santiago (Chile) and R. Krämer of the Institut für Biotechnologie of Jülich (Germany), in the early 1990s made a determined effort to characterize the channel activity of purified ANT and PiC after reconstitution in planar bilayers. Channel activity was observed in the majority of hundreds of BLM experiments. However, the work was complicated by the persistence of traces of contaminant proteins in the preparations, and by the strong variability, in terms of both pore characteristics and pharmacological responses, of the activities observed. The observations were not considered reproducible and reliable enough for publication. To reinforce the point that these carrier proteins can indeed catalyze the transport of ions across membranes, at least under some in vitro experimental conditions, **FIGURE 8** shows some representative current recordings. They help to make another point: the activity elicited from reconstituted carriers is highly variable; conductance values reported for ANT- and PiC-associated pores in the literature and observed by ourselves vary over about two orders of magnitude. While published papers understandably tend to present relatively well-behaved activity, we have often observed irregular, noisy currents that were difficult to distinguish from membrane artifacts. The relationship between these observations in vitro and function in situ is not clear: how often do carriers such as the ANT behave as 25- or 600-pS channels in their native environment? Under what circumstances, for how long, and with what consequences for the mitochondria and the cell? As mentioned, until a few years ago it was considered likely that such activity underlay the permeability transition and cell death, but this seems not to be the prevalent opinion anymore. Thus the take-home message may be a cautionary one.

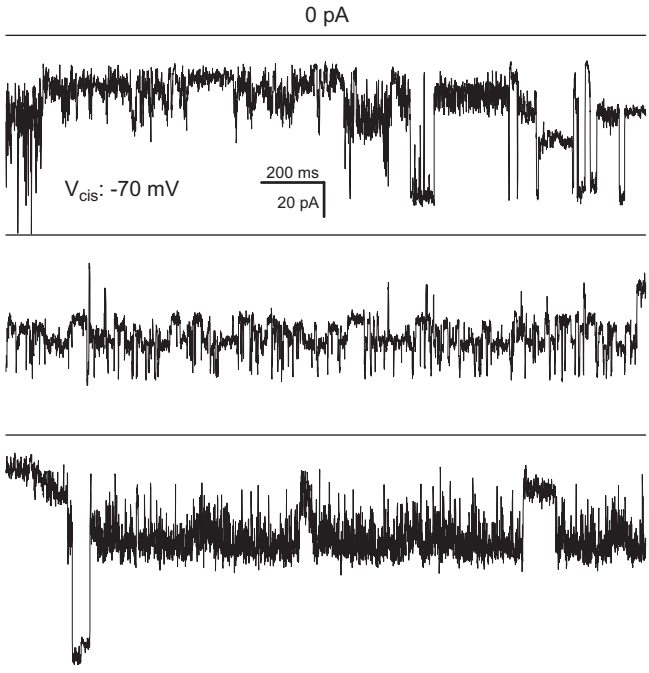

FIGURE 8. Activity of purified adenine nucleotide carrier. Representative current traces recorded at −70 mV in planar lipid bilayer experiments with 100 mM/680 mM KCl gradient are shown, illustrating variability in both conductance and kinetic behavior of purified ANT.

IV. OTHER PUTATIVE MITOCHONDRIAL CHANNELS

A. Uncoupling Proteins: Electrophysiology, Pharmacology, and Pathophysiological Roles

The uncoupling protein (UCP) family, belonging to the superfamily of mitochondrial anion-carrier proteins, contains five members (e.g., Ref. 704). The nature of the ion(s) transported and whether the protein acts as a real ion channel or a carrier are still debated issues; therefore, we briefly discuss UCP proteins as putative channels. UCP1 functions as a thermogenic protein mediating "proton leak" in brown adipocytes (for review, see Ref. 226), while UCP2 and -3 are expressed in various tissues, including skeletal muscle and β-cells. In this latter cell type, the role of UCP2 as a negative regulator of insulin secretion has been established. UCP2 and -3 show high amino acid sequence identity with UCP1, while UCP4 and -5 are less homologous. The proton translocation activity of UCPs requires fatty acids as cofactors, while these modulators do not exert any effect on the chloride channel activity which has been observed by patch-clamping proteoliposomes following reconstitution of UCP1. Huang and Klingenberg (561) observed a slightly inward-rectifying chloride channel displaying a unit conductance of ~75 pS in symmetrical 100 mM KCl. The channel closed at high positive potentials on the matrix side and was sensitive to nucleotides and to the general chloride channel inhibitor DIDS. Mutants of UCP1 that are impaired in proton transport but not in chloride transport have been identified (367). Vice versa, mutations of only two arginines, R83 and R91, abolished chloride transport (366). On the other hand, in an elegant piece of work, native UCP1 has been shown to require long-chain fatty acids (LCFA) for its H^+ transport activity and was proposed to operate as a $LCFA^-/H^+$ symporter (387). The authors show that chloride current through UCP1 is small compared with the currents obtained using LCFA and conclude that chloride is unlikely to contribute significantly to UCP1-mediated uncoupling. Thus this work does not confirm the results obtained with purified and reconstituted protein concerning the relatively high chloride conductance (561). One possibility is that purification and the use of detergents alter the ion-conducting properties of UCP1. UCP2 also forms an anion-conducting pathway in vitro, with the transmembrane domain 2 being reponsible for

channel formation and voltage dependence (1413). The structure of UCP2 has recently been resolved using NMR spectroscopy providing insight into the UCP2 channel pathway and revealing structural similarity to the ANT (156). UCP2 and -3 have also been proposed to contribute to mitochondrial calcium uptake (1322).

The physiological importance and the occurrence of UCP2/3-mediated proton leak is not entirely clear and is still debated, but it has been suggested that it might limit the maximal value of the proton gradient across the IMM. Since ROS production is dependent on the protonmotive force (e.g., Ref. 963), proton leak is expected to limit oxidative damage. In fact, UCP2 has been proposed to regulate cell survival by leading to a decreased formation of mitochondrial ROS, given that lowering of mitochondrial membrane potential (i.e., depolarizing) by proton leak may diminish mitochondrial superoxide production (87, 88, 113, 326). UCP2 overexpression reportedly prevents oxidative injury, while knockout or pharmacological inhibition of UCP2 promotes it in various cell types, suggesting a role for UCP2 in pathological states associated with oxidative stress, including degenerative disease, atherosclerosis, stroke, aging, and cancer. In several cases a transient, small hyperpolarization has been detected that precedes other apoptotic events (1005). This process may promote an increase in intracellular ROS levels, followed by opening of the MPTP, ultimately leading to full-scale apoptosis (see also the case of Kv1.3; sect. III*A5*). Importantly, apoptosis may not occur if mitochondrial hyperpolarization is prevented by uncoupler agents (616). One may therefore speculate that UCP2 contributes to a higher apoptotic threshold and assists survival of cancer cells by modulating mitochondrial membrane potential, inducing a protective mild uncoupling and a consequent decrease in ROS release. Indeed, high expression of UCP2 had been reported to protect from apoptosis (1445) by decreasing mitochondrial ROS production, and an increased ROS production was observed in UCP2 knockout mice (62). UCP2 can be considered a sensor of mitochondrial oxidative stress. On the other hand, its expression increases in response to the mitochondrial oxidative stress caused by electron transport chain inhibitors (442). Interestingly, UCP2 overexpression has been proposed to directly contribute to the Warburg phenotype (1117) and in an orthotopic model of breast cancer, overexpression of UCP2 leads to development of tumors (73).

B. Intracellular Chloride Channel CLIC4

There are seven members of the intracellular chloride channel family (CLICs). CLICs are signal peptide-less proteins with a distant relationship to glutathione-*S*-transferases and are located in various organellar membranes where they play a role in regulation of organelle ion homeostasis and volume (for review, see Ref. 773). CLIC4/mitoCLIC has one predicted transmembrane domain, has both a soluble and a membrane-inserted form, and can be localized to the mitochondrial inner membrane (390), cytoplasm, ER membrane, and the nucleus. Homologs of CLIC4, whose structure was resolved in its soluble form (765), share 85–95% amino acid sequence identity, suggesting that its physiological functions are evolutionarily conserved. Recombinant CLIC4 gave rise to a conductance of 31 pS when studied in 140 mM KCl with the dip-tip technique (772). In another work, recombinant CLIC4, when inserted into planar lipid bilayer, gives rise to a small, 15 pS (in 500/50 mM KCl) poorly selective channel activity, presumably arising from oligomerization of the TM domain (1209). CLIC4, in contrast to CLIC1 and CLIC5, is not inhibited by F-actin, a component of cytoskeleton (1210) but is redox regulated (772).

As to the possible function of CLIC4 in mitochondria, it might contribute to the regulation of the mitochondrial membrane potential, similarly to other mitochondrial Cl^- channels. CLIC4 overexpression induced apoptosis associated with loss of mitochondrial membrane potential, cytochrome *c* release, and caspase activation, suggesting that apoptosis is mediated by mitochondrial dysfunction (391). On the other hand, inhibition of CLIC4 expression by siRNA triggered mitochondrial apoptosis under starvation and enhanced autophagy (1447).

C. Acetylcholine Receptor

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels (e.g., Ref. 239) with those composed of α3 and α7 subunits being expressed also in nonexcitable cells. In addition to the plasma membrane, also rat hippocampus (381), mouse liver (436), and lymphoid human cell line (629) mitochondria were shown to harbor functional nAChRs by using immunolgold labeling exploiting specific antibodies against α3 and α7 subunits. Mitochondria from the wild-type but not $\alpha7^{-/-}$ mice bound α7 nAChR-specific antibody and FITC-labeled a-cobratoxin or Alexa 555-labeled a-bungarotoxin acting on these subunits (629, 436). Interestingly, the presence of nAChRs in mitochondria was revealed in the outer membrane as they colocalized with VDAC and TOM. nAChR agonists (1 mM acetylcholine, 10 mM choline, or 30 nM PNU-282987) impaired intramitochondrial Ca^{2+} accumulation and significantly decreased cytochrome *c* release stimulated with either 90 mM $CaCl_2$ or 0.5 mM H_2O_2. The conclusion of the authors is that nAChRs regulate VDAC-mediated Ca^{2+} transport. No nAChR-like activity has been observed in electrophysiological experiments on OMM preparation so far. It is to note that consistent with the mitochondrial localization of nAChR, cholineacetyltransferase, an enzyme converting choline into acetylcholine, was identified in mitochondria (953).

D. MPV17

MPV17 and its *Saccharomyces cerevisiae* ortholog Sym1 are four transmembrane segment-containing proteins with a predicted mitochondrial localization. However, the NH_2-terminal presequence of Sym1 is not cleavable, and its removal does not affect translocation and effective integration into the IMM. Mutations affecting MPV17 are associated with inherited autosomal mitochondrial DNA depletion syndrome (MDDS) characterized by neuronal disorders, growth retardation, liver failure, and hypoglycemia.

Silencing of an MPV17-like mitochondrial isoform (MPV17l) has been shown to increase mitochondrial ROS generation, depolarization, and apoptosis (707). In knockout mice, lack of MPV17 results in decreased respiration and mitochondrial dysfunction (1355). Whether MPV17 forms ion channels is not known, but recent evidence points to pore-forming capability of its yeast homolog, Sym1, shown to have a role in the structural preservation of the IMM and in maintainence of oxidative phosphorylation (299). Given that the Sym1-related peroxisomal Pxmp2 forms large pores, Dudek and colleagues (1057) tested channel activity in bilayer using Sym1 purified from yeast. In 250 mM KCl, a slightly rectifying cation-selective channel exhibiting slow gating kinetics was recorded with 510 (positive voltages) and 450 pS (negative voltages) conductances. Interestingly, the channel displayed a bell-shaped voltage-dependent P_o, suggesting that it is closed at physiological IMM potentials. The conductance of Sym1 corresponds to a large pore size of ~1.6 nm, but whether metabolites can pass through this channel under physiological conditions remains to be determined. The reported channel activity of Sym1 has properties that are different from those of the channels previously observed by patch clamp of mitoplasts or bilayer experiments using vesicles obtained from VDAC-less yeast mitochondria (118, 1262), which were sensitive to pre-peptides and were tentatively ascribed to the peptide-sensitive channel (see above).

One important aspect of the work of Dudek and colleagues (1057) is the demonstration that Sym1 can be imported into the IMM through the TIM23 complex, independently of the presequence. Thus a novel transport mechanism for a polytopic membrane protein in which internal signals direct the precursor into the inner membrane via the TIM23 complex has been identified. This mechanism might be of relevance also to explain the mitochondrial targeting of other ion channels which do not harbor a classical NH_2-terminal targeting signal (e.g., Kv1.3, IKCa).

E. The Vacuolating Cytotoxin VacA of *Helicobacter pylori*

The vacuolating cytotoxin (VacA) is an important anion-channel forming virulence factor of *Helicobacter pylori* (for reviews, see Refs. 882, 1050). Indeed, low-conductance pore formation by VacA (1311, 1313) has been shown to account for cell vacuolation and for an increase of transepithelial conductivity (1266) and for passive urea permeation (1312). The 88-kDa VacA has two subunits, p55 and p33, the former being required for entry into the target cells while the latter forms a 12-pS chloride channel in 1.5 M KCl when studied in bilayer experiments as recombinant protein (349). Interestingly, VacA has been shown to reach the IMM and cause cytochrome *c* release as well as apoptosis (422). These effects were related to the channel-forming abilities of VacA, since P9A and G14A mutations, resulting in ablation of vacuolization and of channel activity, prevented the mitochondrial effects (1382). VacA p33 (349) was recently shown to be imported to the IMM via the classical TOM/TIM-mediated pathway and to form homohexamers. In another work, both p33 and p55 were found to be imported into the IMM (408). Interestingly, VacA requires the proapoptotic mitochondrial Bax and Bak for its action in this organelle and depending on its channel forming ability, it induces the accumulation of Bax on endosomes and endosome-mitochondria juxtaposition (220). Such VacA channel-dependent accumulation of Bax precedes its activation in the OMM. Importantly, this work raises the possibility of a direct transfer of VacA from PM to endosomes and then to mitochondria, a new mechanism which may be taken into account also when studying other PM channels that end up in the IMM. Altogether, the action of VacA at the IMM is in line with the emerging view that disturbance of ion homeostasis in mitochondria might lead to deleterious effects for the physiology of the whole cell (see above). Whether in the IMM VacA forms channels with properties similar to those observed in the PM or with the recombinant protein remains to be established. However, the small conductance of the channel is expected to prevent its detection at the single-channel level in intact IMM by patch clamp.

F. NMDA Glutamate Receptor in Mitochondria

In vertebrates, ionotropic glutamate receptors (iGluRs) are ligand-gated cation channels that mediate the majority of the excitatory neurotransmission in the central nervous system. Mammalian iGluRs are grouped into four subfamilies according to pharmacological properties and sequence similarities: α-amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA) receptors, kainate (KA) receptors, *N*-methyl-D-aspartate (NMDA) receptors, and delta receptors (713). In the case of NMDA receptors, their permeability to Ca^{2+} is higher than to monovalent cations. Indeed, these receptors gate the cytoplasmic influx of calcium in neurons, participating thus in synaptic communication. On the other hand, excessive Ca^{2+} influx into the cytoplasm through NMDA channels can lead to cell death and has been implicated in neurodegenerative disorders. In a recent piece of

work, NMDA receptor subunits NR2a and NR2b were identified in the IMM using Western blot and immunogold electron microscopy (681). In cells overexpressing NR1-NR2a, treatment with glutamate caused a twofold increase in mitochondrial calcium uptake, even in the presence of MCU inhibitor ruthenium red. Thus the authors proposed that mito NMDA receptors might represent an alternative route for calcium uptake with respect to MCU (681). If so, this might contribute to explain the lack of phenotype of MCU deletion, at least in the nervous system (see above). Further work is required to prove a functional expression of mito NMDA under physiological conditions, to study its ion-conducting properties and its regulation, and to understand its actual contribution to calcium uptake into mitochondria.

G. ASIC1

The neuronally expressed, proton-gated acid-sensing ion channel-1 (ASIC1) (1361) is permeable to Na^+ and Ca^{2+}. Four separate genes encode six different ASIC subunits (1377), i.e., the alternatively spliced transcripts for ASIC1a and ASIC1b, ASIC2a and ASIC2b, as well as ASIC3 and ASIC4. These subunits form homo- or heteromultimeric channels and are activated by an acidic pH (except ASIC2b and ASIC4) (1377). ASIC1a has been described as a postsynaptic proton receptor that influences the intracellular Ca^{2+} concentration in hippocampal neurons (1442). It is well known that excessive accumulation of Ca^{2+} and Na^+ is associated with axonal degeneration (1245). Indeed, increased neuronal Na^+ and Ca^{2+} influxes, proposed to occur through ASIC1a, occur during tissue acidosis in an experimental model of stroke (1403). In a recent study, ASIC1a has been localized to mitochondria by Western blot and expression of EGFP-ASIC1a in cortical neurons. The transport properties of this mitochondrial protein were not defined (1372), but deletion of ASIC1a induced mitochondrial swelling, enhanced Ca^{2+} retention capacity, and elevated oxidative stress. The authors also showed that neurons from ASIC1a$^{-/-}$ mice exhibited impaired MPT. They concluded that mitoASIC1a may serve as a regulator of the MPTP, possibly independently of its channel activity. Alternatively, Na^+ flux across mitoASIC1a might contribute to MPTP opening indirectly, presumably through induction of depolarization, a factor known to foster MTPT activation (1372). While the role of mito ASIC1a, similarly to the mito NMDAR (681) and to the recently identified mitochondrial cannabinoid receptor CB1 (146), is likely to be restricted to tissues of the central nervous system, definition of the ion-conducting properties of ASIC1a in the IMM may be of interest to elucidate its exact contribution to neuronal cell death.

V. CONCLUSION

As a major conclusion, we can state that mitochondrial channels are much more interesting than originally thought! Following identification of VDAC, the field took off starting with a few studies contradicting the dogma that ion channels should not exist in the IMM since ion fluxes mediated by them would compromise energy transduction. By now it has been confirmed by various techniques that numerous ion channels exist both in the OMM and in the IMM which, as demonstrated in many cases, contribute to the correct physiological functioning of mitochondria. Thanks to the very negative membrane potential in mitochondria, strong driving forces exist for ion movements through ion channels in the IMM. Clearly, IMM channels are regulated to ensure undisturbed energy transduction. In fact, by now it is clear, as illustrated in this review, that disturbance of mitochondrial ion homeostasis and/or membrane potential by altered expression and/or pharmacological manipulation of many mitochondrial channels leads to severe mitochondrial dysfuction with consequent cell death.

Many questions in the field remain open, especially regarding targeting of ion channels to the mitochondrial membranes and identification of the molecular entities underlying the observed activities. Despite modern tools like large-scale proteomics, molecular identification of organellar ion channels is still a demanding task, due to the facts that these ion channels are encoded by the nucleus and in most cases do not harbor clear targeting sequences and to their low abundancy and high hydrophobicity rendering proteomic identification extremely difficult. Nonetheless, as illustrated in this review, identification of many channels has been achieved, allowing clarification of their (patho)physiological roles. A few concrete examples point to mitochondrial channels as promising pharmacological targets for influencing pathologies like neuro- or muscular denegerative diseases or cancer (see e.g., MPTP, mito Kv1.3). We believe that with the molecular identification of most mitochondrial ion channels, a new field devoted to large-scale drug screening allowing pharmacological targeting of these ion channels will soon develop.

ACKNOWLEDGMENTS

We are deeply grateful to all co-workers who contributed to the research lines carried out in our laboratories. We thank in particular Drs. L. Biasutto and L. Leanza for precious help during the preparation of the present review. We apologize to all authors whose work is not adequately cited in this review.

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GRANTS

The Italian Association for Cancer Research Grant number 11814 (to I. Szabo), the Cariparo Foundation Excellence

Program (to M. Zoratti), the CNR Project of Special Interest on Aging (to M. Zoratti), PRIN 2011 (2010CSJX4F to I. Szabo and 20107Z8XBW_004 to M. Zoratti), and the EMBO Young Investigator Program (to I. Szabo) are acknowledged for financial support.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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