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ATP-Regulated K^+ Channel in Mitochondria: Pharmacology and Function

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Mitochondria from several tissues contain a potassium-specific channel similar to the ATP-regulated K^+ (K_{ATP}) channel of the plasma membrane. The mitochondrial channel shares with the plasma membrane K_{ATP} channel the sensitivity to sulfonylurea derivatives and some other blockers as well as to channel openers of diverse chemical character. In contrast to the plasma membrane channel, which is blocked by free ATP, the mitochondrial K_{ATP} channel reconstituted into liposomes requires the ATP–Mg complex for inhibition. The mitochondrial K_{ATP} channel, possibly in a concerted action with other K^+ permeability pathways, plays an important role in mitochondrial volume control. Its function in the regulation of the components of the protonmotive force is also suggested.

KEY WORDS: Mitochondria; ATP; potassium channels; pharmacology; sulfonylureas; potassium channel openers.

INTRODUCTION

Adenosine triphosphate-regulated K^+ (K_{ATP}) channels constitute an important class of ionic channels linking cellular bioenergetics to plasma membrane potential (for review see Lazdunski, 1994). They are present in the cell membrane of endocrine, smooth muscle, and skeletal muscle cells as well as in neurons (De Weille, 1993; Takano and Noma, 1993). Using patch-clamp techniques, a similar type of channel, highly selective for K^+ and reversibly inactivated by ATP, was found in the inner membrane of rat liver mitochondria (Inoue *et al.*, 1991). This channel is blocked not only by ATP but also by the antidiabetic sulfonylurea derivative, glibenclamide, giving evidence that the mitochondrial K_{ATP} channel shares some pharmacological properties with K_{ATP} channels found in plasma membranes of various cells (Ashcroft and Ashcroft, 1992). Later on, mitochondrial K_{ATP} channel was partly purified from the inner membrane of rat liver and beef heart mitochondria and was shown to catalyze electrophoretic K^+ flux when reconstituted into phospholipid liposomes (Paucek *et al.*, 1992). Apart from liver and heart, glibenclamide-sensitive potassium transport has recently been discovered in yeast mitochondria (Manon and Guérin, 1993).

Studies on the mitochondrial K_{ATP} channel are complicated by the fact that the mitochondrial inner membrane contains several K^+ transporting systems (Diwan, 1987; Brierley and Jung, 1988) and the differentiation between them is not always simple. It is well known that respiring mitochondria exhibit electrophoretic K^+ uptake, the process known as potassium uniport. Recently, properties of this K^+ uniport have been investigated in more detail (Beavis *et al.*, 1993). Modulation of the activity of potassium uniport by adenine nucleotides has been studied. It was concluded that this uniport activity involved in fact the K_{ATP} channel (Beavis *et al.*, 1993). Further evidence that potassium uniport activity is catalyzed by the K_{ATP} channel was obtained from experiments with the Me^{2+} ionophore A23187. Addition of A23187 in the presence of EDTA increases the permeability of inner mitochondrial membrane to K^+ (Duszyński and Wojtczak, 1977). Later on, it was shown that A23187 plus EDTA induces

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K^+ influx via the potassium uniport which results in mitochondrial swelling (Bernardi *et al.*, 1989; Nicolli *et al.*, 1991). The K_{ATP} channel blocker, glibenclamide, was found to abolish this effect in a dose-dependent manner (Szewczyk *et al.*, 1994). These results suggest that the activity of the mitochondrial potassium uniport could be, at least partly, mediated by the ATP-regulated potassium channel.

This review describes the present state of art concerning pharmacology (Table I) and possible functions of the mitochondrial ATP-regulated potassium channel.

INHIBITORS OF THE MITOCHONDRIAL K_{ATP} CHANNEL

Inhibition by ATP, Other Adenine Nucleotides, and Their Analogs

The mitochondrial K_{ATP} channel is reversibly inactivated by ATP applied to the matrix side of the inner mitochondrial membrane (Inoue *et al.*, 1991; Inoue and Higuti, 1994). The channel activity was half inhibited at 0.8 mM ATP and almost completely blocked at > 2 mM. By contrast, neither ADP nor GTP at 2 mM had a significant effect on the channel activity. Mg^{2+} was not required for ATP blocking. Interestingly, ATP-sensitive currents ran down gradually in inside-out patches, reactivation of the channel being observed after addition and removal of ATP to and from the bathing solution during the run-down period (Inoue *et al.*, 1991).

Further studies on ATP inhibition of mitochondrial K_{ATP} channel were performed after partial purification and reconstitution of the channel into phospholipid liposomes (Paucek *et al.*, 1992). A strong inhibitory effect of ATP on K^+ transport, measured with a fluorescent dye, was observed. Both Mg^{2+} and ATP were required for this inhibition. ATP had no effect in the absence of magnesium, and magnesium had no effect in the absence of ATP. Interestingly, the fact that Mg^{2+} was ineffective in the absence of ATP differed from studies on intact mitochondria where potassium transport was inhibited by Mg^{2+} alone (see Brierley *et al.*, 1994). Similar effects were observed for Ca^{2+}. In the presence of 3 mM Mg^{2+} K_i[ATP] was estimated as 39 μM, and K_i[ADP] as 280 μM. The latter value was found to increase up to 639 μM in the presence of 50 μM ATP. This is consistent with the competition between ATP and ADP for the same binding site, resulting in almost full activity of the channel protein in the presence of 50 μM ATP and 100 μM ADP (in the presence of 3 mM Mg^{2+}) (Paucek *et al.*, 1992).

Inoue *et al.* (1991) observed ATP inhibition of the mitochondrial K_{ATP} channel in the absence of added Mg^{2+}. This discrepancy may be due to the presence of 0.55 mM Ca^{2+} in the assay medium and/or the presence of residual magnesium in the mitoplast preparation. The latter idea is supported by the observation of the "refreshment" of channel activity after ATP addition and removal (Inoue *et al.*, 1991). It is not clear why the inhibition of K_{ATP} channel by ADP was observed after reconstitution into proteoliposomes (Paucek *et al.*, 1992) but not in patch-clamp studies on mitoplasts (Inoue *et al.*, 1991). Recently, it has been reported that both GTP (K_a = 7 μM) and GDP (K_a = 100 μM) are able fully to activate the mitochondrial K_{ATP} channel in the presence of 500 μM ATP, a concentration at which the channel is otherwise completely inhibited (Garlid, 1994).

Because of the presence of several pathways for K^+ movement in the inner mitochondrial membrane (Brierley *et al.*, 1994), demonstration of the functional K_{ATP} channel in intact mitochondria is only possible due to its sensitivity to ATP or to typical K_{ATP} blockers and openers. Potassium ion transport into mitochondria can be measured by following the swelling of mitochondria suspended in isotonic potassium salts. Using this technique, it was demonstrated that K^+ influx was inhibited by adenine nucleotides with low IC_{50} values

Table I. Pharmacology of Mitochondrial K_{ATP} Channel

Inhibitors	Activators
ATP, ADP, AMP[a,b,c]	GDP, GTP[f]
Glibenclamide, glipizide, glisoxepide[a,b,d]	RP 66471, P1060, pinacidil, diazoxide[g]
4-Aminopyridine[a]	
U37883A[e]	
DCCD[b]	

[a] Inoue *et al.*, 1991.
[b] Paucek *et al.*, 1992; ATP and ADP inhibit only in the presence of Mg^{2+} or Ca^{2+}.
[c] Beavis *et al.*, 1993.
[d] Szewczyk *et al.*, 1994, 1995b.
[e] Szewczyk *et al.*, 1995a.
[f] Garlid, 1994; activation observed in the presence of ATP.
[g] Szewczyk *et al.*, 1993a; Belyaeva *et al.*, 1993; Szewczyk *et al.*, 1995b.

of 0.5 and 2.3 μM for ADP and ATP, respectively (Beavis *et al.*, 1993). Surprisingly K^+ transport was also inhibited by AMP (IC_{50} = 8 μM). An inhibition by low concentrations of a nucleotide analog belonging to the triazine dye family, Cibacron Blue F3GA, was also demonstrated (Beavis *et al.*, 1993).

Based on these findings, the following questions may arise:

— where on the channel molecule the nucleotide binding site is located, i.e., whether it may face the outer or the inner leaflet (matrix side) of the mitochondrial inner membrane;
— what is the specificity of interactions of adenine nucleotides with the mitochondrial K_{ATP} channel; in other words why, depending on experimental procedure, different nucleotides affect channel activity with different potency;
— whether ATP is a physiological modulator of the mitochondrial K_{ATP} channel or whether GTP and/or GDP control the channel activity in the presence of ATP;
— why only the ATP-Mg complex and not ATP alone affects channel activity; does this mean that some phosphorylation events are involved in blocking the mitochondrial K_{ATP} channel.

Sulfonylurea Blockers

As in the plasma membrane, the mitochondrial K_{ATP} channel is blocked by a sulfonylurea drug, glibenclamide (Inoue *et al.*, 1991). It was shown that the K_{ATP} channel partly purified and reconstituted into liposomes was sensitive to glibenclamide with K_i of 62 nM in the absence of divalent cations (Paucek *et al.*, 1992). However, Mg^{2+} which alone had no effect on the channel activity was found to reduce the inhibitory potency of glibenclamide (in the presence of 3 mM Mg^{2+} K_i increased to 3.1 μM) (Paucek *et al.*, 1992). This result supports the suggestion that Mg^{2+} may interact directly with the channel protein.

In contrast to the high sensitivity to glibenclamide of the reconstituted mitochondrial K_{ATP} channel, K^+ transport in intact mitochondria appeared to be much less affected by this sulfonylurea derivative (Beavis *et al.*, 1993), as little as 10% inhibition being observed at 70 μM glibenclamide. In our experiments in which K^+ influx into liver mitochondria was enhanced by Mg^{2+} depletion, 50 μM glibenclamide inhibited the flux almost completely (Szewczyk *et al.*, 1994). Similar sensitivity to glibenclamide was observed for potassium influx after energization of mitochondria (Belyaeva *et al.*, 1993). This apparent discrepancy between studies of K_{ATP} channel in intact mitochondria and in liposomes could be explained as follows. As shown by Paucek *et al.* (1992), Mg^{2+} reduces the inhibitory potency of glibenclamide. Thus, the requirement of a relatively high concentration of glibenclamide to abolish the potassium transport into mitochondria could be ascribed to the presence of Mg^{2+} in mitochondrial preparation. In addition, the potency of glibenclamide, a highly hydrophobic compound, depends on its surface concentration. Indeed, by lowering the protein concentration during the experiment it was possible to increase the effectiveness of glibenclamide to block potassium transport (Szewczyk, unpublished observation). In addition, studies on binding of radioactive glibenclamide to mitochondrial membranes revealed the existence of low-affinity binding site only (Szewczyk, unpublished observation).

Non-sulfonylurea Blockers

Plasma membrane K_{ATP} channels are blocked by some non-sulfonylurea drugs (for review see Edwards and Weston, 1993). For example, the α-adrenoreceptor blockers, phentolamine and clonidine, could inhibit K_{ATP} channels in β-cells (Plant *et al.*, 1991). Barbiturates were also shown to inhibit K_{ATP} channels (Kozlowski and Ashford, 1991). In insulinoma cells K_{ATP} channel was also blocked by 8-methoxypsoralen (Szewczyk *et al.*, 1992a) and calcium antagonist TMB-8 (Szewczyk *et al.*, 1992b). Recently, it has been shown that a guanidine derivative U-37883A acts as K_{ATP} channel antagonist (Meisheri *et al.* 1993; Guillemare *et al.*, 1994). This compound was also shown to lower the rate of A23187-induced K^+ uniport activity in mitochondria (Szewczyk *et al.*, 1995b), thus suggesting that it was active against the mitochondrial K_{ATP} channel as well.

It was suggested that U-37883A acts on a binding site different than that for glibenclamide (Ohrnberger *et al.*, 1993). In order to verify whether a similar observation may be true for mitochondria, binding of radioactive derivative of glibenclamide to the inner mitochondrial membrane was studied (Szewczyk *et al.*, 1995a). Binding of [^{3}H]glibenclamide was inhibited by 30 μM glibenclamide but was not affected by U-37883A. This suggests that, indeed, U-37883A binds in mitochondria to a different site than sulfonylurea,

similarly as is the case in the plasma membrane (Ohrnberger *et al.*, 1993).

Using a patch-clamp technique it was shown that 4-aminopyridine blocks mitochondrial K_{ATP} channel (Inoue *et al.*, 1991).

Gauthier and Diwan (1979) were the first to show that the alkylating agent dicyclohexylcarbodiimide (DCCD) partially inhibited K^+ transport in intact mitochondria. No activity of the K_{ATP} channel was found after pretreatment with DCCD of the partly purified potassium channel protein from mitochondria (Paucek *et al.*, 1992).

INTERACTIONS OF POTASSIUM CHANNEL OPENERS WITH MITOCHONDRIA

Plasma membrane K_{ATP} channels are specifically activated by drugs like diazoxide, pinacidil, and minoxidil sulfate, known as potassium channel openers (for review see Edwards and Weston, 1990). Potassium channel openers constitute a chemically diverse group of compounds (Challinor-Rogers and McPherson, 1994). It has been shown that these reagents are able to increase the permeability to potassium ions of various cells containing K_{ATP} channels (Duty and Weston, 1990; Weston and Edwards, 1992).

It has been found that the potassium channel opener RP 66471 induces a decrease of the mitochondrial membrane potential (Szewczyk *et al.*, 1995b). Since neither the inhibition of mitochondrial respiration nor the uncoupling of mitochondria was observed concomitantly, a specific effect on the mitochondrial membrane potential was postulated. It has therefore been concluded that this effect is caused by the increase of permeability of the inner mitochondrial membrane to potassium ions. Interestingly, the effect of RP 66471 was found to be specific. All other potassium channel openers applied, such as Ro 31-6930, KRN 2391, aprykalim and nicorandil, were unable to collapse the membrane potential of energized mitochondria. Comparison of RP 66471-induced depolarization in the presence of various monovalent cations, Li^+, Na^+, K^+, and Rb^+, showed that the amplitude of depolarization in the presence of K^+ was significantly larger than that in the presence of Li^+ and Na^+. However, in the presence of rubidium ions RP 66471 induced a significant depolarization of the membrane, similar to that observed in the presence of K^+.

FUNCTION OF THE MITOCHONDRIAL K_{ATP} CHANNEL

According to the present knowledge, potassium channels in the inner mitochondrial membrane may have a dual physiological function. Firstly, a concerted action of the electrophoretic K^+ uniport and the electroneutral K^+/H^+ exchange is believed to be the main factor responsible for maintaining potassium homeostasis within the mitochondrion and thus to control intramitochondrial osmotic pressure and mitochondrial volume (Bernardi *et al.*, 1992). Regulatory volume changes are regarded as one of the important mechanisms of metabolic control at the mitochondrial level (for review see Halestrap, 1989). Some of these changes are related to the action of hormones which cause an increase of cAMP (glucagon) or calcium (vasopressin and α-adrenergic agonists) concentrations, and to the activation of the mitochondrial respiratory chain. Since changes of mitochondrial volume are sufficient to modulate metabolic processes such as citruline synthesis, pyruvate carboxylation, and fatty acid oxidation (Halestrap, 1989), it is of particular importance to establish whether mitochondrial K_{ATP} channel activity could be, at least partly, responsible for the regulation of mitochondrial metabolism (Halestrap, 1994). Observations that glibenclamide and ATP inhibit mitochondrial swelling whereas K_{ATP} openers potentiate the swelling make it likely that this channel, perhaps together with other potassium pathways, is involved in mitochondrial regulatory volume changes (Szewczyk *et al.*, 1993b; Beavis *et al.*, 1993).

Secondly, as demonstrated previously (Belyaeva *et al.*, 1993, 1994), energization of mitochondria is accompanied by a net uptake of K^+ whereas de-energization in low-potassium media promotes a net K^+ efflux. The electrophoretic K^+ uptake by mitochondria was partly inhibited by glibenclamide and activated by well-known openers of the plasma membrane potassium channel, pinacidil and P1060 (Belyaeva *et al.*, 1993). This was compatible with the hypothesis that potassium uptake upon energization partly compensates electric charge transfer produced by the proton pump and thus enables the formation of ΔpH along with $\Delta\Psi$. This was further substantiated by the observation that the rate of ΔpH formation increases with increasing K^+ concentration in the external medium and thus with increasing rate of K^+ influx (Czyż *et al.*, 1995). The final steady-state value of ΔpH also increases whereas that of $\Delta\Psi$ decreases at increasing K^+ concentration so that the resultant protonmotive force remains practically unchanged (Fig. 1). The

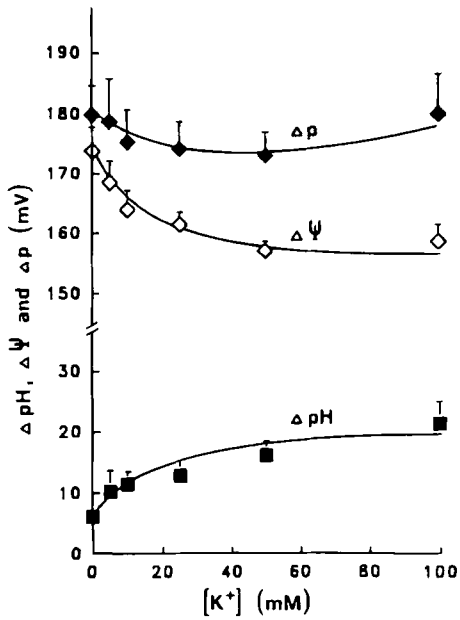

Fig. 1. Effect of K^+ concentration on steady-state values of ΔpH, the transmembrane electric potential (ΔΨ), and the total protonmotive force (Δ*p*) of rat liver mitochondria energized with succinate. The medium contained a mixture of various proportions of 200 mM sucrose and 100 mM KCl containing 0.5 mM EGTA and buffered with 10 mM Tris-HCl (pH 7.4). From Czyż *et al.* (1995).

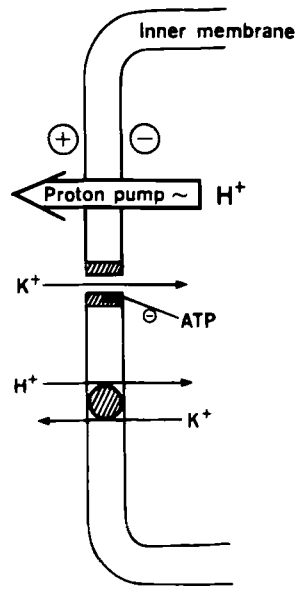

Fig. 2. Proton and potassium fluxes in energized mitochondria. This scheme illustrates a putative role of the K_{ATP} channel in partially compensating the membrane potential and thus enabling additional protons to be pumped out to form a substantial ΔpH. The electroneutral K^+/H^+ exchanger may prevent excessive accumulation of K^+ in the matrix thus contributing to maintaining a proper osmolarity of the inner compartment.

assumption that K^+ transport accounts for the formation of ΔpH was also supported by the observation that both the rate of ΔpH formation and its steady-state level in energized mitochondria are increased by a potent opener of ATP-regulated K^+ channel, RP66471 (Czyż *et al.*, 1995). As shown previously (Szewczyk *et al.*, 1995b), this compound decreases ΔΨ of energized liver mitochondria by increasing the permeability of the inner mitochondrial membrane to K^+. A scheme illustrating this putative role of the mitochondrial K_{ATP} channel is presented in Fig. 2.

All this would also suggest a possible involvement of the mitochondrial K_{ATP} channel in regulation of processes driven by the mitochondrial transmembrane potential, e.g., adenine nucleotide transport or calcium uptake, and ΔpH, e.g., phosphate and pyruvate transport.

FINAL REMARKS AND PERSPECTIVES

Studies on the mitochondrial ATP-sensitive potassium channel started only a few years ago. Hence, a variety of basic information concerning this channel is missing. The mode of interaction of sulfonylureas with mitochondrial K_{ATP} channel has not been characterized yet. Similarly, the mode of activation induced by potassium channel openers is not clear. The physiological role of this channel is still under debate. Recently, the plasma membrane K_{ATP} channel from heart has been cloned and expressed functionally (Ashford *et al.*, 1994). It can be expected that this will facilitate and accelerate investigations of not only plasma membrane K_{ATP} channels but also of the mitochondrial channel.

Interest in the mitochondrial K_{ATP} channel is growing because of both its possible role in mitochondrial energetics and its potential involvement in pathological states like ischemia and anoxia. With regard to this, it would be interesting to search for physiological modulators of this channel other than adenine nucleotides. It would also be important to clarify whether the so-called extrapancreatic effects of antidiabetic sulfonylureas may be due to interaction of this compounds with the mitochondrial ATP-regulated potassium channel.

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