Available online at www.sciencedirect.com
SCIENCE DIRECT
Biochimica et Biophysica Acta 1762 (2006) 202 – 212
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
http://www.elsevier.com/locate/bba

Review

Tissue protection mediated by mitochondrial K^+ channels

Heberty T.F. Facundo, Maynara Fornazari, Alicia J. Kowaltowski*

Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, Brazil

Received 16 March 2005; received in revised form 3 May 2005; accepted 14 June 2005
Available online 1 July 2005

Abstract

Two distinct K^+ uniporters have been described in mitochondria, ATP-sensitive and Ca^{2+}-activated. Both are capable of protecting tissues against ischemia and other forms of injury when active. These findings indicate a central role for mitochondrial K^+ uptake in tissue protection. This review describes the characteristics of mitochondrial K^+ uniport, physiological consequences of this transport, forms of tissue damage in which K^+ channels are implicated and possible mechanisms through which protection occurs.

Keywords: Mitochondria; Potassium; Calcium; Ischemia; Preconditioning; Reactive oxygen

1. Introduction

The description of K^+ uniporters in inner mitochondrial membranes [1] attracted little attention until these channels were identified as the targets of cardioprotective K^+ channel agonists [2]. Since then, a large body of work has confirmed the protective effects of increased mitochondrial K^+ uptake in a variety of forms of cell injury and death [3–8] occurring in different tissues [2,9,10]. Progress has also been made in the comprehension of the physiological effects of these channels and the manner in which they may promote tissue protection against injury. Here, we review the characteristics of mitochondrial K^+ transport, physiological effects of the activity of these channels, forms of tissue protection in which K^+ channels have been implicated and possible protective results of increased mitochondrial K^+ channel activity (reviewed previously in [11–16]).

2. Mitochondrial K^+ transport

K^+, the most abundant cytosolic cation, is present in the mitochondrial matrix at concentrations (~150 mM, [17]) similar to those of the cytosol. Increments in K^+ uniport into the mitochondrial matrix are accompanied by water diffusion and counter anion (mainly phosphate, Pi) uptake, resulting in increased matrix volume (see [15] for review). Thus, K^+ fluxes into and out of mitochondria are commonly followed by light scattering changes promoted by mitochondrial swelling and contraction [15].

2.1. K^+/H^+ antiport

Using light scattering techniques and following the predictions of Mitchell [18], Garlid [19–21] identified a K^+/H^+ exchanger in inner mitochondrial membranes in the late 1970s. Although the transport properties observed were linked to an 82-kDa protein [22], the molecular identity of this transporter has not been further elucidated to date. It is clear, however, that the K^+/H^+ antiporter is a separate entity from the Na^+/H^+ antiporter, a highly selective transporter also present in the inner mitochondrial membrane [23].

Mithocondrial K^+/H^+ antiporters are necessary to maintain organelle integrity, since they prevent excessive matrix swelling caused by continuous K^+ uptake. K^+ ions leak into the mitochondrial matrix in a manner sensitive to the inner membrane potential ($\Delta\Psi$), which confers a negative charge to the matrix relative to extramitochondrial spaces [15]. Matrix volumes could potentially increase continuously due to K^+ leak, leading to mitochondrial membrane rupture

* Corresponding author. Av. Prof. Lineu Prestes, 748, Cidade Universitária, São Paulo, SP 05508-900, Brazil. Fax: +55 11 38155579.
E-mail address: alicia@iq.usp.br (A.J. Kowaltowski).

0925-4439/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbadis.2005.06.003

secondary to mechanical stress. This side-effect of electron transport and H^+ extrusion from mitochondria is counteracted by K^+/H^+ exchangers, which use the H^+ potential as a driving force to transport K^+ out of the matrix [15]. The role of these antiporters in regulating mitochondrial volume is substantiated by the finding that increases in matrix volume stimulate their activity [21].

2.2. ATP-sensitive K^+ channels

Cation uniporters in the inner membrane usually present low permeability constants to ensure the maintenance of oxidative phosphorylation, since the entry of positive charges into the matrix decreases $\Delta\Psi$. Due to $\Delta\Psi$, when transporters are present, cations can theoretically accumulate at concentrations more than three orders of magnitude higher in the matrix than in extramitochondrial media. The activity of the Ca^{2+} uniporter, for example, promotes significant decreases in $\Delta\Psi$ and can lead to intramitochondrial concentrations of up to 1 M [24,25]. The presence of a Ca^{2+} uniporter is only compatible with mitochondrial function because of highly active Ca^{2+} removal pathways and limited in vivo activity due to low affinity relative to Ca^{2+} concentrations in the cytosol [24].

Inoue and co-workers [1] provided unequivocal evidence for the existence of K^+ uniporters in the inner mitochondrial membrane by patch-clamping inner membrane preparations. They found the K^+ uniport was inhibited by ATP, and named these mitochondrial ATP-sensitive K^+ channels (mitoK_{ATP}). Their work was followed by the purification and reconstitution of mitoK_{ATP} channels by Garlid's group [26], an experimental setup that allowed detailed studies of the regulatory properties of this channel. A list of physiological activators and inhibitors as well as the pharmacological agonists and antagonists of mitoK_{ATP} is presented in Table 1.

An undesirable characteristic of most pharmacological mitoK_{ATP} agonists and antagonists is that they present other effects on mitochondrial and cellular function, particularly when used at high concentrations (see Table 1). As an example, diazoxide (DZX), a widely used mitoK_{ATP} agonist because of its selectivity toward mitochondrial channels in heart [2], is a potent inhibitor of succinate dehydrogenase (SDH), when used at concentrations ($\geq$100 μM) not much higher than those required to completely open the channel in isolated mitochondria (30 μM, [27]). 5-Hydroxydecanoate (5-HD), often used as a specific mitoK_{ATP} inhibitor [28], can be converted to 5-HD-CoA in mitochondria, affecting respiration [29] and impeding fatty acid oxidation [30–32]. Based on these findings and difficulties measuring mitochondrial volume changes isotopically, some authors have questioned if the protective effects of mitoK_{ATP} agonists can be attributed to this channel, and even the existence of the channels themselves [33]. While we agree caution is always advisable, we believe the large body of data supporting the presence of these channels and wide variety of effective agonists and antagonists (each with different "toxic" effects) is strongly indicative of their existence and protective nature.

The reason mitoK_{ATP} activity is compatible with the maintenance of oxidative phosphorylation even in the presence of high cytosolic K^+ concentrations became apparent when K^+ fluxes were determined in intact mitochondria [27]. ATP-sensitive K^+ fluxes in heart mitochondria are very slow, readily counteracted by

Table 1
MitoK_{ATP} regulators

Compound	Effect	$K_{1/2}$	Ref.	Observations
ATP	Inhibits	40 μM	[26]	Inhibition requires Mg^{2+} on the cytoplasmic side of the channel
ADP	Inhibits	280 μM	[26]	Requires Mg^{2+}. Activates sarcolemmal K_{ATP}
Palmitoyl CoA	Inhibits	260 nM	[121]	Activates sarcolemmal K_{ATP}
Oleoyl CoA	Inhibits	80 nM	[121]	Activates sarcolemmal K_{ATP}
Mg^{2+}	Inhibits	<1 mM	[122]	Mg^{2+} ions act upon mitoK_{ATP} from the matrix side of the channel
GTP	Activates	7–232 μM	[121]	$K_{½}$ varies with experimental conditions
GDP	Activates	140 μM	[121]	
UDP	Activates	10–13 μM	[36]	
Superoxide radicals	Activate		[77]	Generated experimentally by xanthine/xanthine oxidase
Diazoxide	Activates	0.4–0.8 μM	[2]	Sarcolemmal K_{ATP} $K_{½}$ is >800 μM Concentrations >100 μM inhibit SDH
Cromakalin	Activates	1–1.6 μM	[2]	
BMS191095	Activates	83 nM	[123]	
Nicorandil	Activates	5 μM	[16]	Inhibits SDH at high concentrations
P1075	Activates	70 nM	[124]	
Pinacidil	Activates	12 μM	[27]	Concentrations >50 μM decrease $\Delta\Psi$
Isoflurane	Activates	<1 mM	[125]	
5-HD	Inhibits	45–75 μM	[28]	Converted to 5-HD-CoA, affects fatty acid metabolism
Glyburide (Glybenclamide)	Inhibits	1–6 μM	[28]	Concentrations >5 μM can inhibit respiration
Quinine	Inhibits	<100 μM	[126]	Also inhibits K^+/H^+ exchange
N-ethylmaleimide	Inhibits	<2 mM	[77]	

Physiological (italic) and pharmacological mitoK_{ATP} activators and inhibitors and their half-maximal effective doses are listed.