Current Topics in Biophysics,2007, 30 (suppl B) 22-23

MITOCHONDRIAL ION CHANNELS

A. SZEWCZYK[1], W. JARMUSZKIEWICZ[2], K. DOŁOWY[3]

[1]Nencki Institute of Experimental Biology, Warszawa, Poland;
[2]Adam Mickiewicz University, Poznań, Poland;
[3]Warsaw Agriculture University, SGGW, Poland

Energy generation within the cell is the basic function of mitochondria. Apart from this role, mitochondria are involved in other complex processes such as apoptosis. Recently, an essential position of potassium transport through mitochondrial inner membrane was identified to trigger cytoprotection. This transport is strictly ion channel dependent, and accordingly, resembles to plasma membrane ion channels activity. Potassium ions control mitochondrial metabolism primarily due to regulation of matrix volume. The basic pharmacological properties of mitochondrial potassium channels such as ATP-regulated potassium channel (mitoKATP channel), large conductance Ca^{2+}-activated potassium channel (mitoBKCa channel) were found to be similar to some of the potassium channels present in the plasma membrane of various cell types. Recently, a margatoxin-sensitive voltage gated Kv1.3 channel was identified in T lymphocytes mitochondria.

MITOCHONDRIAL ATP-REGULATED K^+ CHANNEL

The mitoKATP channel was initially described in isolated liver mitochondria. Subsequently, it was also identified in heart, brain, renal, skeletal muscle and human T-lymphocyte. Recently, we have identify mitoKATP channel in amoeba mitochondria. The activity of this channel is modulated by various nucleotides.

The molecular identity of the mitoKATP channel is presently unknown. Immunological studies identify both pore forming Kir6.1 and Kir6.2 subunits in brain mitochondria. It has also been hypothesized that a complex of five proteins (including succinate dehydrogenase) in the mitochondrial inner membrane is capable of transporting K^+ with characteristics similar to those of the mitoKATP channel.

Activity of this channel is modulated by drugs known as potassium channel openers. All of the potassium channel openers applied on mitochondria were previously used to regulate plasma membrane ATP-regulated potassium channel but potassium channel openers such as diazoxide and BMS191095, are considered mitoKATP-selective openers. Similarly, 5-hydroxydecanoic acid has some mitochondrial specificity as mitoKATP channel blocker.

MITOCHONDRIAL LARGE CONDUCTANCE CALCIUM-ACTIVATED POTASSIUM CHANNEL

A putative mitochondrial large conductance Ca^{2+}-activated potassium channel (mitoBKCa channel) was originally described in human glioma cells LN229. This channel, with a conductance of 295 pS, was stimulated by Ca^{2+} and blocked by charybdotoxin. Later the presence of a channel with properties similar to the surface membrane calcium-activated K^+ channel was observed in patch-clamp recordings from cardiac mitoplasts It may contribute to the cardioprotective effect of K^+ influx into mitochondria.

It should be mentioned, that the mitoBKCa channel may offer a novel link between cellular/mitochondrial calcium signaling and mitochondrial membrane potential-dependent reactions. Altered intramitochondrial calcium levels directly affect the potassium permeability of the mitochondrial inner membrane thus modulating the membrane potential. This type of interaction can modulate the efficiency of oxidative phosphorylation in a calcium-dependent manner.

Very likely, the mitochondrial channel has its charybdotoxin/iberiotoxin binding site close to the cytosolic compartment since those compounds as peptides cannot easily enter the mitochondrial matrix space. Consequently, the calcium binding site of the mitoBKCa channel is close to the matrix compartment.

In addition to this classical physiological effect of mitochondrial potassium transport, a pivotal role of mitochondrial potassium channels has been implicated in cardio-and neuroprotection. It is therefore reasonable to expect a possible cytoprotective effect of mitoBKCa

channel activation, probably in the presence of superoxide radicals. Recently, it was shown that cardioprotective effects of estradiol include the activation of mitoBKCa channel in cardiac mitochondria. Additionally, it was suggested that β1 subunit of BKCa channel is present in inner mitochondrial membrane and interact with cytochrome c oxidase subunit I.

It has also been reported that two BKCa channel openers, NS004 and NS1619, inhibit mitochondrial function in human glioma cells due to inhibition of the complex I of mitochondrial respiratory chain. Recently, a channel opener NS1619 was shown to inhibit the function of isolated cardiac mitochondria in similar manner.

CONCLUSION

Variety of observations suggest that mitochondria contributes to cytoprotective phenomenon in various tissues. It seems that mitochondrial potassium channels such as ATP-regulated of Ca^{2+} activated, play the key role in these effects.

ACKNOWLEDGMENTS

Studies described were partially supported by Polish Mitochondrial Network MitoNet.pl.

REFERENCES

Bednarczyk P., Dolowy K. & Szewczyk A. (2005). Matrix Mg^{2+} regulates mitochondrial ATP-dependent potassium channel from heart. FEBS Lett., 579, 1625–1632.

Bednarczyk P., Kicinska A., Kominkova V., Ondrias K., Dolowy K. & Szewczyk A. (2004). Quinine inhibits mitochondrial ATP-regulated potassium channel from bovine heart. J. Membr. Biol., **199**, 63–72.

Debska G., Kicinska A., Dobrucki J., Dworakowska B., Nurowska E., Skalska J., Dolowy K. & Szewczyk A. (2003). Large-conductance K^{+} channel openers NS1619 and NS004 as inhibitors of mitochondrial function in glioma cells. Biochem. Pharmacol., **65**, 1827–1834.

Debska G., Kicinska A., Skalska J., Szewczyk A., May R, Elger C. E. & Kunz W. S. (2002). Opening of potassium channels modulates mitochondrial function in rat skeletal muscle. Biochim. Biophys. Acta, **1556**, 97–105.

Debska G., May R., Kicinska A., Szewczyk A., Elger C. E. & Kunz W. S. (2001). Potassium channel openers depolarize hippocampal mitochondria. Brain Res., **892**, 42–50.

Kicinska A., Swida A., Bednarczyk P., Koszela-Piotrowska I., Choma K., Dolowy K., Szewczyk A. & JarmuszkiewiczW. (2007). ATP-sensitive potassium channel in mitochondria of the eukaryotic microorganism, acanthamoeba castellanii. J. Biol. Chem., (in press)

Szewczyk A., Skalska J., Glab M., Kulawiak B., Malinska D., Koszela-Piotrowska I. & Kunz W. S. (2006). Mitochondrial potassium channels: from pharmacology to function. Biochim. Biophys. Acta, **1757**, 715–720