J Membrane Biol (2007) 215:69–74
DOI 10.1007/s00232-007-9006-3

Modulation of the Permeability Transition Pore by Inhibition of the Mitochondrial K_{ATP} Channel in Liver *vs*. Brain Mitochondria

K. Kupsch · S. Parvez · D. Siemen · G. Wolf

Received: 11 October 2006 / Accepted: 22 January 2007 / Published online: 6 April 2007
© Springer Science+Business Media, LLC 2007

Abstract Inhibition of the mitochondrial K_{ATP} (mitoK$_{ATP}$) channel abrogates the beneficial effects of preconditioning induced by a brief episode of sublethal ischemia. We studied the effect of 5-hydroxydecanoate, a well-known inhibitor of the mitoK$_{ATP}$ channel, on swelling of isolated liver and brain mitochondria. Volume changes were determined by measurement of light absorbance at 540 nm. Mitochondrial swelling induced by adding Ca^{2+} ions correlated with opening of the permeability transition pore as shown by modulation by 1 μM cyclosporin A. In brain mitochondria, 5-hydroxydecanoate did not significantly affect Ca^{2+}-induced swelling. In contrast, 50 or 500 μM 5-hydroxydecanoate increased swelling of liver mitochondria by 9.7 ± 5.1% ($n = 6$, $P = 0.057$) and 29.4 ± 1.4% ($n = 5$, $P < 0.0001$), respectively. The effect of 5-hydroxydecanoate was blocked by cyclosporin A and was dependent on the presence of potassium in the medium. In medium containing 200 μM ATP to inhibit the mitoK$_{ATP}$ channel, 5–hydroxydecanoate did not further increase Ca^{2+}-induced swelling. We conclude that inhibition of the mitoK$_{ATP}$ channel exerts its detrimental effect by facilitation of permeability transition pore opening.

Keywords Mitochondrial K_{ATP} channel · Ischemic preconditioning · 5-Hydroxydecanoate · Mitochondrial permeability transition pore

Introduction

In addition to their function in cell metabolism, mitochondria play a major role in apoptotic and necrotic cell death (Crompton 1999). The release of proapoptotic molecules, such as cytochrome c or apoptosis-inducing factor, from mitochondria triggers the activation of caspases that finally leads to cellular destruction (Gulbins, Dreschers and Bock 2003). This process is associated with opening of the mitochondrial permeability transition pore (PTP), a ''megachannel'' spanning both the inner and the outer mitochondrial membrane. It can exist in various subconductance states. In the fully opened state, it allows molecules up to a molecular weight of 1.5 kDa to pass (Crompton 1999). Accordingly, opening of the PTP leads to a breakdown of the mitochondrial membrane potential, causing failure of oxidative phosphorylation and adenosine triphosphate (ATP) depletion (Hunter, Haworth and Southard 1976). Ca^{2+} is the major physiological activator of the PTP. Other factors that are known to trigger PTP activation are reactive oxygen and nitrogen species, mitochondrial depolarization and high levels of inorganic phosphate (P_i). In contrast, hyperpolarization of the mitochondrial membrane as well as high levels of ATP and adenosine diphosphate (ADP) are known to inhibit the pore (Crompton 1999).

K. Kupsch (✉) · G. Wolf
Institute of Medical Neurobiology, Otto-von-Guericke University Magdeburg, Leipziger Strasse 44, D-39120 Magdeburg, Germany,
e-mail: kathleen.kupsch@medizin.uni-magdeburg.de

S. Parvez · D. Siemen
Department of Neurology, Otto-von-Guericke University Magdeburg, Leipziger Strasse 44, D-39120 Magdeburg, Germany

Present Address:
S. Parvez
Laboratory of Cell and Molecular Signaling, Center for Biomedical Research, The Queen's Medical Center, John A. Burns School of Medicine, University of Hawaii, 96813 Honolulu, HI, USA

Since PTP-mediated cell death is involved in the development of numerous diseases, much effort is spent to investigate modulators of this phenomenon. Recently, we have shown that a second mitochondrial ion channel, the ATP-dependent potassium channel of the inner mitochondrial membrane (mitoK_{ATP} channel), interacts with the PTP (Dahlem et al. 2006). The mitoK_{ATP} channel has been implicated in the mechanism of ischemic preconditioning (IP) (O'Rourke, 2004). IP is a phenomenon in which a brief episode of ischemia protects tissue against a subsequent, otherwise lethal ischemia. The protective effect of IP can be abolished by administration of inhibitors of mitoK_{ATP} channels (Gross and Auchampach 1992), such as glibenclamide and 5-hydroxydecanoate (5-HD). Accordingly, treatment with the selective mitoK_{ATP} channel opener diazoxide mimics the protection mediated by IP (Garcia de Arriba et al. 1999). The mechanisms that are responsible for such effects of mitoK_{ATP} channel modulators are still under debate. Recent studies suggest a correlation between the state of the mitoK_{ATP} channel and the open probability of the PTP (Costa et al. 2006; Dahlem et al. 2006; Facundo, de Paula and Kowaltowski 2005). However, because of the limited specificity of the pharmacological modulators of the mitoK_{ATP} channel, these results are controversial (Hanley and Daut 2005). In the present study, we investigated whether the mitoK_{ATP} channel inhibitor 5-HD affects PTP opening in isolated liver and brain mitochondria. Due to the side effects of 5-HD on metabolic pathways (Hanley et al. 2002), a possible contribution of mitoK_{ATP} channel-independent actions of 5-HD on the opening state of the PTP was also considered in our study.

Materials and Methods

Animals

Procedures for animal use were in strict accordance with the Animal Health and Care Committee of the State Sachsen-Anhalt, Germany. Male Wistar rats (Harlan-Winkelmann, Borchen, Germany) were single-housed and maintained under a 12:12 h light/dark cycle. Before being killed, rats were allowed a 2-week acclimation period and had free access to standard food and water ad libitum.

Isolation of Liver Mitochondria

Male Wistar rats weighing 250–350 g were killed by decapitation. The liver was rapidly removed and washed twice in ice-cold isolation medium containing 250 mM sucrose, pH 7.4 (always adjusted with Tris). After homogenization in a solution of 250 mM sucrose and 1 mM ethylenediaminetetraacetic acid (EDTA, pH 7.4), the resulting suspension was centrifuged at 800 × g for 5 min. The supernatant was decanted and centrifuged at 5,100 × g for 4 min. The resulting pellet was resuspended in a solution of 250 mM sucrose (pH 7.4), gently homogenized by hand and centrifuged at 12,300 × g for 2 min. Homogenization and centrifugation were repeated at 12,300 × g for 10 min. The final pellet was resuspended in a solution of 250 mM sucrose and 0.5 mM EDTA (pH 7.4). It was stored on ice for up to 6 h.

Isolation of Nonsynaptic Brain Mitochondria

Brain mitochondria were prepared from male Wistar rats (6–8 weeks old). Animals were killed by decapitation, and the forebrain was rapidly removed and transferred into ice-cold medium A (225 mM mannitol, 75 mM sucrose, 20 mM 3-[n-morpholino]propanesulfonic acid [MOPS], 1 mM ethyleneglycoltetraacetic acid [EGTA], pH 7.2). After removing meninges and major blood vessels, the brain was minced with scissors, homogenized and centrifuged at 1,330 × g for 3 min. The pellet obtained was resuspended and recentrifuged at 1,330 × g for 3 min. Pooled supernatants were centrifuged at 21,200 × g for 10 min. The pellet was resuspended in 15% Percoll, layered on a Percoll gradient (40% and 23%) and centrifuged at 3,170 × g for 10 min. The mitochondrial fraction located at the interface of the lower two layers was removed and diluted 1:4 with isolation medium A containing 10 mg/ml bovine serum albumin. The Percoll was washed off by two centrifugations at 16,700 × g and 6,700 × g (10 min). The final pellet was resuspended in medium B (225 mM mannitol, 75 mM sucrose, 20 mM MOPS, 0.1 mM EGTA, pH 7.2) and stored on ice.

Measurement of Mitochondrial Swelling

Mitochondrial protein content was determined by the biuret method. Aliquots of mitochondria (liver, 600–800 µg protein/ml; brain, 250 µg protein/ml) were suspended in 1 ml of swelling medium containing 125 mM KCl [125 mM tetraethylammonium (TEA) chloride], 20 mM Tris, 1 mM $MgCl_2$, 1 µM EGTA, 5 mM glutamate, 5 mM malate and 0.1 or 1 mM P_i for brain and liver mitochondria, respectively (pH 7.2). Mitochondrial swelling was monitored by measurement of light scattering at 540 nm by a Varian (Darmstadt, Germany) Cary 3E spectrophotometer equipped with a thermostatted sampling unit (30°C). Permeability transition was induced by addition of $CaCl_2$ (25 or 50 µM) 1 min after starting the experiment. The values for maximum swelling obtained as control and under test conditions were compared by unpaired t-test (two-tailed) using GraphPad Prism (version 3.02; GraphPad Software, San Diego CA).

Results

Addition of 50 μM Ca^{2+} to freshly isolated brain mitochondria incubated in K^+ medium resulted in a rapid decrease in absorbance at 540 nm (Fig. 1a). The effect is known to be due to an increase in mitochondrial volume (Skalska et al. 2005) and is significantly larger than the decline in absorbance observed in the absence of Ca^{2+} (decrease of 2.9 ± 0.6% compared to 6.9 ± 0.3%, $P < 0.001$), which probably reflects a relative dilution of the mitochondrial suspension due to precipitation of mitochondria at the bottom. In the presence of the PTP inhibitor cyclosporin A (CsA, 1 μM), the Ca^{2+}-induced decrease in absorbance was significantly delayed (Fig. 1a), indicating that PTP opening was involved. During a 9-min incubation with Ca^{2+} under control conditions, absorbance decreased to a level of 93.1 ± 0.3% of the basal value ($n = 9$, $P < 0.001$ vs. Ca^{2+}-free). At concentrations up to 500 μM, 5-HD did not change the Ca^{2+}-induced decrease in absorbance (Fig. 1b). The presence of 50 or 500 μM 5-HD in the swelling medium led to a minor increase in Ca^{2+}-induced swelling by 0.8 ± 0.9% ($n = 5$, $P >> 0.05$ vs. control) and 0.4 ± 1.2% ($n = 3$, $P >> 0.05$ vs. control), respectively. Thus, in brain mitochondria, 5-HD did not alter the open probability of the PTP.

In liver mitochondria, addition of 25 or 50 μM Ca^{2+} resulted in a steady decrease in absorbance, reaching 87.8 ± 1.7% ($n = 13$, $P < 0.001$ *vs.* Ca^{2+}-free) or 75.3 ± 3.0% ($n = 10$, $P < 0.001$ *vs.* Ca^{2+}-free), respectively, of the basal value after a 9-min incubation with Ca^{2+} (Fig. 1c). In both cases, swelling was completely inhibited by 1 μM CsA. When swelling was induced by 25 μM Ca^{2+}, treatment with 50 μM 5-HD tended to increase mitochondrial swelling by 9.7 ± 5.1% ($n = 6$, $P = 0.057$) compared to control levels (Fig. 1d, see also Fig. 2c). At a concentration of 500 μM, 5-HD remarkably increased the decline of absorbance by 29.4 ± 1.4% ($n = 5$, $P < 0.0001$). In order to clarify whether the observed increase in mitochondrial swelling induced by 5-HD was due to PTP opening, experiments were repeated in the presence of the PTP inhibitor CsA (1 μM). When liver mitochondria were incubated in medium containing both 5-HD and CsA, addition of 25 μM Ca^{2+} did not result

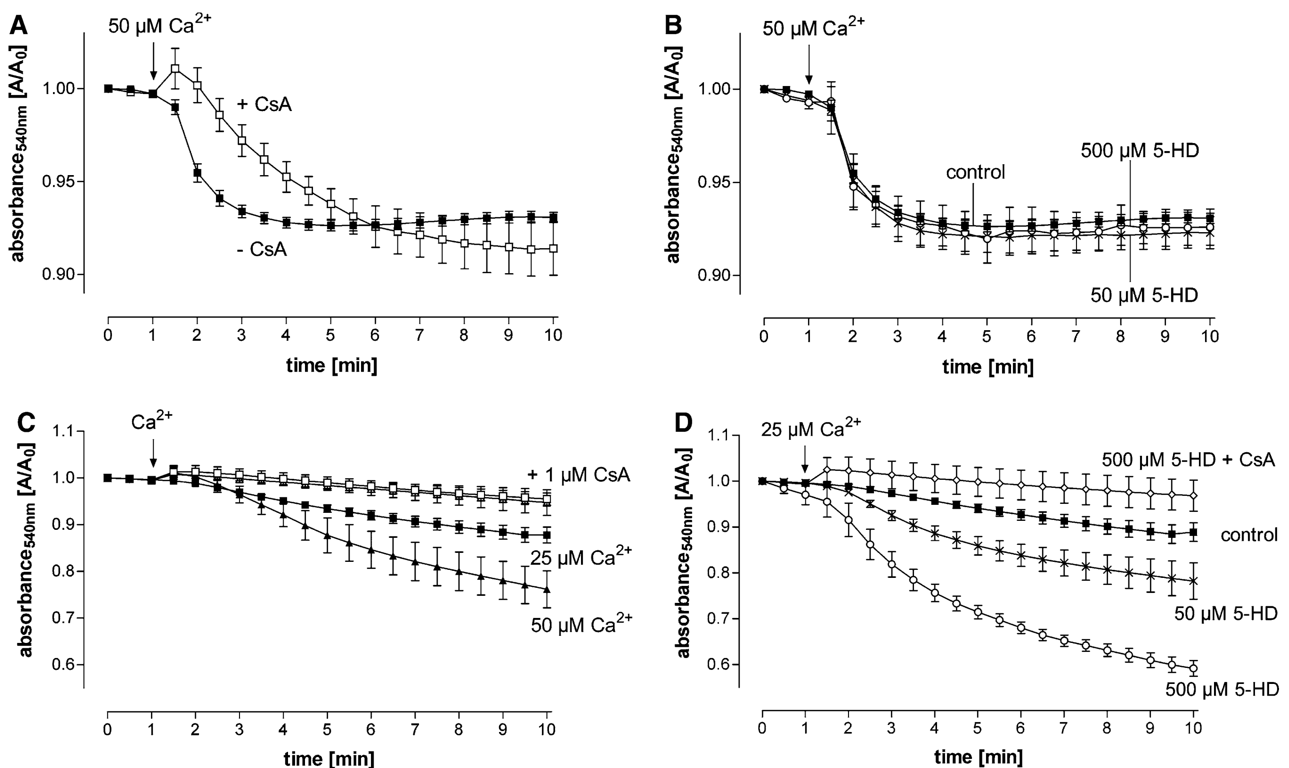

Fig. 1 Effect of 5-HD on Ca^{2+}-induced swelling of mitochondria. Swelling was measured as a decrease in light scattering (percentage of basal value) at 540 nm. Data are means ± standard error of the mean of at least three independent experiments. Control indicates absorbance decrease in the absence of 5-HD. (a) Swelling of brain mitochondria induced by 50 μM Ca^{2+} was delayed by 1 μM CsA, indicating PTP involvement. (b) The mitoKATP channel inhibitor 5-HD at concentrations of 50 μM (×) or 500 μM (○) did not affect the swelling behavior of brain mitochondria. In liver mitochondria (c), swelling induced by 25 μM (■) or 50 μM (▲) Ca^{2+} was completely inhibited by CsA. (d) Increase of Ca^{2+}-induced swelling (■) of liver mitochondria by 5-HD at concentrations of 50 (×) and 500 μM (○). CsA inhibited swelling even in the presence of 500 μM 5-HD (◇), indicating that 5-HD effects on swelling were due to modulation of PTP

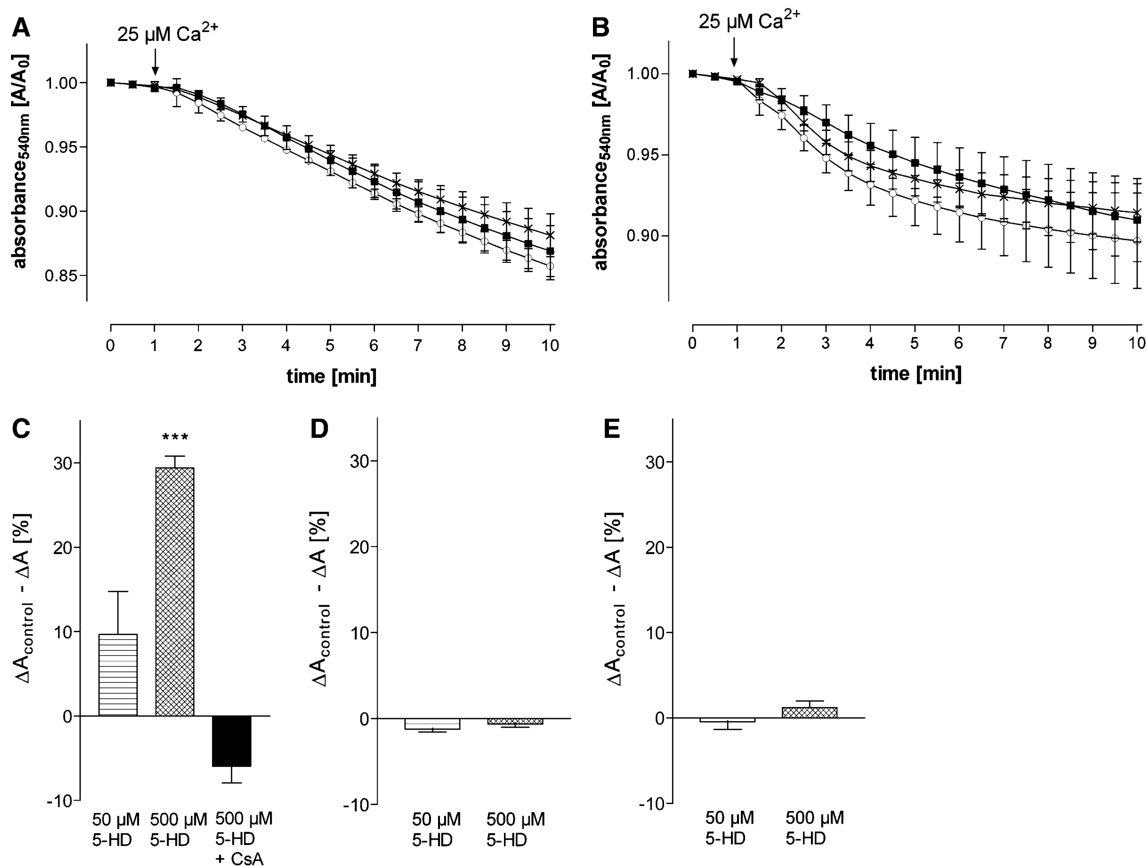

Fig. 2 5-HD increases Ca^{2+}-induced swelling of liver mitochondria in K^+ medium but not in potassium-free medium or in K^+ medium that contains ATP. Data are means ± standard error of the mean of at least three independent experiments. Control indicates absorbance decrease in the absence of 5-HD. ***Difference from control, $P < 0.0001$. (a) 5-HD at concentrations of 50 µm (×) or 500 µm (○) did not affect Ca^{2+}-induced swelling of liver mitochondria in potassium-free medium and (b) in medium containing 200 µM ATP in order to block the mitoK_{ATP} channel (control ■). (c–e) Mean difference between swelling induced by Ca^{2+} in the absence of 5-HD and swelling in the presence of 5 HD in (c) K^+ medium, (d) potassium-free medium and (e) K^+ medium containing 200 µM ATP for inhibition of the mitoK_{ATP} channel (decrease of absorbance without 5-HD is set to zero)

in a decrease in absorbance (Fig. 1d), confirming that 5-HD affects PTP opening and does not have PTP-independent effects on mitochondrial volume. Similar results were obtained when swelling was induced by 50 µM Ca^{2+} (data not shown).

Besides its effect on mitoK_{ATP} channels, 5-HD also influences lipid oxidation of the mitochondria (Hanley et al. 2002). Because a possible action of 5-HD on PTP opening due to interference with metabolic pathways cannot be excluded, experiments were performed in the absence of potassium. Under these conditions, 5-HD at 50 or 500 µM decreased mitochondrial swelling insignificantly by 1.2 ± 0.3% and 0.6 ± 0.4%, respectively ($n = 3$, $P >> 0.05$ each). Hence, in the absence of potassium ions, 5-HD did not affect Ca^{2+}-induced PTP opening in liver mitochondria, indicating that a modulation of potassium homeostasis by 5-HD was required for the activating effect on the PTP (Fig. 2a, see also Fig. 2d).

To further enlighten the role of mitoK_{ATP} channels in 5-HD-induced PTP opening in liver mitochondria, we investigated its effect in medium containing 200 µM ATP in order to block the mitoK_{ATP} channel. Under these conditions, the presence of 5-HD in the swelling medium did not significantly affect the Ca^{2+}-induced decrease of absorbance: 50 µM 5-HD slightly decreased the Ca^{2+}-induced swelling of mitochondria by 0.4 ± 0.9% ($n = 3$, $P >> 0.05$), while 500 µM 5-HD increased swelling by 1.2 ± 0.8% ($n = 3$, $P >> 0.05$). Thus, under conditions that favor the closed state of the mitoK_{ATP} channel, the presence of 5-HD did not further influence the Ca^{2+}-induced PTP opening (Fig. 2b, see also Fig. 2e).

Discussion

MitoK_{ATP} channels have been reported in liver (Inoue et al. 1991) and brain (Bajgar et al. 2001). Their molecular

structure, however, remains unknown, and evidence for their function is largely derived from pharmacological experiments. Available modulators of the mitoK_{ATP} channel have various side effects that may complicate the interpretation of results (Hanley et al. 2002). Thus, one aim of the present study was to carefully check whether a potential effect of the inhibitor used (5-HD) is actually specific for the modulation of the mitoK_{ATP} channel.

We found that in rat liver mitochondria the mitoK_{ATP} channel inhibitor 5-HD significantly enhances the open probability of the PTP. However, apart from blocking the mitoK_{ATP} channel, 5-HD can be metabolized in mitochondria, creating a bottleneck for β–oxidation of fatty acids (Hanley et al. 2005). To exclude that this alternative effect was responsible for the modified swelling behavior, experiments were conducted in medium with TEA substituted for potassium. In contrast to the K_{ATP} channel of the cell membrane, the mitoK_{ATP} channel is not affected by TEA (Paucek et al. 1992). Under potassium-free conditions, 5-HD did not affect Ca^{2+}-induced swelling, suggesting that a modulation of potassium homeostasis is required for the effect of 5-HD. Furthermore, we showed that in the presence of ATP as the physiological inhibitor of the mitoK_{ATP} channel, 5-HD did not further increase Ca^{2+}-induced swelling of rat liver mitochondria. Importantly, while ATP should increase the opening probability of the PTP due to its inhibitory action on the mitoK_{ATP} channel, ATP is additionally known to be a direct inhibitor of the pore (Halestrap, Woodfield and Connern 1997). Indeed, the presence of 200 μM ATP did slightly decrease the Ca^{2+}-induced swelling compared to swelling in medium lacking ATP.

The Ca^{2+}-induced decrease of brain mitochondria was much less pronounced than that of liver mitochondria. Furthermore, CsA did not inhibit but, rather, delayed swelling of brain mitochondria. The relative insensitivity of the PTP of brain mitochondria for inhibition by CsA has been reported before (Brustovetsky and Dubinsky 2000; Chinopoulos, Starkov and Fiskum 2003; Kristal and Dubinsky 1997). In contrast to the results obtained in liver mitochondria, we did not observe an effect of 5-HD on the Ca^{2+}-induced swelling of rat brain mitochondria, indicating that distinct mechanisms underlie the detrimental effect of mitoK_{ATP} channel inhibition on IP of different tissues. However, a recent study of Costa et al. (2006) using different preparation methods and incubation media reports similar effects of mitoK_{ATP} channel modulators on the PTP of liver, brain and heart mitochondria. Thus, the possible interaction between mitoK_{ATP} channel and PTP in brain mitochondria appears to be strongly dependent on the experimental conditions. It is important to stress that the isolation procedure we used yields mitochondria from both neuronal and glial cells. It has been described that neuronal and glial mitochondria differ substantially in their susceptibility to permeability transition (Bambrick et al. 2006). It is, therefore, possible that in our study the treatment with 5-HD facilitated PTP opening in one subfraction of mitochondria, while in another fraction permeability transition was inhibited by 5-HD. In this case, no overall effect on 5-HD on swelling of the mitochondria would be seen. Moreover, though the mitoK_{ATP} channel of brain mitochondria has been reported to be sensitive to 5-HD (Bajgar et al. 2001), recent results suggest that this does not apply in all cases (P. Bednarczyk, personal communication). Keeping this in mind, we cannot exclude that in our experiments 5-HD failed to affect potassium homeostasis of brain mitochondria and, therefore, was not able to influence the opening state of the PTP.

We conclude from our results that inhibition of the mitoK_{ATP} channel by 5-HD increases the sensitivity of the PTP to Ca^{2+} ions. Skalska et al. (2005) reported a similar action of the mitoK_{ATP} inhibitor glibenclamide on the PTP of muscle mitochondria. However, they did find the same effect in potassium-free medium. Hence, the present study is, to our knowledge, the first one in which a PTP-activating effect of mitoK_{ATP} channel inhibition is described. Our results are in accordance with a recent report by Costa et al. (2006) on a protective effect of different mitoK_{ATP} channel activators on Ca^{2+}-induced PTP opening of isolated mitochondria.

The underlying mechanism of the PTP-activating effect of mitoK_{ATP} channel inhibition in liver mitochondria remains unclear. Isolated mitochondria exhibit a membrane potential of around –190 mV (inside negative), generating a large driving force for K^{+} uptake into the mitochondria (Garlid and Paucek 2003). Concordantly, it has been shown that activation of the mitoK_{ATP} channel leads to a depolarization of mitochondria by increasing K^{+} influx, thus reducing the Ca^{2+} influx into mitochondria (Szewczyk, Wojcik and Nalecz 1995). A reduced intramitochondrial Ca^{2+} concentration is known to prevent opening of the PTP. Accordingly, inhibition of mitoK_{ATP} channel by 5-HD might hyperpolarize mitochondria by decreasing K^{+} input, thus increasing the Ca^{2+} influx and facilitating PTP opening. On the other hand, hyperpolarization of mitochondria is commonly considered to be a PTP-inhibiting factor (Bernardi 1992). A further possible explanation is an action of 5-HD on the activity of different ion exchangers of the inner mitochondrial membrane. For instance, a drop in mitochondrial potassium concentration due to inhibition of the mitoK_{ATP} channel should alkalize the mitochondrial matrix because of a reduced activity of the K^{+}/H^{+} exchanger. A rise in pH is known to increase the open probability of the PTP (Halestrap 1991). Furthermore, an alkaline pH elevates the activity of the P_i/OH^- antiporter of the inner mitochondrial membrane and, consequently,

matrix phosphate concentrations. Phosphate is a physiological modulator of the PTP as high phosphate increases the open probability. A different explanation of the interaction between the mitoK_{ATP} channel and the PTP has been suggested by Costa et al. (2006), who reported that inhibition of the PTP by mitoK_{ATP} channel opening can be abolished by inhibitors of protein kinase C (PKCε) as well as by a scavenger of reactive oxygen species. They proposed that mitoK_{ATP} channel activation increases production of H_2O_2, which in turn blocks the PTP by activating PKCε.

In conclusion, the present study demonstrates that the state of the mitoK_{ATP} channel is able to modulate the opening probability of the PTP. Since PTP opening is related to both apoptotic and necrotic cell death (e.g., in ischemia), modulation of this mitochondrial ‘‘megachannel’’ by controlling the state of the mitoK_{ATP} channel may offer therapeutic benefit for various diseases.

References

Bajgar R, Seetharaman S, Kowaltowski AJ, Garlid KD, Paucek P (2001) Identification and properties of a novel intracellular (mitochondrial) ATP-sensitive potassium channel in brain. J Biol Chem 276:33369–33374

Bambrick LL, Chandrasekaran K, Mehrabian Z, Wright C, Krueger BK, Fiskum G (2006) Cyclosporin A increases mitochondrial calcium uptake capacity in cortical astrocytes but not cerebellar granule neurons. J Bioenerg Biomembr 38:43–47

Bernardi P (1992) Modulation of the mitochondrial cyclosporin A-sensitive permeability transition pore by the proton electrochemical gradient. Evidence that the pore can be opened by membrane depolarization. J Biol Chem 267:8834–8839

Brustovetsky N, Dubinsky JM (2000) Limitations of cyclosporin A inhibition of the permeability transition in CNS mitochondria. J Neurosci 20:8229–8237

Chinopoulos C, Starkov AA, Fiskum G (2003) Cyclosporin A-insensitive permeability transition in brain mitochondria: Inhibition by 2-aminoethoxydiphenyl borate. J Biol Chem 278:27382–27389

Costa AD, Jakob R, Costa CL, Andrukhiv K, West IC, Garlid KD (2006) The mechanism by which the mitochondrial ATP-sensitive K^+ channel opening and H_2O_2 inhibit the mitochondrial permeability transition. J Biol Chem 281:20801–20808

Crompton M (1999) The mitochondrial permeability transition pore and its role in cell death. Biochem J 341(pt 2):233–249

Dahlem YA, Wolf G, Siemen D, Horn TF (2006) Combined modulation of the mitochondrial ATP-dependent potassium channel and the permeability transition pore causes prolongation of the biphasic calcium dynamics. Cell Calcium 39:387–400

Facundo HT, de Paula JG, Kowaltowski AJ (2005) Mitochondrial ATP-sensitive K^+ channels prevent oxidative stress, permeability transition and cell death. J Bioenerg Biomembr 37:75–82

Garcia de Arriba S, Franke H, Pissarek M, Nieber K, Illes P (1999) Neuroprotection by ATP-dependent potassium channels in rat neocortical brain slices during hypoxia. Neurosci Lett 273:13–16

Garlid KD, Paucek P (2003) Mitochondrial potassium transport: The K^+ cycle. Biochim Biophys Acta 1606:23–41

Gross GJ, Auchampach JA (1992) Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. Circ Res 70:223–233

Gulbins E, Dreschers S, Bock J (2003) Role of mitochondria in apoptosis. Exp Physiol 88:85–90

Halestrap AP (1991) Calcium-dependent opening of a non-specific pore in the mitochondrial inner membrane is inhibited at pH values below 7. Implications for the protective effect of low pH against chemical and hypoxic cell damage. Biochem J 278(pt 3):715–719

Halestrap AP, Woodfield KY, Connern CP (1997) Oxidative stress, thiol reagents, and membrane potential modulate the mitochondrial permeability transition by affecting nucleotide binding to the adenine nucleotide translocase. J Biol Chem 272:3346–3354

Hanley PJ, Daut J (2005) K_{ATP} channels and preconditioning: A re-examination of the role of mitochondrial K_{ATP} channels and an overview of alternative mechanisms. J Mol Cell Cardiol 39:17–50

Hanley PJ, Drose S, Brandt U, Lareau RA, Banerjee AL, Srivastava DK, Banaszak LJ, Barycki JJ, Van Veldhoven PP, Daut J (2005) 5-Hydroxydecanoate is metabolised in mitochondria and creates a rate-limiting bottleneck for beta-oxidation of fatty acids. J Physiol 562:307–318

Hanley PJ, Mickel M, Loffler M, Brandt U, Daut J (2002) K_{ATP} channel-independent targets of diazoxide and 5-hydroxydecanoate in the heart. J Physiol 542:735–741

Hunter DR, Haworth RA, Southard JH (1976) Relationship between configuration, function, and permeability in calcium-treated mitochondria. J Biol Chem 251:5069–5077

Inoue I, Nagase H, Kishi K, Higuti T (1991) ATP-sensitive K^+ channel in the mitochondrial inner membrane. Nature 352:244–247

Kristal BS, Dubinsky JM (1997) Mitochondrial permeability transition in the central nervous system: Induction by calcium cycling-dependent and -independent pathways. J Neurochem 69:524–538

O'Rourke B (2004) Evidence for mitochondrial K^+ channels and their role in cardioprotection. Circ Res 94:420–432

Paucek P, Mironova G, Mahdi F, Beavis AD, Woldegiorgis G, Garlid KD (1992) Reconstitution and partial purification of the glibenclamide-sensitive, ATP-dependent K^+ channel from rat liver and beef heart mitochondria. J Biol Chem 267:26062–26069

Skalska J, Debska G, Kunz WS, Szewczyk A (2005) Antidiabetic sulphonylureas activate mitochondrial permeability transition in rat skeletal muscle. Br J Pharmacol 145:785–791

Szewczyk A, Wojcik G, Nalecz MJ (1995) Potassium channel opener, RP 66471, induces membrane depolarization of rat liver mitochondria. Biochem Biophys Res Commun 207:126–132