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Physiological aspects of the mitochondrial cyclosporin A-insensitive palmitate/Ca^{2+}-induced pore: tissue specificity, age profile and dependence on the animal's adaptation to hypoxia

Konstantin N. Belosludtsev · Nils-Erik L. Saris · Natalia V. Belosludtseva · Alexander S. Trudovishnikov · Lyudmila D. Lukyanova · Galina D. Mironova

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Abstract Earlier we found that being added to rat liver mitochondria, palmitic acid (Pal) *plus* Ca^{2+} opened a cyclosporin A-insensitive pore, which remained open for a short time. Apparently, this pore is involved in the Pal-induced apoptosis and may also take part in the mitochondrial Ca^{2+} recycling as a Ca^{2+} efflux system (Belosludtsev et al. J Bioenerg Biomembr 38:113–120, 2006; Mironova et al. J. Bioenerg. Biomembr. 39:167–174, 2007). In this paper, we continue studying physiological and regulatory aspects of the pore. The following observations have been made. (1) Cardiolipin has been found to facilitate the Ca^{2+}-induced formation of pores in the Pal-containing liposomal membranes. (2) The opening of Pal/Ca^{2+}-induced pore is accompanied by the release of apoptosis-induced factor (AIF) from mitochondria. (3) The rate of Pal/Ca^{2+}-induced swelling of rat liver mitochondria increases substantially with the age of animals. (4) Although the Pal/Ca^{2+}-induced pore opens both in the liver and heart mitochondria, the latter require higher Pal concentrations for the pore to open. (5) The pore opening depends on the resistance of animals to hypoxia: in the highly resistant to hypoxia rats, the mitochondrial Pal/Ca^{2+}-induced pore opens easier than in the low resistant animals, this being opposite for the classical, cyclosporin A-sensitive MPT pore. The adaptation of the low resistant rats to oxygen deficiency increases the sensitivity of their mitochondria to PalCaP inductors. The paper also discusses a possible role of the mitochondrial Pal/Ca^{2+}-induced pore in the protection of tissues against hypoxia.

Keywords Palmitic acid · Calcium · Hypoxia · Aging · Mitochondrial Ca^{2+}-dependent pore

Abbreviations

CsA	Cyclosporin A
Pal	Palmitic acid
PalCaP	Palmitate/Ca^{2+}-induced pore
MPT	Mitochondrial permeability transition
ROS	Reactive oxygen species

Introduction

Palmitic acid (Pal)—one of the main saturated fatty acids in the cell—is a well-known modifier of the

K. N. Belosludtsev · N. V. Belosludtseva · A. S. Trudovishnikov · G. D. Mironova
Institute of Theoretical and Experimental Biophysics RAS, Pushchino, Moscow Region 142290, Russia

N.-E. L. Saris
Department of Applied Chemistry and Microbiology, University of Helsinki, POB 56, Biocenter 1, FIN-00014 Helsinki, Finland

L. D. Lukyanova
Institute of General Pathology and Pathophysiology RAMS, Moscow 125315, Russia

G. D. Mironova (✉)
Pushchino State University, Pushchino, Moscow Region 142290, Russia
e-mail: mironova40@mail.ru

mitochondria membrane permeability. It was found that Pal promotes the opening of a cyclosporin A-insensitive Ca^{2+}-dependent pore in mitochondria (Sultan and Sokolove 2001a, b; Mironova et al. 2004). This Pal/Ca^{2+}-induced pore (PalCaP) was shown to be different from the mitochondrial permeability transition pore (MPT pore), concerning both regulation and, apparently, the mechanism of formation.

According to our data, formation of PalCaP results from complexation of Ca^{2+} with Pal anions on the matrix side of the inner mitochondrial membrane. At alkaline pH, the affinity of Pal for Ca^{2+} is 1–2 orders of magnitude higher than that of other FFA and phospholipids (Mironova et al. 2001). Moreover, formation of Pal/Ca^{2+} complexes in artificial membranes, planar bilayers (BLM) or liposomes, results in the permeabilization of these membranes (Mironova et al. 2001; Agafonov et al. 2003). It seems that the molecular mechanism of PalCaP opening may relate to the initial stage of Ca^{2+}-induced phase separation of Pal in the lipid bilayer and can be considered as formation of fast-tightening lipid pores upon chemotropic phase transition in the membrane (Agafonov et al. 2007). Further studies showed that, in contrast to the MPT pore, PalCaP closed spontaneously after its opening (this is explained well by the theory of lipid pores; Antonov and Shevchenko 1995) and that different MPT modulators, such as ADP, P_i, CsA, did not influence PalCaP (Sultan and Sokolove 2001a; Mironova et al. 2004; Belosludtsev et al. 2005).

However, there is almost no data concerning PalCaP regulation under various physiological conditions. At the same time, the amounts of Pal and Ca^{2+} that will open the pore are close to physiological ones (Wojtczak 1969; Le-Quoc and Le-Quoc 1989; Mironova et al. 2004). Moreover, the concentration of Pal in mitochondria may increase at certain physiological conditions and pathologies, such as ischemia, diabetes and others (Vork et al. 1993; Mironova et al. 2004; DeFronzo 2004).

In the present study, we have shown that (1) cardiolipin facilitates PalCaP formation in liposomes; (2) the opening of Pal/Ca^{2+}-induced pore is accompanied by the release of apoptosis-induced factor (AIF) from mitochondria; (3) heart mitochondria are more resistant to the inductors of PalCaP than the liver ones; (4) old rats are much more prone to PalCaP opening than the young ones; (5) the possibility of PalCaP opening depends on the resistance of animals to hypoxia: the pore opens easier in the mitochondria of highly resistant to hypoxia rats, which is opposite to what observed in the case of the MPT pore. The adaptation of low resistant rats to oxygen deficiency by intermittent normobaric hypoxia trainings increases the sensitivity of their mitochondria to PalCaP inductors.

Materials and methods

Chemicals All chemicals were purchased from Sigma-Aldrich, St. Louis, MO, U.S.A.

Selection and adaptation of animals in a flow-pressure chamber

Wistar rats were classified according to their resistance to hypoxia on the basis of their behavior in a flow-pressure chamber. For the experiments, two types of animals were selected: highly resistant and low resistant, which was defined by how long they could stand—until the second agonal breath—the conditions of acute hypobaric hypoxia (11.5-km altitude). Highly resistant to hypoxia rats could endure these conditions for 10–15 min, whereas low resistant animals resist them no longer than a minute. The flow-pressure chamber was also used to adapt low resistant rats to oxygen deficiency (an "intermittent normobaric hypoxia" training). The procedure of adaptation consists in the animals inhaling low-oxygen air (10% O_2) for 10 min, this being repeated 5 times with 3-min normal-oxygen breaks once a day. The whole training course lasted 12 days. After the course, the previously low resistant rats became well-adapted to hypoxia and reached the potential of the highly resistant animals (Lukyanova et al. 2007).

Mitochondria isolation

Mitochondria were isolated from the liver of Wistar rats (220–250 g) using a standard differential centrifugation technique (Belosludtsev et al. 2005). The isolation medium contained 210 mM mannitol, 70 mM sucrose, 1 mM EDTA and 10 mM Hepes/KOH buffer (pH 7.4); the washing medium was of the same content, except that EDTA was replaced with 100 μM EGTA. When mitochondria were isolated from the heart, the isolation medium contained 220 mM mannitol, 50 mM sucrose, 2 mM EDTA, 0.2% BSA and 30 mM Hepes/KOH buffer (pH 7.4); the washing medium was the same, except EDTA and BSA. The final suspension contained 90–100 (liver) or 30–50 (heart) mg of mitochondrial protein/ml. The concentration of mitochondrial protein was determined by the Lowry method (Lowry et al. 1951).

Mitochondrial swelling

Mitochondrial swelling was measured as a decrease in A_{540} in a stirred and thermostated cuvette (25°C) using a USB-2000 spectroscopy fiber-optic system (Ocean Optics Inc., USA). The reaction medium contained 210 mM mannitol, 70 mM sucrose, 5 mM succinate, 6 μM EGTA, 1 μM

rotenone, 1 μM CsA and 10 mM Hepes/KOH buffer (pH 7.4). The concentration of mitochondrial protein was about 0.4 mg/ml.

Ca^{2+} uptake by mitochondria and MPT pore opening

The concentration of Ca^{2+} in the reaction medium was measured with an ion-selective electrode. The reaction medium contained 150 mM sucrose, 50 mM KCl, 2 mM KH_2PO_4, 5 mM succinate, 6 μM EGTA, 1 μM rotenone and 10 mM Hepes/KOH buffer (pH 7.4). The concentration of mitochondrial protein was 5 mg/ml. In the experiments, 20 μM Ca^{2+} was added into the reaction medium every 60 sec. After several additions, the concentration of external Ca^{2+} abruptly increased, indicating massive release of the ion from the organelles due to opening of the MPT pore in the inner mitochondrial membrane. The amount of Ca^{2+} necessary for the massive release of the ion from mitochondria (defined as Ca^{2+} capacity) was used as an estimate for the possibility of MPT pore opening.

ROS production

ROS production in the suspension of mitochondria was monitored fluorimetrically with 10 μM 2,7-dichlorodihydrofluorescein diacetate (H_2-DCFDA) and 2 units/ml of horseradish peroxidase (excitation wavelength, 485 nm; emission wavelength, 530 nm) using a Tecan "Infinite-2000" fluorimeter (USA). The reaction medium contained 210 mM mannitol, 70 mM sucrose, 5 mM succinate, 6 μM EGTA, 1 μM rotenone, 1 μM CsA and 10 mM Hepes/KOH buffer (pH 7.4). The concentration of mitochondrial protein was about 0.3 mg/ml.

AIF release

The release of apoptosis-induced factor (AIF) (57 kDa) from mitochondria was analyzed by Western blotting. Briefly, samples for western-blot analysis were subjected to SDS/PAGE (12% gel) electrophoresis and transferred to a PVDF membrane for immunodetection. AIF content was evaluated using primary polyclonal antibodies against AIF (1:2000) and horseradish peroxidase-conjugated secondary antibodies (1:1000).

Liposome permeabilization

Azolectin liposomes (large unilamellar vesicles) loaded with sulforhodamine B (SRB) were prepared using a conventional extrusion technique as described earlier (Agafonov et al. 2003). The release of SRB from liposomes was detected by the increase in fluorescence (excitation wavelength, 565 nm; emission wavelength, 586 nm) measured at 25°C using a USB-2000 spectroscopy fiber-optic system (Ocean Optics Inc., USA).

Results

Cardiolipin increases the Pal/Ca^{2+}-induced permeabilization of azolectin liposomes

As found earlier, the addition of Ca^{2+} to Pal-containing liposomes results in the release of sulforhodamine B from vesicles, and the amount of SRB released is higher when liposomes are formed from the mitochondrial lipids, as compared to azolectin (Mironova et al. 2004). We supposed that the cause was the presence of cardiolipin in the extract of mitochondrial lipids. To test this idea, we measured Pal/Ca^{2+}-induced SRB release from the cardiolipin-containing azolectin liposomes (cardiolipin content, 25%; *w*/*w*), with the pure azolectin vesicles used as a control (Fig. 1). As can be seen, the presence of cardiolipin in the membrane of liposomes substantially increases the Pal/Ca^{2+}-induced SRB release—over the entire range of Pal concentrations examined.

The rate of Pal/Ca^{2+}-induced swelling of liver mitochondria is higher than that of heart mitochondria

In this work, we examined the opening of PalCaP in liver and heart mitochondria. As Fig. 2a shows, 15 μM Pal plus 30 μM Ca^{2+} induced CsA-insensitive swelling in both liver and heart mitochondria. However, the amplitude of swelling of heart mitochondria was significantly lower. At the

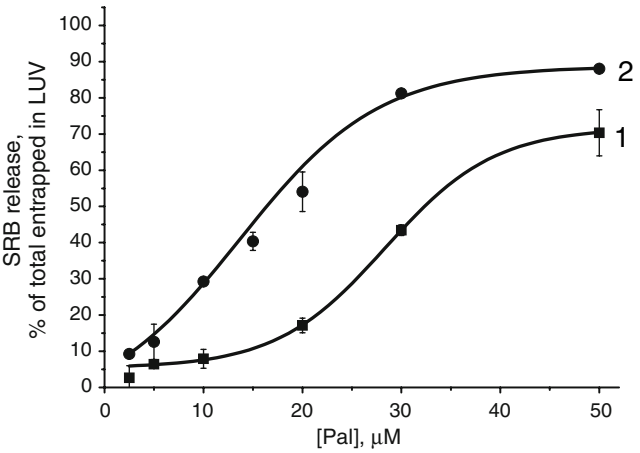
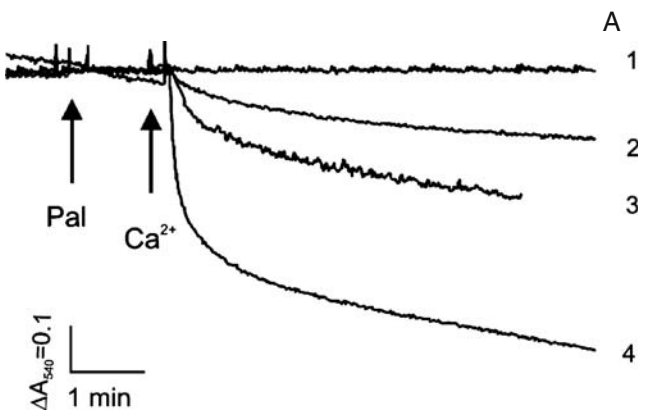
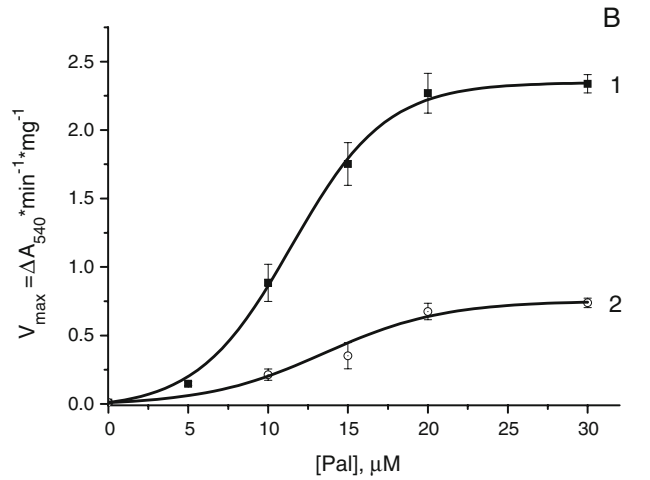
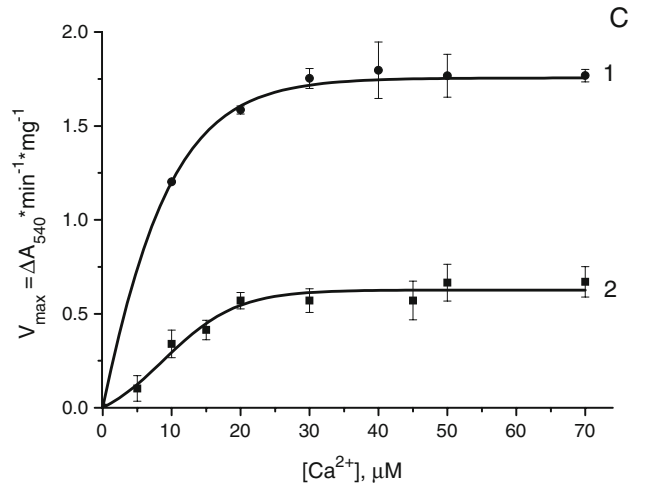


Fig. 1 Dependence of Pal/Ca^{2+}-induced release of SRB from liposomes on the concentration of Pal. The medium contained 40 mM KCl, 5 μM EGTA and 10 mM Tris–HCl (pH 8.5). Concentration of Ca^{2+} was 1 mM. Liposomes were formed from either azolectin (1) or an azolectin/cardiolipin mixture (2); the content of cardiolipin was 25% (*w*/*w*) of total lipids). Mean values ± SD are presented (n=4)







◀ **Fig. 2** Swelling of heart and liver mitochondria induced by Pal and Ca^{2+}. **a** Traces of Pal/Ca^{2+}-induced swelling of heart (1–3) and liver (4) mitochondria. Additions: 1) no additions; 2) 15 μM Pal and 30 μM Ca^{2+}; 3) 30 μM Pal and 45 μM Ca^{2+}; 4) 15 μM Pal and 30 μM Ca^{2+}. **b** Dependence of the rate of liver (1) and heart (2) mitochondrial swelling on the concentration of Pal. Swelling was induced by Pal (5-30 μM) and Ca^{2+} (either 30 or 45 μM, for liver and heart mitochondria respectively). **c** Dependence of the rate of liver (1) and heart (2) mitochondrial swelling on the concentration of Ca^{2+}. Swelling was induced by Pal (either 15 or 30 μM, for liver and heart mitochondria respectively) and Ca^{2+} (10–70 μM). The reaction medium contained 210 mM mannitol, 70 mM sucrose, 5 mM succinate, 5 μM EGTA, 1 μM rotenone, 1 μM CsA and 10 mM HEPES/KOH (pH 7.4)

same time, it did not seem to be a limit in the ability of heart mitochondria to swell: elevation of Pal and Ca^{2+} concentrations up to 30 and 45 μM respectively increased the amplitude of swelling.

The dependences of the rate of Pal/Ca^{2+}-induced swelling of heart and liver mitochondria on the concentration of Pal and Ca^{2+} are given in Fig. 2b–c. The maximal rate of swelling was observed in the presence of 20–30 μM Pal and 30–70 μM Ca^{2+}; however, even at the saturating conditions, liver mitochondria swelled significantly faster than the heart ones.

As the animals mature, PalCaP opens easier

To examine the age dynamics of PalCaP opening, we measured the rate of Pal/Ca^{2+}-induced swelling of liver mitochondria isolated from 1-, 3-, 8- and 18-month-old animals. Figure 3 shows the corresponding rates of swelling plotted versus Pal concentration. As can be seen from the figure, 1-month-old impuberal animals have the highest resistance to PalCaP inductors (Pal and Ca^{2+}), and this resistance decreases with age.

It should be noted that there were no substantial age-related differences in the parameters of mitochondrial respiration and phosphorylation (unpublished data).

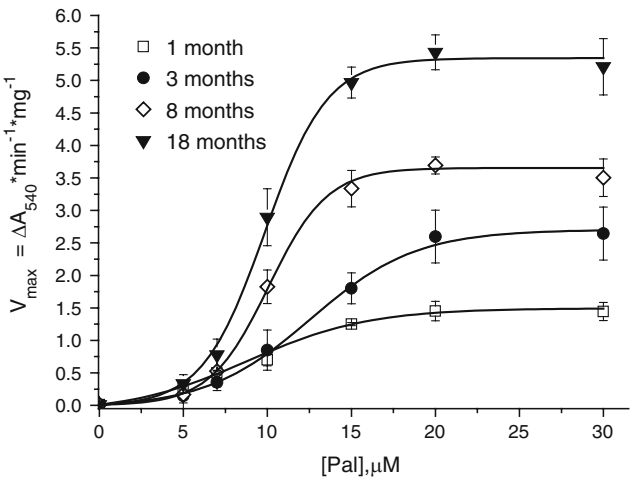


Fig. 3 Dependence of the rate of Pal/Ca^{2+}-induced swelling of liver mitochondria isolated from 1-, 3-, 8- and 18-month old rats on the concentration of Pal. Swelling was induced by Pal (5–30 μM) and Ca^{2+} (30 μM). The reaction medium was the same as in Fig. 2. Mean values ± SD are presented (n=6)

The opening of PalCaP leads to the CsA-insensitive release of AIF from mitochondria

As established earlier, 15 μM Pal plus 30 μM Ca^{2+} induce the opening of PalCaP and the release of cytochrome *c* from mitochondria (Belosludtsev et al. 2006). Now we have found that under the same conditions, apoptosis-inducing factor (AIF) is also released from rat liver mitochondria in a CsA-insensitive way (Fig. 4).

The opening of PalCaP depends on the resistance of animals to hypoxia

It is known that laboratory animals vary significantly in their sensitivity to hypoxic conditions, which is genetically predetermined (Lukyanova et al. 2007). Here we examined the opening of PalCaP in the liver mitochondria of highly resistant, low resistant to oxygen deficiency rats, and hypoxia-adapted animals.

Figure 5a shows the rate of Pal/Ca^{2+}-induced mitochondrial swelling measured for those three types of rats and plotted versus Pal concentration. Mitochondria of highly resistant to hypoxia rats swell faster than those of low resistant animals. However, the adaptation of low resistant rats to the low-oxygen conditions increases the sensitivity of their mitochondria to PalCaP inductors.

Interestingly, an opposite picture is observed in case of the MPT pore. This pore opens easier in mitochondria of the low resistant rats. Comparatively to them, mitochondria of the highly resistant to hypoxia animals reveal a higher Ca^{2+} capacity (Fig. 5b).

Figure 6 shows the dynamics of ROS production by liver mitochondria in the absence (1st curves) and presence (2nd curves) of PalCaP inductors, with the A and B graphs representing the results obtained for the low and highly resistant to hypoxia rats respectively. The data demonstrate that the opening of PalCaP in liver mitochondria of the highly resistant rats leads to the inhibition of ROS production, whereas in the low resistant animals, the production of ROS by mitochondria is stimulated under the same circumstances. It should also be noted that in the highly resistant to hypoxia animals, the rate of mitochondrial ROS production *per se* was slightly higher than that in the low resistant ones.

Fig. 4 Release of apoptosis-inducing factor (AIF) from mouse liver mitochondria induced by the PalCaP opening (15 μM Pal, 30 μM Ca^{2+}). The reaction medium was the same as in Fig. 2

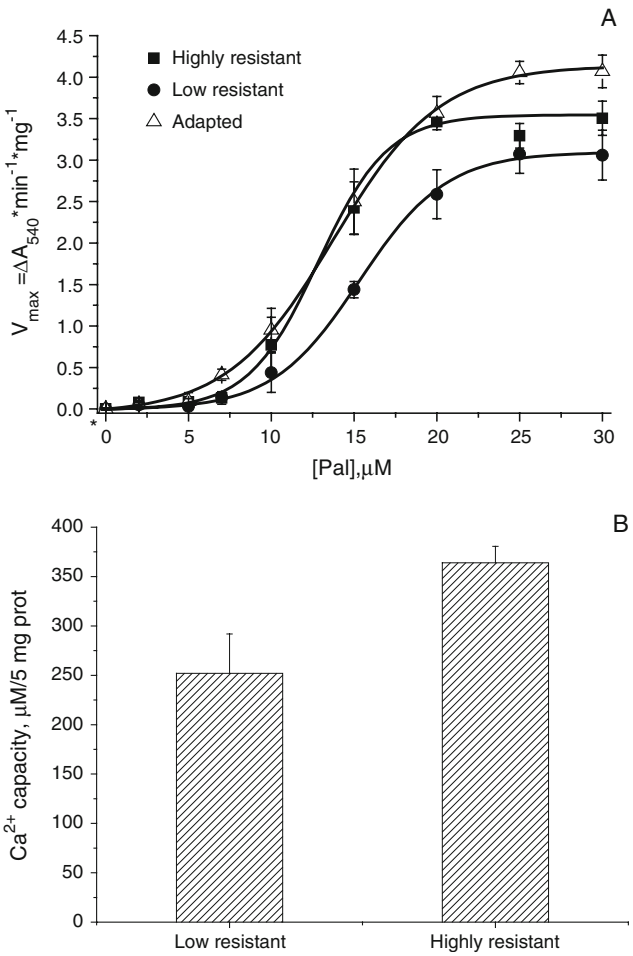


Fig. 5 The possibility of PalCaP and MPT pore to open changes depending on the resistance of rats to hypoxia. **a** Dependence of the rate of Pal/Ca^{2+}-induced swelling of liver mitochondria isolated from highly resistant, low resistant and hypoxia-adapted rats on the concentration of Pal. Swelling was induced by Pal (2-30 μM) and Ca^{2+} (30 μM). The reaction medium was the same as in Fig. 2. **b** Ca^{2+} capacity of liver mitochondria isolated from highly resistant and low resistant to hypoxia rats. The reaction medium contained 150 mM sucrose, 50 mM KCl, 2 mM KH_2PO_4, 5 mM succinate, 6 μM EGTA, 1 μM rotenone and 10 mM Hepes/KOH buffer (pH 7.4). Mean values ± SD are presented (n=4)

Discussion

In this paper we continue studying physiological and regulatory aspects of the mitochondrial palmitate/Ca^{2+}-activated pore. The results presented show that the possibility of PalCaP to open is influenced by the lipid composition of the membrane and depends on the type of tissue and physiological state of the organism (dependence on the age and resistance to hypoxia).

The role of lipid composition of the membrane in formation of PalCaP was considered in our previous papers. The Pal/Ca^{2+}-induced permeabilization of unilamellar liposomes formed from mitochondrial lipids was shown to be

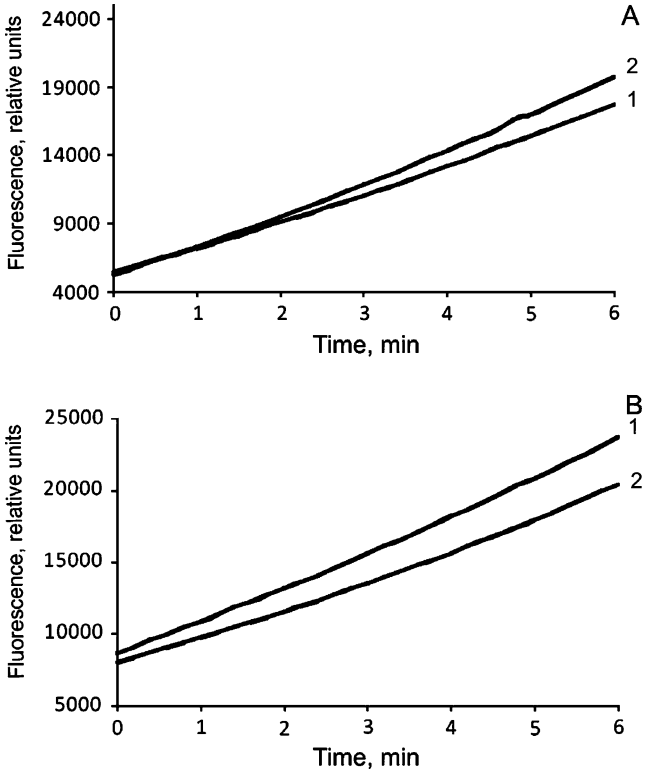


Fig. 6 The effect of PalCaP opening on the generation of H_2O_2 by liver mitochondria isolated from of low resistant (**a**) and highly resistant to hypoxia (**b**) rats. Additions: 1) no additions; 2) 15 μM Pal and 30 μM Ca^{2+}. The reaction medium was the same as in Fig. 2, except that it was supplemented with 10 μM H_2-DCFDA and 2 units/ml of horseradish peroxidase

significantly higher than that of azolectin liposomes (Mironova et al. 2004). It was also found that the incorporation of cholesterol into the liposomal and mitochondrial membranes slightly facilitated the opening of PalCaP (Belosludtseva et al. 2009).

In this paper, we have shown that the Pal/Ca^{2+}-induced permeabilization of liposomes formed from a cardiolipin/azolectin mixture was much more pronounced than that of pure-azolectin vesicles (Fig. 1). Earlier we found that 10-N-nonyl acridine orange, which specifically binds to cardiolipin (Petit et al. 1992), inhibited the opening of PalCaP in mitochondria (Belosludtsev et al. 2006). Thus, cardiolipin seems to be a component of the membrane that can be involved in the formation of PalCaP.

It is known that the lipid composition and physicochemical properties of the mitochondrial membrane can change depending on the type of tissue and physiological state of the organism (Fleischer et al. 1967; Daum 1985). Figure 2 shows that the amplitude and rate of Pal/Ca^{2+}-induced swelling of heart mitochondria are lower than those of liver ones. This may be explained by differences in the lipid composition of liver and heart mitochondria. In liver mitochondria, the level of endogenous fatty acids, including palmitic acid, is higher (Daum 1985). At the same time, the differences in the parameters of swelling may relate to the different number of contact sites, which is larger in the heart mitochondria—due to the presence of creatine kinase (Brdiczka et al. 2006; Speer et al. 2005).

In this paper, we have shown that the opening of PalCaP in the rat liver mitochondria is substantially facilitated as the animals mature and grow old (Fig. 3). According to the literature data, the mitochondrial transmembrane potential drops with age (Hagen et al. 1997), and also changing are the composition and properties of the mitochondrial membrane (Daum 1985). Evidently, these changes may be the cause of mitochondria becoming less resistant to the PalCaP inductors.

Our data on the age-dependence of PalCaP may also have relevance to the programmed cell death, which is known to increase with animal ageing (Lopes et al. 2004; Zhu et al. 2005). Pal was shown to be a physiological activator of apoptosis (Sparagna et al. 2000), and the Pal-induced apoptosis may develop by either caspase-dependent or caspase-independent pathway (Ulloth et al. 2003). Our results demonstrate that PalCaP is accompanied by the release of pro-apoptotic intermembrane proteins: apoptosis-inducing factor (Fig. 4), which induces caspase-independent apoptosis, and cytochrome *c* (Belosludtsev et al. 2006), which triggers caspase-dependent apoptosis. Thus, facilitation of PalCaP opening in the mitochondria of old rats may be the cause of the age-related increase in the intensity of apoptosis.

As follows from the results obtained in this work, PalCaP opening depends on the resistance of animals to hypoxia. In liver mitochondria of the highly resistant to hypoxia rats, PalCaP opens easier than in the organelles of the low resistant animals. The latter, however, can be adapted to hypoxic conditions, becoming quite tolerant to the inductors of PalCaP (Fig. 5a). In contrast to PalCaP, the classical MPT pore opens easier in mitochondria of the low resistant rats (Fig. 5b). These data indicate a difference in the function of these pores and confirm our recent observations that regulation and physiological significance of PalCaP and MPT pore are rather different.

It seems that the physiological activation of PalCaP in mitochondria of the highly resistant and hypoxia-adapted rats is a compensatory mechanism, which protects tissues against ischemic injury. The ischemia-induced tissue damage is known to be caused by the generation of ROS in mitochondria, which can be prevented by the so-called "mild uncoupling effect" (Korshunov et al. 1997; Skulachev 1998a; Brookes 2005). It was suggested earlier that this phenomenon underlies the cardioprotective effect of activators of the mitochondrial ATP-dependent potassium channel, whose involvement in the protection of heart against ischemia/reperfusion can be mediated by activation of the mitochondrial K^+ cycle (Garlid et al. 2003; Krylova et al. 2006; Mironova 2007).

On the other hand, mild uncoupling of oxidative phosphorylation can be provided for by micromolar concentrations of FFA (Skulachev 1998b), and the enhanced expression of mitochondrial uncoupling proteins (UCP-1, UCP-2) would protect tissues against ischemia/reperfusion damage (Mattiasson et al. 2003; Diano et al. 2003; Hoerter et al. 2004). It has also been reported that the FFA-dependent mitochondrial uncoupling is enhanced by ischemic preconditioning (Carreira et al. 2007).

Based on the results of this paper, we suppose that a possible mechanism of animal's adaptation to hypoxia is the activation of a Ca^{2+} cycle, which is mediated by Ca^{2+} uniporter and PalCaP (Mironova et al. 2007) and leads to the mild uncoupling and decreased ROS production in mitochondria (Fig. 6b).

Thus, the data presented indicate that the opening of the CsA-insensitive Pal/Ca^{2+}-induced pore is controlled by the physiological state of the organism, which, in its turn, depends on such factors as animal's age, resistance to hypoxia, and type of tissue. The results suggest that the pore may play a role in such important processes as apoptosis, adaptation to hypoxia and ageing.

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