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Titration of cardiolipin by either 10-*N*-nonyl acridine orange or acridine orange sensitizes the adenine nucleotide carrier to permeability transition

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Abstract Under the action of carboxyatractyloside or fatty acids, adenine nucleotide translocase switches its function from nucleotide carrier to modulator of the opening of a non-specific pore. In addition to the effect of these agents, this modification in activity is, in some way, dependent on the influence of the lipid milieu of the membrane. Cardiolipin is, among other membrane phospholipids, the one that interacts the most with the translocase. This work shows that 10-*N*-nonyl acridine orange and acridine orange, probes for this phospholipid, modify the sensitivity of the translocase to carboxyatractyloside, oleate, and palmitate to induce permeability transition. The results also show that these probes stimulate the release of mitochondrial cytochrome *c*, and increase labeling of the carrier by eosin 5-maleimide. Based on the aforementioned it is proposed that the increase in sensitivity is due to a conformational change in the translocase, induced by the binding of the probe to cardiolipin.

Keywords Mitochondria · Permeability transition · Adenine nucleotide translocase · Cardiolipin · Calcium

Introduction

Permeability transition is a mitochondrial process that occurs after the opening of a transmembrane non-specific pore with a diameter size of roughly 3 nm. This pore permits the efflux of ions and metabolites located in the matrix, even of mitochondrial DNA fragments (Bernardi 1999; Zoratti et al. 2005; García et al. 2005; García and Chávez 2007). The requirements for the opening of such a pore include supraphysiological calcium loads (Brookes et al. 2004) and a wide array of inducing agents; among them are carboxyatractyloside (Gunter and Pfeiffer 1990; Haworth and Hunter 2000) and fatty acids (Schönfeld and Bohnensack 1997; Skulachev 1999). Regarding the chemical nature of the non-specific pore, a number of reports point to the adenine nucleotide translocase (ANT) as the membrane entity involved in the increased permeability (Tikhonova et al. 1994; Brustovetsky and Klingenberg 1996; Wieckowski et al. 2000). The orientation of this carrier (i.e., ANT) across the inner membrane modulates the open/closed cycles of the pore. In this regard, ADP, which fixes ANT on the matrix side, closes the pore whereas the inhibitors atractyloside and carboxyatractyloside, which stabilize ANT in the cytosolic side, stimulate its opening (Pebay-Peyroula et al. 2003). Another factor that contributes to the modulation of the activity of ANT is the phospholipid cardiolipin, located tightly bound to the carrier. Beyer and Klingenberg (1985) demonstrated that ANT has six cardiolipin molecules surrounding the carrier. Furthermore, Hoffmann et al. (1994) have shown that, in a reconstituted system, ANT has an absolute requirement for cardiolipin to perform adenine nucleotide transport. In the same context, several reports have demonstrated that the thyroid hormone controls mitochondrial cardiolipin content. In this regard, mitochondria isolated from hyperthyroid rats show an increase in this phospholipid in the inner membrane (Guerrero et al. 1999; Gredilla et al. 2001). Such an increase is mirrored by an improved non-specific

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permeability (Malkevitch et al. 1997). Conversely, in a previous report, we showed that mitochondria prepared from hypothyroid rats show resistance to undergo permeability transition (Chávez et al. 1998). The latter correlates with the finding that hypothyroid mitochondria have low cardiolipin content (Paradies et al. 1997).

10-*N*-nonyl-acridine orange (NAO) and acridine orange (AO) are appropriate markers for cardiolipin. In the experiments reported here, carboxyatractyloside (CAT), a specific inhibitor of ANT, and oleate and palmitate were used as permeability transition inducing agents. The results show that NAO and AO improve the effect of CAT on mitochondrial Ca^{2+} efflux, as well as on mitochondrial swelling. It is also shown that NAO increases the release of cytochrome *c* and the binding of eosin-5-maleimide to ANT. This latter would indicate a conformational change in the carrier, promoted by the binding of NAO to its tightly bound cardiolipin.

Materials and methods

Kidney mitochondria were prepared from Wistar rats by homogenizing the cortex tissue in 0.25 mM sucrose–1 mM EDTA adjusted to pH 7.3. The last wash was carried out in EDTA-free sucrose medium. Protein was determined by the Lowry method (Lowry et al. 1951). The dye Arsenazo III was used to follow spectrophotometrically mitochondrial calcium movements at 675–685 nm. Mitochondrial swelling was determined following the changes in absorbance at 540 nm. To assess the effect of AO on the labeling of adenine nucleotide translocase, 2 mg of mitochondrial protein was suspended in 3 ml of the basic medium and pre-incubated with the indicated concentrations of AO during 5 min; then, 20 nmol/mg protein of eosin-5-maleimide (EMA) was added (Majima et al. 1993), and incubated during 30 min at 4 °C in darkness. The reaction was stopped by the addition of 30 mM DTT. Mitochondria (100 μg protein) were then subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS) in 12% polyacrylamide, under reducing conditions, and fluorescence was estimated with a UV lamp. Cardiolipin was measured by incubating 250 μg mitochondrial protein in 1 ml of basic medium containing in addition increasing concentrations of NAO and AO. After 10 min incubation, at 25 °C, the mixtures were centrifuged at 18,000×*g*/10 min and the unbound NAO and AO were estimated in the supernatant at 496 nm. The amount of dyes bound was calculated by subtracting the amount found in the supernatant from the total added amount. Release of cytochrome *c* was analyzed according to Correa et al. (2007). Briefly, 2 mg mitochondrial protein was added to 3 ml of the basic mixture; after 5 min incubation, the samples were centrifuged 10 min at 18,000×*g*, the supernatants were precipitated with trichloroacetic acid, the pellets were washed once. Protein (50 μg) was loaded onto SDS-PAGE gels and transferred to a PVDF membrane for immunodetection. Cytochrome *c* content in mitochondria was evaluated using a primary monoclonal antibody against cytochrome *c* (1:1,000 dilution) and an alkaline-phosphatase-conjugated secondary antibody. The basic incubation medium, adjusted at pH 7.3 contained 125 mM KCl, 10 mM succinate, 3 mM phosphate, 10 mM HEPES, 50 μM $CaCl_2$, 100 μM ADP, 4.2 μM rotenone, and 1 μg oligomycin per milligram of protein. Other additions were as indicated in the legends of the respective figures. The incubation mixtures were thermostated at 25 °C and the media were bubbled with O_2 and gently stirred.

Results

Belosludtsev et al. (2006) reported that the binding of NAO to cardiolipin inhibits permeability transition as induced by palmitate. Furthermore, AO and NAO inhibit oxidative phosphorylation, induce a drop in transmembrane potential, and inhibit F1-ATPase activity (Bullough et al. 1989; Maftah et al. 1990). Considering the above, first we examined the effect of these reagents, as well as low concentrations of carboxyatractyloside (CAT), on mitochondrial Ca^{2+} retention. For this, we incubated the mitochondria with different amounts of the fluorescent probes. As shown in Fig. 1, trace a, the addition of 22.5 nmol NAO/mg protein induced a diminution in the amount of Ca^{2+} uptake. This reaction was followed by the release of the cation at a fast rate. A similar result was obtained when mitochondria were incubated in the presence of 15 nmol NAO/mg protein (trace b). However, as shown in trace c, mitochondria retained accumulated Ca^{2+} regardless of the addition of 7.5 nmol NAO/mg. Interestingly, when acridine orange was used instead of NAO (trace d), mitochondria were able to retain accumulated Ca^{2+} even after the addition of 22.5 nmol AO/mg protein. Trace e shows that CAT at the concentration of 0.2 μM was unable to induce matrix Ca^{2+} release.

As known, the phospholipid cardiolipin constitutes an important component of the lipidic annulus of ANT, and is tightly bound to the dimeric protein (Beyer and Klingenberg 1985; Schlame et al. 1991). Considering this, we explored next the possibility that the binding of NAO or AO to cardiolipin would sensitize ANT to CAT-induced permeability transition. First of all, we must take into account that, as shown in Fig. 1, 0.2 μM CAT did not induce Ca^{2+} release, and that neither NAO nor AO, at the amount of 7.5 nmol/mg protein, promoted membrane leakage. As shown in Fig. 2a, 0.2 μM CAT was able to promote Ca^{2+}

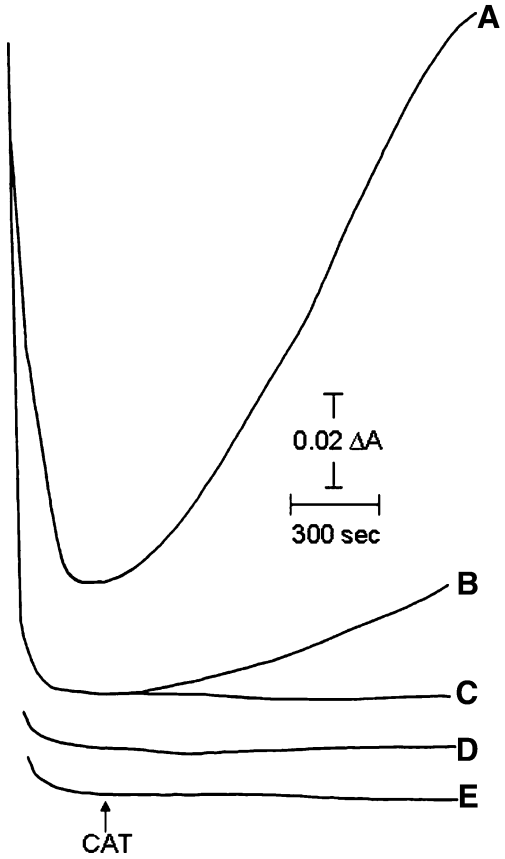

Fig. 1 The effect of NAO, AO, and carboxyatractyloside on mitochondrial Ca^{2+} content. Mitochondrial protein (2 mg) was added to 3 ml of the basic medium, as described under "Materials and methods". The additions of NAO were as follows: in trace *a* 22.5 nmol/mg; in trace *b*, 15 nmol/mg; in trace *c*, 7.5 nmol/mg. In trace *d*, 22.5 nmol/mg of AO were added. Where indicated, in trace *e*, 0.2 μM CAT was added. Temperature 25 °C

efflux when added to mitochondria incubated in the presence of 4.5, 6, and 7.5 nmol NAO/mg, traces B, C, and D, respectively. As seen in Fig. 2b, AO also sensitized ANT to the effect of CAT on pore opening; although, the rate of Ca^{2+} efflux is lower as compared to that observed with NAO. Traces A, B, and C indicate that a Ca^{2+} efflux reaction took place after the addition of 0.2 μM CAT to mitochondria incubated in the presence of 3, 4.5, or 7.5 nmol AO/mg, respectively.

Mitochondrial swelling, in the presence of NAO or AO, was also analyzed to further assess the stimulating effect of the cardiolipin probes on permeability transition. Figure 3a, trace A, shows that 0.2 μM CAT promoted a fast and large amplitude swelling of mitochondria incubated in a medium containing 7.5 nmol NAO/mg. Trace B shows the absolute dependence of Ca^{2+} on this reaction. As observed in trace B, when mitochondria were incubated in a Sr^{2+} medium, instead of Ca^{2+}, NAO was not able to sensitize ANT to the effect of CAT; and swelling took place only after the addition of 50 μM Ca^{2+}. Traces C and D are the controls showing that NAO or CAT alone, respectively, did not induce an increase in mitochondrial volume. Figure 3b shows the effect of AO on CAT-induced swelling. Trace A illustrates that 7.5 nmol AO/mg per se did not induce swelling, trace B shows that this reaction took place after the addition of 0.2 μM CAT. Trace C shows that, similarly to what occurred with NAO, the reaction required Ca^{2+} to induce membrane leakage. However, conversely to what occurs with NAO, 100 μM Ca^{2+} was required to attain mitochondrial swelling.

Next, we decided to explore whether or not the addition of the probes, after CAT, would have similar effects as

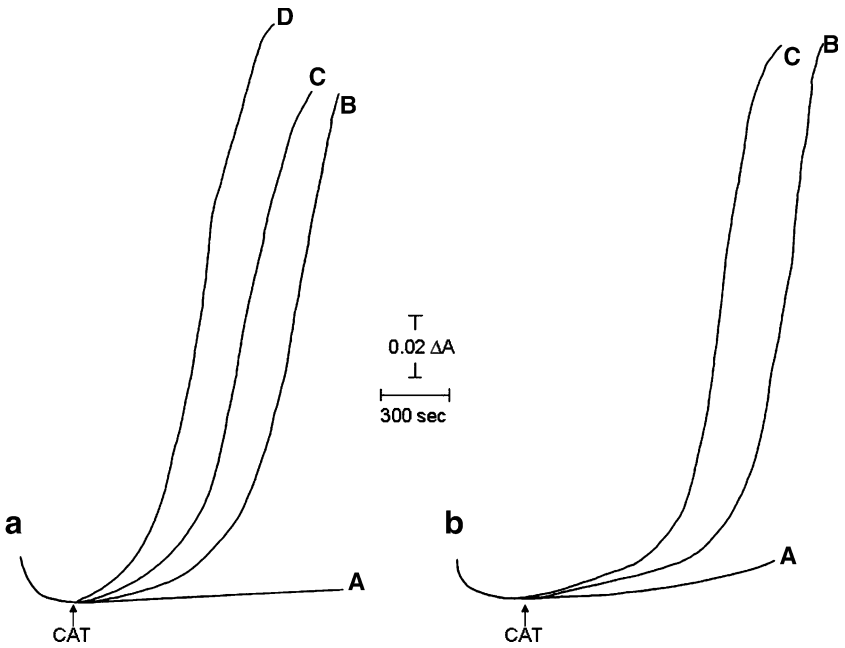

Fig. 2 Calcium release as induced by NAO or AO plus carboxyatractyloside. Mitochondrial protein (2 mg) was incubated in 3 ml of a basic medium, as described under "Materials and methods". In **a**, NAO was added to the incubation medium as follows: traces *B*, *C*, and *D* contained 4.5, 6, and 7.5 nmol/mg protein, respectively. Where indicated, 0.2 μM CAT was added. In **b**, AO was added as follows: traces *B* and *C* contained 4.5 and 7.5 nmol/mg, respectively. CAT was added at 0.2 μM. Temperature 25 °C

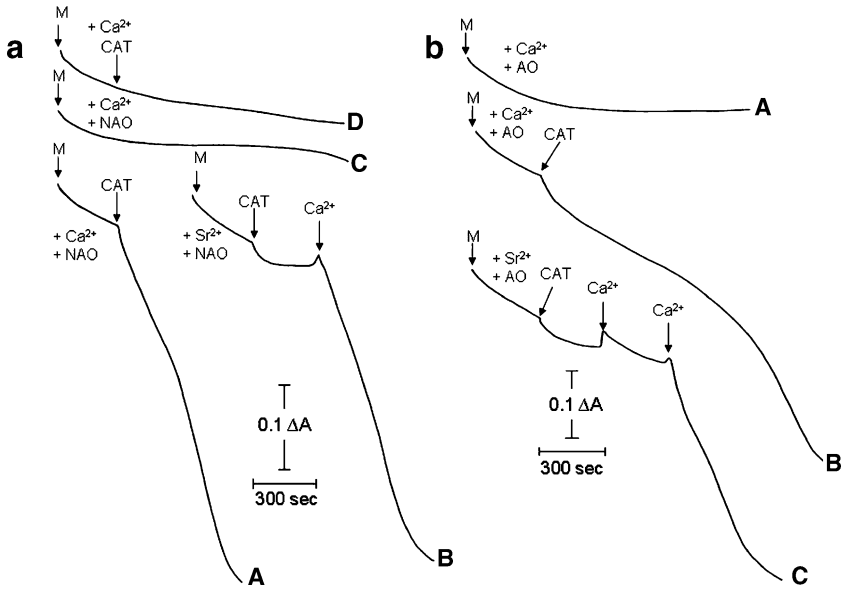

Fig. 3 Mitochondrial swelling induced by NAO or AO plus carboxyatractyloside. Requirement for calcium. Incubation conditions as described for Fig. 2. In **a**, trace *A*, the medium contained 7.5 nmol NAO/mg and 50 μM Ca^{2+}; where indicated, 0.2 μM CAT was added. In trace *B*, the medium contained 7.5 nmol NAO/mg and 50 μM Sr^{2+}; where indicated, 0.2 μM CAT and 50 μM Ca^{2+} were added. In trace *C*, CAT was not added and, in trace *D*, NAO was not added. In **b**, trace *A*, the medium contained 50 μM Ca^{2+} and 7.5 nmol AO/mg. In trace *B*, the medium contained 50 μM Ca^{2+} plus 7.5 nmol AO/mg; where indicated, 0.2 μM CAT was added. In trace *C*, the medium contained 50 μM Sr^{2+}; 0.2 μM CAT and 50 μM Ca^{2+} were added where indicated

when added before the inducer. Figure 4, trace b, indicates that a fast Ca^{2+} release reaction occurred when NAO was added after CAT. However, as seen in trace a, the addition of AO, after CAT, did not induce permeability transition. This could be explained considering that NAO is a penetrant reagent that might titrate cardiolipin located in the inside leaf of the inner membrane, while AO mainly titrates cardiolipin molecules situated in the outside leaf of the inner membrane.

At this stage of the experimental work, the question to answer was whether or not the probes would also stimulate the effect of oleate and palmitate. As known, these reagents also induce permeability transition through a mechanism in which ANT is implicated (Skulachev 1991; Khailova et al. 2006). Figure 5a shows that the cardiolipin probes also facilitate permeability transition induced by 15 μM oleate. Figure 5b shows that with palmitate as inducer, the Ca^{2+} efflux reaction occurs at a slower rate than that observed with oleate.

Titration of mitochondrial cardiolipin by NAO or AO is shown in Fig. 6. As observed, 7.5 nmol NAO/mg titrated approximately 3.4 nmol cardiolipin/mg. Whereas 7.5 nmol AO/mg titrated 2.1 nmol cardiolipin. Such a difference could explain the better effectiveness of NAO to stimulate permeability transition by CAT or fatty acids.

Another question that arose was whether titration of cardiolipin would produce a conformational modification in ANT. To answer this, we used the fluorescent probe eosin-5-maleimide (EMA) to label ANT. Figure 7 illustrates that

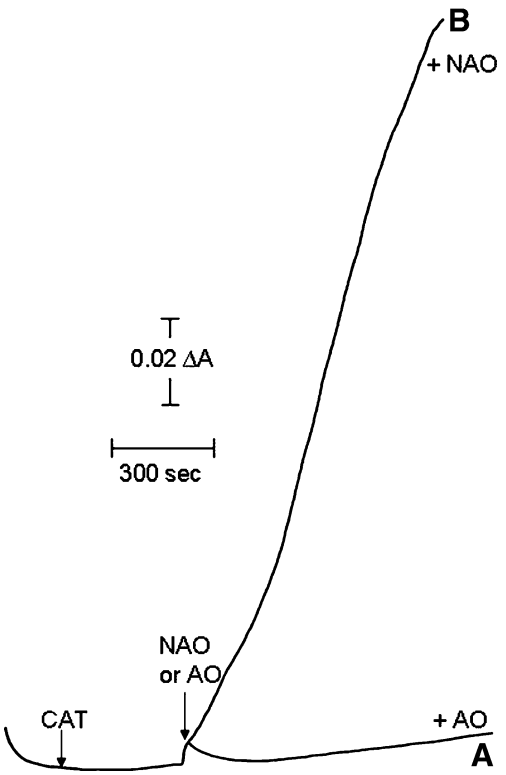

Fig. 4 Effect of NAO and AO on matrix Ca^{2+} content when added after CAT. Experimental conditions were as described for Fig. 2. Where indicated, 0.2 μM CAT and 7.5 nmol/mg of the probes NAO or AO were added

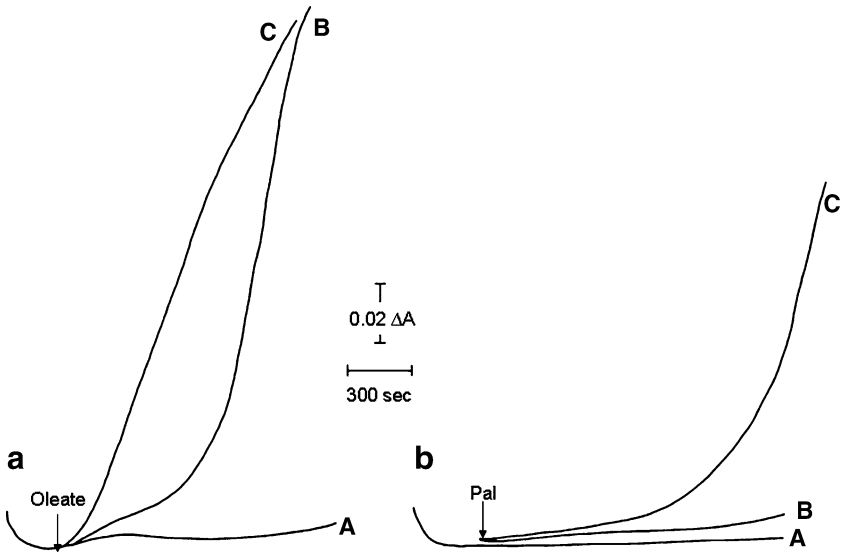

Fig. 5 Effect of NAO and AO on Ca^{2+} release induced by oleate and palmitate. Experimental conditions were as described for Fig. 2. In **a**, trace *C*, 7.5 nmol NAO/mg was added to the incubation mixture; in trace *B*, 7.5 nmol AO/mg was added. Where indicated, 15 μM oleate was added. In **b**, trace *C*, 7.5 nmol NAO/mg was added; in trace *B*, 7.5 nmol AO/mg was added. Where indicated, 15 μM palmitate was added

after the addition of NAO or AO plus Ca^{2+} there was an increase in ANT labeling, indicating that, indeed, a conformational change occurred. It is worthwhile to mention that AO without Ca^{2+} promoted an increase in CAT labeling.

Release of cytochrome *c* from mitochondria is also a characteristic of permeability transition. Thus, the corresponding experiment was performed and the results are shown in Fig. 8. As observed, the release of cytochrome *c* was attained in mitochondria incubated with NAO. Nevertheless, a high amount of release was observed when CAT was added to the incubation mixture. This result reinforces published reports about the deleterious effects of NAO on several mitochondrial functions (Maftah et al. 1990).

Discussion

A number of reports have shown that cardiolipin plays a central role in modulating permeability transition. Studies by Petrosillo et al. (2006) have shown that treatment of mitochondria with cardiolipin hydroperoxide improved non-specific permeability. Kalderon et al. (1995) reported an increased permeability in hyperthyroid rats, which contain a high amount of cardiolipin. Contrasting, we reported that mitochondria isolated from hypothyroid rats, with a low amount of the phospholipid, behave resistantly to CAT-induced pore opening (Chávez et al. 1998). The differences in cardiolipin content between hyper- and hypothyroidism reside in the activity of the mitochondrial cardiolipin synthase. To this regard, Schlame and Hostetler

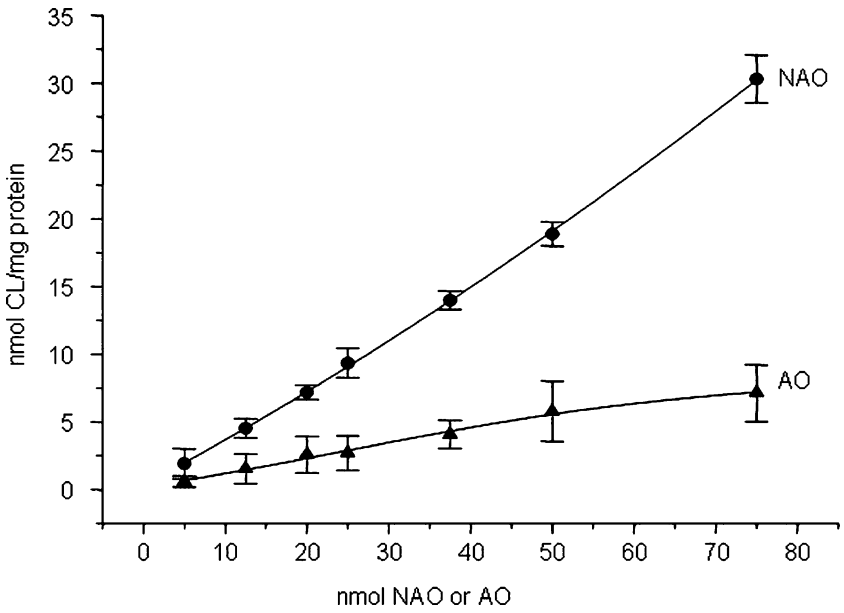

Fig. 6 Titration of mitochondrial cardiolipin by increasing concentrations of NAO or AO. Experimental conditions were as described under "Materials and methods". The values represent the difference from the respective controls without protein addition, considering a stoichiometry of 2 nmol of the probe for 1 nmol cardiolipin

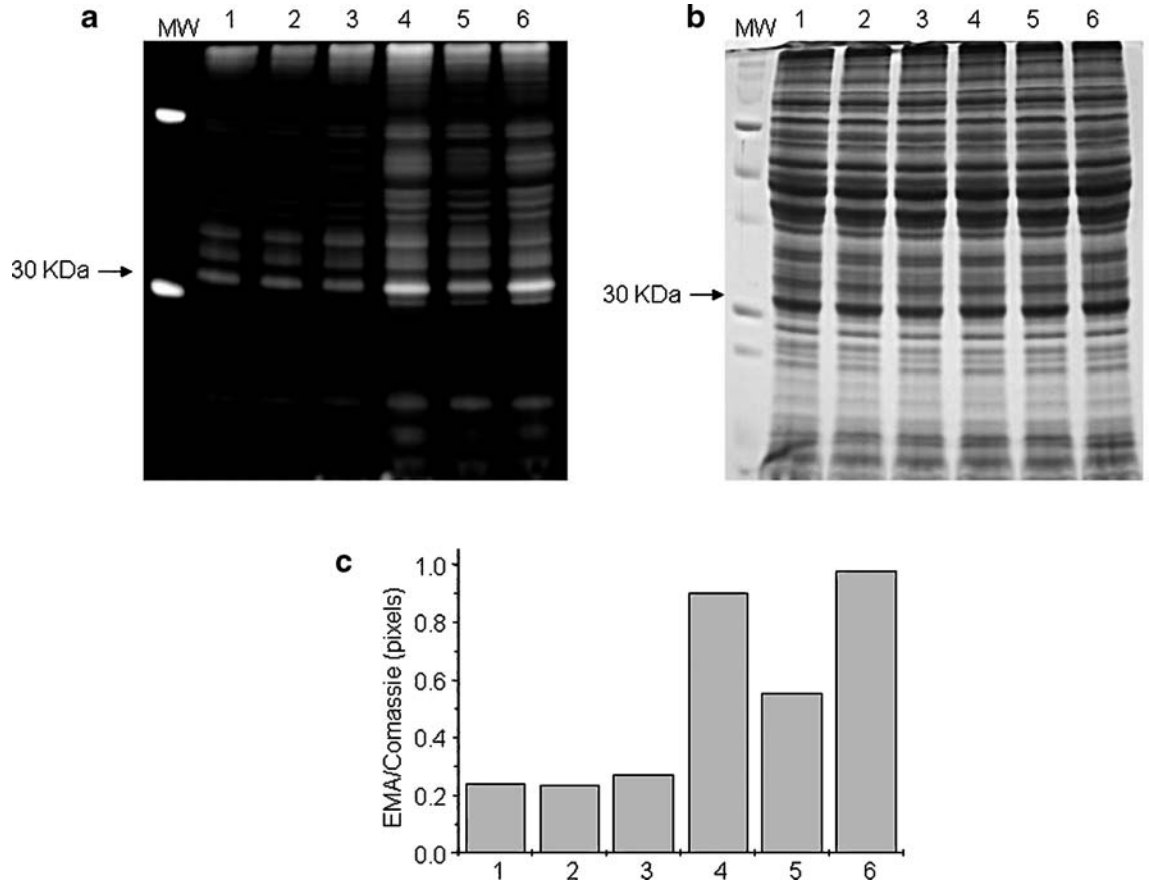

Fig. 7 Influence of the titration of cardiolipin by NAO or AO on the labeling of ADP/ATP carrier by eosin 5-maleimide. Mitochondria (2 mg protein) were incubated in similar conditions as those described for Fig. 2. Other experimental conditions as described under "Materials and methods". **a** The fluorescence profile of labeled mitochondria. Lane *1* shows the labeling of ANT of control mitochondria; lane *2* illustrates the labeling in the presence of 50 μM Ca^{2+}; lane *3* shows the labeling in the presence of 7.5 nmol NAO/mg; lane *4* shows the labeling after treatment with 7.5 nmol/mg NAO plus 50 μM Ca^{2+}; lane *5* shows the labeling of 7.5 nmol AO/mg without Ca^{2+} added; lane *6* illustrates the labeling in the presence of 7.5 nmol AO/mg plus 50 μM Ca^{2+}. **b** The profile of mitochondrial proteins revealed with Coomassie blue. **c** The ratio of the profile of proteins labeled by EMA with respect to the profile of proteins revealed with Coomassie blue

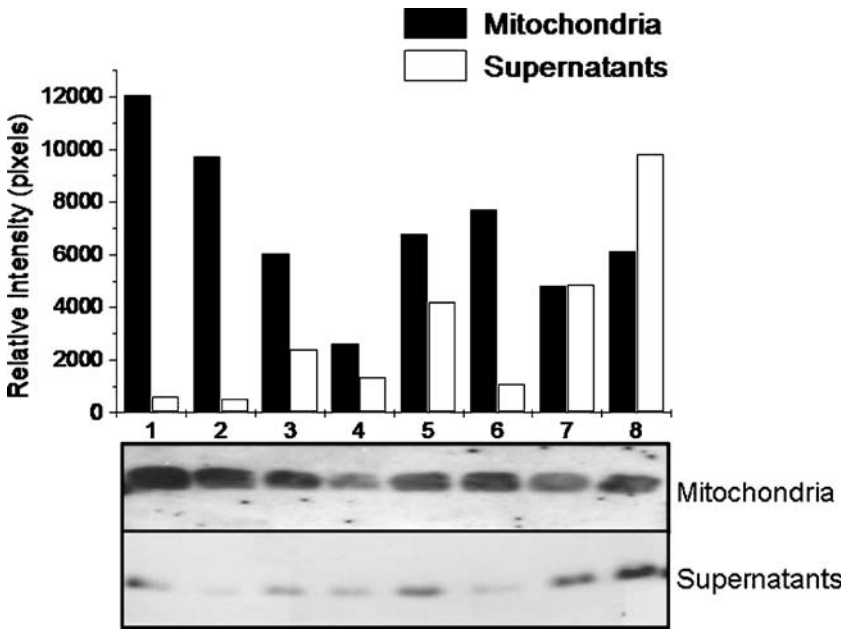

Fig. 8 Induction of cytochrome *c* release by NAO. Cytochrome *c* content in mitochondria and supernatants after NAO incubation. Experimental conditions were as described under "Materials and methods". The numbers at the bottom of the bars indicate: *1*, control mitochondria; *2*, after the addition of 0.2 μM CAT; *3*, after the addition of 7.5 nmol NAO/mg; *4*, after the addition of 15 nmol NAO/mg; *5*, after the addition of 22.5 nmol NAO/mg; *6*, after the addition of 7.5 nmol NAO/mg plus 0.2 μM CAT; *7*, after the addition of 15 nmol NAO/mg plus 0.2 μM CAT, and *8*, after the addition of 22.5 nmol NAO/mg plus 0.2 μM CAT

(1997) reported that the activity of this enzyme is increased in hyperthyroidism and, conversely, decreased in hypothyroidism. An additional report implicating cardiolipin in the mechanism of pore opening is the model proposed by Brustovetsky and Klingenberg (1996). These authors suggest that the binding site for accumulated Ca^{2+}, which is required for pore opening, would be in the negative charges of cardiolipin forming the annulus of ANT. As a result of such an interaction, ANT undergoes a conformational change in such a way that the carrier switches to a non-specific pore.

In this study, we found that the binding of NAO or AO to cardiolipin, tightly bound to ANT, makes this carrier more susceptible to the action of the inducers CAT, oleate, and palmitate. This assumption rests on the fact that 0.2 μM CAT induced membrane leakage to a considerable extent only when added to mitochondria treated with the fluorescent probes. These results may appear controversial to those published by Belosludtsev et al. (2006), indicating that NAO inhibits palmitate-induced permeability transition with a $K_{0.5}$ of approximately 8 nmol probe/mg, a similar amount of NAO to that used in this study. At the moment, we have no explanation for this controversial result. The only comment that we can offer is about the different source of mitochondria, they used mitochondria isolated from liver and our experiments were carried out in kidney mitochondria. An interesting finding was the fact that when the AO probe was added after CAT, matrix Ca^{2+} efflux was not attained; however, this reaction took place when NAO was added after CAT. A plausible explanation for this would be that NAO titrates mainly cardiolipin located in the inner leaf of the membrane, whereas AO would titrate mainly cardiolipin situated in the external side of the inner membrane. Since CAT locks the translocase in the cytosol side, the conformational change that occurs would hide the target sites for AO binding.

The requirement for Ca^{2+} is also an emergent point that must be pointed out. As shown in the swelling experiments in the presence of Sr^{2+}, mitochondrial volume did not increase; this reaction was attained only after the addition of Ca^{2+}.

Release of cytochrome *c*, shown here, after titration of cardiolipin seems to be in agreement with the data published by Ostrander et al. (2001). These authors demonstrated that detachment of cytochrome *c* from the inner membrane corresponds to a diminution in cardiolipin content. Certainly, in our *in vitro* conditions, we cannot consider the above as the cause of cytochrome *c* release. However, it is valid to propose that the binding of the probes to the phospholipid would modify its architecture, favoring release of cytochrome *c* from the membrane.

About the mechanism by which NAO and AO increase the sensitivity to the action of CAT and fatty acids, to induce permeability transition, it seems appropriate to assume that the binding to cardiolipin tightly bound to ANT would induce a configurational change in the translocase. This change may expose more target sites for binding of the inducers. This assumption is based on the experiment showing that a high amount of label, by EMA, was found in ANT after incubation of mitochondria with the probes. Indeed, we cannot discard completely that, for example, NAO may bind to another phospholipid species, like phosphatidyl serine and phosphatidyl inositol; however, the affinity constant for cardiolipin is lower, i.e., 2×10^{-6} M, than that found for these phospholipids, 7×10^{-4} M, being the stoichiometry 2 mol NAO per mol cardiolipin and 1 mol NAO per mol phosphatidyl serine or phosphatidyl inositol (Petit et al. 1992).

Finally, regarding the role of ANT in permeability transition, we do not rule out the report by Bernardi et al. (2006) indicating that the adenine nucleotide translocase is not a molecular component of the permeability transition pore, but is rather a modulator. However, in the context of our work, a conformational change in the putative modulator, as induced through the binding of the fluorescent probes to cardiolipin, should induce pore opening.

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