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Mechanism accounting for the induction of nonspecific permeability of the inner mitochondrial membrane by hydroperoxides

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The effect of antioxidants on the nonspecific permeability of the inner mitochondrial membrane induced by cumene hydroperoxide or Ca^{2+} has been studied. Butylated hydroxytoluene, butylated hydroxyanisole and 2,2,5,7,8-pentamethyl-6-chromanol, taken at a concentration up to 50 μM, suppress the cumene hydroperoxide-induced accumulation of lipid peroxidation products. In the same range of concentrations, these antioxidants inhibit the activation of nonspecific permeability by cumene hydroperoxide or Ca^{2+}. Propyl gallate, being less effective under such conditions, fails to affect the induction of nonspecific permeability. Additionally, 2,2,5,7,8-pentamethyl-6-chromanol at a concentration decreasing the accumulation of lipid peroxidation products by 70% has been shown not to increase the lag period of nonspecific permeability induction. Higher antioxidant concentrations, while leading to an increase in the lag period of nonspecific permeability induction, cause but minor suppression of lipid peroxidation. From the results obtained we can assume that free radicals formed in the course of hydroperoxide decomposition or on mitochondrial redox complex interact directly with a system responsible for nonspecific permeability or with regulating components of this system.

Introduction

The ability of hydroperoxides to increase ion permeability of the inner mitochondrial membrane is now well-established [1–4]. Recently, it has been demonstrated that transition of the inner membrane to the state of nonspecific permeability for low-molecular-weight solutes ($M_r < 1500$) [3–5] can account for the activation of ion fluxes by hydroperoxides.

Permeability transition induced by hydroperoxides is attributed to the reversible opening of the Ca^{2+}-activated non-specific pore. Ca^{2+} and hydroperoxides, acting as synergists, induce the opening of the (hypothetical) pore, which causes the dissipation of $\Delta\Psi$ and the loss of intramitochondrial low-M_r solutes [3,4,6].

Two mechanisms accounting for nonspecific pore opening by hydroperoxides seem to be most probable. The first is related to hydroperoxide metabolism by an enzyme complex, containing glutathione peroxidase, glutathione reductase and transhydrogenase [7] with no free-radical products being formed (Fig. 1). Such metabolism of hydroperoxides leads to the oxidation of glutathione and pyridine nucleotides, their oxidized forms, according to some authors [1,8], being able to increase, directly or indirectly, ion permeability of the inner mitochondrial membrane.

The second mechanism is related to hydroperoxide decomposition, leading to formation of radical products [10] and subsequent initiation of LP [9].

We have shown earlier that there exists a correlation between the cumene hydroperoxide-induced increase in mitochondrial nonspecific permeability and the accumulation of LP products [11]. Moreover, it has been demonstrated that the free-radical scavenger, BHT, suppressing LP, also prevents nonspecific permeability increase.

Abbreviations: $\Delta\Psi$, mitochondrial inner membrane potential; TPP^+, tetraphenylphosphonium; MDA, malonic dialdehyde; LP, lipid peroxidation; CuOOH, cumene hydroperoxide; BHT, butylated hydroxytoluene; BHA, butylated hydroxyanisole; PG, propyl gallate; PMC, 2,2,5,7,8-pentamethyl-6-chromanol; RLM, rat liver mitochondria.

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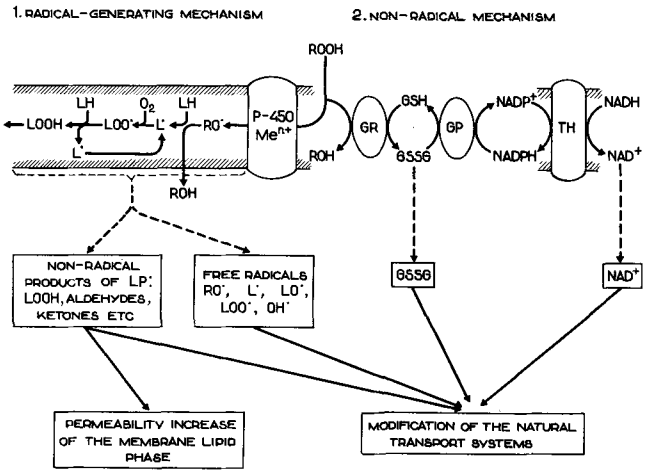

Fig. 1. Scheme of possible ways of increasing the ion permeability of the inner mitochondrial membrane by hydroperoxides. Abbreviations: LH, lipids; ROOH, hydroperoxide; GP, glutathione peroxidase; GR, glutathione reductase; TH, transhydrogenase; *P*-450, cytochrome *P*-450; Me^{n+}, transition metals.

BHT displays the inhibitory effect not only when nonspecific permeability is activated by cumene hydroperoxide but by Ca^{2+} as well [12,13].

The above data indicate that free-radical reactions are an obligatory intermediate link in nonspecific permeability activation, with the effect of exogenous organic hydroperoxides being due to their metabolism according to the free-radical mechanism. To confirm this assumption, we must first exclude the possibility of a BHT nonspecific (not related to its antioxidant properties) effect on the nonspecific permeability system.

Here we may proceed from the data available on the ability of BHT to alter physical parameters [14,15] and ion permeability of the lipid bilayer [16–18], and also to affect the activity of enzymes [19,20]. Secondly, it is still an open question whether an increase in nonspecific permeability results from the interaction between free radicals formed during hydroperoxide decomposition, and the nonspecific pore or some other component controlling its activity; or whether the activators are nonradical products of LP (Fig. 1).

To resolve the problem, we have compared the influence of various antioxidants on the induction of nonspecific permeability of the inner mitochondrial membrane by cumene hydroperoxide or Ca^{2+} and on LP.

Materials and Methods

Rat liver mitochondria were isolated by differential centrifugation [21]. The incubation medium contained 250 mM sucrose, 250 μM EDTA and 5 mM Hepes (pH 7.4). The final washing of the mitochondria was performed in the absence of EDTA. The protein concentration was assayed by the biuret method with bovine serum albumin as a standard. Changes in the transmembrane potential were evaluated by the distribution of TPP^+ between the incubation medium and the mitochondrial matrix with a TPP^+-selective electrode [22]. O_2 concentration in the incubation medium was measured polarographically with a Clark-type electrode. LP intensity was estimated by lipid hydroperoxide accumu-

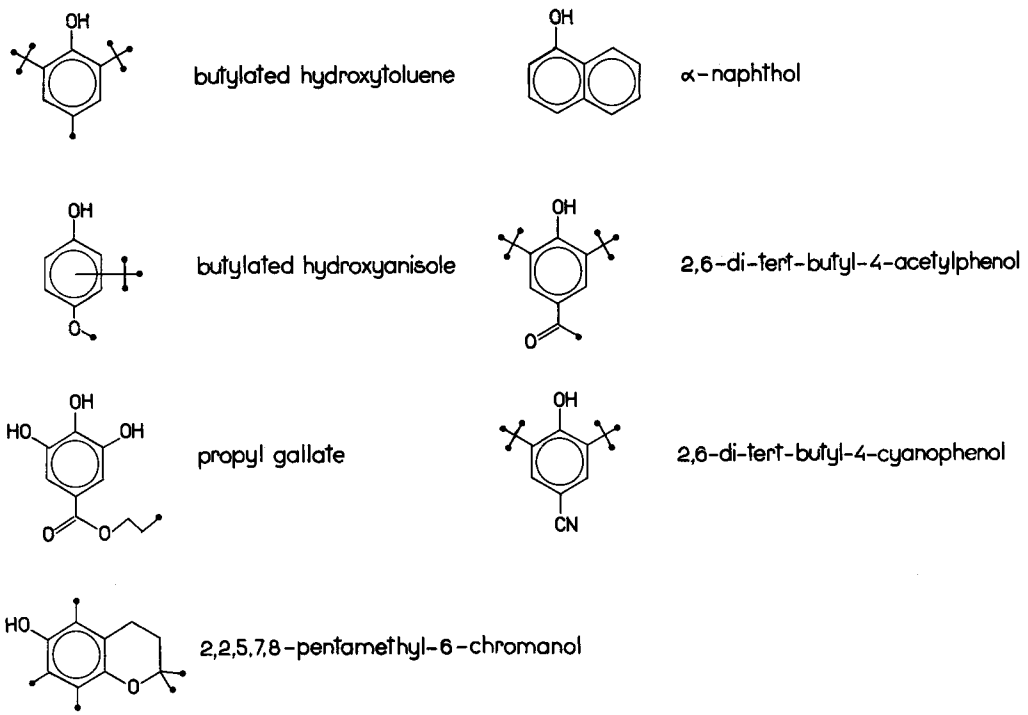

Fig. 2. Chemical structures of the antioxidants used in the work.

lation, according to the modified method of Asakawa [23,24].

Mitochondria were incubated in a standard medium, containing 10 mM Mes-Tris (pH 7.4), 10 mM H_3PO_4, 0.5 mM $MgCl_2$, $CaCl_2$ (10 nmol/mg protein). The osmolarity of the incubation medium (300 mosM) was attained by adding a corresponding amount of sucrose. Antioxidants (ethanol solution) were added into the incubation medium immediately after the mitochondria. Ethanol itself (maximal concentration used in experiments) had no effect on the processes under study.

Partition coefficients of antioxidants in the octanol-water system were calculated according to Rakker [25].

Changes in the incubation medium are indicated in the legends to the figures. The mitochondrial protein concentrations were 2 mg/ml during the LP products assay and 1 mg/ml during the respiration rate assay.

Results

Antioxidants used in the work were: BHT, BHA, PG, PMC, α-naphthol, 2,6-di-*tert*-butyl-4-acetylphenol and 2,6-di-*tert*-butyl-4-cyanophenol (Fig. 2).

Earlier, we have shown that activation of nonspecific permeability by CuOOH is critically dependent on the $\Delta\Psi$ value [26]. A lowering of $\Delta\Psi$ reduces the lag period of nonspecific permeability induction. Since some antioxidants are capable of increasing the bilayer lipid conductivity for H^+ [17], at the initial stage of our work the effect of antioxidants on the mitochondrial respiration rate in state 4 was studied. As seen from Fig. 3, an increase in the concentration of 2,6-di-*tert*-butyl-4-cyanophenol (curve 1), α-naphthol (curve 2) and 2,6-di-*tert*-butyl-4-acetylphenol (curve 3) up to 50 μM results in the significant acceleration of mitochondrial respiration. This attests to their ability to act as classical protonophores in causing $\Delta\Psi$ dissipation. Therefore, for further studies we have used only BHT, BHA, PG and PMC, which produce only a slight effect on the respiration rate of mitochondria in state 4 (curves 4–7).

Antioxidative activity of these agents was evaluated by their inhibitory effect on LP, initiated in de-energized mitochondria by the addition of CuOOH. The addition of CuOOH results in the rapid accumulation of LP products (Fig. 4a, curve 1). The addition of BHA in increasing concentrations causes a sharp reduction of LP products formed during a 12 min incubation (Fig. 4a, curves 2, 3). It is obvious from Fig. 4b, where the dependence of LP products accumulation versus antioxidants concentration is shown, that low concentrations of BHT, BHA and PMC effectively suppress LP.

Despite its high antioxidative activity in a homogeneous (methyloleate) system [27,28], which is similar to the BHT one, PG exhibits less pronounced antioxidative effect (curve 1) under present experimental conditions than BHT does. The value of partition coefficient

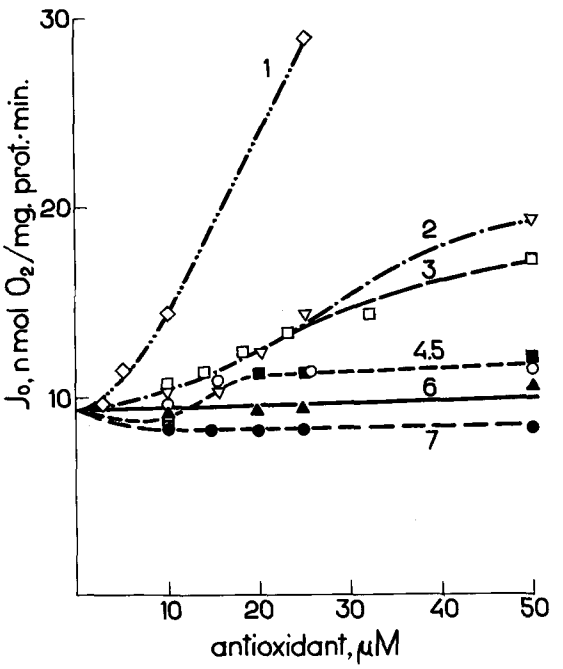

Fig. 3. Effect of the antioxidants on the respiration rate of mitochondria in state 4. For experimental conditions, see "Materials and Methods". The incubation medium was additionally supplemented with 10 mM succinate and 2 μM rotenone. (1) 2,6-Di-*tert*-butyl-4-cyanophenol; (2) α-naphthol; (3) 2,6-di-*tert*-butyl-4-acetylphenol; (4,5), PG or BHA; (6) PMC; (7) BHT.

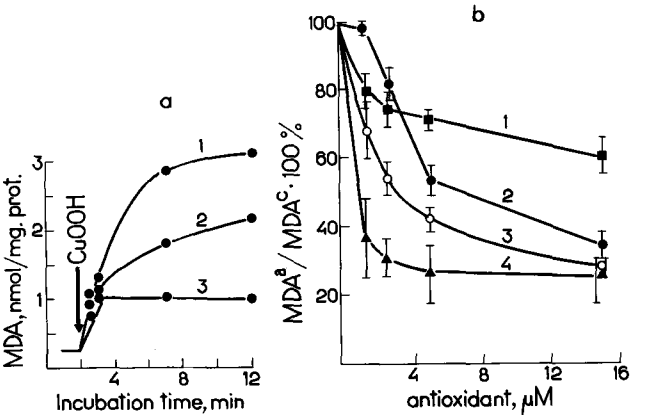

Fig. 4. Effect of the antioxidants on the accumulation of LP products induced by CuOOH in the de-energized mitochondria. For experimental conditions, see Materials and Methods. The incubation medium was additionally supplemented with 1.5 μM CCCP. (a) The effect of BHA on the kinetics of the LP products accumulation. The arrow indicates the addition of 200 μM CuOOH. (1) control; (2) in the presence of 2 μM BHA; (3) in the presence of 15 μM BHA. (b) concentrational dependence of the suppression of LP products accumulation by antioxidants; MDA^a is the amount of MDA formed in the presence of the antioxidant; MDA^c is the amount of MDA formed in the absence of antioxidant. The amount of MDA was determined 12 min after the addition of 200 μM CuOOH. (1) PG; (2) BHT; (3) BHA; (4) PMC. The data are expressed as means ± S.E. of six determinations with the separate mitochondrial preparations. 100% = 2.6 (nmol MDA/mg protein) ± 0.4.

between the aqueous and hydrophobic phases for PG (lg $P = 2.509$) is less than those for BHT, PMC and BHA (lg $P = 6.195$; 4.483 and 3.684, respectively) which are localized preferably in the membrane phase [29]. This fact might account for the failure of PG to provide better protection against LP. However, some other factors, e.g., limited diffusion of PG to the sites of free-radical generation, can not be excluded. Figs. 5 and 6 show the effect of the antioxidants on the mitochondrial respiration rate increase induced by CuOOH or Ca^{2+}. Mitochondrial preparations vary in their sensitivity to nonspecific permeability inductors. Accordingly, different concentrations of CuOOH and Ca^{2+} were used so as to provide close time dependences of the non-specific permeability induction in different mitochondrial preparations. As seen from Fig. 5a (curve 1), an addition of CuOOH increases the mitochondrial respiration rate which, after a certain lag period, attains a stationary value. When added to mitochondria, Ca^{2+} exerts an analogous effect. If nonspecific permeability is induced by CuOOH, the stationary respiration rate conforms to the maximal uncoupling of the mitochondrial suspension. The addition of the uncoupler fails to increase the respiration rate. In the case of nonspecific permeability induction by Ca^{2+}, the stationary respiration rate observed in the experiment is not maximal. The addition of the uncoupler causes a further increase in the rate. PG in a concentration up to 50 μM (higher concentrations lead to mitochondria uncoupling) fails to prevent respiration stimulation by CuOOH (Fig. 5b, curve 1). At the same time, PMA, BHA and BHT, which at low concentrations effectively suppress LP (Fig. 4b, curves 2–4), demonstrate a strongly pronounced inhibitory effect (Fig. 5b, curves 2–4). In the case of nonspecific permeability induction by Ca^{2+}, PMC, BHA and BHT exhibit an analogous effect and abolish the respiration rate increase (Fig. 6, curves 2–4). PG has little, if any, effect on the acceleration of respiration by Ca^{2+} (curve 1).

The correlation between the effectiveness of antioxidants to suppress LP and to prevent the nonspecific permeability increase enables us to assume that free radical reactions are involved in the nonspecific permeability induction as an intermediate step.

Free radicals, arising from hydroperoxide decomposition (Fig. 1) or formed by mitochondrial redox-systems, can attack directly the nonspecific pore or a component, regulating its activity. On the other hand, radicals can affect the pore through non-radical products of lipid peroxidation. To distinguish between these two possibilities we compared the PMC effect on the accumulation of the LP products and on the activation of nonspecific permeability by CuOOH, the activation being monitored by the change of $\Delta\Psi$. Synchronous measurements of the energy-dependent accumulation of TPP^+ by mitochondria and accumulation of the LP

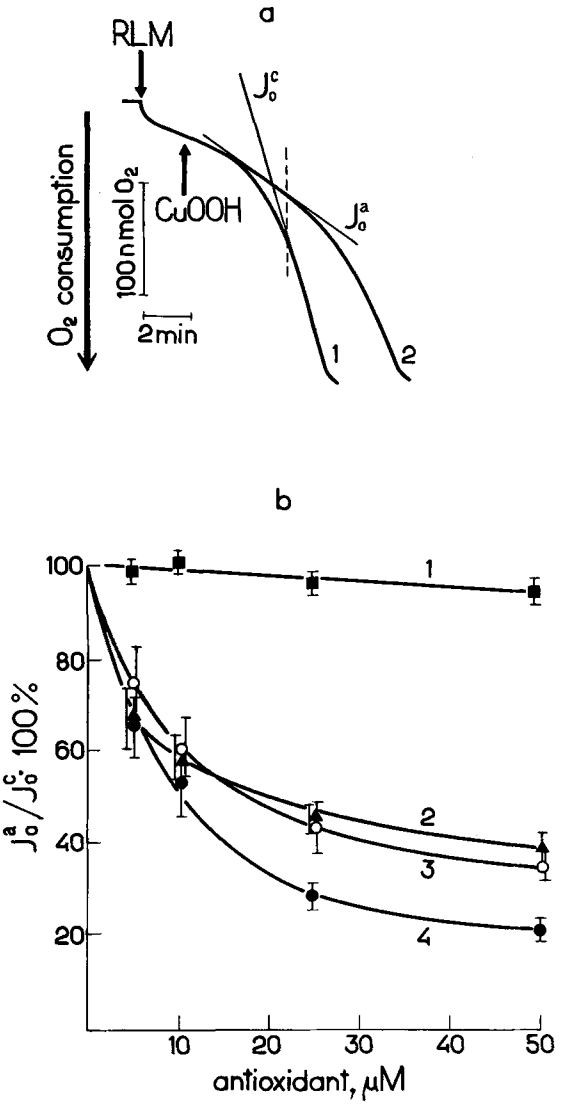

Fig. 5. Effect of the antioxidants on the mitochondrial respiration rate increase by CuOOH. For experimental conditions, see Materials and Methods. The incubation medium was additionally supplemented with 10 mM succinate and 2 μM rotenone. (a) The effect of BHT on the kinetics of oxygen consumption by the mitochondrial suspension. The arrows indicate the addition of RLM and 200 μM CuOOH. (1) control; (2) in the presence of 10 μM BHT. (b) Concentrational dependence of the suppression of mitochondrial respiration rate increase by antioxidants. J_0^a is the mitochondrial respiration rate in the presence of the antioxidant. J_0^c is the mitochondrial respiration rate in the absence of the antioxidant. The mitochondrial respiration rate was determined at a moment when the maximum respiration rate in the control was attained. CuOOH (200–300 μM) was added 2 min after the mitochondria. (1) PG; (2) PMC; (3) BHA; (4) BHT. The data are expressed as means ± S.E. of six determinations with the separate mitochondrial preparations (100% = 71.4 (nmol O_2/mg protein per min) ± 5.3; J_0 in state 4 = 10.8 (nmol O_2/mg protein per min) ± 1.0.

products show the process of de-energization of the inner mitochondrial membrane to be correlated in time with accumulation of the LP products (Fig. 7a,b, curves 1). The lower level of LP products in this case, compared with that of the de-energized mitochondria, can be attributed to the antioxidative action of QH_2 of the

mitochondrial respiratory chain and partial utilization of CuOOH and lipid hydroperoxides by glutathione peroxidase. As seen from Fig. 7b, curve 2, the addition of 5 μM of PMC suppresses the formation of LP products by 72%. This agrees well with the action of the same PMC concentration on LP in the de-energized system – 74% inhibition (Fig. 4). However, in spite of the consideralbe suppression of the LP products accumulation, the lag period of the nonspecific permeability induction fails to increase (Fig. 7a, curve 2). However, the rise of the antioxidant concentration up to 50 μM, causing no further pronounced suppression of the LP products accumulation, leads to an increase in the lag-period of the nonspecific permeability induction (Fig. 7a,b, curves 3). Thus, considerable variations in the amount of LP products of a non-radical nature fail to produce any appreciable effect on the nonspecific permeability induction. Consequently, non-radical products of LP do not appear to be activators of nonspecific permeability of the inner mitochondrial membrane. The nonspecific permeability induction may be attributed to a direct attack by free radicals of a system, providing for nonspecific conductivity, or its regulating components.

In this respect, the ability of free radicals to readily oxidize thiol groups [30–32] suggests that mitochondrial protein SH groups, modification of which results in the induction of non-specific permeability [33], may be the target for a free radical attack.

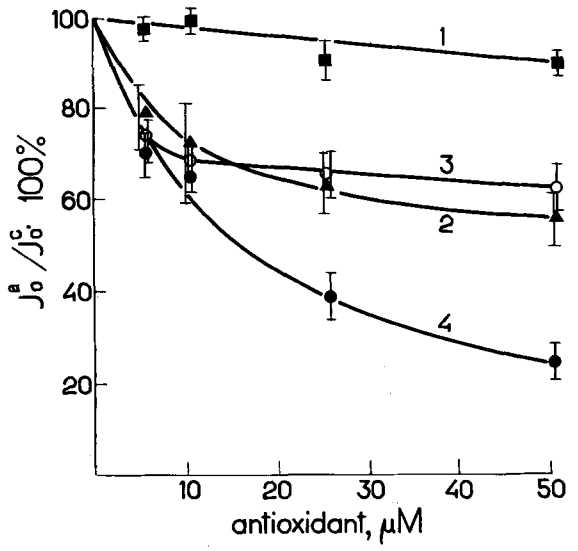

Fig. 6. Effect of the antioxidants on the mitochondrial respiration rate increase by Ca^{2+}. For experimental conditions, see Materials and Methods. The incubation medium was additionally supplemented with 10 mM succinate and 2 μM rotenone. J^a is the mitochondrial respiration rate in the presence of the antioxidant. J_0^c is the mitochondrial respiration rate in the absence of the antioxidant. The mitochondrial respiration rate was determined at a moment when the maximum respiration rate in the control was attained. Ca^{2+} (20–40 nmol/mg protein) was added 2 min after the mitochondria. (1) PG; (2) PMC; (3) BHA; (4) BHT. The data are expressed as means ± S.E. of six determinations with the separate mitochondrial preparations (100% = 45.2 (nmol O_2/mg protein per min) ± 4.6; J_0 in state 4 = 13.2 (nmol O_2/mg protein per min) ± 0.7.

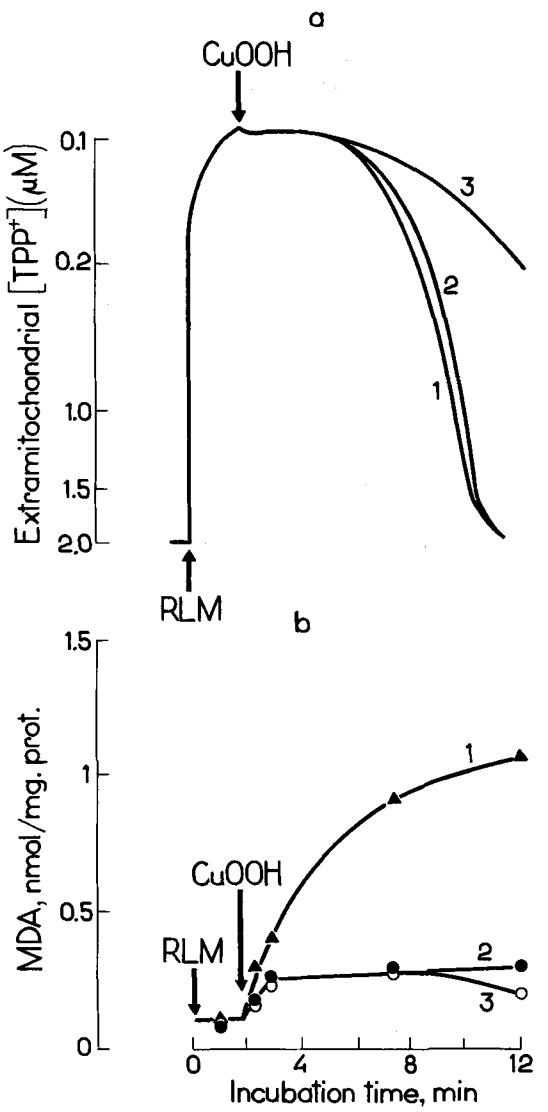

Fig. 7. Effect of PMC on the $\Delta\Psi$ decrease (a) and the accumulation of LP products (b), induced by CuOOH. For experimental conditions, see Materials and Methods. The incubation medium was additionally supplemented with 10 mM succinate, 2 μM rotenone and 2 μM TPP^+. Arrows indicate the addition of RLM and 250 μM CuOOH. (1) Control; (2) in the presence of 5 μM PMC; (3) in the presence of 50 μM PMC.

Discussion

The assumption on the involvement of free radicals in the nonspecific permeability induction is inferred from the following facts: (1) The mitochondria are recognized as one of the main cellular generators of partially reduced oxygen species (O_2^-, H_2O_2 and $OH^\cdot$) which are produced mainly at the level of the QH_2 cytochrome *c* oxidoreductase and the NADH dehydrogenase [34,35]. (2) Addition to mitochondria of organic

hydroperoxides (*t*-BuOOH, CuOOH) leads to the generation of highly reactive organic radicals [10], which initiate chain reaction of LP [9,11].

(3) The well-known free-radical scavenger BHT is able to prevent induction of nonspecific permeability by Ca^{2+} [12,13], SH groups oxidizing agents [13,36] or cumene- and *t*-butyl hydroperoxides [11,13].

According to Carbonera and Azzone [13], the increase in the mitochondrial nonspecific permeability induced by Ca^{2+} and SH-group-oxidizing reagents is related to the increase in the formation of oxygen radicals. In the case of the induction of nonspecific permeability by organic hydroperoxides, generation of alkyl and alkoxyl radicals in a cytochrome P_{450}- and transition metal-mediated reaction [10,37] takes place. At the same time, the validity of the above interpretation was questioned because of the ability of BHT to modify biological membranes [14–18], that is, a property not connected with the antiradical activity of BHT. The data of the present work support the proposal that free radical reacitons are one of the intermediate steps in the regulation of the nonspecific permeability induced by CuOOH or Ca^{2+} [11–13]. Free radicals are known to be capable of initiating a free-radical chain reaction of lipoperoxidation [38] in the mitochondrial membrane. We have shown earlier that accumulation of the LP products effected in mitochondria by CuOOH fails to destroy the permeability barrier properties of the lipid bilayer [11].

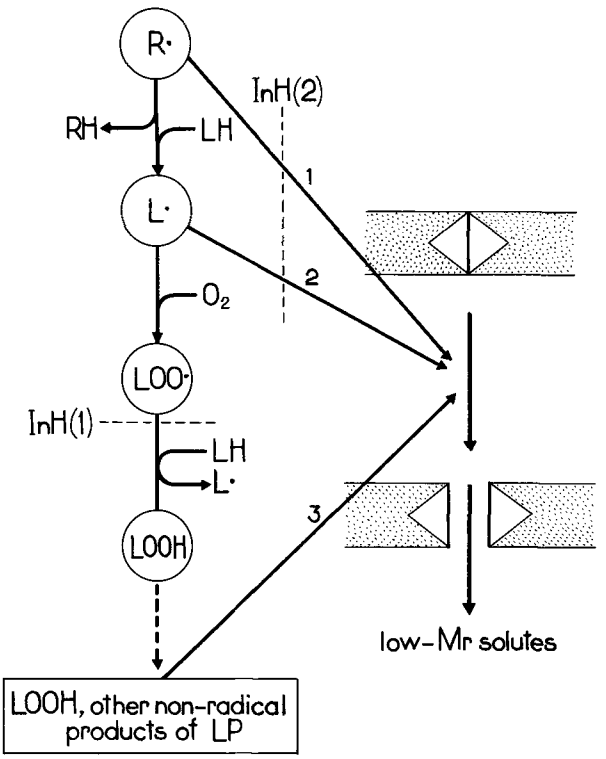

Fig. 8. Scheme of possible ways of nonspecific permeability activation by free radicals. An initiator radical, R^0, initiates the free-radical chain oxidation of lipids (LH) and accumulation of LP non-radical products (LOOH, aldehyde, ketones, alkanes, etc.). The activation of a system responsible for nonspecific permeability may result from the action of LP non-radical products (arrow 3), or from a direct attack of this system by free radicals (arrows 2 and 1). InH (1) – low concentrations of the antioxidants. The effect at the stage of propagation. InH (2) – high concentrations of the antioxidants. Additional effect at the stage of initiation.

The results obtained during experiments on a comparison of the effect produced by different concentrations of antioxidant on LP and nonspecific permeability activation (Fig. 7) enable us to omit from consideration the regulatory role of LP non-radical products. This is in conformity with the data obtained earlier on the absence of a correlation between the LP products accumulation and the increase in mitochondrial ion permeability induced by Ca^{2+} [12].

Thus, the accumulation of LP products only reflects the intensification of free radical processes, activating nonspecific permeability, as shown in Fig. 8.

From this point of view, the difference in the efficiency of LP inhibition and of nonspecific permeability suppression by antioxidants may be explained assuming that low concentrations of antioxidants react preferably with lipid peroxyl radicals ($LOO^{\cdot}$) causing the inhibition of LP at the stage of propagation (the chair-breaking action). At the same time, antioxidants at higher concentrations are also capable of trapping primary radicals at the stage of chain initiation, leading to the suppression of nonspecific permeability induction (the initiation-preventing action). On the other hand, it could not be excluded that particular types of radical, formed as a result of cuOOH decomposition, have different reactivities to target molecules. Such a possibility is based on the data of Van der Zee et al. [39] demonstrating that LP and K^+ leakage, induced by *t*-butyl hydroperoxide in red blood cells, is not causally related (*t*-butylalkoxyl radical causes LP, whereas the *t*-butylperoxyl radical is responsible for K^+ leakage) and it is possible to dissociate these processes by using different radical scavengers.

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