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Biochimica et Biophysica Acta 1564 (2002) 207–213

BIOCHIMICA ET BIOPHYSICA ACTA
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Photodynamic activation of ion transport through lipid membranes and its correlation with an increased dielectric constant of the membrane

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Received 22 November 2001; received in revised form 20 March 2002; accepted 18 April 2002

Abstract

Illumination of biological membranes with visible light in the presence of membrane-active sensitizers (e.g. rose bengal) is known to inactivate transport proteins such as ion channels and ion pumps. In some cases, however, illumination gives rise to an activation of transport. This is shown here for ion channels formed by alamethicin in lipid membranes, and for porin channels, which were isolated from the outer membrane of *E. coli* (OmpC) and from the outer membrane of mitochondria (VDAC) and were reconstituted in lipid membranes. An activation (in the form of an increased conductance) was also observed in the presence of the cation carriers valinomycin and nonactin. The activation phenomena were only present, if the membranes were made from lipids containing unsaturated double bonds. Activation was reduced in the presence of the antioxidant vitamin E. We suggest that the activation of the different transport systems has a common physical basis, namely an increase of the dielectric constant, ε_m, of the membrane interior by the presence of polar oxidation products of photodynamically induced lipid peroxidation. Experimental evidence for an enhanced dielectric constant was obtained from the finding of a light-induced increase of the membrane capacitance in the presence of rose bengal.

Keywords: Photosensitization; Biological membrane; Ion channel; Ion carrier; Membrane capacitance

1. Introduction

Membrane damage has been considered as an important part of photosensitized cellular modifications finally leading to cell death by apoptosis or necrosis [1–3]. The photodynamic treatment of biological membranes, that is, their illumination by visible light in the presence of photosensitizers, causes a multitude of different effects. Of primary interest has so far been a loss of membrane functions such as the inactivation of membrane enzymes, of membrane channels or of other transport pathways for ions, amino acids or sugars. There are, however, also reports on activation phenomena such as an enhanced opening rate of ion channels [4–10]. In some cases, activation was observed at short times of illumination and was followed by inactivation at longer times.

The photodynamic treatment may be considered as a special kind of oxidative stress to the cell. This is in line with the observation that activation of ion transport systems has also been observed after application of other types of oxidizing stress such as the addition of hydroperoxides [11,12] or after exposition to ionizing radiation [13–15].

The present communication intends to understand activation phenomena on the basis of membrane electrostatics. We show that photodynamic activation is a general phenomenon which may be observed for different transport mechanisms such as ion channels and ion carriers. We also show that activation is closely related to photodynamically induced lipid peroxidation. A general concept is described which explains activation on the basis of an enhanced dielectric constant, ε_m, of the membrane interior caused by lipid peroxidation. Finally, the suggested photodynamically induced increase of ε_m is experimentally confirmed via an enhanced membrane capacitance.

2. Materials and methods

All experiments were performed by using planar lipid membranes as a model system for biological membranes. The membranes were doped with well-established model compounds acting either as a channel-former (alamethicin)

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0005-2736/02/$ - see front matter
PII: S0005-2736(02)00452-2

or as ion carriers (valinomycin or nonactin). Alternatively, cellular ion channels (porins) were isolated from the outer membranes of *E. coli* and from mitochondria of *Neurospora crassa* and were reconstituted in planar lipid membranes.

2.1. Membranes and sensitizers

Membranes were formed from lipids of different oxidizability across a hole in the septum of a Lexan (polycarbonate) or Teflon (polytetrafluoroethylene) cuvette. The septum separates two aqueous phases accessible for electrodes. The diameter of the hole varied from 0.2 to 3 mm depending on the kind of measurement.

Diphytanoyllecithin, a fully saturated lipid, dioleoyllecithin and dilinoleoyllecithin with one and two double bonds, respectively, were obtained from Avanti Polar Lipids (Birmingham, AL, USA). A 0.5–1% solution was prepared in *n*-decane (standard for gas chromatography; Fluka, Buchs, Switzerland). In addition, the membrane-forming solution usually contained 0.5 mM of the sensitizer rose bengal (disodium salt, 95%; Aldrich, Milwaukee, WI, USA). For comparison, some experiments were performed with the following sensitizers: a water-soluble mixture of single- and double-sulfonated Zn–phthalocyanine prepared according to the procedure of Ali et al. [16], Al–phthalocyanine (Aldrich), merocyanine 540 (Sigma, Deisenhofen, Germany), and methylene blue (Fluka). The effect of the antioxidant vitamin E (Fluka) was studied by its addition to the membrane-forming solution (1–2 mg/ml).

2.2. Model compounds

The ion carriers valinomycin and nonactin were from Boehringer (Mannheim, Germany) and were added to the membrane-forming solution [17]. The channel-forming peptide alamethicin (Sigma) was added to the aqueous phases on both sides of the membrane [15].

2.3. Reconstitution of porins

Solutions of the detergent-solubilized porins OmpC [18] and LamB (maltoporin) [19] from the outer membrane of *E. coli*, as well as of the mitochondrial porin from *N. crassa*, the voltage-dependent anion channel (VDAC) [20], were diluted in 1–2% genapol and were added in small amounts to the aqueous phases on both sides of a membrane containing the photosensitizer. The spontaneous incorporation of single porin molecules into the membrane was either detected via the stepwise increase of the electric current (single-channel experiments) or via the more or less continuous increase of the electric current (multi-channel experiments) [21,22]. Photodynamic activation is characterized by an enhanced rate of channel incorporation.

2.4. Experimental procedures

The current across the membrane was amplified by using current/voltage converters (10^5–10^6 V/A in the case of multi-channel- and of carrier-experiments, 10^9 V/A in the case of single-channel experiments). The signal was finally transferred into a computer equipped with analog/digital board DAS-1602 (Keithly Metrabyte, Taunton, MA, USA). The digitized data were analyzed by using the software package Asyst (Keithly Metrabyte).

Capacitance measurements were performed by application of linear voltage ramps (triangle wave) to the membrane [23]. The signal—after amplification and rectification—is directly proportional to the membrane capacitance. In view of the comparatively large changes observed, the compensation circuit (see Ref. [23]) could be omitted.

Photodynamic modifications of the membrane (with different transport systems incorporated) were studied by illuminating the membrane and its surrounding annulus with a conventional light source (60 W), which was focused onto the membrane.

All experiments were performed at room temperature.

3. Results

Activation of ion channels has so far been observed on cellular ion channels in native biological membranes (see Introduction). The use of model membranes and of well-defined peptide channels provides more detailed information on the mechanistic aspects of the activation process. This has been shown previously at inactivation studies of ion channels formed by gramicidin A and of polyene channels [24,25]. Contrary to these types of channels, which show continuous inactivation even at small light intensities and short illumination times, the conductance induced by alamethicin channels exhibits a light-induced increase which is followed by a decrease to values much smaller than the initial conductance value before illumination (Fig. 1). The increase is clearly induced by alamethicin, since the conductance of unmodified lipid membranes is several orders of magnitude lower (see conductance values mentioned in the legends of Figs. 1 and 2). The light-induced transient conductance increase disappears in the presence of the antioxidant vitamin E. A continuous inactivation of the conductance is found in this case (Fig. 1).

A light-induced increase of the membrane conductance is also observed in the absence of specific transport systems. This was first shown by Mirsky et al. [26] with haematoporphyrin dimethylether as a sensitizer and is confirmed here for rose bengal. Even in the dark, addition of the sensitizer to the membrane-forming solution gives rise to an increase of the normal (basic) membrane conductance (of about 10^{-7} S/cm^2) by at least one order of magnitude (see data in the legend to Fig. 2). We think that this is due to the disturbance of the bilayer structure by the comparatively

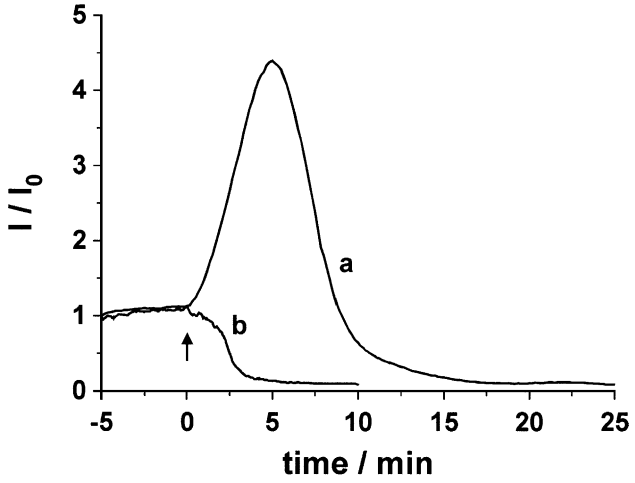

Fig. 1. Photodynamic activation and inactivation of alamethicin channels. The ratio I/I_0 of the current I normalized to the initial current I_0 is plotted as a function of time. The membranes were formed from 1% solutions of dioleoyllecithin in decane containing 0.5 mM rose bengal. The membrane separated two aqueous solutions of 1 M NaCl and 0.25 μM alamethicin. Experiments were performed in the absence (a) and presence (b) of 2 mg/ml vitamin E in the membrane-forming solution. A constant voltage of 55 mV was applied to the membrane. The initial membrane conductance was about 4×10^{-3} S/cm^2 in both cases. Illumination was started at time zero (arrow).

large concentration of the dye. Illumination of the membrane leads to a further increase of the conductance shown in Fig. 2. We suspect that this increase is due to a modification of the membrane interior by products of photodynamically induced lipid peroxidation (see Discussion). The conductance increase of the unmodified lipid structure shows great variations. Fig. 2 illustrates two extreme cases. A further consequence of this photomodification is a reduced membrane stability. The survival time of the membranes formed from dioleoyllecithin—after start of illumination—was found to be of the order of a few minutes up to a maximum of 1 h at the applied light intensities. The light-induced increase of the basic membrane conductance may, however, be neglected at all other experiments presented. This holds either in view of the large conductance values induced by the specific transport systems or in view of the comparatively short time period of illumination.

Figs. 3 and 4 illustrate the light-induced response of lipid membranes observed in the presence of two different types of porin channels, OmpC from the outer membrane of *E. coli* and VDAC from the outer mitochondrial membrane of *N. crassa*. In both cases, photodynamically induced channel activation is observed. The behaviour of OmpC is illustrated on the level of single ion channels. Fig. 3a shows the current trace for a membrane formed from dioleoyllecithin. The fluctuations observed in the dark indicate the presence of one or two channels. After the start of illumination and a short delay period, a pronounced increase in the rate of channel incorporation is apparent. This is a typical result out of 10 largely identical experiments. If, however, the membrane is formed from saturated diphytanoyllecithin, the fluctuation behaviour of the membrane before and after illumination remains largely identical, that is, there is no light-induced increase in the number of open channels (Fig. 3b). The two lipids differ in their oxidizability, which seems to play an important role in the light-induced increase of the rate of channel incorporation (see Discussion).

A light-induced increase of the current—illustrated by a multi-channel experiment (Fig. 4)—was also observed in the presence of the mitochondrial VDAC instead of the bacterial OmpC. Similar results were obtained with the

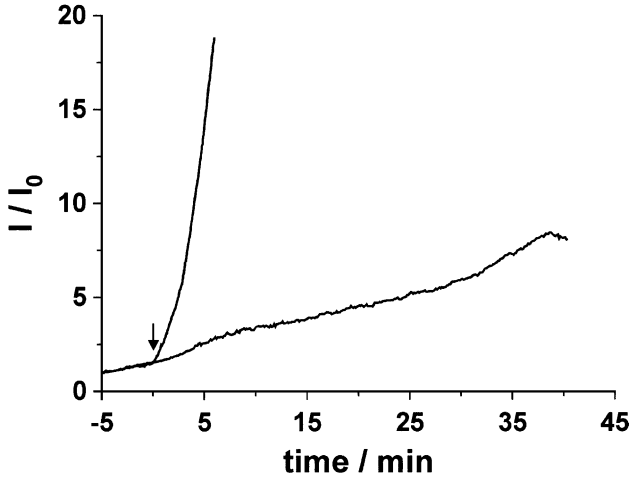

Fig. 2. Light-induced increase of the current I (normalized to the initial current I_0) of unmodified membranes formed from dioleoyllecithin (with 0.5 mM rose bengal in the membrane-forming solution) across a hole of 1 mm diameter. The membrane separated two aqueous solutions of 1 M KCl. The two experiments illustrate the behaviour of two membranes with different life times of about 5 and 35 min after start of illumination. The initial conductance values were 2×10^{-6} and 4×10^{-6} S/cm^2, respectively, measured at an applied voltage of 50 mV.

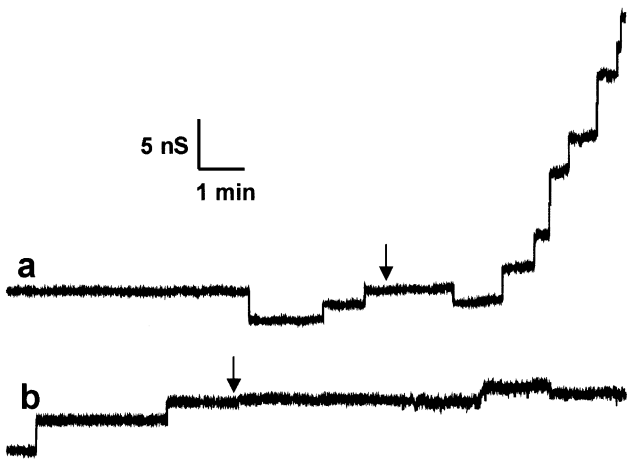

Fig. 3. Single-channel fluctuations of OmpC channels following continuous illumination of the membrane (arrow). (a) Membrane formed from dioleoyllecithin in a solution of 0.6 ng OmpC/ml in 1 M KCl; (b) membrane formed from diphytanoyllecithin in a solution of 6 ng OmpC/ml in 1 M KCl. The membrane-forming solution (in addition to the lipid) contained 0.5 mM rose bengal in both cases. The electric current was measured at a band width of 30 Hz.

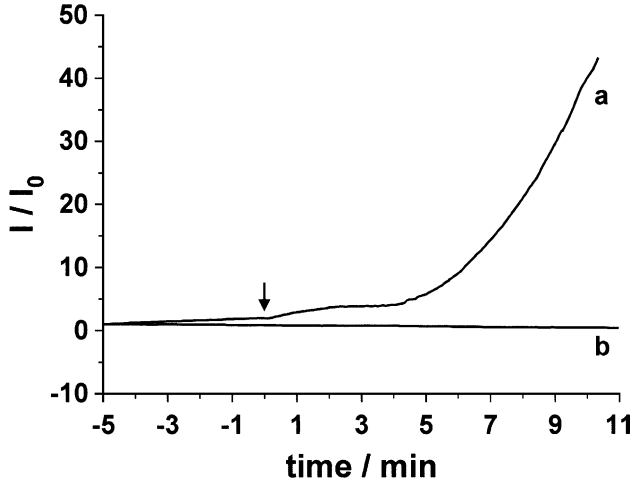

Fig. 4. Light-induced increase of the current I (normalized to the initial current I_0) in the presence of the membrane porin VDAC. The ion channels were reconstituted in lipid membranes formed from either a 1:1-mixture of dioleoyllecithin and dilinoleoyllecithin (a) or diphytanoyllecithin (b) in n-decane containing in addition 0.5 mM rose bengal. A constant voltage of 15 mV was applied to the membrane which separated two aqueous solutions of 1 M KCl and 33 ng/ml protein. The initial current was $I_0 = 1.1 \times 10^{-7}$ A (a) and 4×10^{-7} A (b) (at a membrane diameter 0.5 mm), which corresponds to about 1500 (6000) open channels.

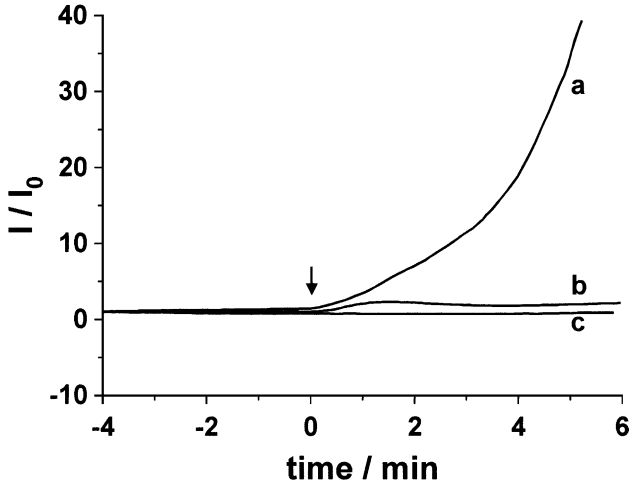

Fig. 5. The photodynamic effect on the membrane current in the presence of the ion carrier nonactin. The membranes were formed from 1% solutions of either dioleoyllecithin (a,b) or diphytanoyllecithin (c) in decane containing 0.5 mM rose bengal and 2×10^{-4} M nonactin. The membrane separated two aqueous solutions of 1 M KCl. The influence of the antioxidant vitamin E was studied by adding 2 mg/ml to the membrane-forming solution (b).The initial conductance values (at a voltage of 50 mV) were 4.8×10^{-4} S/cm^2 (a), 1.1×10^{-4} S/cm^2 (b) and 1.5×10^{-4} S/cm^2 (c). Illumination was started at time zero (arrow).

porin LamB from the outer membrane of *E. coli* (data not shown).

The increase of the current shown in Fig. 4 was also present, if illumination was limited to 1 min only. A continuous rise of the current was observed after the end of illumination which was virtually identical to that during continuous illumination.

A light-induced conductance increase is also observed, if membranes formed from dioleoyllecithin are doped with ion carriers of the valinomycin type (Figs. 5 and 6). This is a confirmation of similar experiments by Mirsky et al. [26], which, however, were performed by using a different sensitizer and a different lipid. The conductance increase is strongly reduced in the presence of vitamin E and disappears completely, if the membrane is formed from the saturated lipid diphytanoyllecithin of low oxidizability.

We think that there is a common physical basis for the different activation phenomena. They are believed to reflect photomodification of the lipid matrix of the membrane. The arguments outlined in the following section are based on light-induced lipid peroxidation which—due to the accumulation of polar products—is thought to increase the dielectric constant, ε_m, of the membrane interior.

To test this hypothesis, the response of the membrane capacitance, C, was investigated. As shown in Fig. 7, the result clearly depends on the oxidizability of the lipid used for membrane formation. In the case of dioleoyllecithin, the capacitance is found to increase after the start of illumination, while in the case of diphytanoyllecithin, C remains fairly constant. Rather, a very small (but significant) decrease of C is observed, which is caused by a very slow, light-induced transition of small parts of the membrane from the bilayer state into the thicker, coloured (multi-lamellar) state of the membrane. A transition in opposite direction (i.e. from the multi-lamellar to the bilayer state) is normally observed throughout the thinning process of the membrane.

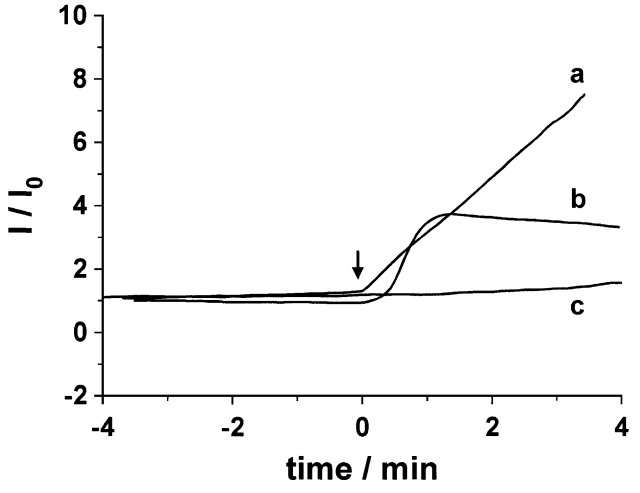

Fig. 6. The photodynamic effect on the membrane current in the presence of the ion carrier valinomycin. The membranes were formed from 1% solutions of either dioleoyllecithin (a,b) or diphytanoyllecithin (c) in decane containing 0.5 mM rose bengal and 10^{-4} M valinomycin. The membrane separated two aqueous solutions of 1 M KCl. The influence of the antioxidant vitamin E was studied by adding 1 mg/ml to the membrane-forming solution (b). The initial conductance values (at a voltage of 50 mV) were 1.9×10^{-3} S/cm^2 (a), 7×10^{-3} S/cm^2 (b) and 2.5×10^{-4} S/cm^2 (c). Illumination was started at time zero (arrow).

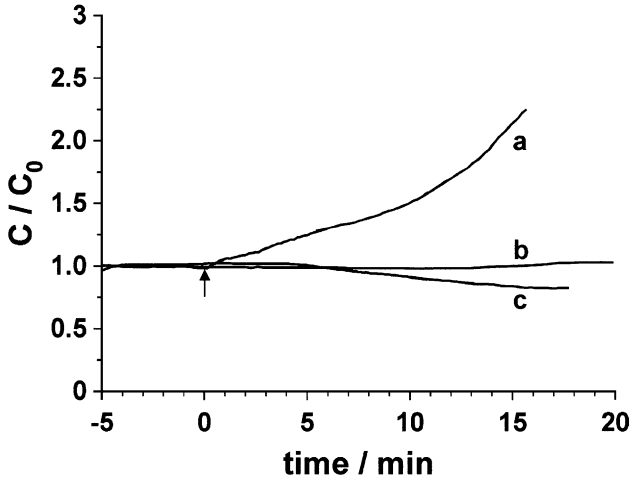

Fig. 7. The response of the membrane capacitance following illumination of the membrane in the absence (curve b) or presence (curves a and c) of 0.5 mM rose bengal in the membrane-forming solution. The membranes were either formed from dioleoyllecithin (curves a and b) or from diphytanoyllecithin (curve c) in the presence of 1 M KCl in water. Illumination was started at time zero (arrow).

We do not know the origin of the light-induced reversal of this process which, however, is a less important side-effect of sensitizer action.

Summarizing, the results presented in Fig. 7 show a light-induced increase of the capacitance, but only for the unsaturated lipid and in the presence of the sensitizer.

It is a well-known experience confirmed throughout numerous publications that the membrane may be approximated by a plate condenser according to

$$C = \varepsilon_m \varepsilon_0 A/d \quad (1)$$

where ε_m = dielectric constant of the membrane, ε_0 = permittivity of space, A = membrane area, d = membrane thickness.

The membrane area was found to remain largely unaffected throughout the photodynamic treatment of the membrane, apart from the small side-effect mentioned above. (The latter moreover leads to a small reduction of C, that is, it slightly diminishes the enhancement of C.) The conclusion of a fairly constant membrane area is based on measurements with comparatively large membranes (of 3 mm diameter), which allow good visible control of the black state and of the planar arrangement of the membrane.

In view of the approximate constant membrane area, the light-induced enhancement of C (by more than a factor of 2) must be due to an increase of ε_m/d (cf. Eq. (1)). The following argument supports a modification of ε_m as essential contribution.

The capacitance of lipid membranes formed from solutions of lipids in decane was found to depend on the chain length of the fatty acid residues. The dependence is, however, less than linear [27]. Though a small variation of d due to chemical modifications of the lipid cannot be excluded, a variation by a factor of more than 2 (as would be required to explain the increase of C) can hardly be imagined. This would require fragmentation of the lipids to an extent incompatible with the stability of a planar lipid membrane. Therefore, the strong enhancement of C is suggested to reflect mainly a photodynamically induced increase of the dielectric constant ε_m by accumulation of polar products of photooxidized lipids.

An increase of the membrane capacitance after illumination of lipid membranes in the presence of haematoporphyrin dimethylether was also observed by Mirsky et al. [26] and was interpreted as an increase of the membrane area induced by surface-active photoproducts. In the present communication, however, the membrane area (contrary to Mirsky et al. [26]) was carefully controlled and was found to remain virtually constant.

The results so far presented were obtained in the presence of the sensitizer rose bengal. We think, however, that the principal findings may be generalized for other membrane-active sensitizers. This is supported by our previous finding of a largely identical behaviour of the plasma membrane of opossum kidney cells after illumination in the presence of different sensitizers [28]. Throughout the present study, further support for a generalization was obtained from experiments performed with alamethicin in the presence of the following sensitizers: a water-soluble mixture of single- and double-sulfonated Zn–phthalocyanine, Al–phthalocyanine, merocyanine 540, and methylene blue. In all cases, a qualitatively similar behaviour as in the case of rose bengal (see Fig. 1) was observed, that is, activation followed by inactivation of the conductance (data not shown).

4. Discussion

The present communication reports on photodynamically induced activation phenomena of the electric conductance observed with three completely different classes of transport systems for ions in lipid membranes: model channels formed by the peptide alamethicin, reconstituted cellular ion channels from three kinds of porins, and the potassium carriers valinomycin and nonactin. In all cases, an increase of the conductance was found at short times of irradiation, as long as inactivation (alamethicin) can be neglected. This holds in spite of the completely different structure of the various systems. We suspect therefore that activation is a general phenomenon which is based on a light-induced modification of the lipid environment of the different transport systems rather than on an "improvement of transport efficiency" by chemical modification of the transporting molecules.

Our conclusion is supported by the absolute requirement of unsaturated lipids for the different activation phenomena (see Figs. 3–6) and by the considerable reduction of the amplitude of the effects observed in the presence of the antioxidant vitamin E (see Figs. 1, 5, and 6). Both phenom-

ena are typical for photodynamically induced lipid peroxidation [29–31].

A physical property, which is known to be of profound influence for ion transport across biological membranes, is the dielectric constant ε_m. This is due to the low value of ε_m (of the order of two) in the membrane interior as compared with $\varepsilon_a \approx 80$ in the aqueous phases on both sides of the membrane. As a consequence, there is a large electrostatic energy difference for ions between water and membrane interior, which leads to extremely low ion concentrations in the membrane interior [32,33]. Efficient ion transport across biological membranes is only possible, if the positive electrostatic energy difference is (at least partly) compensated by other molecular (e.g. hydrophobic) interactions as in the case of lipophilic ions or ion carriers [34,35]. An increase of the dielectric constant inside the membrane may substantially reduce the electrostatic energy difference. A simple estimate based on the Born equation (modified for thin lipid structures by Parsegian [32]) shows that a 50% increase of ε_m leads to an enhancement by almost three orders of magnitude of the rate constant of translocation of ion carrier complexes of the valinomycin type across the membrane interior [14]. Though application of this theory—in view of its simplifying assumptions—is inadequate for a quantitative comparison with experimental data, it allows a qualitative understanding of the underlying physical principle.

The situation is less clear for ion channels that provide for aqueous pathways across the lipid structure. An increase of ε_m may, however, be expected to influence all kinds of charged particles and even of neutral, polar groups, which—via their intrinsic dipole moments—interact with the dielectric properties of the membrane. Therefore, the incorporation into the membrane of any (at least partly) polar substance and its conformation inside the membrane may be imagined to depend on ε_m. This also holds for cellular ion channels, which belong to the class of integral membrane proteins. They differ from cytoplasmic proteins by a comparatively large percentage of hydrophobic amino acid residues. Though they are less frequent, the polar amino acid residues of integral membrane proteins will also experience the strong gradient of ε_m at the membrane/water interface (in a similar way as discussed above for simple ions). In the case of ion channels, their incorporation into the membrane, their conformation as well as their gating behaviour might be affected by an increase of ε_m.

So far, however, there is little experimental evidence available of how this may lead to an activation of the ion channels considered. In the case of alamethicin, similar activation phenomena as presented here were observed after X-ray exposition of the membrane and its aqueous environment [15]. No influence on channel gating and on the single-channel properties was observed. Activation was explained by an increase of the partition coefficient of alamethicin monomers between membrane and water, which was correlated with an experimentally detected increase of the membrane capacitance. The photodynamically induced modifications shown in Fig. 1 are similar to those found after X-ray exposition [15]. This may serve as an indication that both types of oxidative damage lead to identical functional consequences for alamethicin channels.

While there is sufficient evidence for the oxidized lipid environment to be responsible for the activation of alamethicin channels (see above), the inactivation process rather seems to be the result of a chemical modification of the peptide. This is again concluded from the corresponding X-ray study [15], where evidence was provided for the amino alcohol phenylalaninol in position 20 (the only aromatic group of the alamethicin sequence) to be of special importance.

In the case of porins, photomodification of the membrane leads to an increase of the rate of channel incorporation into the membrane. This is clearly apparent from Fig. 3a, where channel incorporation is detected via the stepwise increase of the electric current. The figure also indicates that the amplitude of the conductance steps is more or less identical before and after illumination of the membrane. This was confirmed by a more detailed inspection of the amplitudes and shows that the single-channel conductance is largely unaffected by the photodynamic treatment.

Our results and their interpretation are in accord with previous findings of a considerable enhancement of the rate of channel incorporation, if membranes are formed from oxidized cholesterol. In fact many single-channel studies on porins were performed by using this oxidized lipid to increase the rate of channel incorporation (by several orders of magnitude compared with membranes formed from lecithin [36]). The increase of the channel activity after photooxidation of the lipids, which was observed throughout the present study, appears as a logical consequence of these previous findings, which have not been explained so far, and for which our interpretation should also hold.

We suggest that the driving force for the enhanced transport activity of all investigated systems, after a photodynamic (or other oxidative) treatment of the membrane, is the increase of the dielectric constant, ε_m, of the membrane interior (see discussion above). Such an increase was indeed detected via the increase of the membrane capacitance (cf. Fig. 7 and its discussion). We think that the increase of ε_m is due to an accumulation of polar products of lipid peroxidation in the membrane. Photodynamically induced lipid peroxidation appears well established in the literature [29–31]. Our suggestion is supported by the finding that both, the photodynamically induced increase of the transport efficiency, as well as the increase of the membrane capacitance, were found to depend on the oxidizability of the lipid used for membrane formation.

The present study was performed by using artificial lipid membranes. We think, however, that the main conclusions are also valid for native biological membranes. This is supported by previous findings of our group on photodynamically induced transient activation phenomena of

ion channels in the plasma membrane of OK-cells (see Fig. 4 of Ref. [10]), which are accompanied by an increase of the membrane capacitance (see Fig. 3 of Ref. [37]).

Acknowledgements

The studies on the porins would not have been possible without the support by R. Benz (University of Wuerzburg). The authors thank him and his technical assistant Bettina Schiffler for providing us with preparations of the detergent-solubilized porins mentioned in the text. Preliminary experiments on some aspects of the study were performed by the students H. Kühn, H. Küpper, P. Polzer and E. Seiradake throughout our special course on membrane biophysics.

The authors also like to thank the Deutsche Forschungsgemeinschaft (Az. Sta 236/4-3) for financial support of the study.

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