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The inner mitochondrial membrane contains ion-conducting channels similar to those found in bacteria

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Patch-clamp experiments were performed on rat liver mitochondria inner membranes. Application of voltage gradients of either polarity revealed the presence of several different conductances, ranging up to 1.3 nS in symmetrical 150 mM KCl. Evidence is presented that at least those higher than 0.3 nS are substates of the highest conductance channel. Increasing matrix-side-positive (unphysiological) transmembrane voltage gradients favored the switch of the 1.3 nS channel to operation in lower conductance states. The size of these conductances, the presence of substates and the channel behavior are strongly reminiscent on one hand of the observations on the membrane of protoplasts from the gram-positive bacterium *Streptococcus faecalis*, [Zoratti, M. and Petronilli, V. (1988) FEBS Lett. 240, 105–109], and on the other of some properties of previously described channels of mitochondrial origin.

Patch-clamp; Ion channel; Voltage dependence; Conductance substate; (Rat liver mitochondria)

1. INTRODUCTION

Little attention has generally been given to the possible presence of ion channels in the inner mitochondrial membrane, since their operation was deemed to be incompatible with the maintenance of the steep electrochemical gradients required for energy conservation via the chemiosmotic mechanism. In recent years, however, the evidence has mounted that such channels do exist. Aside from the special case of the Fo sector of the proton ATPase, the best known is probably the calcium uniport [1], which has long been considered a bona fide channel because of its high conductance and because it is blocked by the bulky Ruthenium red cation [2,3]. Evidence for an electrophoretic pathway of anion flux has also existed for a long time [4,5], but the work has only recently been re-evaluated and completed by Garlid's group, which has studied the regulation of the anion uniporter in detail [6–8]. Cation-conducting electrophoretic pathways, activated by membrane stretch and Mg^{2+} depletion, also appear to exist ([4]; Bernardi et al., personal communication). Finally, the application of the techniques of cellular electrophysiology has resulted in the report [9,10] that the membrane of mitoplasts from cuprizone-induced giant mouse liver mitochondria contains a 107 pS (in 150 mM KCl) channel, which opens mainly at potentials in the unphysiological (i.e., matrix-side-positive) range. A second channel, obtained as a contamination in Fo preparations and studied after reconstitution in planar lipid bilayers, with a conductance of 165 pS in 100 mM NaCl, might or might not be the same molecular species [10]. Thieffry et al. [11], using the dip-tip technique, observed a channel with four conductance states, separated by 100, 220 and 220 pS conductance steps in 150 mM NaCl, and concluded that it originated from the mitochondrial membranes. The probability of operation in one or another of the conductance states was voltage-dependent, with lower conductance states favored at potentials closer to zero.

The outer mitochondrial membrane is well known to harbor a high density of pore-forming voltage-dependent porins (VDAC), which have recently been studied in situ by electrophysiological techniques [12–14]. The outer membrane of gram-negative bacteria contains similar porins [15]. Both spheroplasts from gram-negative bacteria [16] and protoplasts from gram-positive ones ([17]; Zoratti et al., unpublished observations) have been reported to possess high conductance (up to several nS) stretch-activated channels with several conductance substates.

We have also investigated the electrical properties of the inner mitochondrial membrane by the patch-clamp technique [18]. It exhibited several conductances, with values ranging from about 30 pS to more than 1 nS in 150 mM KCl. At least those higher than about 300 pS

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appear to be due to partial (lower) conductance states of a giant 1.3 nS channel. The electrophysiological behavior of the inner mitochondrial membrane thus resembles that of bacterial protoplasts.

2. MATERIALS AND METHODS

Rat liver mitochondria, prepared as previously reported [19] were suspended in 30 mM TrisCl, pH 7.2, and sown on the glass bottom of the patch-clamp apparatus (List PCT) incubation chamber. Treatment with hypoosmolar solutions of this sort is well known to cause swelling of the mitochondria, leading to the disruption of the outer membrane and to the formation of mitoplasts [9,20]. After being allowed to stand for 3–4 min to become attached to the glass, the mitoplasts were washed with several volumes of medium (150 mM KCl, 0.1 mM $CaCl_2$, 20 mM Hepes/K^+, pH 7.2). The largest objects (diameters up to 3–4 μm) were selected as targets. The swollen mitoplasts often displayed the 'cap' already described [9,21], which is thought to represent remnants of the outer membrane still covering limited areas. All seals were formed either on vesicles without this cap or on the cap-free portion of the surface. Results did not differ in the two cases. In all the work reported here both the micropipette (uncoated; Hilgenberg 11411 glass) and the bath contained the medium specified above. Data were obtained either in the mitoplast-attached configuration or from membrane patches resulting from disgregation of the rest of the vesicle or obtained by withdrawing the pipette. Current records and current amplitude histograms obtained under the two configurations were indistinguishable. The seal showed a marked tendency to collapse at applied potentials higher than 50 mV (either polarity), but occasionally voltages as high as 160 mV could be applied for a short time. The current signals were amplified by an EPC-7 (List) control unit, filtered at 3 kHz (Frequency Devices 902 LPF), recorded using a Racal 4 analogical recorder, and subsequently digitized using an Indec L-11/73-70 data acquisition and processing system. Software developed in P. Hess' group was used to process the data. Current amplitude histograms were constructed by computerized treatment of the digitized current level in record segments ranging up to a maximum total of 614 000 data points. The current intensities at all data points were determined with reference to a cursor manually positioned at the zero-current level, memorized and sorted into bins. The bin width was automatically adjusted each time the histogram was visualized, depending on the desired display characteristics. Amplitude histograms of the total current flowing through a patch upon application of voltage pulses are presented in fig.3. These were constructed positioning the baseline cursor at the zero-potential current level, and including all the data points of the voltage pulse after relaxation of the capacitive (dis)charge. The plots therefore present the sum, over a period of time, of the currents flowing through all the open channels in the patch. On the contrary, the histograms in fig.4 were constructed by measuring and sorting currents flowing through individual channels. One-step events (i.e., current level variations taking place on the timescale of the sampling interval) were considered to reflect a change in the conductance state of one channel. The baseline cursor was positioned at the current level prevailing before and/or after the single event, and the current conducted was measured. Fig.1A exemplifies the positioning of the cursors for the measurement of the current for the whole patch (solid lines) and for a single channel (dotted lines). Only selected events were chosen when determining single-channel current histograms. Therefore, unlike the histograms of fig.3, those in fig.4 do not constitute a quantitative assessment of the relative probability of appearance of the various conductance levels.

Voltages given are those on the matrix side of the patched membrane, assigning the zero potential level to the pipette. Cations entering (or anions leaving) the mitochondrial matrix side are considered to produce a negative (downward) current. Conductances stated were calculated assuming ohmic current–voltage relationships.

3. RESULTS

In all our experiments and at all applied potentials, of either sign, the results were consistent with the presence of several channel conductances in the membrane, ranging from 30 pS or less to about 1.3 nS. The baseline current exhibited the amplitude, stability and noise characteristics expected for a seal established on a low-conductance biological membrane, with seal resistances often as high as 10 GΩ (not shown). The higher conductances were generally quite active: often a characteristic flickering behavior, associated with rapid channel transitions between states of different conductance, was well in evidence, contributing to the broadening of current amplitude histograms (see below). Fig.1 presents a few examples from the current records, showing the most commonly encountered conductances, which are mentioned in the figure legends. The giant 1.3 nS conductance is shown in fig.1B,C, while fig.1D (see also fig.1E) illustrates the presence of a ca. 107 pS conductance. The latter was observed more frequently at positive applied voltages. Burst kinetics, often observed, are illustrated in fig.1F. Some of the evidence for the presence of substates of the high-conductance pore(s) is illustrated by fig.1A,C,H.I. The event in fig.1I was preceded and followed by more than 500 ms of inactivity, making the simultaneous opening and closing of more than one channel extremely unlikely. The lower current levels during the event must therefore be attributed to substates. Fig.1A,H show a channel closure, followed by rapid transitions to and from a still lower current level. If the latter were to be ascribed to the operation of a second channel, again an unlikely coincidence in time would have to be assumed. In fig.1C, fast opening events occurred only while the major channel was closed, again suggesting that they were due to substates. Behaviors of these types were common. A membrane-strech-induced opening in a *S. faecalis* protoplast [17] is shown in fig.1L for comparison purposes: the similarity with fig.1I is evident. The mitochondrial conductances could not be activated by membrane stretch like their bacterial counterparts [16,17]. They were often active from the onset, and our attempts to activate them in other cases led to the collapse of the high-resistance seal.

To study the voltage dependence of the conductances a pulse protocol was used, applying 1- or 2-s voltage pulses of equal magnitude but opposite sign, separated by 0.1 s at zero potential, in an alternating fashion. Fig.2A–C presents exemplary current records. Fig.3 presents the total patch current amplitude histograms constructed from all the positive and negative portions of the record of the same experiment used for fig.2A–C. At positive (unphysiological) potentials conductance levels are prominent which are much less evident at negative voltages. They are emphasized by the arrows. Fig.4 presents amplitude histograms constructed from

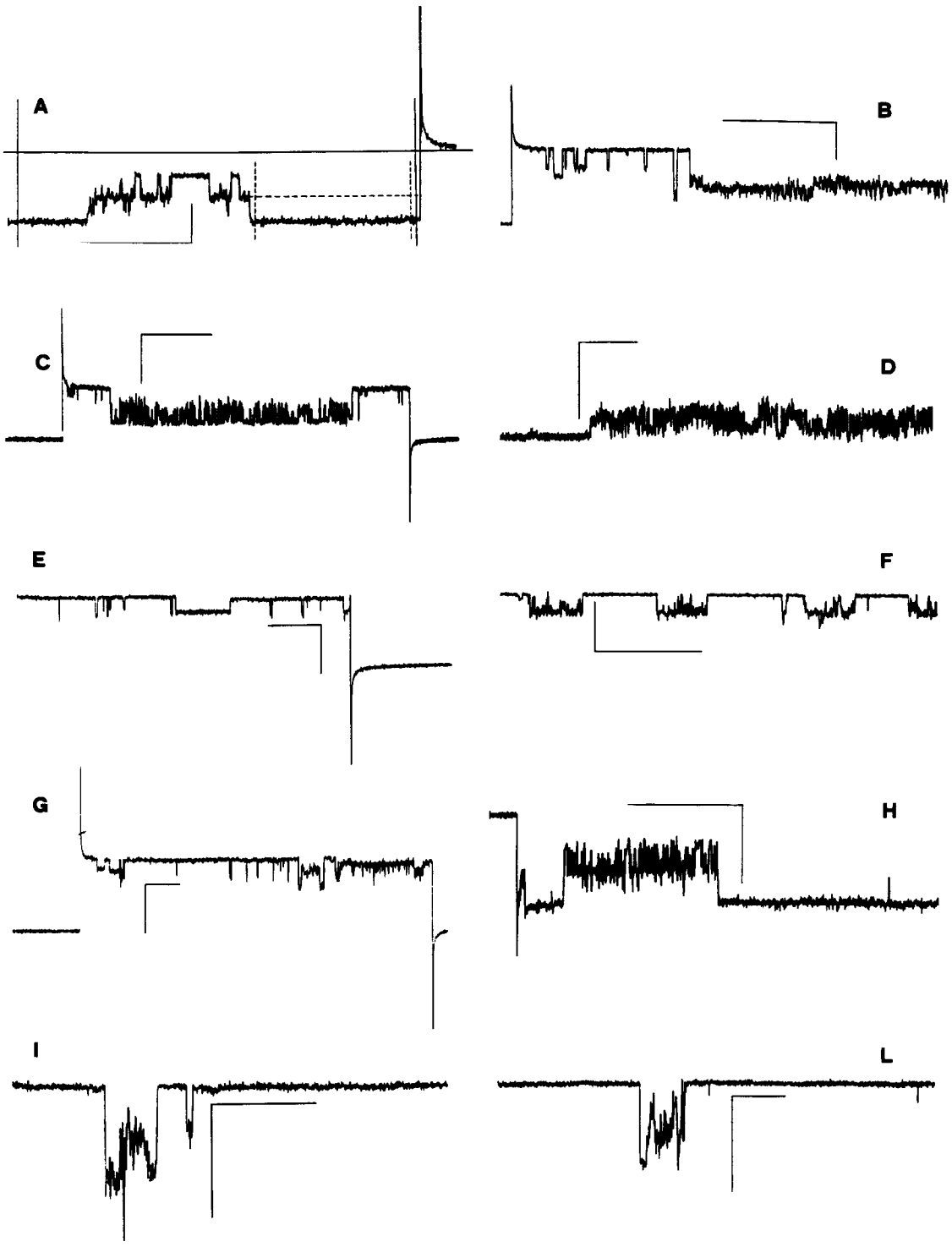

Fig.1. Typical current records. All traces were recorded from symmetrically bathed excised patches. Capacitive current spikes upon voltage jumps appear in traces A–C,E–H. Digital sampling frequency: 20 kHz unless otherwise specified. Bars: 50 pA, 100 ms unless otherwise specified. (A) V = −30 mV, followed by transition to 0 mV. Time bar: 50 ms. Current bar: 25 pA. Conductances appearing (closures): ca. 530, 470 pS (1 nS total). The positioning of measuring cursors is illustrated (see section 2). (B) V = +51 mV (from 0). Conductances (closures): ca. 500, 680, 1300 pS. The long event begins with a ca. 1.0 nS step, with subsequent flickers over a conductance range of about 300 pS. (C) V = +31 mV pulse between intervals at 0 applied voltage. Sampling rate: 10 kHz. Conductances: ca. 1.3 nS closure, with substate (flickering) events of about 700 pS (final step: 1 nS). (D) V = +160 mV. Conductance: ca. 107 pS. Notice the presence of lower levels. (E) V = +40 mV, followed by a step to 0. Conductances: two brief closures of ca. 500 and 310 pS were followed by a longer closure of ca 410 pS and an opening event of ca. 310 pS (difference: ca 100 pS), and by two more events of ca 500 and 310 pS. (F) V = −40 mV (openings). Conductance: ca. 450 pS. (G) V = +40 mV pulse, bracketed by intervals at 0 mV. Major conductances (closures): ca. 220, 310, 450 and 800 pS. (H) V = −40 mV (from 0). Conductance levels (closures): ca. 450 and 530 pS. (I) V = −40 mV. Conductances: opening step of main event: 1.3 nS; minor event: ca. 540 pS. (L) From a *S. faecalis* protoplast membrane, for comparison with trace I. V = −20 mV. Conductance (in 350 mM KCl, opening step): ca. 2.2 nS.

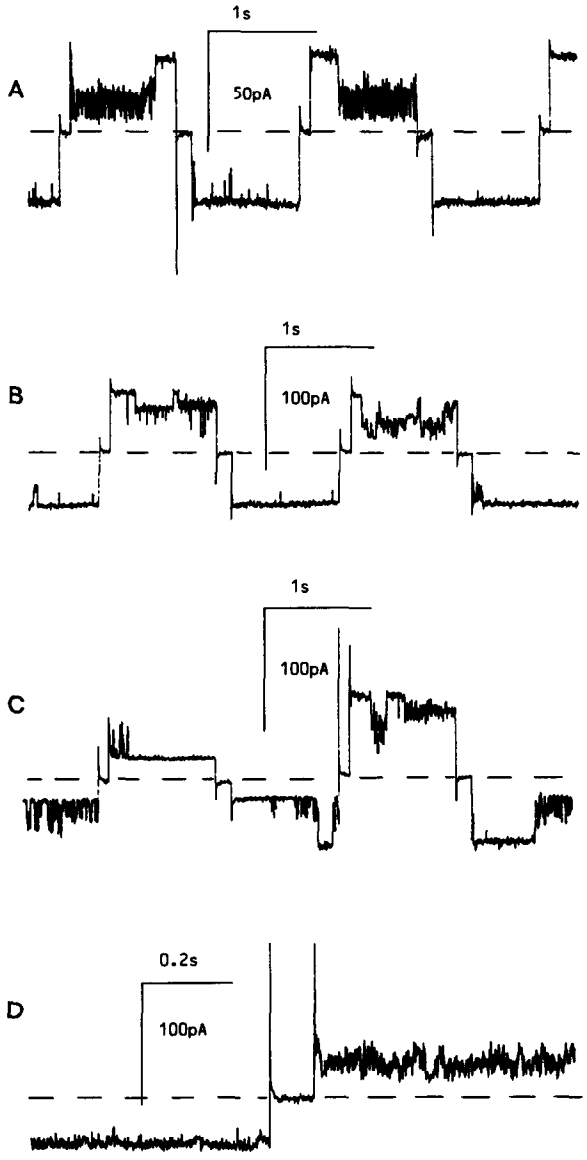

Fig.2. Alternate-sign voltage pulse experiment. Examples. Voltage pulses are separated by 0.1 intervals at 0 mV. Traces A–C and trace D are from two different experiments. Capacitive (dis)charge currents were not compensated. The dashed lines indicate the zero voltage and current level. Digitizing frequency. A–C: 4 kHz, D: 10 kHz. Time bars: A–C: 1 s; D: 0.2 s. Current bars: A: 50 pA; B–D: 100 pA. Voltages: A,D: ±20 mV; B: ±30 mV; C: ±40 mV. Major conductances appearing: A: at +20 mV (upper): ca. 1260 pS, with a flickering band of ca 630 pS. At −20 mV, a brief event of ca. 550 pS. B: at +30 mV: ca. 450, 350, 860 pS. At −30 mV: ca. 550 pS. C: at −40 mV: ca. 650, 450, 1000 pS.

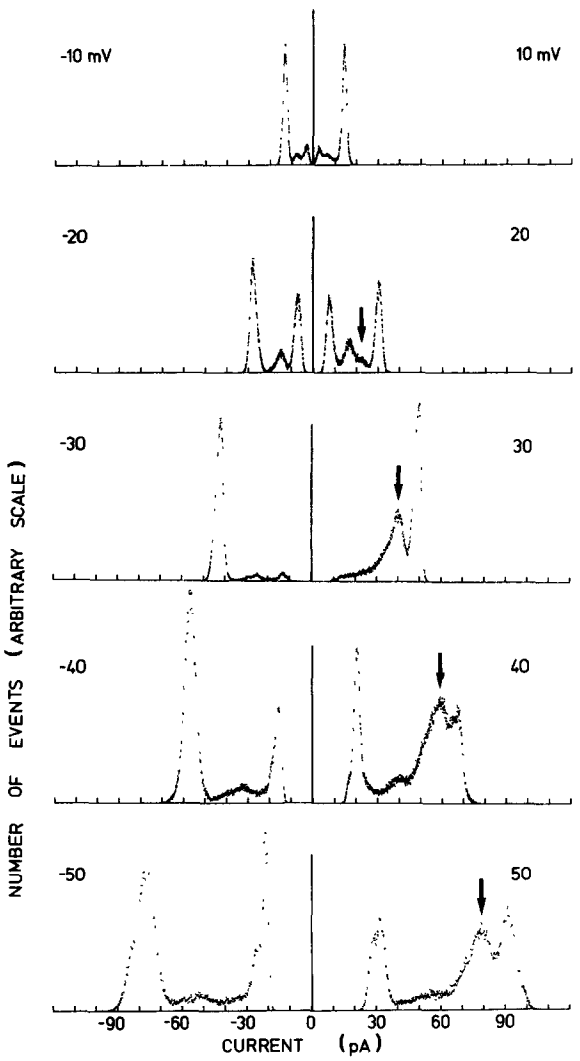

Fig.3. Total patch current amplitude histograms. From the same patch used for fig. 2A–C. The applied voltage (in mV) is indicated. Arrows: see text.

single events in the same records used for fig.3 as discussed in section 2. In most cases the single-step transitions used to construct the histogram were closures from maximal current levels. It follows therefore that the absence of a particular peak on one of the single-event histograms does not mean that the corresponding conductance was seldom upon, but rather the opposite.

The single-event histograms indicate the presence of at least six conductances in the mitoplast membrane. Others are 'hidden' under the rather broad peaks, including ones of about 50, 100 and 200 pS. Smaller conductances, unresolved at the gain and potential values used, probably contribute to the broadening of the amplitude histogram peaks. Conductance steps of about 550 pS were frequently observed, especially at positive potentials (fig.1A,B,H,I; fig.2A,B; fig.4). Direct measurement of step current amplitude on the current records yielded a large number of closely spaced values throughout the range: the conductance limits of the various channels or substates apparently were not sharply defined, a characteristic precedented in some porins [22]. The wealth of current sizes represented a serious obstacle to the determination of current/voltage relationships for the single conductances. The general behavior is at least approximately ohmic, as described by the symmetry of the plots in figs 2 and 3.

Only one giant channel was present in the patch of figs 2–4. The total patch current histograms show that

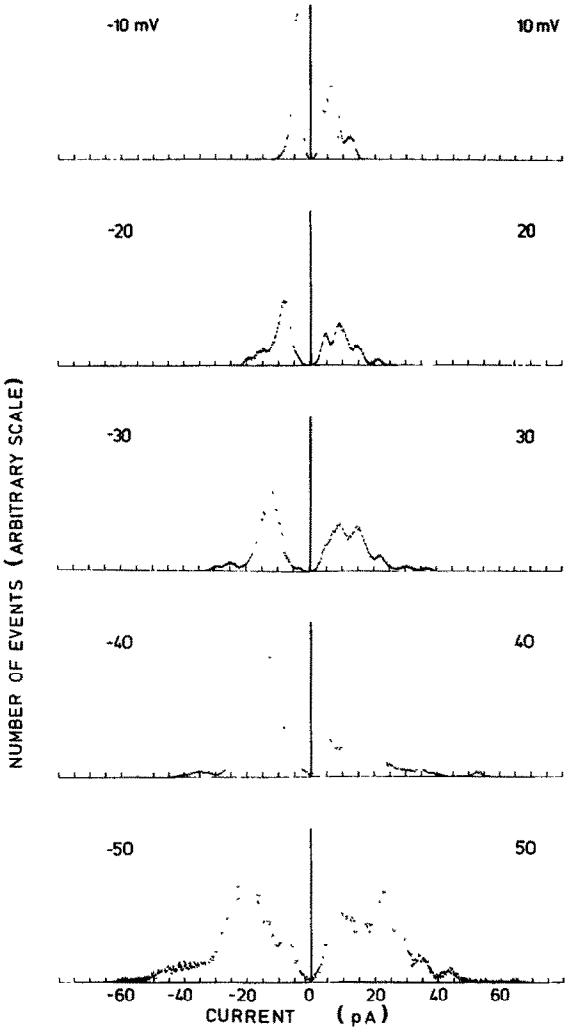

Fig.4. Single-event current amplitude histograms. From the same records used for fig.3. The applied transmembrane voltage is indicated.

the maximal patch conductance was 1.8–2 nS; it increased somewhat after collection of the data at ±10 mV as the seal (initial resistance: about 8 GΩ) became looser. A measure of the leak current is given by the distance between the origin and the first points of the histograms in fig.3. The maximal current flowed for a high fraction of the time at all applied potentials, as indicated by the size of the corresponding peaks in fig.3. It is therefore likely that it was sustained by all the channels in the patch, simultaneously open. The leak conductance was about 0.4 nS ($R = -2.5$ GΩ) during most of the experiments, so that the sum of the patch channel conductances may be taken as 1.4–1.6 nS. The single conductance histograms (fig.4) and the current records (fig.1B,C) show that a channel was present, and was closing at positive applied voltages, with a conductance of about 1.3 nS. It follows that the total patch current (including leak current) above, e.g., 35 pA at V = 50 mV must have been carried in part by conductance substates of the giant channel. It follows also that all conductances between approximately 0.3 and 1.1 nS contributing to the single-event amplitude histograms of fig.4 correspond to conductance substates of the 1.3 nS channel. The currents appearing in the total amplitude histograms (fig.3, arrows) obtained at positive applied potentials, and much less evident in those obtained at negative potentials, correspond to conductances in the range 0.8–1.1 nS, i.e., they must be carried at least in large part by substates of the giant channel, partially closed at positive potentials. The same results were obtained in the two other experiments, conducted according to the pulse protocol described above, in which the membrane patch contained only one giant channel. That the sign of the applied potential has a considerable effect on the behavior of some of the conductances is also evident from records such as the one in fig.2D, in which the increased flickering at positive potentials is clearly visible.

4. DISCUSSION

The observations summarized above indicate that the membrane of rat liver mitoplasts can exhibit a number of different electrical conductances. At least those between 0.3 and 1.1 nS have been deduced to represent partial conductance states of a giant 1.3 nS channel. More positive (unphysiological) potentials favor the operation of the substates at the expense of the highest conductance state. The effect of transmembrane potentials in what is widely believed to be the physiological range, i.e., about −180 mV ([23,24]; contrast [25,26]) unfortunately could not be studied because the seal usually collapsed at lower voltages.

The only previous comparable patch-clamp study [9], on mitoplasts from cuprizone-enlarged mouse liver mitochondria, reported the presence of only one 107 pS channel. The nature of the membrane on which we established high-resistance seals in an important point to examine in this context: the question arises as to whether we might have obtained current records from outer mitochondrial membranes. We believe this not to be the case. The osmotic shock treatment (followed by washing) is known to eliminate most of the outer membrane [20]. Furthermore, we avoided 'cap' regions [9]. Importantly, the resistances of the seals we established were in the several GΩ range. Tedeschi and co-workers reported instead that seals on the outer membrane of cuprizone-enlarged mouse liver mitochondria have resistances of only 10–500 MΩ [13,14], due to the presence of 100–1000 mitochondrial porin molecules per patch [12]. We never observed a progressive conductance increase during a voltage pulse, as described by Kinnally et al. for experiments on the outer membrane. Also, the 107 pS conductance reported by Sorgato et al. [9] to be characteristic of the inner mem-

brane appeared frequently in our records (fig.1D,E). We believe therefore that the seals were established on inner mitochondrial membranes.

Some of the conductances we observed were in the range normally associated with porin-type channels [15]. Rat liver mitochondria outer membrane porins (VDAC) reconstituted in black lipid bilayers, have a conductance of 0.45 nS in 100 mM KCl [27], i.e., about 0.67 nS in 150 mM KCl, about one-half of the maximal value of 1.3 nS we observed. Reconstituted VDAC channels characteristically decrease their conductance as the absolute value of the applied transmembrane potential increases [27]. Tedeschi and co-workers reported that in experiments on the native outer membrane its conductance either showed a decline on both sides of zero applied voltage, or, more often, it exhibited an increase at positive (our convention) potentials, with a decrease occurring instead in the negative range ([12–14]; see footnote in [14]). Neither voltage dependence scheme was followed in our experiments: the partial conductance states of the 1.3 nS channel were favored by increasing positive potentials, while the open probability of the highest conductance state remained high throughout the negative potential range we explored. It is therefore unlikely that the pore we observed is the VDAC (porin), yet a possibility remains that this might be the case. Porins from mammalian mitochondria insert into lipid bilayers as single channels [28,29], but those from fungi frequently do so as multiplets (often triplets), and form extended arrays in the membrane [28]. The presence of multiplets might account for some of the properties of the conductances we observed. The voltage dependence of the giant channel resembles instead that reported by Thieffry et al. [11] for the 540 pS channel they observed and its substates.

Conductance steps of this size, as well as of 100 and about 200 pS, were frequently observed in our experiments, especially as closures at positive potentials. We have concluded they are due to a substate of the 1.3 nS channel, yet they were also sometimes observed as isolated events (fig.1D,I). We offer therefore the speculation that the giant 1.3 nS channel may be actually composed of subunits, possibly capable of existing as independent ion-conducting pores, and functioning in a cooperative manner when aggregated. This model, similar to the one we proposed for bacterial channels [17], accounts for the variety of high conductances observed and for their substate-like behavior. Models of channels formed by multiple conducting subunits have been proposed before (e.g. [14,30,31]). An abundance of partial conductance states has been suggested to be indicative of a 'barrel-stave' structure [32]. An attractive possibility is that these giant channels may be localized at intermembrane contact sites, which have been proposed as the sites of important mitochondrial transport processes, in particular protein translocation [33,34]. They would presumably remain associated with the inner mitochondrial membrane throughout the osmotic shock procedure and the removal of the outer membrane.

The electrophysiological behavior described above presents strong analogies with the one exhibited by bacterial membranes. Conductances of various sizes, ranging up to a few nS, are present in the only membrane of *S. faecalis* protoplasts and in the inner membrane of *E. coli* spheroplasts ([16,17]; Zoratti et al. and Ghazi et al., unpublished observations). These conductances often give rise to high and noisy, flickering patch currents. A striking characteristic of the large bacterial channels is that they are activated by membrane stretch [16,17]. An analogous behavior could not be demonstrated with mitoplast membranes. However, the membranes used in this work were initially subjected to osmotic shock. Furthermore, suction was applied to establish the gigaseal. Bacterial stretch-activated channels become permanently activated if subjected to repeated stretch cycles (Zoratti et al., unpublished); a similar situation might prevail with mitoplasts and prevent the observation of stretch-induced activation. It is clear at any rate that bacteria and mitochondria harbor channels with similar characteristics, which presumably also share a common evolutionary origin, a common placement in the membrane systems and common functions. Just what these functions might be remains to be explored. The transport of large molecules (proteins, genetic material) [33–37] appears at this point to be a likely candidate, in both systems, for the largest channel complex. Some of the conductances we observed might also be tentatively identified with the uniports recently described ([8]; Bernardi et al., personal communication), which are believed to play a key role, together with the K^+/H^+ and Na^+/H^+ antiporters, in the regulation of the osmotic pressure in mitochondria [38]. The pH, Mg^{2+} concentration and membrane stretch have been identified as the main factors controlling the operation of these uni- and antiports, thus providing an initial clue to the factors which might control the conductances we observed. Useful clues might also be provided by the observations on the VDAC channels [39]. The question arises as to whether rare, random operation of these channels might be partly responsible for the 'leaks' which cause part of the respiration by resting isolated mitochondria [40].

The electrical activity described in this report must be closely controlled in vivo, by factors which need to be understood. Nonetheless, the picture of the inner mitochondrial membrane as a nearly impassable permeability barrier, concerned only with the business of energy conservation, ought to be reconsidered. The presence of these channels is one more fact underscoring the role of mitochondria as integrated cellular components, connected to and interacting with other cell compartments and structures [36].

NOTE ADDED IN PROOF

While this paper was under review, very similar results were reported by Kinnally et al. [41].

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