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ION CHANNELS, RECEPTORS AND TRANSPORTERS

Modulation of the hepatocyte rough endoplasmic reticulum single chloride channel by nucleotide–Mg^{2+} interaction

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Abstract The effect of nucleotides on single chloride channels derived from rat hepatocyte rough endoplasmic reticulum vesicles incorporated into bilayer lipid membrane was investigated. The single chloride channel currents were measured in 200/50 mmol/l KCl *cis*/*trans* solutions. Adding 2.5 mM adenosine triphosphate (ATP) and adenosine diphosphate (ADP) did not influence channel activity. However, MgATP addition inhibited the chloride channels by decreasing the channel open probability (Po) and current amplitude, whereas mixture of Mg^{2+} and ADP activated the chloride channel by increasing the Po and unitary current amplitude. According to the results, there is a novel regulation mechanism for rough endoplasmic reticulum (RER) Cl^- channel activity by intracellular MgATP and mixture of Mg^{2+} and ADP that would result in significant inhibition by MgATP and activation by mixture of Mg^{2+} and ADP. These modulatory effects of nucleotide–Mg^{2+} complexes on chloride channels may be dependent on their chemical structure configuration. It seems that Mg–nucleotide–ion channel interactions are involved to produce a regulatory response for RER chloride channels.

Keywords Chloride channels · Rough endoplasmic reticulum · Bilayer lipid membrane · Single channel properties · MgATP–MgADP

Abbreviation

HEPES	4-(2-Hydroxyethyl) piperazine-1-ethanesulfonic acid N-(2-hydroxyethyl) piperazine-N′-(2-ethanesulfonic acid) potassium salt
RER	Rough endoplasmic reticulum
mitoK_{ATP}	Mitochondrial ATP-sensitive K^+ channel
DIDS	4,4′-Diisothiocyanatostilbene-2,2′-disulfonic acid
CFTR	Cystic fibrosis transmembrane conductance regulator
VDAC	Voltage-dependent anion channel

Introduction

Several major classes of chloride channels have been described based on their structural or functional differences and modulation by signaling molecules. The channel gating functions might be modulated by quite separate structural elements such as nucleotides. Nucleotides have been reported to influence the activity of chloride-permeable anion channels. There are reports that show some of the intracellular anionic

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channels are activated by nucleotides [3], although reports of the inhibitory effect of nucleotides on these channels also exist [16, 18].

Using patch–clamp and bilayer lipid membrane methods, anion selective channels with different single channel properties have been observed in rough endoplasmic reticulum [3, 18] and the inner mitochondrial membrane [16, 24, 37]. Published data indicate that anion channel activities are regulated by a variety of modulatory mechanisms [2, 15–17]. An anion-selective 108 pS channel was observed in patched mitoplasts from rat brown adipose tissue in symmetric 150 mmol/l KCl. The channel was partially inhibited in a reversible manner by purine nucleotides including adenosine triphosphate (ATP) and adenosine diphosphate (ADP) [15]. Recently, a "maxi" mtCl channel was characterized in the mitochondrial inner membrane of a colon tumor cell line. The channel was voltage-dependent with a conductance of 400 pS in symmetrical 150 mmol/L KCl. It was inhibited by several compounds including 4,4′-diisothiocyanatostilbene-2,2′-disulfonic acid (DIDS), Mg^{2+}, and ATP [7], whereas Bégault and Edelman reported an ATP-activated Cl^- channel using reconstituted endoplasmic reticulum-enriched pancreatic microsomes [3]. Accordingly, Clark et al. found anion channels with different conductances and gating behaviors in rat brain endoplasmic reticulum [5].

A putative RER chloride-selective channel was described in rat hepatocytes using bilayer lipid membrane by Eliassi et al. [10]. However, pharmacological modulation of the RER chloride channels is not clear. Thus far, four families of anion channels have been described. They are the ClC family (voltage-dependent Cl^- channels), the CLIC family (Cl^- intracellular channels), the ABC family, and the ligand-gated anion channel family [29]. Assignment of the RER chloride channels to one of the known families of chloride channels remains to be elucidated.

Given the role of intracellular Cl^- channels in cell homeostasis, it is of great interest to identify signals that are involved in the regulation of channel-gating behavior. In order to understand the effects of nucleotide, we attempted to characterize the electrophysiological and pharmacological properties of the rat hepatocyte RER chloride channels incorporated into a planar lipid bilayer.

Materials and methods

Materials

4-(2-Hydroxyethyl) piperazine-1-ethanesulfonic acid N-(2-hydroxyethyl) piperazine-N′-(2-ethanesulfonic acid) potassium salt (HEPES), sucrose, potassium chloride, Tris, HCl, MgATP, ATP (as disodium salt), magnesium, ADP (as sodium salt), and DIDS were purchased from Sigma. MgADP was prepared by mixing of ADP and magnesium that we called it as mixture of ADP and Mg^{2+}. n-Decane was obtained from Merck. Salts and all solvents were analytical grade.

RER isolation

Rough microsomes (RM) derived from RER of rat hepatocytes were prepared as previously described [1, 10, 12, 26]. Briefly, male Wistar rats weighting 200±20 g were used. All experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH publication no. 80-23, revised 1996). Rats were anesthetized with ether and livers were rapidly excised and homogenized in 0.25 M sucrose (4 °C). The homogenate was filtered through surgical gauze, and the filtrate was centrifuged at 8,700×*g* for 10 min at 4 °C (Beckman model J-21B). Next, the supernatant was further centrifuged (Beckman LB-M ultracentrifuge) at 43,000×*g* for 6 min at 4 °C, and the subsequent supernatant was centrifuged at 110,000×*g* for 1 h at 4 °C. The pellet from the 300,000×*g* sucrose gradient centrifugation was resuspended in 0.25 M sucrose, 3 mM imidazole, and 0.5 mM pyrophosphate, pH 7.4. Subsequently, the suspension was centrifuged at 140,000×*g* for 60 min twice. The obtained pellet was resuspended in 0.25 M sucrose and 3 mM imidazole and the centrifugation was repeated for 40 min. RMs were stored in 10 μl aliquots in 0.25 M sucrose/3 mM imidazole, pH 7.4 at −80 °C for future use.

L-α-Phosphatidylcholine extraction

L-α-Phosphatidylcholine (L-α-lecithin) was extracted from fresh egg yolk according to the protocol described by Singleton and Gray [10, 27].

Electrophysiological studies

Experiments were performed using a planar lipid membrane technique. Bilayer lipid membrane (BLMs) were formed in a 200 μm diameter aperture drilled in a Delrin cup (Warner instrument Corp., Hamden, CT, USA), which separated two chambers *cis* (cytoplasmic side)/*trans* (luminal face). The chambers contained 200/50 mMKCl (*cis*/*trans*) solutions. The pH on both sides was adjusted to 7.4 with Tris-HEPES. BLMs were painted using a suspension of L-α-lecithin in n-decane at a concentration of 25 mg/ml. Formation and thinning of the bilayers were monitored by capacitance measurements and optical observations. Typical capacitance

values ranged from 200 to 400 pF. Single channel currents were measured with a BC-525A amplifier (Warner Instrument). The *trans* chamber was voltage-clamped relative to the *cis* side which was grounded.

Electrical connections were made by Ag/AgCl electrodes and agar salt bridges (3 M KCl). All recordings were filtered at 1 kHz using a four-pole Bessel filter, digitized at a sampling rate of 5 kHz and stored on a personal computer for off line analysis by Pclamp9 (Axon Instruments Inc). The channel unitary conductance was calculated from the current–voltage relationship. The channel open probability (Po) was calculated using standard event detection algorithms in Pclamp9. Po was calculated from the segments of the continuous recordings lasting 50 s. Data are expressed as the means ± standard error measurement. The significance of the differences was determined by a Student's paired *t* test. The permeability ratios for Cl^- and K^+ were calculated according to the Goldman–Hodgkin–Katz voltage equation.

Results

Single chloride channel properties

Purified RER vesicles were incorporated into planar lipid bilayers. Using 200 mM KCl in the *cis* and 50 mM KCl in the *trans* chamber solutions following resulting single channel activity was recorded at various membrane voltages. Figure 1a shows recordings of Cl^- channels reconstituted in the bilayer at various holding potentials of −50 to +50 mV. The results in Fig. 1a indicate a zero current potential value close to −30 mV, the equilibrium potential expected for Cl^- ions under the prevailing ionic conditions. RER Cl^- channels had measured reversal potentials (Erev) of −31±2 mV (n=15) in asymmetrical KCl solutions (50 mM *trans* and 200 mM *cis*). At 0 mV under steady-state conditions, cations and anions flow from the *cis* to the *trans* chamber along their own concentration gradients. However, at voltages negative to −30 mV, Cl^- ion flow generated a negative current. With the Goldman–Hodgkin–Katz equation, the RER Cl^- channel was determined to be ~17 times more selective for Cl^- than K^+.

The current–voltage relationship curve is shown in Fig. 1b. The current–voltage relationship of the unitary Cl^- channel did not exhibit rectification and was ohmic at all voltages in the experiments. With 200 mM KCl *cis*/50 mM *trans*, the slope conductance of the inward current was 115± 4 pS (n=15). We found that the channel current amplitude varied with potential. When a positive-holding potential is applied, consequently, the ER luminal side is positive with respect to the cytoplasmic side, and the channel current amplitude tends to increase (Fig. 1a and b). Clearly, channel activity was voltage dependent with more activity at the more positive potential values.

The effect of voltage on channel activity was investigated by measuring the channel open probability as a function of voltage in asymmetrical Cl^- conditions (200 mM KCl *cis*/50 mM KCl *trans*). Figure 1c shows the average steady-state open probability at holding potential for the full open conducting state obtained from five different experiments. The Po of the channel was low (ranging from 0.02 to 0.11). Po of the channels at 0 mV was 0.02±0.01. Transitions from an open state to the closed state could be observed. Whereas, the current–voltage plot for this channel (Fig. 1b) was linear, the mean open probability–voltage relationship curve was changed as a nonlinear pattern by changing the applied voltage. A one-way ANOVA test result revealed significant differences between Po and membrane potential measured from different experiments in asymmetrical solutions (p<0.05).

Pharmacological properties of RER Cl^- conductance

Effects of chloride channel blocker

To study the effect of the drugs, we used regular single chloride channels having a classical stable, constant opening behavior and current amplitude. The channel pharmacological properties were next investigated by testing the effect of DIDS. Figure 2 shows that addition of 0.1 mM DIDS to the *cis* chamber resulted in a significant inhibition of channel activity at +40 mV (n=4). A significant current block at 0.1 mM DIDS would thus confirm that the reconstitution of the channel recorded here was a Cl^- permeable anion channel. It should be indicated that DIDS is a well-known inhibitor of Cl^- channels [21–23, 31].

Effects of ATP and ADP on channel activity

To characterize whether channel activity could be modulated by nucleotides, we performed further experiments in which the action of ATP and ADP on channels incorporated in lipid bilayers were investigated. We examined the effects of ATP on RER Cl^- conductance over a wide range of concentrations (0.1, 0.25, 0.5, 1 and 2.5 mM; n=5 for each concentration). Figure 3 presents single channel recordings of +40 mV under control conditions (a) and after the addition of 2.5 mM ATP to the *cis* side (b). The effect of ATP was not accompanied by significant changes in the channel conductance and open probability with unitary current amplitude of 6.3±0.7 pA and 0.06±0.03 (n=5) in the presence of ATP, as compared to 7.1±0.4 pA and 0.08±0.02 in control conditions, respectively (p>0.05). Accordingly, ATP at 0.1, 0.25, 0.5 and 1 mM did not affect the channel activity (data not shown).

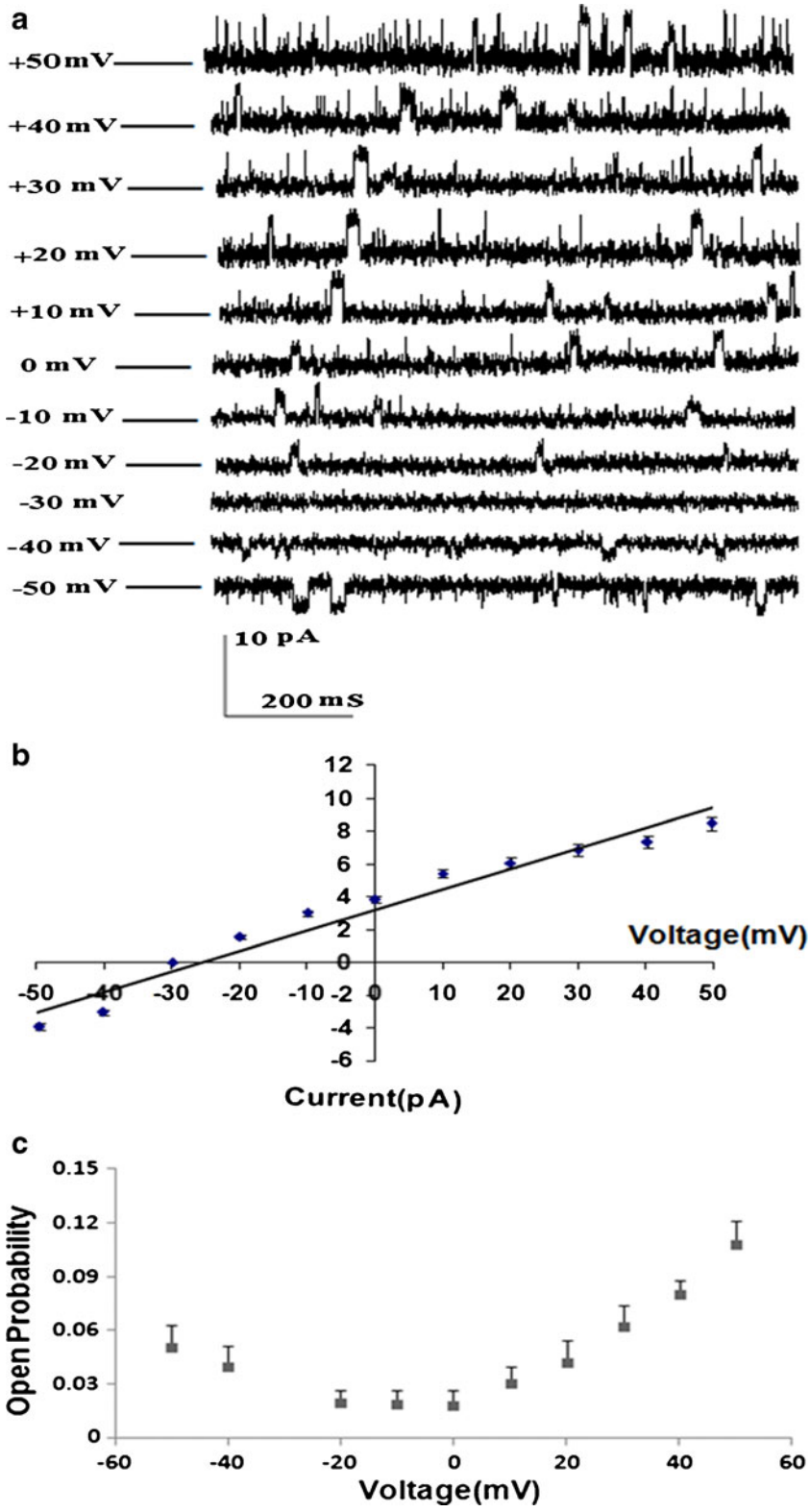

Fig. 1 Single channel properties of an anionic channel from rat RERs. **a** Single channel recordings in 200/50 mMKCl (*cis*/*trans*) gradient after reconstitution of RER hepatocyte vesicles in planar lipid bilayer at potentials ranging from −50 to + 50 mV. The lines on the left indicate the closed state of the channels. **b** Current–voltage relationships for single channel recordings. Each *point* represents the means ± SEM of six different experiments. **c** Open probability (Po) as a function of voltage. Each *point* represents the average open probability as a function of voltages in five different experiments

In supplementary experiments, the addition of 2.5 mM ADP in the *cis* face failed to modify channel conducting or gating behavior. The unitary current amplitude and Po for +40 mV were estimated at 7.1±0.4 pA and 0.08±0.02 (n=5) in control conditions (a) compared with 6.8±0.5 pA and 0.05±0.03 (n=5) after the addition of ADP to the *cis* solution (Fig. 3c). The amplitude of the currents and probability of opening under control conditions and after addition of 2.5 mM ADP were not significantly influenced (p>0.05).

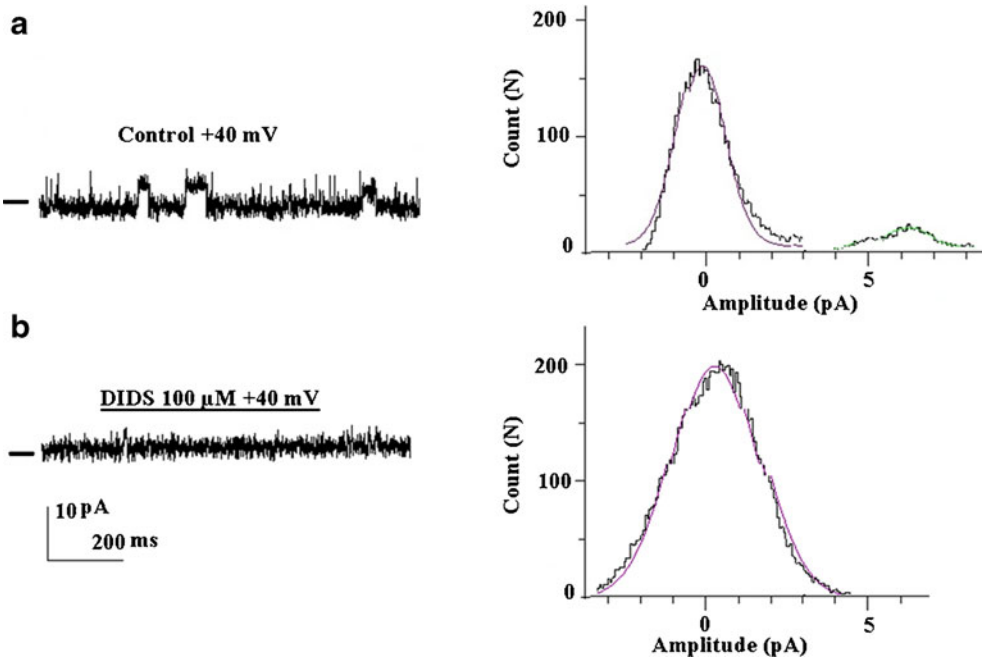

Fig. 2 The effect of DIDS on channel gating behavior at +40 mV. Single channel recordings of under control conditions (**a**; 200/50 mM KCl; *cis*/*trans*), and immediately after addition of DIDS to *cis* side 0.1 mM (**b**; $n=4$). The *lines on the left* indicate the closed state of the channels

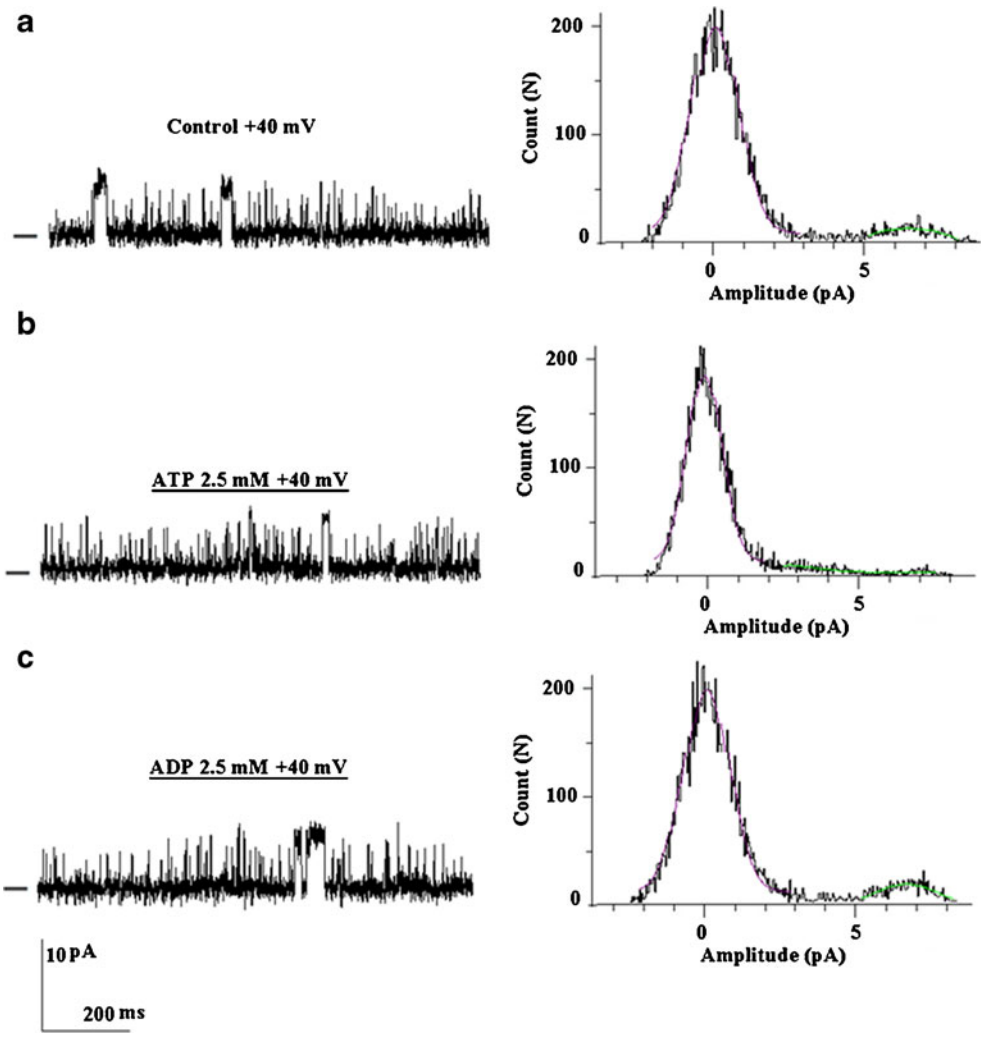

Fig. 3 The effect of ATP and ADP on channel gating behavior at +40 mV. Single channel recordings under control conditions (**a**; 200/50 mM KCl; *cis*/*trans*), and immediately after *cis* addition of ATP (**b**; $n=5$) and ADP 2.5 mM (**c**; $n=5$). Shown on the *right* are amplitude histograms fitted with superimposed Gaussian curves. The *lines on the left* indicate the closed state of the channels

Effects of MgATP and mixture of Mg^{2+} and ADP on channel activity

Next, we examined the possibility of regulation of the channel incorporated in BLM by Mg ATP. Figure 4 illustrates typical unitary current traces recorded at +40 mV before (a) and after the addition of 2.5 mM MgATP to the *cis* solution (b). Addition of MgATP significantly decreased channel openings. It was shown that both the gating and the conducting behavior of the RER Cl^- conductance were influenced by the MgATP added to the *cis* side of the channel. The Po and current amplitude of the reconstituted Cl^- channel were shown to be different before and after the addition of MgATP, e.g., analysis of channel activity revealed that the values of Po and the current amplitude at +40 mV were respectively 0.08±0.02 and 7.1±0.4 pA under control conditions (Fig. 4a). Figure 4b clearly shows that the values of these parameters in the presence of 2.5 mM MgATP (n=4) were blocked to 0.02±0.01 (p<0.01) and 4.2±0.2 pA (p<0.05), respectively.

As described previously, channel activity was not affected by ATP, but these results indicate that MgATP inhibited the channel openings. Next, we examined the possibility of direct channel modification by Mg^{2+}. Hence, when 2.5 mM Mg^{2+} was added to the *cis* solution at +40 mV, the conductance and open probability of the channel were not changed significantly (n=4, data not shown).

In contradiction to MgATP, we observed that the application of 2.5 mM mixture of Mg^{2+} and ADP at the *cis* face induced an activating effect on the Cl^- channels. Figure 4c represents the effects of mixture of Mg^{2+} and ADP added to the *cis* chambers on the activity of single Cl^- permeable anion channels at +40 mV. We found that Po and current amplitude were significantly increased by mixture of Mg^{2+} and ADP present in the *cis* compartment, to 0.08±0.02 and 7.1±0.4, respectively, under control conditions compared with 0.31±0.03 and 12.8±0.9 when mixture of Mg^{2+} and ADP was added to the *cis* side (p<0.01, n=5).

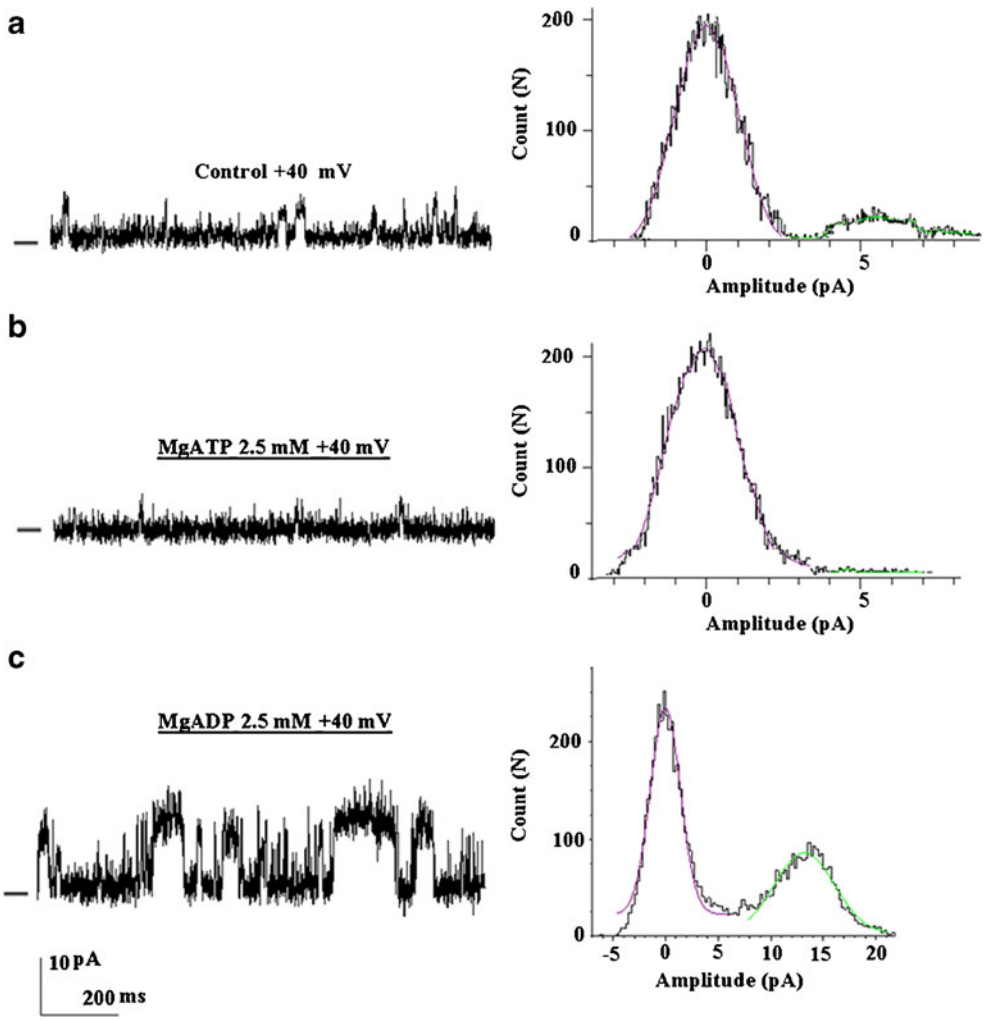

Fig. 4 The effect of MgATP and mixture of Mg^{2+} and ADP on channel gating behavior at +40 mV. Single channel recordings under control conditions (**a**; 200/50 mM KCl; *cis*/*trans*), and immediately after *cis* addition of MgATP and mixture of Mg^{2+} and ADP 2.5 mM. Shown on the *right* are amplitude histograms fitted with superimposed Gaussian curves. The *lines on the left* indicate the closed state of the channels. Summarized data show current amplitudes and Po of reconstituted channels in absence or presence of MgATP (**b**; n=4) and mixture of Mg^{2+} and ADP (**c**; n=5). Data are means ± SEM. Significant differences in the open probability value and amplitude is observed

Discussion

This study revealed that RER vesicles, when incorporated in planar lipid membrane, produce characteristic chloride currents. This chloride conductance has properties different from those attributed to CLIC, because the CLICs are insensitive to chloride channel blocker DIDS [19, 29, 35]. When reconstituted in a planar lipid bilayer, the properties of CFTR [14, 20, 34] are also distinct from the present Cl^- channel. They differ markedly in single channel conductance and sensitivity to DIDS. The CFTR-related Cl^- channel is insensitive to DIDS [20, 34].

Our observed chloride channels had a conductance higher than some of the reported chloride channels from cardiac sarcoplasmic reticulum [18] and rat brain endoplasmic reticulum anion channels [5]. VDACs in the mitochondrial outer membrane exhibit a large conductance, 0.45–0.58 nS with a bell-shaped current–voltage relationship in 0.1 M KCl [4, 6, 33] and thus are incompatible with these results.

A Cl^- selective channel was characterized by Eliassi et al. after the incorporation of rat hepatocytes RER vesicles into a BLM. The channel showed fast flickering kinetic and voltage dependent properties, with a mean conductance of 164±5 pS and an open probability value ranging from 0.9 at 0 mV to 0.4 at +60 mV in 200 mM *cis*/50 mM *trans* KCl conditions [10]. This channel shows gating behavior and a voltage dependency, which are inconsistent with the results presented here. This variance could be due to an actual separation of these channels; thus, two different types of chloride channels are arguably expressed in hepatocyte RER membranes. Probably similar to the mitochondrial inner membrane, a variety of chloride conductance is present in the RER membrane. Several anion channels with different conductance have also been reported in mitochondria [24, 37]. We cannot rule out the possibility that the origin of this discrepancy may be related to the effects of BLM composition differences. It is well established that the function of membrane proteins does depend on the lipid membrane composition [25].

Along with previous reports for ion channels from sheep cardiac mitoplasts [30], our channel activity incorporated into BLM was unaffected by ATP, ADP and Mg^{2+}. In accordance with this work, Malekova et al. described single chloride conductance ranging from 104 to 172 pS in mitochondrial inner membrane vesicles in which none of the chloride channels were modified by either 1 mM ATP or 1 mM ADP applied to the *cis* solution [21]. Contrary to this report, Klitsch and Siemen observed an anion-selective 108 pS channel in patched mitoplasts from rat brown adipose tissue in symmetric 150 mmol/L KCl. The channel was partially inhibited in a reversible manner by purine nucleotides, including ATP and ADP [15]. ATP (0.5–2 mmol/L) was reported to inhibit the chloride channels derived from isolated rat heart mitochondrial vesicles from the one side of BLM (*cis*) and not from the other side, but subsequent application of ADP to the same channel did not inhibit it [16].

On the basis of these findings, Mg^{2+}, ATP, and ADP individually do not affect the RER Cl^- channel activities, but when the study was carried out in the presence of ADP or ATP combined with Mg^{2+}, it led into a modulation of the studied channel. These influences may be occurring at an adenine–nucleotide binding site that is accessible depending on their chemical structure configuration, resulting in changes in the channel structure. On the other hand, these data may allow us to conclude that depending on the chemical structure, magnesium–nucleotide compounds are capable of blocking or activating Cl^- permeable RER anion channels. Nevertheless, the present observations remain compatible with the findings obtained by Thevenod et al. from the membrane of rat pancreatic and parotid zymogen granules, where inhibition or stimulation of Cl^- conductance by nucleotides seemed to be independent of the cation present in the medium and therefore inherent to Cl^- conductance [28]. Compared to the RER chloride channels, Kominkova et al. have studied the effects of $MgCl_2$ on the ATP-induced chloride current decrease. $MgCl_2$, in a concentration-dependent manner, significantly reversed the ATP inhibitory effect [16].

In a previous study, we also demonstrated the activation of endoplasmic reticulum K^+ channels by mixture of Mg^{2+} and ADP in bilayer lipid membrane experiments [1]. Elevated levels of intracellular MgADP, as occurs under metabolic stress [8, 13] could effectively couple the intracellular metabolic pathways with ion channel function. The microsomal Cl^- channels, probably the same as K_{ATP} channels [13, 32, 36], are also involved in metabolic stress conditions. It has been suggested that RER is involved in metabolic stress. In metabolic stress, the concentration of intracellular ATP drops while the levels of intracellular ADP rise [32]. The magnesium ion is an important divalent cation in cells [16]. We may assume that the magnesium–ADP–Cl^- channel interactions observed in our study play a role in metabolic stress conditions. Accumulating evidence indicates that the ER controls a wide range of cellular processes such as stress responses and apoptosis [9, 11]. It seems that, under normal physiological conditions, hepatocyte RER Cl^- channels exist mainly in a closed, inactive form. However, during metabolic stress states, as the intracellular MgADP concentration rises, they open resulting in an enhanced inward chloride current.

In conclusion, similar to mitochondrial ion channels, the RER chloride channels may have been associated with the effects on cells during metabolic stress. We suppose that there is a cross-talk between cytosolic metabolism changes and ER lumen mediated by ER membrane ion channels. Our

data show that cytosolic nucleotides–Mg^{2+} complexes can substantially increase or decrease RER Cl^- conductance, depending on the nature of the nucleotide–Mg^{2+} complex.

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