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Amiloride-insensitive sodium channels are directly regulated by actin cytoskeleton dynamics in human lymphoma cells

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ABSTRACT

Sodium influx mediated by ion channels of plasma membrane underlies fundamental physiological processes in cells of blood origin. However, little is known about the single channel activity and regulatory mechanisms of sodium-specific channels in native cells. In the present work, we used different modes of patch clamp technique to examine ion channels involved in Na-transporting pathway in U937 human lymphoma cells. The activity of native non-voltage-gated sodium (NVGS) channels with unitary conductance of 10 pS was revealed in cell-attached, inside-out and whole-cell configurations. NVGS channel activity is directly controlled by submembranous actin cytoskeleton. Specifically, an activation of sodium channels in U937 cells in response to microfilament disassembly was demonstrated on single-channel and integral current level. Inside-out experiments showed that filament assembly on cytoplasmic membrane surface caused fast inactivation of the channels. Biophysical characteristics of NVGS channels in U937 cells were similar to that of epithelial sodium channels (ENaCs). However, we found that amiloride, a known inhibitor of DEG/ENaC, did not block NVGS channels in U937 cells. Whole-cell current measurements revealed no amiloride-sensitive component of membrane current. Our data show that cortical actin structures represent the main factor that controls the activity of amiloride-insensitive ENaC-like channels in human lymphoma cells.

1. Introduction

Sodium transport through ion channels in plasma membrane plays an important role in water-salt homeostasis, cell volume regulation and modulations of membrane potential in living cells. Specific changes in membrane permeability for monovalent ions underlie fundamental physiological processes in cells of blood origin and may be coupled with a variety of clinical pathologies [1]. In recent years, leukemia-lymphoma cell lines are extensively used as appropriate cellular models to study the role of ion-transporting systems in hematologic malignancies. Particularly, systemic analysis of monovalent ion fluxes and water balance in U937 lymphoma cells postulated specific modulations of integral channel permeability for Na^+ implicated in apoptotic water-salt cellular regulations [2]. An important question arises about the functional expression and regulation of sodium-specific channels underlying physiological reactions in human lymphoma cells.

To date, various physiological aspects and molecular basis of sodium transport in apical membranes of renal epithelia are well-established [3,4]. Particularly, epithelial Na^+ channels (ENaCs) represents the rate-limiting step for Na^+ reabsorption in the distal nephron, lungs, and colon [5–7]. In other non-excitable cells, including cells of blood origin, the membrane pathways providing selective sodium influx are much less understood. Electrophysiological studies revealed the activity of NVSG channels in myeloid blood cells, particularly in primary macrophages [8–10]. ENaC transcripts have been previously detected in human leukemic cell lines including proerythroblastic TF1, erythroblastic leukemia HEL and myeloblastic U937 [11,12]. Taken together, these results allowed us to speculate that ENaC channels may be involved in

Abbreviations: CytD, cytochalasin D; DEG/ENaC, degenerin/epithelial Na^+ channel; $NMDG^+$, *N*-methyl-D-glucamine$^+$; NVGS channel, non-voltage-gated sodium channel; P_o, channel open probability.

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sodium-transporting pathway in monocytic blood cells and their transformed counterparts. In the same time, the single channel behavior and regulation of sodium channels in human leukemia-lymphoma cells remains largely unknown. In frame of functional approach, promising data on native channel fingerprint may be obtained with the use of patch clamp technique.

One of the most important questions is to reveal physiological pathways that modulate non-voltage-gated sodium channel activity in the plasma membrane [7]. In epithelia, an involvement of cytoskeleton elements and some actin-binding proteins in the control of ENaC functions have been repeatedly documented [13–15]. However, molecular mechanisms that couple channel activity with submembranous microfilaments are still not understood. Previously, we have employed human erythroleukemia K562 cell line to examine an involvement of membrane-cytoskeleton coupling in channel regulation and cellular mechanotransduction [16,17]. Convincing evidence indicated an essential role of actin dynamics in the activation of sodium-selective channels in K562 cells which display properties of multipotent blood cell precursor [10,18,19]. The present study was designed to examine functional expression and actin-dependent gating of Na-specific channels in U937 lymphoma cells [20,21]. Our data show that sodium influx through amiloride-insensitive sodium channels in plasma membrane of U937 cells is directly controlled by the dynamics of submembranous actin structures.

2. Materials and methods

2.1. Cell culture

The human histiocytic lymphoma cell line U937 (Russian Cell Culture Collection, Institute of Cytology, St.Petersburg, Russia) were grown in RPMI-1640 medium containing 10% fetal bovine serum (Biolot, Russia) and 40 μg/ml gentamycin at 37 °C and 5% CO_2. For patch clamp measurements the cells were seeded on coverslips, coated with poly-DL-lysine (Sigma, USA).

2.2. Electrophysiology

Cell-attached, inside-out and whole-cell modes of the patch clamp technique [22] were employed to examine functional properties of native channels in plasma membrane. The patch clamp setup was based on HEKA EPC-8 (HEKA, Germany) amplifier and Zeiss Axiovert 40 CFL inverted microscope (Carl Zeiss MicroImaging, Germany). Pipettes were pulled from borosilicate glass capillaries (BF-150-110-10) at a P-97 puller (Sutter Instrument, USA). Resistance of the pipettes filled with standard solution was in range of 3–5 MOhm in whole-cell mode and 5–12 MOhm in other configurations. Ion currents through single channels were recorded at various levels of holding membrane potential. Whole-cell ramp currents were elicited by 1000-ms voltage pulses (from +20 to −80 mV) from a holding potential of +20 mV. For leakage current substraction in whole-cell records we use equimolar substitution of Na^+ with impermeable $NMDG^+$ cations in external solution. The membrane voltage was determined as the potential of the intracellular membrane side minus the potential of the extracellular one.

Channel open probability (P_o) was determined using following equation: $P_o = I/iN$, where I is the mean current determined from the amplitude histograms, i is the unitary current amplitude and N is the number of functional channels in the patch. Data are presented as mean ± SEM (n – number of experiments) and were compared using standard paired Student's t-test, $p < 0.005$ was considered significant.

2.3. Solutions

The standard external solution contained (mM): 145 NaCl, 2 $CaCl_2$, 1 $MgCl_2$, and 10 HEPES/TrisOH. Pipettes were filled with the external solution in cell-attached and inside-out experiments. Potassium bath solution containing (mM) 140 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES/KOH was used in cell-attached recordings to nullify the resting membrane potential. Cytosol-like solution (contacting with the intracellular membrane side) contained (mM) 140 K-Aspartate, 5 NaCl, 2 EGTA/KOH, 1 $MgCl_2$, 20 HEPES/TrisOH and the corresponding amount of $CaCl_2$ (0.176 mM) to establish free calcium concentration at the level of 0.01 mkM (pCa 8). pH of all solutions was set at 7.3. The purified G-actin isolated from the rabbit skeletal muscle [22] was stored in the low ion strength solution (2 mM Tris–HCl, 0.1 mM $CaCl_2$, 0.2 mM ATP, 0.02% NaN_3, pH 7.5) and used for 5 days. An aliquot of G-actin stock solution was added to the bath to the final concentration of 300 μg/ml.

3. Results

3.1. Activity of sodium-selective channels in intact cells and excised membrane fragments

To define single channel properties in intact cells we performed cell-attached patch clamp experiments with sodium (145 mM Na^+-containing solution) as the main cation in the patch pipette. In 6 of 23 of stable patches we observed inwardly directed currents representing the activity of the non-voltage-gated sodium (NVGS) channels in human lymphoma U937 cells. Fig. 1 demonstrates an example of background activity of NVGS channels at various holding membrane potentials. Mean current–voltage relationship corresponds to the unitary conductance of 10.4 ± 0.7 pS and indicates preferential permeability for sodium. Further, sodium channels with identical characteristics were recorded in inside-out experiments on U937 cells (10.6 ± 1.3 pS, n = 5). Sodium-selective channels of similar conductance (10–12 pS) were described earlier in rat macrophages and K562 leukemia cells [8–10].

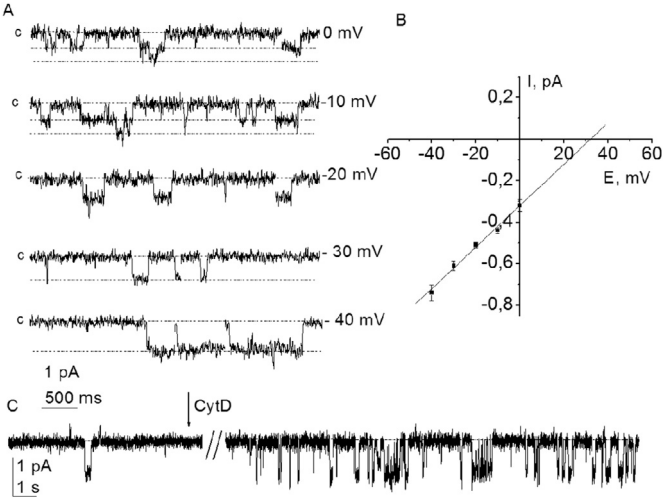

Fig. 1. The activity of non-voltage-gated sodium (NVGS) channels in plasma membrane of U937 lymphoma cells. (A) Cell-attached current records at different membrane potentials (indicated near the traces), c – closed state. (B) Mean current–voltage relationship of sodium channels calculated from 6 experiments. Unitary conductance is 10.4 ± 0.7 pS, reversal potential – +34.5 ± 4.9 mV. (C) An increase of channel activity in response to actin disrupter CytD (10 μg/ml) added to the bath solution; currents recorded at −40 mV.

In most patches on U937 cells, the open probability value (P_0) of NVGS channels was low and no spontaneous increase of channel activity was observed under control conditions. In the same time we found that the activity could be drastically increased by the application of F-actin destructor cytochalasin D (CytD; Fig. 1C). This effect was studied in following experiments using cell-attached, inside-out and whole-cell patch configurations.

3.2. Role of submembranous actin cytoskeleton in regulation of non-voltage-gated sodium channels in U937 cells

Firstly, possible involvement of actin cytoskeleton in channel functioning was analyzed on single current level in cell-attached patches. We found that extracellular application of CytD (10 μg/ml) resulted in an activation of NVGS channels in U937 cells. Fig. 2 shows the representative experiment illustrating the development of the CytD effect on membrane currents in intact cell.

A significant increase of P_0 was observed in 1–3 min after CytD addition; thereafter the channels remained active and were not affected by the following wash-out of the reagent. An activation of NVGS channels in response of F-actin disassembly was observed in 35% of cell-attached patches ($n = 17$). Mean unitary conductance of sodium channels activated by CytD was 10.6 ± 0.7 pS ($n = 6$); extrapolated value of reversal potential was +32.5 ± 4.1 mV. In some experiments, typical outward potassium currents were also observed in the membrane patch (Fig. 2). As shown in cell-attached and inside-out recordings, the activity of potassium channels were not affected by application of actin destructors in U937 cells.

It is reasonable to assume that cytoskeleton integrity may control mechanosensitive channel function in plasma membrane of blood cells [16,23]. Earlier, cytochalasins were considered as potential activators of stretch-activated channels in mammalian cells. Therefore, we specially checked the effect of mechanical stimulus (suction) on sodium currents recorded from cell-attached and inside-out patches. Importantly, membrane stretch did not induce NVGS channel activity on U937 cells. Our observations indicate that channel gating is directly coupled with actin cytoskeleton and is independent on the mechanical status of plasma membrane. Activation of the NVGS channels seems to be due to disassembly or fragmentation of membrane-attached actin filaments. Indeed, similar effect of channel activation in response to actin disruption was observed in inside-out experiments when cytochalasin was applied to the cytoplasmic side of the membrane fragments (Fig. 3; mean unitary conductance 9.9 ± 0.9 pS). Single channel parameters measured for spontaneous and CytD-induced activity were very close in intact cells and membrane fragments.

Our electrophysiological data show that NVGS channel behavior in U937 cells and particular phenomenon of cytoskeleton-dependent activation are similar to those obtained earlier in leukemia K562 cells. Previously, the experiments on excised patches with the use of cytoskeletal proteins allowed us to develop an experimental model suitable for studying the involvement of actin dynamics in ion channel regulation [9,24]. Specifically, we applied globular (G)-actin in the following inside-out patch experiments on U937 cells (Fig. 3). Native G-actin is known to polymerize rapidly with the increase in ionic strength. We tested the effect of polymerizing actin on the activity of NVGS channels induced by cytochalasin in excised membrane fragment.

The injection of G-actin (at a final concentration of 0.3 mg/ml) to the cytosol-like solution resulted in a rapid inactivation of sodium channels. Inhibition of sodium channel activity was developed during 2–3 min, accordingly with proposed time needed for actin filament formation in Mg-containing solution [18]. The amplitudes of the single currents were not affected, whereas P_0 values reduced to zero (Fig. 3). Importantly, the addition of preformed actin filaments to the cytoplasmic side of the membrane had no effect on channel activity. Our results suggest that cortical actin structures play a pivotal role in regulation of NVGS channels in U937 cells. Further whole-cell experiments with cytoskeleton disrupters support our conclusion (Fig. 4A, B). Extracellular application of CytD resulted in significant increase of integral currents representing sodium channel activity; this was confirmed by following replacement of Na^+ ions in the external solution by impermeable $NMDG^+$ (Fig. 4A). CytD-induced steady-state currents provided a suitable model to test potential pharmacological inhibitor of the channels.

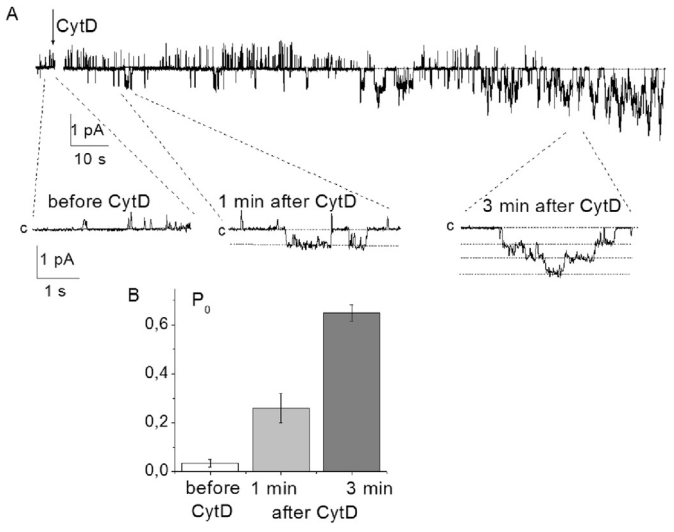

Fig. 2. Activation of NVGS channels in intact cells induced by actin cytoskeleton-disrupting treatment. (A) The development of the effect of cytochalasin application in cell-attached experiment; holding membrane potential is −20 mV. Fragments of current records in the extended time frame are shown below. Outward currents represent the activity of potassium channels. (B) Summary graph of mean P_0 values before and after CytD application ($n = 6$).

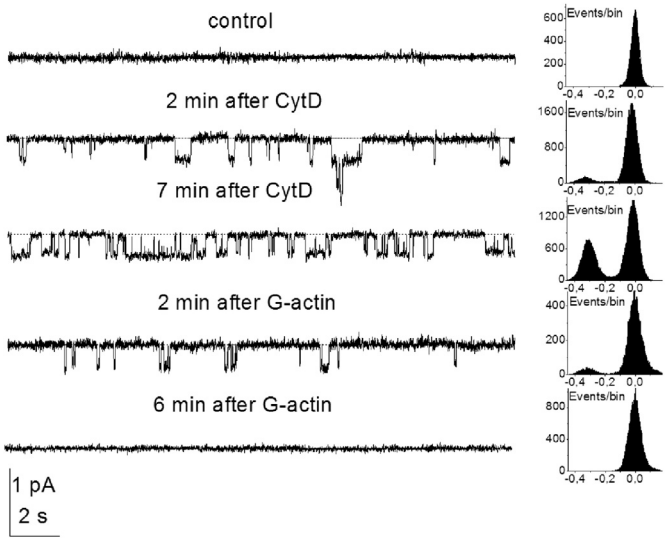

Fig. 3. NVGS channels in membrane fragments are regulated by assembly and disassembly of submembranous actin filaments. Currents recorded from representative inside-out patch at −30 mV in the control and after addition of CytD (10 μg/ml) followed by G-actin application (0.3 mg/ml) to the cytosol-like solution. All-point amplitude histograms indicate that the amplitude of single channel openings remain unchanged; unitary conductance is 10.8 pS.

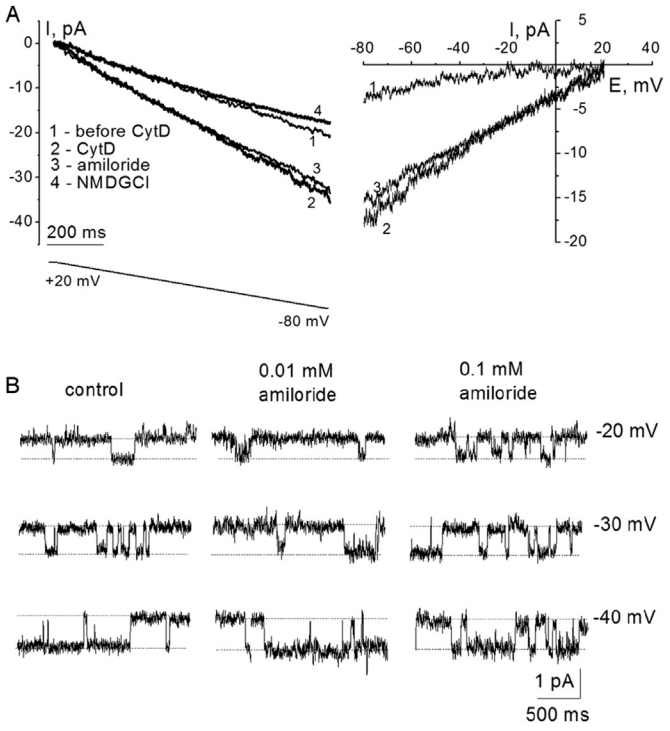

Fig. 4. NVGS channels in U937 cells are not blocked by diuretic amiloride. (A) Whole-cell recordings reveal no inhibition of membrane current by amiloride (up to100 μM). Whole-cell currents evoked with a voltage ramp (1000 ms pulses from +20 to −80 mV) before (on the left) and after (on the right) leakage substraction. (B) Single channel currents induced by CytD in whole-cell experiment before (control) and after addition of amiloride to the external solution.

3.3. Estimation of sensitivity of sodium channels to amiloride

As shown in our experiments, biophysical properties of NVSG channels in monocyte-macrophage cells are close to those of ENaC [7,25]. Reverse transcriptase–polymerase chain reaction (RT-PCR) analysis confirmed the presence of mRNA for alpha-, beta- and gamma-hENaC subunit (α-, β-, and γ-ENaC) in human U937 lymphoma cells; sizes of amplification products corresponded to the calculative ones (Supplementary data). These data together with the previous reports of ENaC expression in leukemia cell lines [10–12] allow us to suppose that sodium currents represent ENaC activity in U937 cells.

In whole-cell experiments, we examined the sensitivity of NVGS channels to diuretic amiloride that is known as typical inhibitor of the renal ENaC channels. Importantly, no inhibition of integral ramp currents was observed after application of amiloride (10 and 100 μM, Fig. 4A). Further, the insensitivity of NVGS channels to amiloride was directly confirmed using single current recordings (Fig. 4B). In some whole-cell experiments, the peculiar measurements of single currents were possible due to relatively small number of functioning channels in cell membrane and formation of extra tight seal contact between the recording pipette and the plasma membrane. Thus, we had a unique opportunity to record single channels in whole-cell membrane before and after application of amiloride to the external side of the membrane. Amiloride at concentrations of 10 and 100 μM had no effect on the amplitude and kinetics of the channel openings (Fig. 4B). Moreover, our experiments revealed no amiloride-sensitive component of current in whole-cell membrane. We can conclude that amiloride-insensitive ENaC-like channels are functionally expressed in U937 cells.

4. Discussion

In the present study, non-voltage-gated Na-selective channels in plasma membrane of cultured human lymphoma U937 cells have been identified and examined using patch clamp technique. Single channel currents were analyzed under quasi-physiological conditions in cell-attached patches, then in excised membrane fragments and in whole-cell membrane. The results obtained in various modes of patch clamp experiments convincingly evidenced unique functional characteristics of amiloride-insensitive NVGS channels in U937 monocyte-like cells. Sodium channels displaying similar conductance and pharmacological properties were characterized earlier in primary macrophages [8] and promyeloid K562 cells [9,10,18]. Collectively, our data reveal functional activity of ENaC-like channels possibly implicated in water-salt regulations and membrane signaling in myeloid blood cells. The results obtained indicate that actin-based regulatory mechanism underlies activation and inactivation of non-voltage-gated channels in plasma membrane of monocytes-macrophage cells.

Our RT-PCR analysis confirmed an expression of alpha-, beta-, gamma-ENaC subunits in U937 cells (Fig. S1). ENaC subunits have been detected on mRNA and protein level in various non-epithelial tissues whereas channel activity in plasma membrane remained much less determined. Particularly, ENaC transcripts have been detected in leukemia and lymphoma cells [6,11,12]. Functional characteristics of NVGS channels in U937 cells are rather close to those of ENaCs with the exception of amiloride sensitivity. Integral and single current recordings clearly indicate no block of the channels by amiloride in lymphoma cells just as it was previously shown for so called “atypical” ENaC in transporting epithelia [26,27]. Whole-cell current measurements also revealed no amiloride-sensitive component of membrane current. According to classical point of view, renal ENaCs are typically inhibited by submicromolar concentrations of diuretic amiloride and their derivatives [3,25]. Therefore, amiloride-blockable currents were considered to represent ENaC activity in electrophysiological assays on various experimental models. Nowadays, this concept that traditionally considers amiloride block as the main criterion of ENaC activity has to be updated [27]. Several studies reported significantly lower sensitivity of ENaC to amiloride in lung epithelia and endothelial cells [5,28–31]. One can assume that amiloride-insensitive ENaCs are functionally expressed in human lymphoma cells.

Our data consistently show that the mechanism controlling channel activity involves actin polymerizartion at the cytoplasmic membrane surface rather than interaction of the channel with preformed filaments; the latter model was proposed for amiloride-sensitive renal ENaC [13,14]. We can conclude that actin-gated ENaC-like channels in leukemia-lymphoma cells are opened in response to microfilament disassembly and closed by actin assembly. It is plausible that similar mechanism mediates cytoskeleton-dependent modulation of ENaCs in multiple transporting epithelia. Numerous studies reported an involvement of actin cytoskeleton in short-term ENaC regulations. An increase of P_0 induced by actin disruption has been repeatedly shown for renal ENaCs in various experimental models including native epithelia and expression systems [14,15]. Several lines of evidence documented an interaction between of ENaCs and F-actin network in polarized reabsorbing epithelia [32–35]. Nevertheless, functional coupling of ENaC activity with submembranous actin dynamics remained an open question. It seems promising that experimental approaches developed in our studies would be applied to uncover molecular mechanisms of actin cytoskeleton-dependent regulation of the channels in renal epithelial cells.

Previously, sodium-specific channels possibly implicated in cell volume regulation in U937 lymphoma cells have been theoretically predicted [2]. Our patch clamp experiments actually demonstrated functional activity of native channels mediating sodium influx in plasma membrane. It could be also suggested that activation of NVGS channels increased passive Na permeability and may cause membrane depolarization in various non-excitable cells. We found that sodium influx through NVGS channels in U937 cells is crucially dependent on submembranous actin cytoskeleton. The data strongly support actin-dependent channel gating shown previously in K562 cells as the only experimental model [18]. It is reasonable to assume that cortical cytoskeleton may be a critical regulator of membrane potential in cells of blood origin similarly to mechanism discussed earlier for epithelial tissues [36].

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.03.167.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.03.167.

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