Polyamines have been shown to participate in the rectification of cloned inwardly rectifying potassium channels, a class of potassium channel proteins that conducts inward current more readily than outward current. Here, basalophil leukemia cells were used to determine the effects of polyamines on a native, inwardly rectifying potassium current. Rat basophil leukemia cells were cultured in the presence of two different polyamine biosynthesis inhibitors, and both the electrophysiological properties and the polyamine levels were monitored. Treatment with α-difluoromethylornithine, a specific ornithine decarboxylase inhibitor, resulted in no significant change of electrophysiological properties. In contrast, treatment with 5′-(1Z)-4-amino-2-butenyl]-methyl-amino]-5′-deoxyadenosine (MDL73811), an inhibitor of S-adenosylmethionine decarboxylase, resulted in increased outward currents through inwardly rectifying potassium channels while intracellular putrescine was markedly increased and spermidine and spermine levels were decreased. Fluctuations of intracellular polyamine concentrations as imposed by MDL73811 were directly translated in an altered cell excitability. Based on these results we conclude that the rectification properties of native inwardly rectifying potassium channels are largely controlled by intracellular spermine.

Rectification of cloned inwardly rectifying potassium channels (IRKs) depends on two processes: (a) a fast voltage-dependent block of the open channel pore by internal Mg2+ ions (1, 2), and (b) a much slower voltage-dependent block of the open channel by cytoplasmic polyamines, in particular spermidine and spermine (3–5). The block by polyamines (PAs) is important, as it controls the shape of the current-voltage relationship in strong IRKs such as IRK1, HIR, or hIRK (6–8), where outward currents reach a maximum with increasing depolarizations and then shut down completely. PA block creates a physiologically important region of negative slope conductance at potentials just above the potassium equilibrium potential, EK, which first limits and then terminates the stabilizing effects of strong IRKs on the membrane potential (9).

Weakly rectifying IRKs, such as ROMK1, are more than 4 orders of magnitude less sensitive to spermidine or spermine, and their mild rectification properties are mainly controlled by Mg2+ ions (10–12).

PA block is not restricted to IRKs. Block at micromolar concentrations has been reported for a subfamily of glutamate receptors where the rectification properties of Ca2+-permeable forms of the α-amino-3-hydroxy-5-methyl-isoxazolepropionate receptor are controlled by intracellular spermine (13–15). In addition, intracellular polyamines were found to bind to and modulate voltage-gated and Ca2+-gated K+ channels (16, 17).

Putrescine, spermidine, and spermine are essential for cell growth and differentiation (18). Membrane proteins that depend on polyamines for proper function are exposed to a wide range of intracellular polyamine concentrations, since biosynthesis is regulated by growth factors, mitogens, and hormones. Polyamine biosynthesis is usually enhanced during cell growth but may also be increased in brain after excessive electrical stimulation of neurons or after epileptic episodes (19, 20). Pharmacological manipulations that inhibit polyamine biosynthesis result in decreased growth rates and/or cell death. The importance of polyamines in malignant cell growth has made their biosynthetic enzymes prime targets for therapeutic interventions leading to the development of potent inhibitors for key enzymes in polyamine metabolism. The most widely studied inhibitors include α-difluoromethylornithine (DFMO) for ornithine decarboxylase, which catalyzes the formation of putrescine from L-ornithine, and 5′-[(1Z)-4-amino-2-butenyl]-methyl-amino]-5′-deoxyadenosine (MDL73811), which inhibits S-adenosylmethionine decarboxylase, the enzyme that provides aminopropyl groups for the synthesis of spermidine and spermine from putrescine (21).

In the present study, DFMO and MDL73811 were used as pharmacological tools to manipulate the internal polyamine content of rat basophil leukemia (RBL-1) cells. RBL-1 cells were selected because their major membrane current is an inwardly rectifying K+ conductance (22). This conductance has been shown recently to originate from a strong inward rectifier, rIRK1, with 94% homology to the cloned mouse IRK1 channel (6, 23). Here, we show for the first time that the rectification properties of native IRK channels are controlled by intracellular spermine and can be changed by pharmacological manipulation of the intracellular spermine level.
Experimental Procedures

Materials—Putrescine, spermidine, spermine, and 1,7-diaminoheptane were from Sigma. RPMI 1640 medium, penicillin-streptomycin, and fetal calf serum were from Life Technologies, Inc. DFMO and MDL73811 were gifts from Marion Merrell Dow, Inc. Putrescine, spermidine, spermine, and 1,7-diaminoheptane were from Sigma. RPMI 1640 medium, penicillin-streptomycin, and fetal calf serum were from Life Technologies, Inc. DFMO and MDL73811 were gifts from Marion Merrell Dow, Inc. Putrescine, spermidine, spermine, and 1,7-diaminoheptane were from Sigma. RPMI 1640 medium, penicillin-streptomycin, and fetal calf serum were from Life Technologies, Inc. DFMO and MDL73811 were gifts from Marion Merrell Dow, Inc.

Cell Culture and Treatments—RBL-1 cells were grown in RPMI 1640 medium supplemented with 10% fetal calf serum, streptomycin (10 μg/ml), and penicillin (10 units/ml) and maintained at 37 °C in 5% CO₂. RBL-1 cells were replated either at low densities (5–8 × 10⁵ cells/ml) or at a 5 times higher density into 6-well culture plates for determination of intracellular polyamines. For treatment with polyamine biosynthesis inhibitors, the culture medium was replaced 24 h after plating by medium supplemented with appropriate inhibitor concentrations. DFMO and MDL73811 were used in aqueous stocks. During treatment the culture medium was replaced daily. Control cell cultures were handled the same way. Prior to electrophysiological recordings or HPLC measurements cells were allowed to recover for at least 8 h after the last medium change.

Determination of Intracellular Polyamine Levels—Cellular polyamine concentrations were determined as described previously (24). In brief, cells were washed twice with ice cold phosphate-buffered saline, scraped from wells, and frozen at −80 °C. Thawed samples were sonicated, and proteins were precipitated with perchloric acid. After the addition of 1,7-diaminoheptane as internal standard, samples were neutralized with K₂CO₃ and polyamines were derivatized with 5-di-methylamino-napthalene-1-sulfonyl chloride.

Derivatized polyamines were partially purified with Sep-Pak C₁₈ cartridges. Samples were further fractionated by HPLC, employing a Partisil-10 ODS column, utilizing one of two elution methods. The first method employed acetonitrile in water as mobile phase. The column was equilibrated with 56% acetonitrile. One minute after sample injection a linear gradient to 78% acetonitrile over 10 min was carried out. The gradient was then increased to 86% acetonitrile over 10 min, followed by 90% acetonitrile for 15 min. The second procedure, which provides enhanced resolution of putrescine (25), utilized as mobile phases 92.5% acetonitrile, 7.5% methanol (Solvent A) and 10 mM monopotassium phosphate (pH 4.4, Solvent B). First, the column was equilibrated with 35% Solvent A and 65% Solvent B. One minute after sample injection a linear gradient to 60% Solvent A was carried out. The gradient was then increased to 90% Solvent A over 5 min and held there for an additional 20 min. Column effluent was monitored with a fluorescence detector using excitation and emission filters of 305–395 and 435–650 nm, respectively.

Authentic putrescine, spermidine, and spermine standards were carried through the entire procedure to establish column retention times and calibration curves for each polyamine. Concentrations were expressed as pmol of polyamine/μg of DNA and given as means ± S.E. DNA concentrations were measured according to the method of Burton (26).

Electrophysiology—Membrane currents were measured in the whole cell version of the patch clamp technique (31) using an Axoclamp 1B amplifier (Axon Instruments, Foster City, CA). Pipettes had resistances of 2–5 MΩ when filled with (in mM): 130 potassium aspartate, 10 NaCl, 4 CaCl₂, 2 MgCl₂, 10 HEPES, and 5 d-glucose (pH 7.4). All recordings were done at room temperature. The seal resistance was usually higher than 10 GΩ. The input resistance of cells included in the analysis was 2–6 GΩ. Capacitive currents were evoked by small voltage clamp pulses of −5 mV from a holding potential of 0 mV and compensated by the analogue circuit of the amplifier. The readout of the compensation circuit was taken as an estimate of the membrane capacitance and used to normalize current amplitudes and calculate current densities. Such capacitance measurements give an estimate of cell size, since the specific membrane capacity is assumed to be rather constant at 1 μF/cm². Current recordings were not corrected for leak. If not otherwise stated, they were filtered at 1 kHz and sampled at 5 kHz for off-line analysis. PCclamp programs were employed for data acquisition and analysis. Data were analyzed after stable whole cell recordings were obtained, generally after about 2 min. Data are given as mean values ± S.E.

Results

Whole cell patch clamp recordings in RBL-1 cells reveal large inwardly rectifying K⁺ currents that are blocked by external Ba²⁺ in the micromolar concentration range (Fig. 1A). With 4.4 mM potassium in the extracellular bath solution, current amplitudes at −140 mV were on average −786.5 ± 61.4 pA (n = 20). Since the IRK current is by far the dominating membrane current expressed in RBL-1 cells the small outward current component flowing through these channels is easily identified. Fig. 1B illustrates a typical steady state I-V relationship measured in RBL-1 cells. Outward currents are seen in potential range slightly more positive than the reversal potential for potassium ions (from −70 to −30 mV; Eᵣ = −87 mV) with a maximum at −55 mV. At more positive potentials the outward...
current becomes smaller, producing a negative slope conductance and a characteristic “hump” in the I-V relationship. This negative slope conductance observed in the I-V relationship is characteristic for outward currents flowing through “strong” inward rectifier channels (Fig. 1B). Similar IRK currents have been reported in RBL cells (22, 23).

Polyamines Regulate Outward Currents through IRK Channels—DFMO and MDL73811 were used to manipulate intracellular polyamine concentrations in RBL-1 cells. Treatment of RBL-1 cells with 500 μM DFMO for 2 days resulted in a decrease of the internal spermine concentration by 85%, from 765 and 252 nM to 121 and 31 nM, respectively (Table II and Fig. 2A). At the same time the internal spermidine concentration increased in cells treated RBL-1 cells (Fig. 2B). Similar IRK currents have been reported in RBL cells (22, 23).

The effects on the rectification properties of IRK currents were analyzed by studying I-V relationships in RBL cells cultured in the presence of DFMO and MDL73811. Treatment of RBL-1 cells with 500 μM DFMO produced no obvious alterations in the I-V relationships even though the internal spermidine concentration had decreased (Fig. 2A). Current amplitudes measured at −55 mV were −0.074 ± 0.073 pA/pF in control (n = 33) and −0.032 ± 0.033 pA/pF in DFMO-treated cells (n = 16). However, when RBL-1 cells were treated with 50 μM MDL73811 to decrease both the internal spermine and spermidine concentrations much larger outward current amplitudes were observed between −70 and −15 mV (Fig. 2A). Current amplitudes at −55 mV were 1.54 ± 0.13 pA/pF (n = 26; Fig. 2B) with slightly smaller inward currents. At resting potentials of −140 mV the current density was −28.52 ± 1.67 pA/pF for cells treated with 50 μM MDL73811 (n = 26). In control cells, −35.35 ± 3.05 pA/pF (n = 35) were measured (Fig. 2A). A similar reduction of inward current amplitudes could be observed for all other groups treated with either DFMO or combinations of DFMO and MDL73811 (Table I) and might reflect a decrease in protein biosynthesis imposed by MDL73811 and DFMO on rapidly growing cells.

Passive electric properties such as input resistance or resting membrane potential were not different between control and MDL73811- or DFMO-treated cells. The resting membrane potential was −66.6 ± 0.62 mV in control cells (n = 33), −69.27 ± 0.33 mV in cells treated with 50 μM MDL73811 (n = 29) and −68.31 ± 0.52 mV in cells treated with 500 μM DFMO (n = 16). One parameter showing a statistically significant deviation, however, was cell capacitance. Treatment with 50 μM MDL73811 increased the cell capacitance from 24.01 ± 1.27 pF (n = 20) to 33.65 ± 2.73 pF (n = 20; Table I). The reported differences in cell size do not invalidate our conclusion that outward currents through IRK channels are increased under MDL73811 treatment, since all electrophysiological data are
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Whole cell current amplitudes and PAS in RBL-1 cells exposed to DFMO and MDL73811

IRK currents were measured in the whole cell version of the patch clamp technique. Peak amplitudes were measured for the potentials indicated in pA/pF. Determinations of intracellular PAS were performed with the HPLC technique and given as pmol/µg of DNA. All data are expressed as means ± S.E. of n determinations.

| Current amplitudes | Polyamines |
|---------------------|------------|
|  -55 mV             |  -140 mV   |
| Control             |            |
| -0.074 ± 0.073      | 5.12 ± 1.82|
| (n = 35)            | (n = 35)   |
| DFMO (500 µM)       | 2.26 ± 2.26|
| -0.032 ± 0.033      | 57.57 ± 6.67b|
| (n = 15)            | (n = 15)   |
| MDL73811 (50 µM)    | 440.14 ± 98.92b|
| 1.54 ± 0.13a        | 108.51 ± 8.62b|
| (n = 26)            | (n = 26)   |
| MDL73811 (500 µM)   | 684.40 ± 67.16b|
| 1.02 ± 0.16a        | 97.94 ± 2.39b|
| (n = 12)            | (n = 12)   |
| MDL73811 (500 µM) + | 57.52 ± 23.45|
| DFMO (500 µM)       | 140.03 ± 8.12a|
| 0.38 ± 0.14a        | 45.51 ± 4.76b|
| (n = 10)            | (n = 10)   |
| MDL73811 (500 µM) + | 31.40 ± 11.85|
| DFMO (500 µM)       | 153.74 ± 5.82b|
| 0.56 ± 0.09a        | 48.82 ± 4.04b|
| (n = 21)            | (n = 21)   |

*Significant differences in current amplitudes from control values calculated with p < 0.05 by single factor analysis of variance followed by a one-tailed Dunnett’s test.

*Significant differences in polyamine contents from control values with p < 0.05 calculated by single factor analysis of variance and a two-tailed Dunnett’s test.

Table I

| RBL-1 cells | Polyamines |
|-------------|------------|
| Cell capacitance | Putrescine | Spermidine | Spermine |
| pF | µM | µM | µM |
| Control | 24.03 ± 1.27 | 11.1 | 18.48 ± 0.91 | 8.52 | 765 | 252 |
| (n = 20) | (n = 4) | (n = 4) | (n = 4) | (n = 4) |
| DFMO (500 µM) | 21.2 ± 1.23 | 9.06 | 18.05 ± 2.94 | 4.59 | 114 | 567 |
| (n = 20) | (n = 4) | (n = 4) | (n = 4) | (n = 4) |
| MDL73811 (50 µM) | 33.65 ± 2.73a | 18.3 | 20.48 ± 2.72 | 492 | 121 | 31.3 |
| (n = 20) | (n = 4) | (n = 4) | (n = 4) | (n = 4) |

*Significant difference in the capacitance of MDL73811 treated cells from control cells calculated with p < 0.05 by single factor analysis of variance and Dunnett’s test. Note that DNA contents were not significantly different among the three groups presented.

normalized with respect to cell capacitance and therefore cell size.

To define the pharmacological conditions that could give us maximal outward currents we also examined cells treated for 48 h with 500 µM MDL73811 and cells treated with a combination of 50 µM MDL73811, 500 µM DFMO or 500 µM MDL73811, 500 µM DFMO. Data analyzed with respect to polyamine content and electrophysiological properties are summarized in Table I. Treatment of RBL-1 cells with 50 or 500 µM MDL73811 proved to be most effective, resulting in a large increase in outward current through inward rectifier channels in response to a pronounced decrease of internal spermine concentrations (Table I).

To estimate the turnover in the intracellular polyamine pool the time course of the developing MDL73811 effect was examined (Fig. 3A). RBL-1 cells were treated for various times with 50 µM MDL73811, and changes in outward currents were monitored at −55 mV. In 50 µM MDL73811 outward currents reached a plateau after about 3 days. These data are contrasted with outward currents in cells cultured in the presence of 50 µM DFMO, where outward currents fluctuate around base line (Fig. 3A). Although these experiments indicate that the maximal outward current was developed after about 3 days, most of the data presented in this paper were acquired from cells exposed for only 2 days for two reasons: (a) short exposure times were used to minimize the cytotoxicity reported for MDL73811, and (b) after 2 days cell densities were most suitable for electrophysiological experiments in this fast growing cell line.

To exclude nonspecific drug effects the dose-response relationship was analyzed by treating RBL-1 cells for 48 h with different concentrations of MDL73811. Outward currents at −55 mV were increased by 50% with 54 nM MDL73811 (Fig. 3B). This is about 10 times lower than the K_i value of about 600 nM found for MDL73811 and rat S-adenosylmethionine decarboxylase in an in vitro assay (27). Similar experiments were done to determine concentration-dependent effects of MDL73811 on intracellular polyamines. After exposing RBL-1 cells for 48 h to different MDL73811 concentrations, cells were harvested, and the polyamine content was analyzed by means of HPLC. Mean values of intracellular polyamine levels were plotted against MDL concentrations and fitted by Hill equations. The estimated IC_50 values were 62.0, 45.1, and 5.9 nM for putrescine, spermidine, and spermine, respectively (Fig. 4).

Intracellular Application of Spermine Decreases Outward Currents through IRK Channels—If the increase in outward currents under MDL73811 treatment is mainly due to a decline in intracellular spermine, then addition of spermine to the cytoplasm of spermine deprived RBL-1 cells should restore the outward current pattern of untreated control cells. Fig. 5A shows steady state I-V relations recorded immediately after establishing the whole cell configuration in RBL-1 cells treated for 2 days with MDL73811 (con MDL) and 37 min after perfusion with a pipette solution containing 100 µM spermine. Dur-
ing the time course of the experiment with spermine added to the cytoplasm via the patch pipette, the outward current “hump” that could be blocked completely by 50 mM Ba$^{2+}$ ($n = 5$; inset to Fig. 5A) decreased gradually with time. Since the diffusion rate of spermine from the pipette reservoir into the cell is limiting, it is assumed that recordings made immediately after breaking into the cell ($t = 0$) are similar to those made with spermine in the pipette solution (as shown in Fig. 3, A and B). The steady increase in intracellular spermine concentrations under such recording conditions is reflected in gradually decreasing outward currents. Outward currents were stable when cells were perfused with standard pipette solution, whereas a time- and concentration-dependent decline in outward currents was observed by addition of spermine to MDL73811-treated cells (Fig. 5B). The observed decrease could be characterized by fitting monoexponential equations. Time constants were 34 min for perfusion of cells with 100 mM exogenous spermine ($n = 3$) and 98 s in experiments done with 1 mM spermine in the recording pipette ($n = 10$; three independent experiments). When inward currents were monitored at $-40$ mV during the time course of such experiments, they proved to be stable as expected for application of a strongly voltage-dependent blocker such as spermine (Fig. 5B, lower panel).

Outward Currents through Inward Rectifier Channels Stabilize Membrane Potentials of RBL-1 Cells—Inward rectifier currents mediate the resting $K^+$ conductance in RBL-1 cells. Increasing amounts of outward current conducted by such channels should have a highly stabilizing effect on the resting membrane potential. This was demonstrated using whole cell recordings done under current clamp conditions immediately after gaining access to RBL-1 cells treated with 50 mM MDL73811. Voltage responses were limited in amplitude to $40$ mV for depolarizing current injections up to $+5$ pA. On average, cells were depolarized by $20.36 \pm 1.28$ mV ($n = 3$) with
DFMO (2 days) and the rather low concentrations used. On the other hand, we suspect that this difference is due to the short exposure time to spermidine stores are no longer replenished (see Ref. 18). We note that spermine content actually increased. Usually, a small reduction in spermidine levels while the internal spermine content is increased, leading to a reduction in spermidine levels. We have previously developed in experiments with heterologous IRK channels in RBL-1 cells. Treatment with DFMO has been shown by it itself has negligible effects on recombinant IRK1 channels (5).

In contrast, MDL73811 led to a decline of both spermidine and spermine to the accumulation of large amounts of putrescine. While the decrease in spermidine levels was of the same magnitude as that observed with DFMO, spermine levels were increased by DFMO but decreased by MDL73811. Since significant increases in outward currents were observed only following MDL73811 treatment, we can conclude that intracellular spermine is the major determinant of outward currents in RBL-1 cells. The proposed higher efficiency of spermine in blocking native IRK channels is further supported by data on recombinant IRK1 channels (5).

The interaction of the various polyamines and Mg²⁺ at their common binding site(s) in the channel pore is not very well defined. This has to be taken into account for all experiments done with MDL73811 in which the internal putrescine concentration is decreased by about 100 times. The voltage-dependent block exerted by putrescine on IRKs, however, is rather shallow (4). A significant interaction of high internal putrescine concentrations with IRKs should be reflected in a reduction of IRK.
inward currents in a voltage range between ~80 and ~100 mV, where the block by spermine and spermidine is weak. Inward currents in MDL73811-treated cells, however, were not different from currents in DFMO-treated cells. For this reason the interaction of putrescine with the polyamine-Mg\(^{2+}\) binding site must be rather weak, as predicted from experiments with cloned IRK channels where the affinity for putrescine was found to be much lower than that for the higher charged polyamines (3, 4).

A significant problem with the use of enzyme inhibitors such as MDL73811 is the possibility that the observed changes in outward currents are due either to cytotoxic side effects (29) or to nonspecific drug interactions. A decreased cell viability should become evident in more depolarized resting membrane potentials of MDL73811-treated cells. There were no signs of cytotoxicity as measured by analysis of resting membrane potentials. In general, MDL73811 is considered a very effective and specific inhibitor of polyamine biosynthesis (21). Three arguments are in favor of a specific interaction of MDL73811 with its enzyme target, S-adenosylmethionine decarboxylase, under our experimental conditions: (a) the MDL73811 effect developed slowly with time as expected for manipulations of metabolic turnover rates; (b) 54 nM MDL73811 were sufficient to increase outward currents by 50% (this sensitivity is even higher than the reported “in vitro” \(K_i\) of MDL73811 for S-adenosylmethionine decarboxylase (600 nM)); and (c) exogenous spermine could be used to replace authentic intracellular polyamines depleted by the pharmacological regimen.

Moreover, the reported data show clearly that pharmacologically induced changes in polyamine metabolism are directly translated into physiological response schemes. In RBL-1 cells, IRKs are mainly used to clamp the membrane potential at negative values to maintain a large driving force for Ca\(^{2+}\) influx, essential for stimulus-secretion coupling in nonexcitable RBL-1 cells (30). Low concentrations of intracellular spermine allow for large outward currents, thereby stabilizing negative membrane potentials. High internal spermine concentrations, in contrast, destabilize RBL-1 cells and lower the threshold for membrane depolarizations. Any spermine concentration change is therefore directly translated into an altered cell excitability.

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Regulation by Spermine of Native Inward Rectifier K Channels in RBL-1 Cells
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