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Tolbutamide-Sensitive Potassium Conductance in the Basolateral Membrane of A6 cells

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Abstract. K^+ channels sensitive to intracellular ATP (K_{ATP} channels) have been described in a number of cell types and are selectively inhibited by sulfonylurea drugs. To look for the presence of this type of K^+ channel in the basolateral membrane of tight epithelia, we have used an amphibian renal cell line, the A6 cells, grown on filters. After the selective permeabilization of the apical membrane with amphotericin B, the basolateral conductance was studied under voltage-clamp conditions. Tolbutamide inhibited 65.8 ± 6.3% of the barium-sensitive current. The tolbutamide-sensitive conductance had an equilibrium potential of −83 ± 1 mV and was inward rectifying in spite of the outwardly directed K^+ gradient. Similar results were obtained with glibenclamide. The half-inhibition constants were 25.7 ± 3.0 μM and 0.114 ± 0.018 μM for tolbutamide and glibenclamide, respectively. To study the relation between cellular ATP and the activity of this conductance, A6 cells were treated with glucose (5 mM) and insulin (250 μU/ml). This maneuver significantly increased the cellular ATP and abolished the tolbutamide-sensitive conductance. A sulfonylurea-sensitive K^+ conductance is present and active in the basolateral membrane of A6 cells. This conductance appears to be modulated by physiological changes of intracellular ATP.

Key words: Potassium channel — Adenosine triphosphate — Sulfonylureas — A6 cells — Basolateral membrane

Introduction

In the basolateral membrane of tight epithelia, both a "resting" and an osmotically induced potassium conductance have been described (Germann, Ernst & Dawson, 1986). These basolateral potassium conductances (G_K) are the recirculating pathway for K^+ accumulated into the cell by the basolateral Na/K ATPase and they are involved in the regulation of cell volume (Dawson, 1987; Eveloff & Warnock, 1987). We have characterized these two types of G_K in the basolateral membrane of A6 cells (Broillet & Horisberger, 1991). The volume-activated G_K is outward rectifying and highly sensitive to barium and quinidine. The "resting" G_K (which can be defined as the conductance present when the osmotically induced K^+ conductance is not activated), however, was found to be barium sensitive and inward rectifying.

Recently, a family of K^+ channels sensitive to the intracellular concentration of ATP, the K_{ATP} channels, have been described in a variety of tissues (*for review*: Nichols & Lederer, 1991). These K_{ATP} channels are inhibited by the binding of ATP at the intracellular side of the membrane. The presence of K_{ATP} channels has been demonstrated in the membrane of cardiac (Noma, 1983), skeletal (Castle & Haylett, 1987) and smooth muscle cells (Standen et al., 1989; Kovacs & Nelson, 1991; Davies, Standen & Stanfield, 1991 (review)), of insulin-secreting cells (Ashcroft, Harrison & Ashcroft, 1984; Cook & Hales, 1984), of central neurons and peripheral nerves (Ashford et al., 1988; Mourre, Widmann & Lazdunski, 1990).

Concerning epithelial cells, K_{ATP} channels have also been described in the apical membrane of several segments of the renal tubule (Wang, Schwab & Giebisch, 1990; Wang et al., 1990; Wang, Sackin & Giebisch, 1992). There is recent evidence for the presence of K_{ATP} channels also in the basolateral membrane of the proximal tubule (Tsuchiya et al., 1992).

The K_{ATP} channels are specifically blocked by sulfonylurea drugs such as tolbutamide or glibenclamide as shown by single channel recordings

(Zünkler et al., 1988; Satoh, Yamada & Taira, 1991). These drugs are extensively used in the treatment of non-insulino-dependent diabetes mellitus because they promote insulin secretion. The sulfonylureas can inhibit the K_{ATP} channels when applied inside or outside the cells; they may act by binding to a specific site on the channel or to a very closely associated protein (Trube, Rorsman & Ohno-Shoshaku, 1986).

To detect the presence of K_{ATP} channels in the basolateral membrane of tight epithelia, we have tested the effects of these specific K_{ATP} channels blockers on the basolateral G_K of renal epithelial cells (A6). We found that a significant part of the basolateral G_K was sensitive to sulfonylureas. To determine if this conductance could be regulated by physiological changes of intracellular ATP, we tried to modulate intracellular ATP using glucose and insulin. Glucose has been shown to be one of the main metabolic substrates used along the distal nephron (Uchida & Endou, 1988), and insulin, to increase glucose metabolism in the epithelial renal cells (Fidelman et al., 1982). Insulin and glucose treatment induced both an increase in intracellular ATP and a decrease of the sulfonylurea sensitive conductance.

Materials and Methods

Cell Culture

The experiments were performed on the clone A6-2F3 obtained by limiting dilution of A6 cells (Verrey et al., 1987). The culture techniques have been described in detail in another paper (Broillet & Horisberger, 1991). Briefly, A6-2F3 cells, at passages 88–98, were grown on collagen-coated Transwell® permeable filters of 4.7 cm^2 (Costar, Cambridge, MA). The cells were used for electrical measurements after 7 to 35 days of culture in an amphibian medium (Handler et al., 1979) supplemented with 5% fetal calf serum (PAA, Linz, Austria), 10^{-7} M dexamethasone (Sigma, St. Louis, MO), 100 U/ml penicillin G, 130 μg/ml streptomycin.

Solutions and Drugs

For the apical membrane permeabilization experiments, the solution (A) used to perfuse the apical side of the epithelium contained (in mM): 92 K-gluconate, 1 Na-gluconate, 1 $MgSO_4$, 10 MOPS. The pH of the [3-N-Morpholino propanesulfonic acid] (MOPS)-buffered apical solution was adjusted to 7.0 with NaOH. In the "cell swelling" experiments, 25 mM Cl^- was added in solution A (gluconate replacement); the cation content was kept constant. The solution (B) used to perfuse the basolateral side of the epithelium contained (in mM): 3 K-gluconate, 19.4 NaCl, 55.6 Na-gluconate, 1 $MgCl_2$, 25 $NaHCO_3$, 0.8 NaH_2PO_4, 1.8 $CaCl_2$. For the experiments performed with intact epithelia, the same amphibian Ringer (C) was used on both sides: 75 NaCl, 3 KCl, 1 $MgCl_2$, 25 $NaHCO_3$, 0.8 NaH_2PO_4, 1.8 $CaCl_2$. The bicarbonate-containing solutions were gassed with 95% O_2 and 2% CO_2 (pH 7.4). From a stock solution of 5 mg/ml, amphotericin B (Fungizone®, Squibb: amphotericin 50 mg/Na-cholate 41.2 mg/$NaHPO_4$ 2.52 mg) was added to the apical solution to a final concentration of 10.8 μM. All solutions containing amphotericin B were protected from light. When used, barium (5 mM) was added as $BaCl_2$ to the basolateral solution while keeping Na^+ and Cl^- concentration constant by adjustment of NaCl and Na-gluconate concentration. Tolbutamide was obtained from Serva (Heidelberg, Germany). Glibenclamide was kindly provided by Seloc AG (Liestal, Switzerland). Tolbutamide and glibenclamide were dissolved in dimethyl sulfoxide (DMSO) to make stock solutions of 200 mM and then diluted to the desired final concentrations before each experiment. When used these two inhibitors were added to the basolateral perfusing solution. The maximal DMSO concentration (1%) had no detectable effects on transepithelial current-voltage (*I-V*) curves. Glucose (5 mM) and 250 μU/ml insulin (Sigma) were also added to the basolateral solution. Amiloride (Sigma) was added to the apical solution (C) at a concentration of 5 μM. All the experiments were performed with solutions at a temperature of 28°C.

Electrical Measurements

The electrical measurements were performed in a modified Ussing chamber which allowed for the continuous perfusion of both the apical and the basolateral sides of the epithelium at a flow rate of 10 ml/min. A current-voltage clamp apparatus (Physiologic Instrument VCC 600, San Diego, CA) was used for the transepithelial electrical measurements. The characteristics of the chamber and the principles of the electrical measurements have already been described in detail in a previous paper (Broillet & Horisberger, 1991). The Transwell® filter was placed in the measurement chamber and solutions A and B were perfused. The transepithelial potential (V_t) was clamped at −60 mV and the short-circuit current was measured every minute by clamping V_t to 0 mV for 3 sec. Then amphotericin B (10.8 μM) was added in the solution A to permeabilize the apical membrane. After stabilization of the transepithelial current, *I-V* curves were obtained by generating square pulse voltage changes and monitoring the corresponding currents. Starting from −60 mV the holding potential was set for 3-sec periods to 0, −20, −40 mV and then to −80, −100 and −120 mV with a return to −60 mV between each step.

In another set of experiments the short-circuit current (I_{sc}) was measured in intact A6 cells with amphibian Ringer (C) on both sides of the epithelium. The I_{sc} was measured under control conditions, after inhibition of Na^+ transport by 5 μM amiloride (apical), or after basolateral exposure to 500 μM tolbutamide or 5 mM barium (*see* Fig. 6).

ATP Measurement

To determine the effects of apical membrane permeabilization and basolateral glucose-insulin treatment, intracellular ATP content was measured at the end of 24 electrophysiological measurements. Cell metabolism was stopped by removing the apical perfusing solution and adding 1 ml ice-cold Tris acetate (0.1 M)–EDTA (2 mM) buffer (4°C, pH 7.75). The cells were scraped from the permeable filter in 2.5 ml of Tris acetate–EDTA buffer (final volume) using a disposable cell scraper (Costar, Cambridge, MA) and then sonicated on ice for 10 sec at 40 W (Branson Sonifier). ATP content was determined by a microchemiluminescence assay using a firefly luciferase assay kit (BioOrbit 1243-

107, MBV, Vevey, Switzerland) according to the manufacturer's specifications (Thore, 1979) with a luminometer (LKB-Wallac 1251, Finland). Light production was linear between 10^{-12} and $5 \cdot 10^{-8}$ M of ATP. ATP content was measured in the diluted sonicate extract from each filter in duplicate and averaged.

The total amount of protein recovered after cell scraping was quantified by a Lowry protein assay in triplicate (Lowry et al., 1951). Bovine serum albumin (Sigma) was used as a standard.

Data Analysis

The half-inhibition constant (K_i) of tolbutamide and glibenclamide was obtained by fitting the concentration-effect relationships of each experiment to a Michaelis-Menten kinetic by a least-square fit method and a simplex algorithm (Nelder & Mead, 1965). The data are presented as mean values ± SEM. Differences between means were analyzed using the Student's t-test for paired experiments unless otherwise specified.

Results

Basolateral Potassium Conductance

After the permeabilization of the apical membrane, the I-V curves, reflecting the basolateral membrane properties, were similar to those obtained under "resting" conditions, showing inward rectification, as described in a previous paper (Broillet & Horisberger, 1991). The conductance sensitive to the basolateral addition of 5 mM barium was considered as the K^+ conductance (5 mM barium inhibited 63.9 ± 2.9% of the total transepithelial conductance (n = 18)). The I-V curve of the barium-sensitive current was inward rectifying with conductances of 0.14 ± 0.02 mS/cm^2 at −10 mV and 0.21 ± 0.03 mS/cm^2 at −110 mV (n = 18, $P < 0.002$) and a reversal potential of −73 ± 2 mV (n = 18).

Effect of K_{ATP} Channel Inhibitors

Tolbutamide

When increasing concentrations of tolbutamide were added to the basolateral solution, a dose-dependent reduction of the transepithelial conductance was observed (Fig. 1). At 0 mV, 2 mM tolbutamide inhibited 65.8 ± 6.3% (n = 7) of the 5 mM barium-sensitive current and the K_i for tolbutamide was 25.7 ± 3.0 μM (n = 6) (Fig. 2). The tolbutamide-sensitive current (I_{tolb}: difference of the transepithelial current (I_t) with or without 2 mM tolbutamide) was 4.3 ± 0.3 μA/cm^2 at 0 mV and of −2.3 ± 0.2 μA/cm^2 at −120 mV, with a mean equilibrium potential of −83 ± 1 mV (n = 12). I_{tolb} was slightly inward rectifying (Fig. 3A) in spite of the outwardly directed K^+ gradient. In contrast to what had been observed with barium (Broillet & Horisberger, 1991), no time-dependent component of the block by tolbutamide (at concentrations ranging from 10 μM to 2 mM) could be detected. The tolbutamide

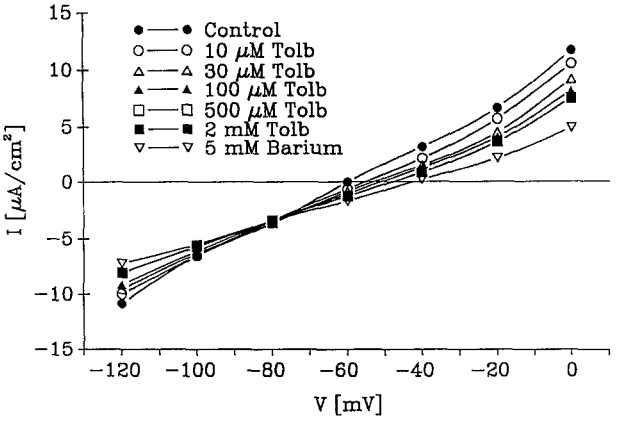

Fig. 1. Effects of tolbutamide on the basolateral conductance (a representative experiment). Transepithelial I-V curves were recorded after apical membrane permeabilization, in the presence of a 92 to 3 mM apical to basolateral K^+ gradient. Increasing tolbutamide concentrations were added to the basolateral solution, and I-V curves were recorded after 5 min equilibration for every tested concentration. To estimate the total basolateral potassium conductance, 5 mM Ba^{2+} was also added in the basolateral solution at the end of the experiment.

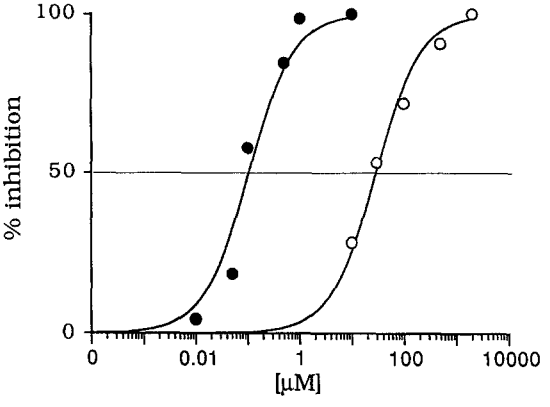

Fig. 2. Dose-dependent inhibition of the basolateral conductance by tolbutamide and glibenclamide. Inhibition is expressed as a percentage of maximal inhibition of the transepithelial current at 0 mV. The curves are the best fit to the following equation:

$$\% \text{ inhibition} = 100 \cdot C/(K_i + C)$$

where C is the inhibitor concentration and K_i is the half-inhibition constant. For these two representative experiments, the best fitting K_i were 29.3 ± 2.8 μM and 0.106 ± 0.021 μM for tolbutamide and glibenclamide, respectively.

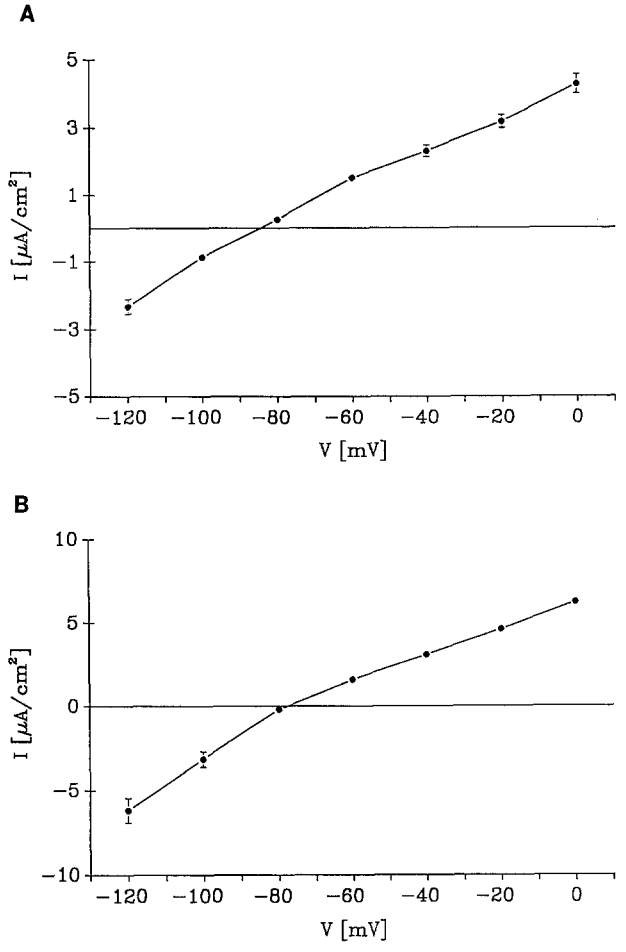

Fig. 3. Current-voltage relations of sulfonylurea-sensitive current. Transepithelial *I-V* curves were recorded after apical membrane permeabilization, in the presence of a 92 to 3 mM apical to basolateral K^+ gradient. (*A*) The tolbutamide-sensitive current (mean values ± SEM of 12 experiments) is the difference between the current measured in the presence or in the absence of 2 mM tolbutamide. (*B*) The glibenclamide-sensitive current (mean values ± SEM of 9 experiments) is the difference between the current measured in the presence or in the absence of 100 μM glibenclamide. Both *I-V* curves were slightly inward-rectifying and had reversal potentials close to the K^+ equilibrium potential.

effect was totally reversible up to a concentration of 500 μM. No significant effect of tolbutamide could be detected in the presence of 5 mM barium (I_{sc} with 5 mM barium 5.9 ± 0.2 μA/cm² *vs.* 6.1 ± 0.6 μA/cm² with 5 mM barium and 500 μM tolbutamide (n = 4, NS)). This indicated that the tolbutamide-sensitive conductance was blocked by 5 mM barium.

Glibenclamide

Very similar effects were obtained with glibenclamide. The K_i was 0.114 ± 0.018 μM at 0 mV (n = 5) (Fig. 2). Glibenclamide (100 μM) inhibited 56.4 ± 2.6% (n = 7) of the Ba^{2+}-sensitive conductance. This inhibition was not significantly different from the one obtained by the addition of 2 mM tolbutamide to the basolateral solution. The glibenclamide-sensitive current (I_{glib}), defined as the difference between I_t with or without 100 μM glibenclamide (Fig. 3*B*), was also inward rectifying with an equilibrium potential of −79 ± 1 mV (n = 9).

Effect of Tolbutamide after Cell Swelling

Under cell swelling conditions, obtained in the presence of 25 mM Cl^- in the apical solution during the permeabilization, a large outward-rectifying transepithelial conductance could be observed. This G_K was barium and quinidine sensitive (the experimental conditions and the intrinsic characteristics of the volume-activated G_K had been described in a previous paper (Broillet & Horisberger, 1991)). Under these conditions 500 μM tolbutamide had no significant effect on the transepithelial current (171.9 ± 25.9 μA *vs.* 169.6 ± 10.9 μA/cm² at 0 mV and −74.1 ± 2.9 μA/cm² *vs.* −74.0 ± 2.9 μA/cm² at −120 mV in the absence or in the presence of tolbutamide, respectively (n = 5, NS). The basolateral addition of 100 μM glibenclamide gave similar results (*data not shown*).

Glucose and Insulin Experiments

A 15 min basolateral treatment with 5 mM glucose and 250 μU/ml insulin induced a decrease of I_t from 15.4 ± 1.7 to 11.4 ± 0.7 μA/cm² (n = 17, $P < 0.002$) at 0 mV and from −17.3 ± 1.2 to −14.0 ± 0.9 μA/cm² at −120 mV (n = 17, $P < 0.0001$). Under these specific conditions, no significant tolbutamide inhibition of I_t could be observed on the transepithelial *I-V* curves (11.7 ± 0.9 *vs.* 11.5 ± 1.0 μA/cm² at 0 mV and −14.3 ± 1.2 *vs.* −13.9 ± 1.4 μA/cm² at −120 mV (n = 13, NS)) (*see* example in Fig. 4). Similar results were obtained with 100 μM glibenclamide (*data not shown*).

ATP Measurement

To confirm the effect of glucose and insulin on the ATP store of the cells, we measured the intracellular ATP concentration before and after treatment with glucose and insulin on permeabilized cells.

ATP content was similar before and after apical membrane permeabilization (Fig. 5). The 15 min basolateral treatment with glucose and insulin significantly increased the ATP content (Fig. 5). Using 10 μm for the height of the cells, (Tousson et al., 1989) we could estimate intracellular ATP concentrations to 0.91 ± 0.08 mM, 0.96 ± 0.06 mM ATP before and

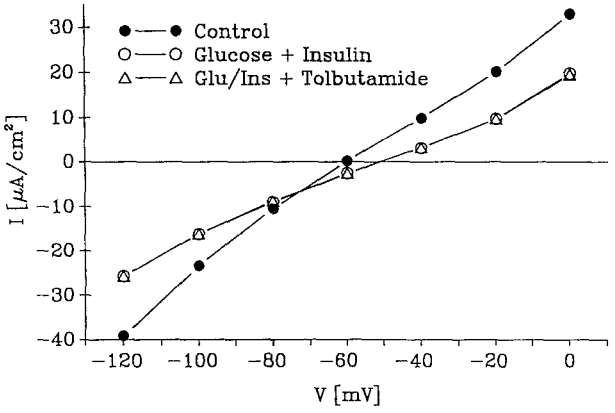

Fig. 4. Effect of glucose and insulin on the basolateral conductance (a representative experiment). The apical membrane was permeabilized in the presence of a 92 to 3 mM apical to basolateral K^+ gradient. The transepithelial current-voltage relations were recorded before (control) and after a 15 min basolateral perfusion of 5 mM glucose and 250 μU/ml insulin, with or without 500 μM tolbutamide in the basolateral solution. Glucose and insulin treatment decreased the basolateral conductance, and tolbutamide had no more effect after this treatment.

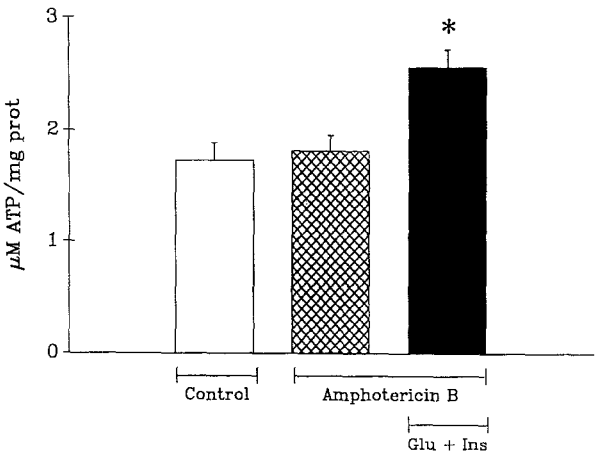

Fig. 5. Effect of glucose and insulin on the intracellular ATP content. ATP content [μM/mg of protein] was measured after the apical membrane permabilization (*Amphotericin B*) with or without treatment with glucose and insulin (*Glu + Ins*). To estimate possible effects of amphotericin B, ATP content was also measured before apical membrane permeabilization (*Control*). Measurements in the three experimental conditions were always performed in parallel (* $P < 0.002$, paired Student's *t*-test, $n = 8$).

after apical membrane permeabilization respectively, and to 1.36 ± 0.08 mM ($n = 8$) after glucose and insulin treatment.

Tolbutamide-Sensitive Conductance in NonPermeabilized Cells

In six experiments performed on intact A6 cells (example in Fig. 6) with symmetrical apical and basolateral amphibian Ringer (C), the control I_{sc} was 8.2 ± 0.2 μA/cm². Amiloride (5 μM, apical) inhibited 5.7 ± 0.3 μA/cm² of the control I_{sc}, a value that represents the transepithelial Na^+ transport. Basolateral addition of tolbutamide (500 μM) and barium (5 mM) inhibited 1.6 ± 0.2 ($P < 0.001$) and 3.9 ± 0.2 ($P < 0.001$) μA/cm², respectively. With the assumption of a 3 Na^+ to 2 K^+ stoichiometry of the Na-K pump, the current across the basolateral membrane is carried for one-third by the electrogenic Na-K pump and for two-thirds by the K^+ ions recirculating across the basolateral membrane. Thus, sudden inhibition of all the basolateral K^+ conductance should result in an immediate two-thirds reduction of I_{sc} (Nielsen, 1979). A 68% inhibition of the amiloride-sensitive I_{sc} was indeed observed with barium. Tolbutamide also induced a significant reduction of I_{sc} amounting to 41% of that observed with barium. As the basolateral membrane potential is not controlled in nonpermeabilized cells, the reduction of I_{sc} due to partial inhibition of the basolateral G_K is expected to be smaller than the fractional reduction of this conductance. The driving force for K^+ ions across the residual K^+ conductance is increased because the basolateral membrane is depolarized by inhibition of the K^+ conductance. Thus, the part of the basolateral G_K due to tolbutamide-sensitive channels is expected to be greater than 40% of the total K^+ conductance; the precise value, however, cannot be determined when the basolateral membrane is not voltage clamped.

Discussion

In the present study we have investigated the effects of sulfonylurea agents on the basolateral potassium conductances of A6 cells. These drugs have been shown to selectively block K_{ATP} channels in several cell types (Belles, Hescheler & Trube, 1987; Sturgess et al., 1985; Beech & Bolton, 1989). When the A6 cells were not swollen, two-thirds of the "resting" G_K were sensitive to tolbutamide and glibenclamide. This is pharmacological evidence that a large part of the "resting" basolateral G_K is constituted of K_{ATP} channels. In contrast, we could not detect any effect of tolbutamide or glibenclamide on swollen cells. Thus, K_{ATP} channels do not participate in the volume-activated G_K. However, considering the very large size of the basolateral outward-rectifying G_K, our results did not exclude the presence of the relatively small sulfonylurea-sensitive G_K under cell swelling conditions.

The half-inhibition constant that we have measured in A6 cells was 25 μM for tolbutamide. This value was slightly larger than the one published for pancreatic β-cells: 7 μM (Trube et al., 1986), but

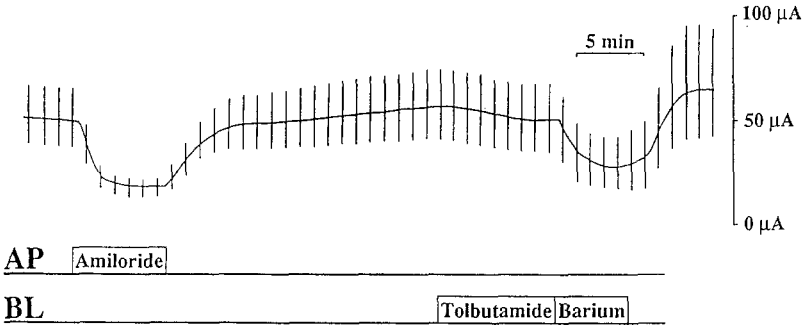

Fig. 6. Original recording of the short-circuit current (I_{sc}) of an intact A6 epithelium (4.71 cm^2). Square pulses of voltage (±20 mV, 3 sec) were generated every minute. The nonpermeabilized cells were first exposed to a symmetrical amphibian Ringer solution and then successively to 5 μM amiloride apical (*AP*), to 500 μM tolbutamide basolateral (*BL*) and finally to 5 mM barium as shown in the figure.

smaller than the one observed in heart cells: 400 μM (Belles et al., 1987). Glibenclamide, the most potent of the sulfonylurea agents has an affinity 100–1,000 times larger than tolbutamide, in heart, smooth muscle and β cells (Zünkler et al., 1988; Standen et al., 1989). Similarly in A6 cells, glibenclamide was 250 times more potent than tolbutamide.

To demonstrate that sulfonylurea-sensitive G_K was indeed sensitive to physiological modification of intracellular ATP concentration, we tested the effects of glucose and insulin addition (in order to stimulate ATP production) on the basolateral G_K. Glucose and insulin treatment induced a significant increase in ATP_i within 15 min. Within the same time we observed the disappearance of sulfonylurea inhibitory effects on the basolateral conductance. The simultaneous occurrence of the changes in ATP_i and in the basolateral G_K is additional evidence for a physiological role of K_{ATP} channels in the basolateral membrane of these kidney cells.

In cardiac and skeletal muscle cells (Noma, 1983; Findlay, 1987; Davies et al., 1991) the K_i for ATP is 20–500 μM. As ATP_i is usually in the millimolar range, as we have found in A6 cells, these K_{ATP} channels should be inactivated under normal conditions. However, ATP is not uniformly distributed in the cell cytoplasm (Pfaller et al., 1984), the precise ATP concentration near the cell membrane is difficult to estimate and it is not clear whether a change in ATP_i concentration is the only controlling factor. Changes in other intracellular constituents, such as intracellular Ca^{2+} or Mg^{2+} concentration (Findlay, 1987), intracellular pH (Misler, Gillis & Tabcharani, 1989) or even the ADP/ATP ratio (Cook & Hales, 1984; Ribalet & Ciani, 1987; Nichols, Ripoll & Lederer, 1991), may be important in explaining K_{ATP} channel regulation.

In single channel studies, the current-voltage relations for K_{ATP} channels were found to be linear over most of the potential range with an inward-rectification appearing only at high positive membrane potentials in cardiac cells (Noma, 1983; Cook & Hales, 1984; Findlay, 1987), in skeletal muscle cells (Woll, Lönnendonker & Neumcke, 1989) and in pancreatic β-cells (Trube et al., 1986). More clearly, inward-rectifying K_{ATP} channels have been described in cardiac cell membrane (Trube & Hescheler, 1984). These patch-clamp studies were done in the presence of high K^+ concentrations on both sides of the cell membrane. In our experiments, done in the presence of a large outwardly directed K^+ gradient, an outward-rectifying G_K was expected. On the contrary, we could observe a slightly inward-rectifying G_K. These results are similar to those of Belles et al. (1987) who obtained linear current-voltage relation with whole-cell recordings on cardiac cells.

The physiological role of this basolateral ATP-sensitive G_K is not yet determined. In the absence of cell swelling, this G_K could be responsible for the maintenance of membrane potential. Its inward-rectifying properties may prevent excessive K^+ loss from shrunken cells. Observation of the tolbutamide effect in (nonpermeabilized) "normal" cells indicates that in Na^+ transporting cells, a significant part of the basolateral K^+ conductance is due to tolbutamide-sensitive channels. From their results on the proximal tubule, Tsuchiya et al. (1992) have proposed that the ATP sensitivity of these channels is responsible for the coupling between Na/K ATPase activity and the basolateral G_K. An increase in Na/K ATPase activity would result in a decrease of intracellular ATP concentration which would activate K_{ATP} channels. A similar mechanism might operate in tight epithelia.

In summary, we have found that a large part of the "resting" inward-rectifying basolateral membrane K^+ conductance resulted from an inward-rectifying sulfonylurea-sensitive G_K. This G_K could be modulated by variations in the intracellular concentration of ATP and was active in Na^+ transporting cells.

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