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COMMENTARY

Intracellular Targets for Antidiabetic Sulfonylureas and Potassium Channel Openers

*Adam Szewczyk**

NENCKI INSTITUTE OF EXPERIMENTAL BIOLOGY, POLISH ACADEMY OF SCIENCES, DEPARTMENT OF MUSCLE BIOCHEMISTRY, 02-093 WARSAW, POLAND

ABSTRACT. Antidiabetic sulfonylureas and potassium channel openers affect the activity of the ATP-regulated potassium channel (K_{ATP} channel) present in the plasma membrane of various cells. This causes a broad spectrum of physiological responses, including the modulation of insulin release from pancreatic B-cells and the relaxation of smooth muscle. Recently, new targets for antidiabetic sulfonylureas and potassium channel openers were found in membranes of organelles, such as mitochondria and zymogen- and insulin-containing granules. By acting on these targets, the drugs modulate, independently of K_{ATP} channel activity, insulin release from pancreatic B-cells, and they regulate K^+ transport in mitochondria and zymogen granules. The interaction of sulfonylureas and potassium channel openers with intracellular targets gives additional basic information about their properties. Additionally, these studies could be important because of the medical applications of sulfonylureas and potassium channel openers. BIOCHEM PHARMACOL 54;9:961–965, 1997. © 1997 Elsevier Science Inc.

KEY WORDS. sulfonylureas; potassium channel openers; ATP; insulin; mitochondria; zymogen granules

Sulfonylureas have been used successfully since the 1950s as oral hypoglycemic agents to treat non-insulin-dependent diabetes mellitus (NIDDM) [1]. The family of antidiabetic sulfonylureas includes such compounds as glibenclamide, glipizide, and tolbutamide. The therapeutic effect of these drugs, e.g. an increase of the insulin level in blood, results primarily from the binding of the sulfonylurea to a high affinity site in the plasma membrane of pancreatic B-cells, known as the SUR† [2]. The molecular mechanism of sulfonylurea action, however, is not fully understood. It is believed that the SUR is a structural component of the B-cell K_{ATP} channel [3]. Binding of sulfonylureas to the SUR causes closure of the K_{ATP} channel, leading to membrane depolarization and a further influx of Ca^{2+} through the voltage-dependent Ca^{2+} channels. This initiates a chain of events leading to the release of insulin from pancreatic B-cells by exocytosis. Recently, a pancreatic SUR has been cloned that should lead to a detailed mechanism of sulfonylurea action on B-cells [3, 4].

Antidiabetic sulfonylureas exhibit a pleiotropic action outside pancreatic B-cells, the so-called extrapancreatic effect (for review, see Refs. 5 and 6). At least part of the observed effects are connected with the sulfonylurea-sensitive K_{ATP} channels present in the plasma membrane of various cells, including smooth, cardiac, and skeletal muscle cells, and in neurons [7].

The activity of the K_{ATP} channels is also affected by substances such as cromakalim, diazoxide, and pinacidil, otherwise known as potassium channel openers [8]. By contrast to the blocking properties of sulfonylureas, potassium channel openers activate the K_{ATP} channels. In other words, these substances lead to physiological responses opposite to that exerted by sulfonylureas; for example, diazoxide inhibits insulin release from pancreatic B-cells [9].

Over the past years, hundreds of observations concerning the effects of sulfonylureas on cellular metabolism have been accumulated. Some of these effects could support the hypoglycemic action of long-term sulfonylurea administration. For instance, glyburide augments the extraction of insulin by the liver, and such an effect may prevent the development of sustained high levels of insulin in blood perfusing the peripheral tissues [10]. Stimulation of glucose transport and glucose metabolism was also observed upon incubation with sulfonylureas [11, 12]. Sulfonylurea drugs stimulate glycolytic and inhibit gluconeogenic pathways in the liver [13]. Glibenclamide *in vivo* augments skeletal growth [14]. Moreover, glipizide affects placental insulin receptors and the phospholipid content of this tissue [15]. Stimulation of glucose uptake and an increased plasma membrane content of glucose transporters in skeletal muscle cells by the sulfonylureas have also been observed [16].

The intracellular interactions of sulfonylureas, not involving closure of the plasma membrane K_{ATP} channels

* Correspondence: Dr. Adam Szewczyk, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Department of Muscle Biochemistry, 3 Pasteur str., 02-093 Warsaw, Poland. Tel. (48-22) 22-28-31; FAX (48-22) 22-53-42.

†*Abbreviations:* K_{ATP} channel, plasma membrane ATP-regulated potassium channel; mitoK_{ATP} channel, mitochondrial ATP-regulated potassium channel; mitoSUR, mitochondrial sulfonylurea receptor; and SUR, sulfonylurea receptor.

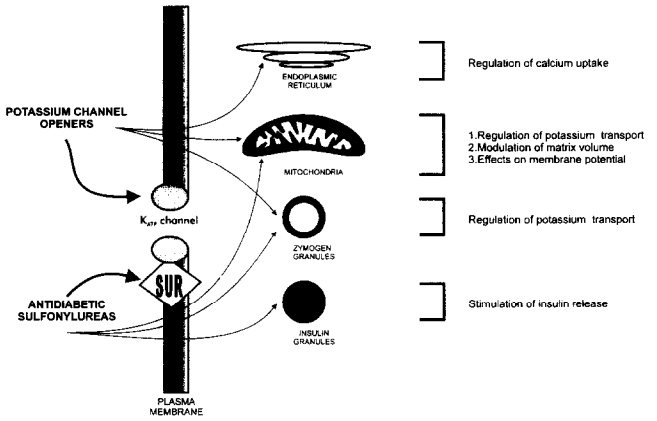

FIG. 1. Interactions of antidiabetic sulfonylureas and potassium channel openers within the cell. SUR = the sulfonylurea receptor.

and affecting insulin release from pancreatic B-cells, will be described in this review (Fig. 1). Additionally, I would like to focus on recently described intracellular targets of sulfonylurea and potassium channel openers due to the discovery of the intracellular K_{ATP} channel. Some of the intracellular effects of antidiabetic sulfonylureas and potassium channel openers are important because of their therapeutic application.

THE INTRACELLULAR SULFONYLUREA RECEPTOR IN INSULIN SECRETING CELLS

A large portion of antidiabetic sulfonylureas, despite their interaction with the plasma membrane of pancreatic B-cells, are internalized and bound to intracellular membranes [17]. Moreover, sulfonylureas can induce insulin release at fixed membrane potentials without Ca^{2+} entry into the cell, and this suggests that these drugs may have intracellular modes of action [18]. Binding studies with [^{3}H]glibenclamide show that in insulinoma cells the majority (> 90%) of glibenclamide binding proteins are localized in intracellular membranes with only minor levels (< 10%) found in plasma membranes [18]. The functional role of these intracellular binding sites is still not elucidated.

It was shown recently that antidiabetic sulfonylureas promote exocytosis of insulin by direct interaction with an intracellular target [19]. Capacitance measurements of exocytosis show that glibenclamide, glipizide, and tolbutamide can potentiate exocytosis of insulin-containing granules not involving closure of the K_{ATP} channel [19]. This is confirmed by the observation that the stimulatory action of the sulfonylureas on exocytosis is not the result of the voltage-gated Ca^{2+} currents being increased. The stimulatory action of tolbutamide is reversibly abolished by the protein kinase C inhibitor bis-indolylmaleimide or when protein kinase C is fully activated by exposure of the B-cells to phorbol 12-myristate-13-acetate. By contrast, activation of protein kinase A is not required for the stimulatory effect of the sulfonylureas. The mechanism by which sulfonylureas stimulate exocytosis, without affecting K_{ATP} channels, remains unclear. The effects of sulfonylureas are observed at concentrations only slightly higher than those required to block the K_{ATP} channel, and these are within the range of therapeutic doses.

The effect of glibenclamide on insulin release in permeabilized B-cells is completely antagonized by the potassium channel opener diazoxide [20]. The above observations can be explained by the direct interaction of sulfonylureas with a protein involved in the exocytotic machinery and affecting insulin release. Finally, the interaction of sulfonylureas and potassium channel openers with ion transport present in the granular membrane cannot be excluded. A similar proposal is drawn from studies on zymogen granules as described below. Interestingly, it is suggested that in depolarized B-cells the effect of sulfonylureas on exocytosis may account for as much as 75% of the total stimulatory action of sulfonylureas upon insulin release [19].

A similar role of the K_{ATP} channels in exocytosis, as in pancreatic B-cells, is proposed for growth hormone release from adenohypophysis [21]. It is a matter of further investigation if there also is an intracellular target for sulfonylureas affecting growth hormone release from adenohypophysis. On the other hand, the presence of sulfonylurea binding protein in intracellular granule membrane does not appear to be a universal property of secretory tissue. For example, specific glibenclamide binding sites in adrenal gland chromaffin granules are not detected (Szewczyk A and Lobanov NA, unpublished observations).

POTASSIUM CHANNEL OPENERS AND ZYMOGEN GRANULES

The properties of transporters (or channels) of monovalent cations in the membrane of isolated pancreatic zymogen granules have been characterized [22]. This was performed with an assay measuring bulk cation influx driven by a proton diffusion potential [22]. Monovalent cation conductances have the sequence $Rb^+ > K^+ > Na^+ > Cs^+ > Li^+$. The conductance is inhibited by Ca^{2+}, Mg^{2+}, Ba^{2+}, quinine, and quinidine. Sensitivity to glibenclamide and tolbutamide is also observed. Over 50% of the K^+ conductance is inhibited by millimolar concentrations of ATP or MgATP. The inhibition by MgATP, but not by ATP itself, is reversed by the K^+ channel opener diazoxide. The inhibitory effect of nucleotides is probably due to noncovalent interactions, as these can be mimicked by nonhydrolyzable analogs of ATP and by ADP. The reversal of MgATP inhibition by diazoxide may be mediated by phosphorylation, as it is not affected by dilution and is blocked by the protein kinase inhibitor H7. To summarize, the properties of the K^+ conductance of pancreatic zymogen granule membranes are similar to those found for the K_{ATP} channels of the plasma membrane.

The transport of K^+ by granules is also measured indirectly by ionophore-induced lysis of the isolated secretory granules when suspended in a solution containing KCl [23].

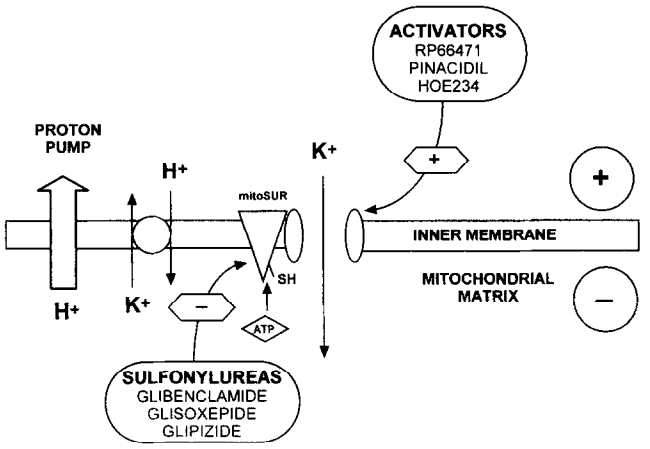

FIG. 2. Sulfonylurea sensitive K^+ fluxes in energized mitochondria. This scheme illustrates a putative role of the mitoK_{ATP} channel, sensitive to sulfonylureas and potassium channel openers, in compensating the $\Delta\Psi$ and enabling additional protons to be pumped out to form a substantial ΔpH. The electroneutral K^+/H^+ antiporter prevents accumulation of K^+ in the mitochondrial matrix, thus maintaining a proper osmolarity of the inner compartment. mitoSUR = the mitochondrial sulfonylurea receptor.

The K^+ transport is shown to be inhibited by physiological levels of ATP in a dose-dependent manner and is not reversed by ADP. The sulfonylurea tolbutamide (0.5 mM) also reduces ionophore-dependent lysis by 46%. The ATP sensitivity of K^+ transport is influenced by pH (increased ATP sensitivity with decreasing pH) and KCl concentration (increased ATP sensitivity with increasing concentration of KCl). Additionally, preincubation with phospholipase A_2 or lysophospholipids produces a significant decrease, through an unknown mechanism, in the granule K^+ transport. However, it is not likely that this inhibition is due to a change in membrane fluidity, as arachidonic acid and octanol do not have comparable effects.

These results confirm the presence in pancreatic acinar cells of a granule-associated K^+ transport that is ATP and sulfonylurea sensitive. The probable role of this K^+ transport could be a contribution to granule swelling as a step in exocytotic membrane fusion [23].

MITOCHONDRIAL ATP-REGULATED POTASSIUM CHANNEL

A K^+ selective and ATP-sensitive ionic channel was found in rat liver mitochondria using the patch clamp technique (Fig. 2) [24]. Later, the channel was partly purified and reconstituted into proteoliposomes (this can be done also from heart mitochondria) [25]. Independent studies using yeast mitochondria show similar glibenclamide-sensitive potassium transport [26].

The properties of the mitoK_{ATP} channel have been summarized elsewhere (for review, see Refs. 27 and 28). Briefly, the mitoK_{ATP} channel is reversibly inactivated by ATP and is also blocked by the antidiabetic sulfonylurea derivative glibenclamide. A rundown of the mitoK_{ATP} channel is observed to be similar to that of the plasma membrane K_{ATP} channel. GTP and GDP reverse the inhibition of the mitoK_{ATP} channel by ATP.

It is reported for intact mitochondria that the potassium electrogenic transport (K^+ uniport) induced by magnesium depletion is also blocked by glibenclamide in a concentration-dependent manner [29]. Other antidiabetic sulfonylureas also were able to block K^+ uniport induced in this way [30].

Equilibrium binding studies were performed using ^{3}H-labeled glibenclamide to characterize the interactions of glibenclamide with the inner mitochondrial membrane [29]. Garlid and co-workers [25] describe the inhibition of the mitoK_{ATP} channel by glibenclamide in a reconstituted system with an IC_{50} of 62 nM. This suggests the presence of high-affinity binding sites in the inner mitochondrial membrane. By contrast, only a single class of low-affinity binding sites for glibenclamide in intact mitochondria has been observed (mitoSUR), with a K_D of 4 μM [29]. The use of [^{125}I]glibenclamide led to the identification of the mitoSUR as a 28-kDa polypeptide (Szewczyk A and Wójcik G, unpublished observation). Moreover, in intact beef heart mitochondria the K_D for glibenclamide binding (300 nM) is one order of magnitude lower than that for rat liver mitochondria [29].

The mitoSUR, coupled to K^+ transport, is not the only mitochondrial protein interacting with sulfonylureas. Glibenclamide and tolbutamide are found to be inhibitors of rat liver, heart, and skeletal muscle carnitine palmitoyl transferase [31]. The concentration of glibenclamide that produces 50% inhibition of the enzyme is 40 μM [31].

The mitoK_{ATP} channels are also blocked by some non-sulfonylurea inhibitors of plasma membrane K_{ATP} channels. It has been shown that a guanidine derivative, U-37883A, acts as a K_{ATP} channel antagonist [32], and this compound is also shown to inhibit the K^+ uniport activity in rat liver mitochondria [33], thus suggesting that it is active against the mitoK_{ATP} channel as well. On the other hand, the K_{ATP} channel of insulinoma cells is blocked by the calcium antagonist TMB-8 [34], but this drug is not active on the mitoK_{ATP} channel [30].

The potassium channel opener RP66471 induces a decrease of the mitochondrial membrane potential [35]. Neither the inhibition of mitochondrial respiration nor the uncoupling of mitochondria is observed concomitantly. Hence, a specific effect on the membrane potential caused by the increase of permeability of the inner mitochondrial membrane to potassium ions is postulated. Interestingly, the effect of RP66471 is found to be specific. Other potassium channel openers applied, such as Ro 31-6930, KRN 2391, aprykalim, and nicorandil, are unable to collapse the membrane potential of energized mitochondria. A comparison of RP66471-induced depolarization in the presence of various monovalent cations (Li^+, Na^+, K^+, and Rb^+) shows that the amplitude of depolarization in the presence of K^+ is significantly larger than that in the presence of Li^+ and Na^+. Recently, some other potassium

channel openers also were shown to activate, within a nanomolar concentration range, the K^+ transport in mitochondria [30, 36, 37].

The physiological function of the mitoK_{ATP} channels is not clear because of confusing regulation of this channel. The physiological concentration of matrix ATP should block the mitoK_{ATP} channel constantly. One may speculate that only a dramatic decrease of the matrix ATP level would activate the channel, but this would only lead to permanent inhibition of mitochondrial metabolic activity due to membrane depolarization. Therefore, ATP probably plays the role of an endogenous inhibitor of the mitoK_{ATP} channel, but "ATP depletion" is not the physiological process leading to channel activation. More likely, other effectors, such as GTP or GDP, are involved in the fine activation of mitoK_{ATP} channel activity [27].

On the basis of accumulated data, the mitoK_{ATP} may have a dual physiological function. First, a concerted action of the K^+ uniport and the electroneutral K^+/H^+ exchanger could be the main factor responsible for maintaining potassium homeostasis within the mitochondrion and thus to controlling intramitochondrial osmotic pressure and mitochondrial volume. Mitochondrial volume changes are regarded as one of the important regulatory mechanisms of metabolic control at the mitochondrial level (for review, see Refs. 38 and 39). It is of particular importance to establish whether mitochondrial K_{ATP} channel activity could be, at least partly, responsible for the regulation of mitochondrial metabolism. Observations that glibenclamide and ATP inhibit mitochondrial swelling whereas K_{ATP} openers potentiate the swelling make it likely that this channel, perhaps with other potassium pathways, is involved in mitochondrial regulatory volume changes.

Second, energization of mitochondria is accompanied by a net uptake of K^+, partly inhibited by glibenclamide, and activated by potassium channel openers such as pinacidil and P1060 [40]. This is compatible with the hypothesis that potassium uptake upon energization may compensate, in part, for the electric charge transfer produced by the proton pump and thus enable the formation of ΔpH along with $\Delta\Psi$. In fact, it was found that the rate of ΔpH formation increases with increasing K^+ concentration in the external medium and thus with an increasing rate of K^+ influx [41]. The final steady-state value of ΔpH also increases, whereas that of $\Delta\Psi$ decreases at increasing K^+ concentration so that the resultant protonmotive force remains practically unchanged. The assumption that K^+ transport accounts for the formation of ΔpH is also supported by the observation that both the rate of ΔpH formation and its steady-state level in energized mitochondria are increased by the potassium channel opener RP66471 [41]. As shown previously [35], this compound decreases $\Delta\Psi$ of energized liver mitochondria by increasing the permeability of the inner mitochondrial membrane to K^+.

To summarize, these results suggest a possible involvement of the mitoK_{ATP} channel in the regulation of processes driven by the transmembrane potential and ΔpH, for example adenine nucleotide transport or phosphate transport in mitochondria.

TARGET IN THE SARCOPLASMIC RETICULUM?

The potassium channel opener BRL38227 and glibenclamide directly act on intracellular calcium stores in airway smooth muscle [42]. The effects of BRL38227 and glibenclamide were investigated in permeabilized cells using $^{45}Ca^{2+}$ effluxes. BRL38227 reduces the loading of the inositol ($InsP_3$)-sensitive intracellular store by 26.5%; this effect is antagonized by glibenclamide. BRL38227 itself does not release calcium and has no effect on GTP-induced calcium release. Glibenclamide also reduces calcium loading of the intracellular store and enhances calcium release. These results suggest that BRL38227 has a direct effect on intracellular calcium handling.

CONCLUSIONS

Both sulfonylureas and potassium channel openers have important applications in the treatment of diabetes mellitus and hypertension. The search for efficacious drugs considered only the plasma membrane K_{ATP} channels and/or SUR as the main targets for physiological response. Recent observations of the effects of sulfonylureas and potassium channel openers on cellular organelles suggest that one also has to take into account the intracellular targets for these drugs. The potential benefits of such interactions involve, for example, a better understanding of the exocytosis processes in pancreatic B-cells. However, additional targets for these drugs such as mitochondria may lead to adverse changes in cellular bioenergetics leading, in turn, to cell death. Hence, a rational drug design must consider the new intracellular targets identified for antidiabetic sulfonylurea and potassium channel openers.

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