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Introduction

A new class of K^+ channels that link membrane potential to the bioenergetic situation of the cell has been recently discovered (Noma 1983). These K^+ channels (K_{ATP}) are normally closed at physiological intracellular ATP concentrations and open upon a diminution of $[ATP]_{in}$. These channels have been shown to be present in pancreatic ß-cells (Ashcroft et al. 1984; Cook and Hales 1984; Rorsman and Trube 1985a; Rorsman and Trube 1985b), cardiac ventricular cells (Noma 1983; Trube and Hescheler 1984) and skeletal muscle (Spruce et al. 1985; Spruce et al. 1986; Spruce et al. 1987). They might also be present in the central nervous system (Ashford et al. 1988; Bernardi et al. 1988) and in smooth muscle (Quast 1988; Quast and Cook 1988).

The ATP-sensitive K+ channel is the receptor for sulfonylureas

Sulfonylureas are hypoglycemic agents that are widely used in the treatment of diabetes mellitus (Loubatières 1977). It has been shown that sulfonylureas act principally by decreasing K^+ permeability in the ß-cell membrane (Ferrer et al. 1984; Gylfe et al. 1984; Henquin, 1977; Henquin 1980; Matthews and Shotton 1982; Meissner et al. 1979; Rorsman and Trube 1985a), thus leading to ß-cell membrane depolarization, increased Ca^{2+} influx and insulin secretion (Gylfe et al. 1984; Henquin and Meissner, 1984; Lambert et al. 1986; Boyd, 1988). Both $^{86}Rb^+$ flux techniques and electrophysiological methods have recently demonstrated that sulfonylureas block K_{ATP} channels in pancreas and cardiac ventricular cells with high specificity (Belles et al. 1987; Dunne et al. 1987; Fosset et al. 1988a; Schmid-Antomarchi et al. 1987a; Schmid-Antomarchi et al. 1987b; Sturgess et al. 1985; Trube et al. 1986) (Fig. 1A and B). However, all sulfonylureas currently used in the treatment of type 2 diabetes are not equally active. Concentrations for half-maximum inhibition of $^{86}Rb^+$ efflux from b-cells are found over 6 orders of magnitude depending on the structure of the sulfonylurea used ($K_{0.5}$ = 0.06 nM for glibenclamide and 40 mM for carbutamide) (Schmid-Antomarchi et al. 1987a). The rank order of potency to block the K_{ATP} channel from ATP-depleted insulinoma cells, determined for a series of sulfonylureas, is glibenclamide > glipizide > gliquidone > glisoxepide > glibornuride > gliclazide > chlorpropamide and tolbutamide > carbutamide (Schmid-Antomarchi et al. 1987a) (Fig. 1C). Glibenclamide, because it is a very

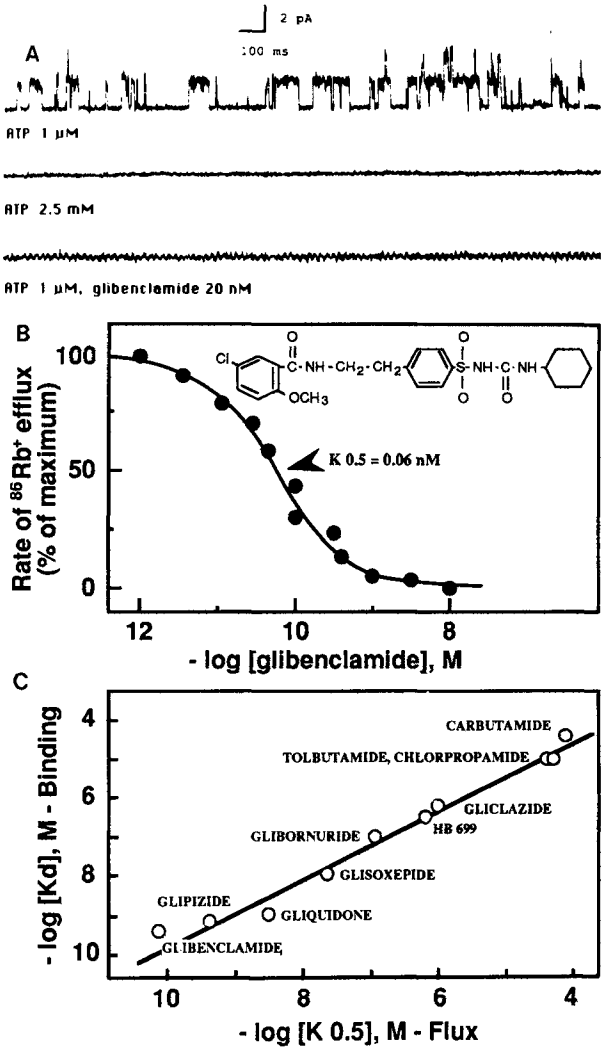


Fig. 1. Insulinoma RINm5F cells. A Single channel currents recorded from inside-out patches. An upward deflection in the traces corresponds to an inward current. The membrane potential was -60 mV. ATP-regulated K^+ channels are opened at low concentrations of ATP and could be blocked at high concentration (2.5 mM) of $[ATP]_{in}$ or by glibenclamide. B Inhibition by glibenclamide of ATP-sensitive $^{86}Rb^+$ efflux from RIN cells. Time of ATP depletion was 20 min ($[ATP]_{in}$ = 0.4 mM). Time of $^{86}Rb^+$ efflux was 1 min. C Correlation between inhibition by various hypoglycemic drugs of $[^3H]$glibenclamide binding and $^{86}Rb^+$ efflux in RINm5F insulinoma cells. K_d (half-inhibition of $[^3H]$glibenclamide binding by hypoglycemic drugs is plotted *versus* $K_{0.5}$ (half-inhibition of ATP-sensitive rate of $^{86}Rb^+$ efflux) (Schmid-Antomarchi et al. 1987a).

potent blocker of K_{ATP} channels (Schmid-Antomarchi et al. 1987a, b), more potent than tetrodotoxin or saxitoxin for the voltage-sensitive Na^+ channel, has been used successfully to identify biochemically the sulfonylurea receptor. Affinities (K_d) for the different sulfonylureas measured with the [^{3}H]glibenclamide binding assay were found to be nearly perfectly correlated to efficacy ($K_{0.5}$) for K_{ATP} channel blockade (Schmid-Antomarchi et al. 1987a) (Fig. 1). Sulfonylurea receptors with very similar properties have also been identified in chicken and guinea-pig cardiac ventricular microsomes (Fosset et al. 1988a). These results suggest that the sulfonylurea receptor is closely linked, if not identical, to the K_{ATP} channel. The notion that the K_{ATP} channel is the receptor for sulfonylureas is consistent with findings showing that the K_{ATP} channel in excised membrane patches is readily blocked by the very potent sulfonylurea glibenclamide or by the less potent tolbutamide, i.e. without the need of soluble second messengers (Dunne et al. 1987; Fosset et al. 1988a; Schmid-Antomarchi et al. 1987a; Schmid-Antomarchi et al. 1987b; Sturgess et al. 1985; Trube et al. 1986).

Activation of the K_{ATP} channel by uncoupling of oxydative phosphorylation or by directly lowering $[ATP]_{in}$ reduces the duration of the action potential and is believed to induce arythmia in the heart (Trube and Hescheler 1984; Fosset et al. 1988a). These deleterious effects are reversed by treatment with sulfonylureas (Fosset et al. 1988a). Under physiological conditions however, sulfonylurea treatment does not appear to have any effect on the cardiac action potential, indicating that the channel is then permanently closed by the high intracellular ATP concentration and casting doubt on a role of the K_{ATP} channel in this tissue as a sensor of intracellular ATP variations as in pancreatic ß-cells.

Sulfonylurea receptors are also present in brain cells. Rat and pig microsomes specifically bind sulfonylureas with half-maximum values that correlate closely with the values found for ß-cell microsomes (Bernardi et al. 1988; Geisen et al. 1985; Lupo and Bataille 1987; Mourre et al. 1989) (Fig. 2A), suggesting the presence of K_{ATP} channels in the central nervous system. The five main structures containing the highest concentrations of receptors were the substantia nigra, the globus and central pallidus, the motor neocortex and the molecular layer of the cerebellar cortex. In the hippocampus, the highest level of binding sites was found in stratum lucidum of CA_3 where the mossy fibers make synaptic contacts with the proximal part of the apical dendrite of CA_3 neurons. There were high densities of receptors in CA_3 and intermediate densities in CA_1 and CA_2 (Fig. 2B). The high affinity of glibenclamide for its receptor in pig brain (0.8 nM) has been used to both affinity label and purify

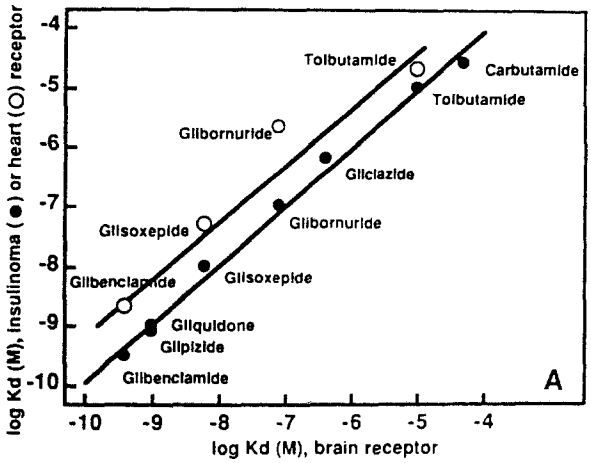
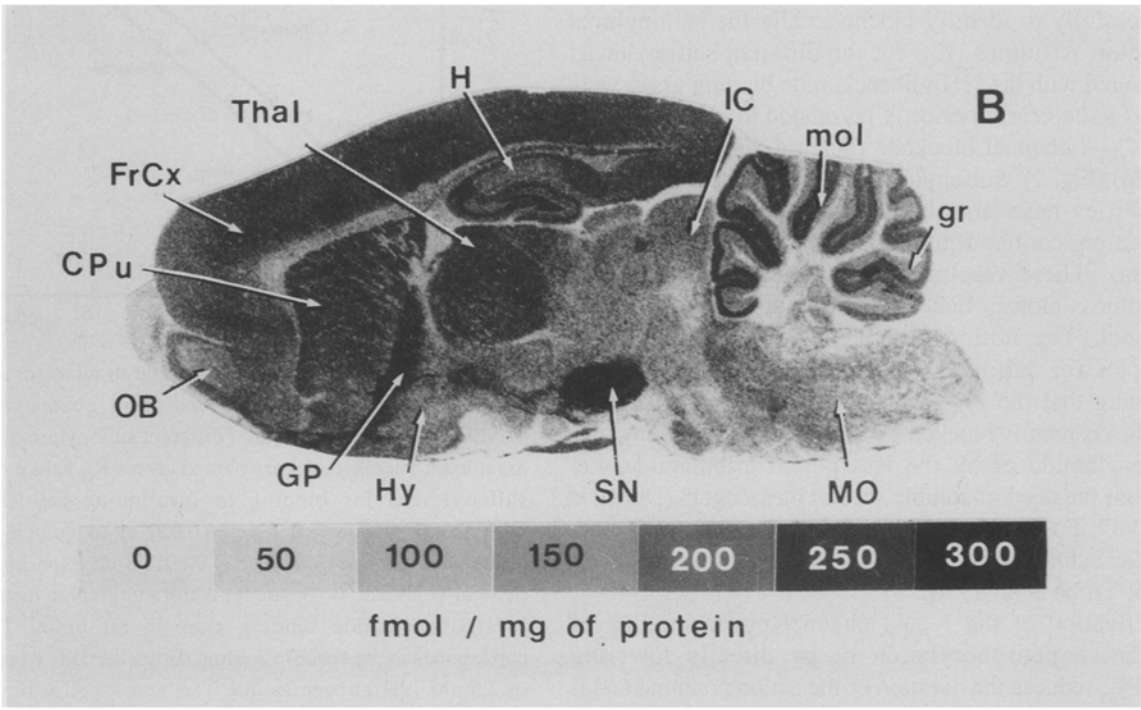


Fig. 2. A Binding of [^{3}H]glibenclamide to microsomes from rat brain, from insulinoma cells and from guinea-pig hearts. Correlation curve. K_d values of different sulfonylureas for binding to rat brain microsomes were plotted *versus* K_d values of different sulfonylureas for binding to insulinoma cell (RINm5F) microsomes (slope = 0.98; r = 0.99) or to guinea-pig heart microsomes (slope = 0.98; r = 0.99). Both experiments were done in duplicate. B (opposite) Autoradiographic distribution of [^{3}H]glibenclamide binding sites in rat brain. The scale corresponds to the specific binding. Brain sections were incubated in 2.5 nM [^{3}H]glibenclamide. The non-specific binding was identical to the background of the tritium-sensitive film (not shown). CPu, caudate putamen; FrCx, frontal cortex; GP, globus pallidus; Gr, granular layer of the cerebellar cortex; H, hippocampus; Hy, hypothalamus; IC, inferior colliculus; Mo, medulla oblongata; mol, molecular layer of the cerebellar cortex; OB, olfactory bulb; SN, substantia nigra; Thal, thalamus.

the sulfonylurea receptor. Both affinity labelling and purification indicate that the putative sulfonylurea-sensitive K_{ATP} channel is a protein of 150 kDa (Bernardi et al. 1988) (Fig. 3). The latter value corresponds well to the molecular mass of the sulfonylurea receptor in insulinoma cells of 125 and 140 kDa, estimated by affinity labelling (Kramer et al. 1988 and Fig. 3). Reconstitution of the receptor in artificial membranes should definitely clarify whether the receptor has K^+ conducting properties.

Fig. 3. (opposite) Sodium dodecylsulfate/polyacrylamide gel electrophoresis of the purified [^{3}H]glibenclamide receptor in pig brain (A) and autoradiographic pattern of photoaffinity labelling carried out with active [^{3}H]glibenclamide (3 nM) purified binding fractions from pig brain in the presence (lane B) and in the absence (lane C) of 300 nM glibenclamide and from insulinoma RINm5F microsomes in the presence (lane D) or in the absence (lane E) of 300 nM glibenclamide. For lanes A to E, same patterns were obtained when running gels without or with the presence of the reducing agent 2-mercaptoethanol.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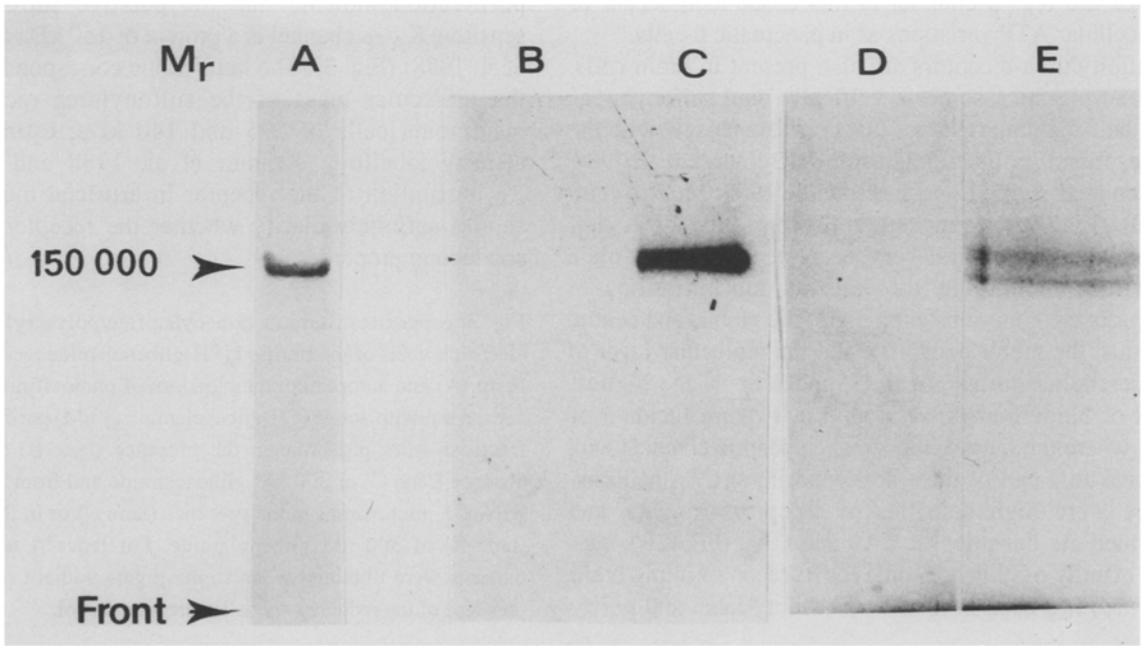
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Phosphorylation of the ATP-sensitive K^+ channel by kinase C

Stimulation of insulin secretion by carbohydrates such as glucose and glyceraldehyde is accompanied by depolarization of the ß-cell membrane and by an increase of diacylglycerol synthesis (Wollheim et al. 1988). Exogenous kinase C stimulators such a 4-ß-12-phorbol-myristate-13-acetate (PMA) and 1,2-didecanoyglycerol (DC_{10}) also depolarize ß-cells, raise free cytosolic Ca^{2+} and stimulate insulin secretion. The membrane depolarization induced by PMA and DC_{10} is transient and lasts 2 to 3 minutes. In cell-attached membranes patches, it was shown that membrane depolarization was paralleled by a transient reduction of the probability of K_{ATP} channel opening. As during a period a 5 min after kinase C activation by PMA or DC_{10}, intracellular ATP levels did not diminish significantly, it was concluded that membrane depolarization is not the result of K_{ATP} channel block by raised intracellular ATP, but is mediated by a kinase C catalyzed phosphorylation leading to K_{ATP} channel blockade. These observations obviously raise questions about the regulatory role of intracellular ATP in the control of ß-cell membrane potential and insulin secretion (Wollheim et al. 1988).

When the ß-cell is treated with PMA for a period longer than 5 min, the initial channel inhibition is followed by a marked increase of K_{ATP} channel activity in cell-attached patches (Ribalet et al. 1988; de Weille et al. 1989). Also in insulinoma cells that were intracellularly perfused with a solution containing 2 mM ATP, it was shown that both PMA and 1-oleyl-2-acetylglycerol (OAG), induce membrane hyperpolarization (Fig. 4B) and reduce membrane resistance. These effects are due to K_{ATP} channel activation and are antagonized by subsequent treatment with glibenclamide (de Weille et al. 1989). Interestingly, K_{ATP} channel activity induced by "long-term" treatment with PMA or OAG (>5 min, in our experiments) is observed even in the presence of an otherwise blocking concentration of 2 mM ATP. Once activated by kinase C, the channel looses the property of being regulated by $[ATP]_{in}$. At first sight, K_{ATP} channel activation as a result of long-term kinase C stimulation seems difficult to reconcile with a regulatory role of glycolysis. However, it is shown that cytosolic-free Ca^{2+} may activate phospholipase C resulting in diacylglycerol synthesis and kinase C activation (Eberhard and Holz 1988). If it is assumed than an increase of diacylglycerol synthesis following glucose stimulation in ß-cells is the

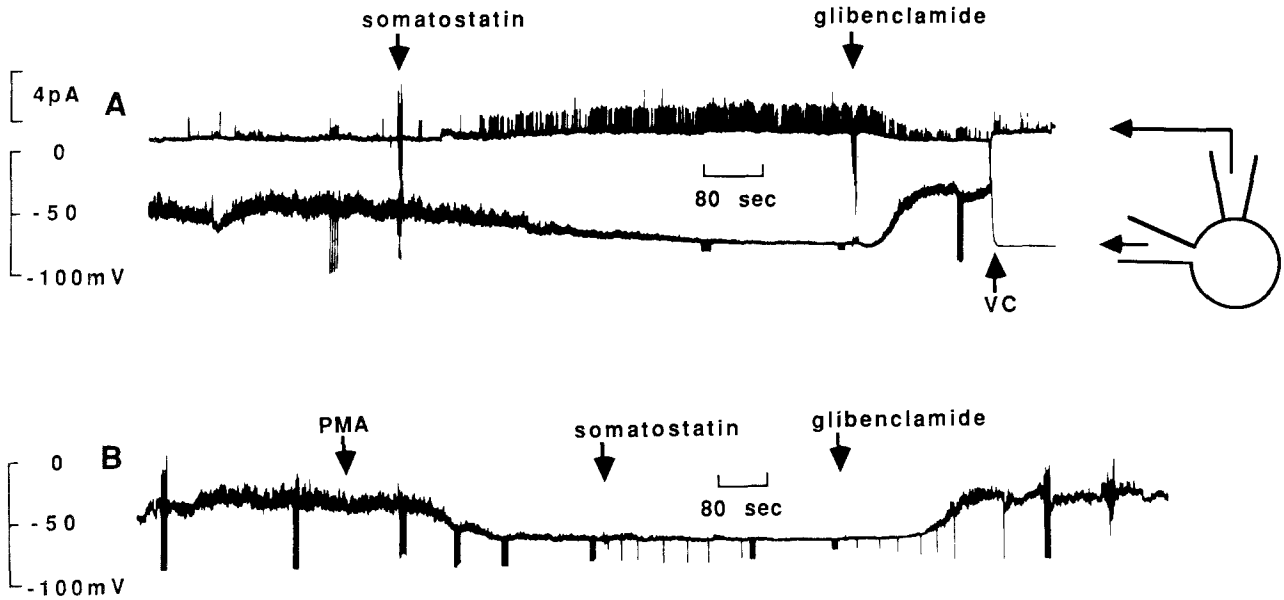

Fig. 4. Somatostatin hyperpolarizes RINm5F cells by activating K_{ATP} channels. Membrane potentials of RINm5F were recorded using the whole-cell tight-seal technique. The recording pipette contained 150 mM KCl, 2 mM ATP, 2 mM EGTA, 0.5 mM $MgCl_2$ and 100 mM GTP. Membrane resistance was estimated by a series of 5 small hyperpolarizing current pulses. **A** Single channel currents were recorded by a second pipette in the cell-attached configuration clamped at 0 mV (see inset). The somatostatin-evoked hyperpolarization was seen to be paralleled by the activation of K^+ channels that could be blocked by 100 nM of glibenclamide. After cell membrane depolarization induced by glibenclamide, the dialyzing pipette was voltage-clamped to -70 mV (vc) showing that channel block by glibenclamide was not voltage-dependent.**B** Protein phosphorylation. Stimulation of kinase C activity by 1 mM PMA hyperpolarizes the ß-cell membrane. Additional application of 100 nM somatostatin does not further reduce membrane resistance. 2 mM intracellular ATP.

result rather than the cause of K_{ATP} channel closure, then phosphorylation-induced K_{ATP} channel reopening may be thought to limit glucose-induced Ca^{2+} influx. According to this view, intracellular ATP and free Ca^{2+} have opposite effects on K_{ATP} channel activation and insulin secretion. Alternatively, the phosphorylation pathway may form part of a regulatory system that is controlled by extracellular factors that have not yet been identified.

The role of kinase C in the regulation of the K_{ATP} channel and cell function is apparently rather complex. However, similar types of effects of PMA involving both activation or inhibition of channel activity have now also been observed for L-type Ca^{2+} channels in cardiac and smooth muscle cells (Lacerda et al. 1988; Van Renterghem et al. 1988; Fish et al. 1988).

Regulation of the ATP-sensitive K+ channel in ß-cells by hormonal peptides

Galanin is a 29 amino acid peptide that was isolated initially from porcine intestine (Tatemoto et al. 1983). The peptide is also present in the pancreas (Amiranoff et al. 1987; Dunning et al. 1986) and in the central nervous system (Ahrén et al. 1988; Rökaeus 1987). In the pancreas, galanin inhibits insulin secretion *via* membrane hyperpolarization and lowering of cytosolic free Ca^{2+} (Ahrén et al. 1986; McDonald et al. 1985).

It has been demonstrated that the galanin-induced membrane hyperpolarization is the result of K_{ATP} channel opening, which could be blocked by glibenclamide (de Weille et al. 1988). As K_{ATP} channel activation by galanin could be obtained both with internally perfused ß-cells and excised patches, in the absence of cAMP, it seems improbable that the adenylate cyclase system is involved in the activation of the K_{ATP} channel by galanin (de Weille et al. 1988). It was shown that pretreatment of insulinoma cells by pertussis toxin also prevented activation of the K_{ATP} channel by galanin (Dunne et al. 1989). Hence, galanin probably inhibits insulin secretion from pancreatic ß-cells by opening the K_{ATP} channel *via* an activation of a pertussis toxin sensitive G protein, leading to hyperpolarization and inhibition of Ca^{2+} influx. Intracellular cAMP levels and hence adenylate cyclase activity are reduced by galanin via a pertussis toxin sensitive G protein (Amiranoff et al. 1988). This effect may also contribute to the inhibition of insulin secretion by a yet unknown mechanism not directly involving K_{ATP} channel regulation.

Another important hormone with hyperglycemic properties is somatostatin, a 14 aminoacid that inhibits secretion from pituitary (Lewis et al. 1986; Pennefather et al. 1988; Yamashita et al. 1988) and pancreatic cells (Pace and Tarvin 1981) and serves as a neurotransmitter in the central nervous system (Epelbaum 1986). The somatostatin-evoked inhibition of secretion from pituitary and possibly pancreatic cells may pass via multiple pathways including (i) inhibition of voltage-dependent Ca^{2+} channels (Lewis et al. 1986; Luini et al. 1986), (ii) inhibition of adenylate cyclase activity (Lebrun et al. 1982) and (iii) activation of an inwardly rectifying K^+ conductance (Lewis et al. 1986; Luini et al. 1986).

In whole cell recordings from insulinoma cells intracellularly perfused with a solution containing 2 mM ATP and 100 mM GTP (Fig. 4A), it was shown that somatostatin induced membrane hyperpolarization by an activation of K_{ATP} channel (de Weille et al. 1989). Somatostatin failed to hyperpolarize the ß-cell when GTP was absent in the perfusate. Furthermore, somatostatin-stimulated $^{86}Rb^+$ efflux from ß-cells was prevented by pertussis toxin pretreatment, suggesting that a G protein mediates the somatostatin response (Fosset et al. 1988b). As electrophysiological experiments were done in the absence of cAMP, it is clear that the adenylate cyclase system is not involved in the coupling between somatostatin receptor occupancy and K_{ATP} channel activation (de Weille et al. 1989). As is the case for galanin, inhibition of insulin secretion by somatostatin is due to an activation of the K_{ATP} channel *via* a *pertussis* toxin sensitive G protein. Somatostatin reduction of intracellular cAMP may also play a role in the inhibition of secretion. It is not yet known whether the voltage-dependent L-type Ca^{2+} channel in ß-cells is affected by somatostatin.

In summary, it has been shown that the K_{ATP} channel plays a central role in the functioning of the pancreatic ß-cell, as both intracellular and extracellular factors lead to the modulation of its activity. It is not known whether the K_{ATP} channel plays as important a role in other tissues in which it has been identified such as the brain, the cardiac muscle or the striated muscle, since modulation of the channel in those tissues by (neuro) peptides has not yet been demonstrated.

Physiological role of sulfonylurea-sensitive K^+ channels

The physiological role of K_{ATP} channels in the pancreatic ß-cell seems clear. In the absence of extracellular glucose, the pancreatic ß-cell is electrically silent. At physiological glucose concentrations, K_{ATP} channels close and membrane resistance increases (Atwater et al. 1978), giving rise to generation of action potentials and Ca^{2+} ion influx. The ensuing secretion of insulin by ß-cells ultimately leads to a reduction of blood glucose levels.

In brain and muscle, a negative feedback system requiring a sensor of intracellular ATP is difficult to envisage, as the channel only seems to be expressed in those tissues under extreme conditions such as ischemia

or uncoupling of oxydative phosphorylation. It has been suggested (Spruce et al. 1987) that the K_{ATP} channel in muscle might serve to reduce Ca^{2+} influx and contraction during periods of exhaustion, thus limiting further ATP utilization. However during ischemia of the heart, shortening of the action potential and of the refractory period as a result of K_{ATP} channel activation, although it prevents excessive Ca^{2+} entry which may lead to cell death, also leads to arythmia and fibrillation, which can hardly be considered as a physiologically useful response. Moreover, pretreatment with sulfonylureas apparently protects the heart against these deleterious effects, indicating that the supposed beneficial role of the K_{ATP} channel in counteracting effects of a sharp decrease of intracellular ATP may even turn out to be counterproductive.

Induction of ischemia in the brain rapidly creates an hyperpolarizing phase which is probably associated with conscience loss (Hansen 1985; Fujiwara et al. 1987). This hyperpolarization is eliminated by glibenclamide (Mourre et al. 1989) and is probably due to the activation of a K_{ATP} channel following a decrease of $[ATP]_{in}$ due to brain ischemia. In the brain, because the interstitial space is much smaller than the intracellular volume, opening of K_{ATP} channels will lead to sustained K^+ efflux which would create extracellular K^+ accumulation, depolarization of synaptic terminals, and release of citotoxic amino acids such as glutamate which will lead to death of hippocampal neurones. These effects again, which would be directly linked to opening of K_{ATP} channels following decrease of ATP, are not particularly favorable.

All the considerations mentioned above suggest that the K_{ATP} channel may generally serve other goals than making a link between membrane polarization and intracellular ATP levels.

In view of the findings that K_{ATP} channel activity in ß-cells is modulated by hormones such as galanin and somatostatin (Fig. 5), it now seems possible that K_{ATP} channels are the targets of extracellular messengers in heart and brain tissue as well. Future research will tell us whether K_{ATP} channels actually constitute a class of sulfonylureas-sensitive and peptide-activatable K^+ channels that also turn out to have ATP-sensitivity.

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References

Ahrén B, Arkhammar P, Berggren P-O, Nilsson T (1986) Galanin inhibits glucose-stimulated insulin release by a mechanism involving hyperpolarization and lowering of cytoplasmic-free Ca^{2+} concentration. Biochem Biophys Res Commun 140:1059-1063

Ahrén B, Rorsman P, Berggren P-O (1988) Galanin and the endocrine pancreas. FEBS Lett 229:233-237

Amiranoff B , Servin AL, Rouyer-Fessard C, Couvineau A, Tatemoto K, Laburthe M (1987) Galanin receptors in a hamster pancreatic b-cell tumor : identification and molecular characterization. Endocrinology 121:284-289

Amiranoff B, Lorinet A, Lagny-Pourmir I, Laburthe M (1988) Mechanism of galanin-inhibited insulin release, occurrence of a pertussis-toxin-sensitive inhibition of adenylate cyclase. Eur J Biochem 177:147-152

Ashcroft FM, Harrison DE, Ashcroft SJH (1984) Glucose induces closure of single potassium channels in isolated rat pancreatic b-cells. Nature 312:446-447

Ashford MLJ, Sturgess NL, Trout NJ, Gardner NJ, Hales CN (1988) Adenosine-5'-triphosphate-sensitive ion channels in

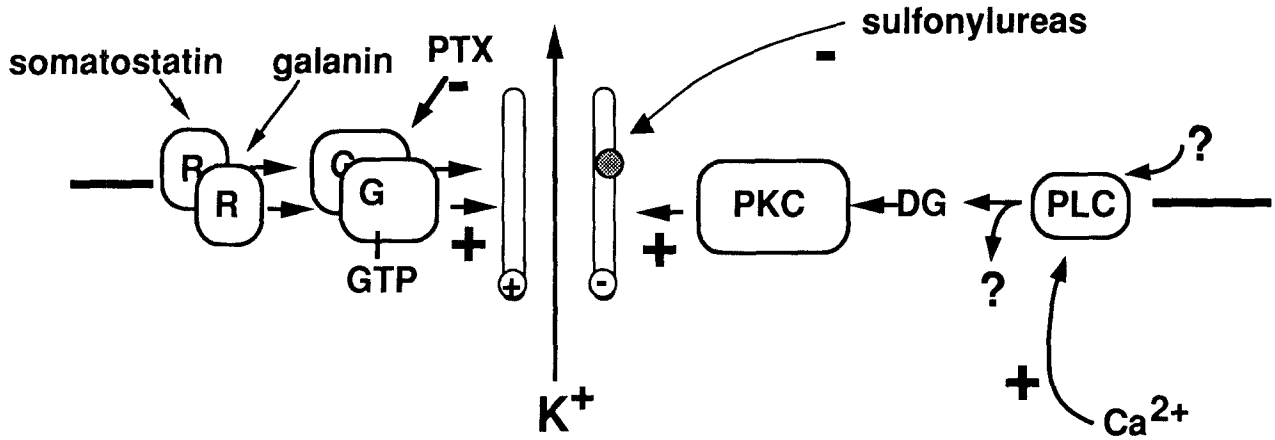

Fig. 5. Different types of regulation of the K_{ATP} channel. The K_{ATP} channel is inhibited (-) by sulfonylureas. Somatostatin and galanin activate the K_{ATP} channel (in b-cells) *via pertussis* toxin (PTX) sensitive G-proteins (G). Stimulation and diacylglycerol (DG) synthesis activated the K_{ATP} channel. Phospholipase C (PLC) may be stimulated by either intracellular Ca^{2+} or extracellular factors.

neonatal rat cultured central neurones. Pflügers Arch 412:297-304

Atwater J, Ribalet B, Rojas E (1978) Cyclic changes in potential and resistance of the b-cell membrane induced by glucose in islets of Langerhans from mouse. J Physiol 278:117-139

Belles B, Hescheler J, Trube G (1987) Changes of membrane currents in cardiac cells induced by long whole-cell recordings and tolbutamide. Plügers Arch 409:582:588

Bernardi H, Fosset M, Lazdunski M (1988) Characterization, purification and affinity labelling of the brain [^{3}H]glibenclamide binding protein, a putative neuronal ATP-regulated K^+ chnanel. Proc Natl Acad Sci USA 85:9816-9820

Boyd AE (1988) Sulfonylurea receptors, ion channels fruitflies. Diabetes 37:847-850

Cook DL, Hales N (1984) Intracellular ATP directly blocks K^+ channels in pancreatic b-cells. Nature 311:271-273

Dunne MJ, Illiot MC, Petersen OH (1987) Interaction of diazoxide, tolbutamide and ATP^{4-} on nucleotide-dependent K^+ channels in an insulin-secreting cell line. J Memb Biol 99:215-224

Dunne MJ, Bullett MJ, Guodong L, Wollheim CB, Petersen OH (1989) Galanin activates nucleotide-dependent K^+ channels in insulin-secreting cells *via* a *pertussis* toxin-sensitive G-protein, EMBO J 8:413-420

Dunning BE, Ahren B, Veith RC, Böttcher G, Sundler F, Taborski GJ (1986) Galanin : a novel pancreatic neuropeptide. Am J Physiol 251:E127-E133

Eberhard PA, Holz RW (1988) Intracellular Ca^{2+} activates phospholipase C, TINS 11:517-520

Epelbaum J (1986) Somatostatin in the central nervous system : physiology and pathological modifications. Prog Neurobiol 27:63-100

Ferrer R, Atwater I, Omer EM, Goncalves AA, Croghan PC, Rojas E (1984) Electrophysiological evidence for the inhibition of potassium permeability in pancreatic b-cells by glibenclamide. Quart J Exp Physiol 69:831-839

Fish RD, Sperti G, Colucci WS, Chapham DE (1988) Phorbol ester increases the dihydropyridine-sensitive calcium conductance on a vascular smooth muscle cell line. Circulation Res , 62:1049-1054

Fosset M, de Weille JR, Green RD, Schmid-Antomarchi H, Lazdunski M (1988a) Antidiabetic sulfonylureas control action potential properties in heart cells via high affinity receptors that are linked to ATP-dependent K^+ channels. J Biol Chem 263:7933-7936

Fosset M, Schmid-Antomarchi H, de Weille JR, Lazdunski M (1988b) Somatostatin activates glibenclamide-sensitive and ATP-regulated K^+ channels in insulinoma cells via a G protein. FEBS Lett 242:94-96

Fujiwara N, Hagashi H, Shimoji K, Yoshimura M (1987) Effects of hypoxia on rat hippocampal neurones *in vitro*. J Physiol 384:131-151

Geisen KH, Hitzel V, Ökonomopulos R, Pünter J, Summ HD (1985) Inhibition of [^{3}H]glibenclamide binding to sulfonylurea receptors by oral antidiabetics. Arzneim -Forsch 35:707-712

Gylfe E, Helmann B, Sehlin J, Täljedal IB (1984) Interaction of sulfonylurea with the pancreatic b-cell. Experientia 40:1126-1134

Hansen AJ (1985) Effects of anoxia on ion distribution in the brain. Physiol Rev 65:101-148

Henquin JC (1977) Possible mechanism of tolbutamide acute stimulation and secondary inhibition of insulin release by perfused rat islets. Diabetologia 13:401.

Henquin JC (1980) Tolbutamide stimulation and inhibition of insulin release : studies of the underlying ionic mechanisms in isolated rat islets. Diabetologia 18:151-160

Henquin JC, Meissner HP (1984) Significance of ionic fluxes and changes in membrane potential for stimulus-secretion coupling in pancreatic b-cells. Experientia 40:1043-1052

Henquin JC, Bozem M, Schneer W, Nenquin M (1987) Distinct mechanisms for two amplification systems of insulin release. Biochem J 246:393-399

Kramer W, Okonomopulos R, Punter J, Summ HD (1988) Direct photoaffinity labeling of the putative sulfonylurea receptor in rat b-cell tumor membranes by [^{3}H]glibenclamide. FEBS Lett 229:355-359

Lacerda AE, Rampe D, Brown AD (1988) Effects of protein kinase C activators on cardiac Ca^{2+} channels. Nature 335:249-251

Lambert DG, Hughes K, Atkins TW (1986) Insulin release from a cloned hamster b-cell line (HIT-T_{15}).The effects of glucose, amino acids, sulfonylureas and colchicine. Biochem Biophys Res Commun 140:616-625

Lebrun P, Malaisse WJ, Herchuelz A (1982) Evidence for two distinct modalities of Ca^{2+} influx into pancreatic b-cell. Am J Physiol 242:E59-E66

Lewis DL, Weight F, Luini A (1986) A guanine nucleotide-binding protein mediates the inhibition of voltage-dependent calcium current by somatostatin in a pituitary cell line. Proc Natl Acad Sci USA 83:9035-9039

Loubatières A (1977) Effects of sulfonylureas on the pancreas, in The Diabetic Pancreas (Volk BW, Wellman RE, eds) pp 489-515, Bailliere Tindall, London

Luini A, Lewis D, Guild S, Schofield G, Weight FJ (1986) Somatostatin, an inhibitor of ACTH secretion, decreases cytosolic-free calcium and voltage-dependent calcium current in a pituitary cell line. Neurosci 6:3128-3132

Lupo B, Bataille D (1987) A binding site for [^{3}H]glipizide in the rat cerebral cortex. Eur J Pharmacol 140:157-169

Matthews EK, Shotton PA (1982) A dual effect of tolbutamide on ^{86}Rb efflux from rat pancreatic islets in vitro, J Physiol 329:68P

McDonald TJ, Dupre J, Tatemoto K, Greenberg GR, Radzink J, Mutt V (1985) Galanin inhibits insulin secretion and induces hyperglycemia in dogs. Diabetes 34:192-196

Meissner HP, Preissler M, Henquin JC (1979) Possible ionic

mechanisms of the electrical activity induced by glucose and tolbutamide in pancreatic b-cells. In: Diabetes (Waldhäusl WK, ed) pp 166-171, Excerpta Medica, Amsterdam

Mourre C, Ben Ari Y, Bernardi H, Fosset M, Lazdunski M (1989) Antidiabetic sulfonylureas : localization of binding sites in the brain and effects on the hyperpolarization induced by anoxia in hippocampal slices. Brain Res, in press

Noma A (1983) ATP-regulated K^+ channels in cardiac muscle. Nature 305:147-148

Pace C, Tarvin JT (1981) Somatostatin : Mechanism of action in pancreatic islet b-cells. Diabetes 30:836-842

Pennefather PS, Heisler S, MacDonald JF (1988) A potassium conductance contributes to the action of somatostatin-14 to suppress ACTH secretion. Brain Res 444:346-350

Quast U (1988) Inhibition of the effects of the K^+ channel stimulator cromakalim (BRL 34915) in vascular smooth muscle by glibenclamide and forskolin. Naunyn-Schmiedelberg's Arch Pharmacol 337:suppl RF2

Quast U, Cook NS (1988) Potent inhibitors of the effect of the K^+ channel opener BRL 34915 in vascular smooth muscle. Br J Pharmacol 93:204P

Ribalet B, Eddlestone GT, Ciani S (1988) Metabolic regulation of the K(ATP) and a maxi-K(U) channel in the insulin-secreting RINm5F cell. J Gen Physiol 92:219-237

Rökaeus Å (1987) Galanin : a newly isolated biologically active neuropeptide. Trends Neurosci 10:158-164

Rorsman P, Trube G (1985a) Evidence that glucose-induced depolarization in the pancreatic b-cells involves the closure of an ATP-dependent K^+ channel. Acta Physiol Scand 124:147

Rorsman P, Trube G (1985b) Glucose dependent K^+ channels in pancreatic b-cells are regulated by intracellular ATP. Pflügers Arch 405:305-309

Schmid-Antomarchi H, de Weille JR, Fosset M, Lazdunski M (1987a) The receptor for antidiabetic sulfonylureas controls the activity of the ATP-modulated K^+ channel in insulin-secreting cells. J Biol Chem 262:15840-15844

Schmid-Antomarchi H, de Weille JR, Fosset M, Lazdunski M (1987b) The antidiabetic sulfonylurea glibenclamide is a potent blocker of the ATP-modulated K^+ channel in insulin secretin cells. Biochem Biophys Res Commun 146:21-25

Spruce AE, Standen NB, Stanfield PR (1985) Voltage-dependent ATP-sensitive potassium channels of skeletal muscle membrane. Nature 316:736-738

Spruce AE, Standen NB, Stanfield PR (1986) Rubidium permeability of ATP-dependent potassium channels of frog skeletal muscle. J Physiol , 378:105P

Spruce AE, Standen NB, Stanfield PR (1987) Studies of the unitary properties of adenosine-5'-triphosphate-regulated potassium channels of frog skeletal msucle. J Physiol , 382:213-236

Sturgess N, Ashford MLJ, Cook DL, Hales CN (1985) The sulfonylurea receptor may be an ATP-sensitive potassium channel. Lancet 8453:474-475

Tatemoto K, Rökaeus ÅÅ, Jörnvall H, McDonald TJ, Mutt V (1983) Galanin - a novel biologically active peptide from porcine intestine. FEBS Lett 164:124-128

Trube G, Hescheler J (1984) Inward-rectifying channels in isolated patches of the heart cell membrane : ATP-dependence and comparison with cell-attached patches. Pflügers Arch 401:178-184

Trube G, Rorsman P, Ohno-Shosaku T (1986) Opposite effects of tolbutamide and diazoxide on the ATP-dependent K^+ channel in mouse pancreatic b-cells. Pflügers Arch 407:493-499

Van Renterghem C, Romey G, Lazdunski M (1988) Vasopressin modulates the spontaneous electrical activity in aortic cells (line A7r5) by acting on three different types of ionic channels. Proc Natl Acad Sci USA 85:9365-9369

De Weille JR, Schmid-Antomarchi H, Fosset M, Lazdunski M (1988) ATP-sensitive K^+ channels that are blocked by hypoglycemic sulfonylureas in insulin secreting cells are activated by galanin, an hyperglycemic hormone. Proc Natl Acad Sci USA 85:1312-1316

De Weille JR, Schmid-Antomarchi H, Fosset M, Lazdunski M (1989) Regulation of ATP-sensitive K^+ channels in insulinoma cells. Activation by somatostatin and kinase C, the role of cAMP. Proc Natl Acad Sci USA 86:in press

Wollheim CB, Dunne MJ, Peter-Riesch B, Bruzzone R, Pozzan T, Petersen OH (1988) Activators ofprotein kinase C depolarize insulin-secreting cells by closing K^+ channels. EMBO J 7:2443-2449

Yamashita N, Shibaya N, Ogata E (1988) Requirements of GTP on somatostatin-induced K^+ current in human pituitary tumor cells. Proc Natl Acad Sci USA 85:4924-4928