Metabolite-Regulated ATP-Sensitive K^+ Channel in Human Pancreatic Islet Cells

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In patch-clamped surface cells of human islets, we identified an inwardly rectifying, voltage-independent K^+ channel that may be a crucial link between substrate metabolism and depolarization-induced insulin secretion. It is the major channel open at rest. It closes on exposure of the cell to secretagogue concentrations of glucose or other metabolic fuels and oral hypoglycemic sulfonylureas but reopens on addition of either a metabolic inhibitor that prevents substrate utilization or the hyperglycemic sulfonamide diazoxide. Onset of electrical activity coincides with channel closure by the secretagogues. In excised patches, the activity of this channel is inhibited at its cytoplasmic surface by ATP. These results suggest that in humans, as in rodents, *1*) rises in cytoplasmic ATP levels during substrate metabolism trigger K^+-channel closure and cell depolarization and 2) clinically useful sulfonamides modulate glucose-induced insulin secretion, in part by affecting a readily identifiable resting conductance pathway for K^+.
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A proposed mechanism of glucose-induced insulin secretion in rodent islets is that glucose metabolism promotes the generation of metabolic intermediates. This results in decreased resting K^+ permeability (P_{K^+}) and membrane depolarization. Membrane depolarization, in turn, promotes voltage-dependent Ca^{2+} entry and calcium-dependent insulin granule exocytosis (see refs. 1–3 for reviews). The most likely candidate for the resting P_{K^+} is an inwardly rectifying, voltage-independent K^+ channel that closes during the cell's metabolism of glucose. This channel is inhibited at its cytoplasmic surface by micromolar concentrations of ATP, hence earning the title *K^+(ATP) channel* (1–4); it is also a major site of action of hypo- and hyperglycemia-inducing drugs (5,6).

Studies of the mechanism of stimulus-secretion coupling in human islets are few due to the scarcity of viable tissue (7). Recently, techniques for mass isolation of viable human islets have been developed for islet transplantation (8). With small aliquots of such preparations of islets, we describe the metabolic gating of a similar K^+(ATP) channel in cell-attached patches of metabolically active, cultured human islets. The results confirm and extend previous reports of the existence of this channel in human islet and human insulinoma cells (9,10). This work has been presented in abstract form (11,12).

Calcium 1 mM = 4 mg/dl	Glucose 1 mM = 18 mg/dl

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MATERIALS AND METHODS

Islets (100–150 μm diam) were isolated and purified by collagenase digestion and Ficoll-gradient separation techniques from pancreases newly harvested from life-supported cadavers (see ref. 8 for details). Purified islets were incubated in HEPES-buffered CMRL-1066 tissue-culture medium (Gibco, Grand Island, NY), enriched with 10% heat-inactivated fetal bovine serum, 0.5% penicillin, and 0.5% streptomycin in 5% CO_2/95% air for 1–4 days at 24°C, and then brought up to 37°C for plating on cover glasses and subsequent culturing for 3–8 days at 37°C. Individual cover glasses were transferred to the recording chamber containing solutions at room temperature (20–23°C) or body temperature (35–37°C); the latter temperature was maintained with a thermistor-controlled flowing water jacket. Single-channel recording was done with conventional patch-clamp techniques standard for our laboratory on surface cells of islets clearly identifiable under the phase-contrast microscope as brownish hemiellipsoids 100–150 μM diam that were free of acinar fragments or debris (4). The data acquisition and analysis setup was identical to that previously

used in our rat islet studies (4). Currents were filtered at 0.9 kHz and sampled at 2 kHz. To standardize nomenclature, the clamping potential (V_c) is defined as the negative of the potential of the interior of the pipette with respect to the bath ground; hence, a potential of V_c = +20 mV depolarizes the patch by 20 mV. The true membrane potential across the cell-attached patch is the membrane potential across the remainder of the cell minus V_c. The average number of channels open in a patch is noted by convention as I/i; it is equal to the number of channels in the patch times the probability of an individual channel being open ($N \cdot P_o$). We measured this quantity by an interactive graphics-based analysis system with level crossings to determine when 1, 2, 3, and more channels were open and averaging the results for a 20-sec to 2-min segment of record.

The standard extracellularlike solution (ES) contained (in mM) 144 NaCl, 5.5 KCl, 2.5 $CaCl_2$, 1 $MgCl_2$, and 25 HEPES titrated to pH 7.3 with NaOH. The standard intracellularlike solution (IS) contained (in mM) 144 KCl, 2 $MgCl_2$, no added $CaCl_2$, and 25 HEPES titrated to pH 7.15 with KOH; 1 mM EGTA was added in some experiments. Solutions were modified by iso-osmotic replacement of the predominant salt with the test substance.

Islets from six single-donor preparations were used. In each, islets comprised >90% of the tissue volume. In thin sections, most peripheral cells of fixed islets stained with aldehyde fuchsin, indicating good insulin content. Aliquots of islets from each batch, tested under standard conditions (8), responded to a rise in perifusate glucose concentration from 3.3 to 16.66 mM, with peak insulin secretion (at 5 min) nearly 5 times baseline and sustained secretion >2.5 times baseline.

RESULTS

Physiological gating of metabolically regulated, ATP-sensitive K^+ channel. Figure 1 identifies a metabolically regulated K^+ channel in cell-attached patches of membrane of surface cells of cultured human islets. In ~50% of all stable patches formed with IS in the pipette and glucose-free ES in the bath, an inward channel current is readily apparent at or near the cell's resting potential (V_c = 0). From observations of this channel over a wide range of V_c (at least ±70–80 mV from rest), it appears that the channel activity is not voltage dependent and that the channel current is inwardly rectifying. Its zero current (or reversal) potential (E_{rev}) is 70–75 mV, and its maximum slope conductance (γ_s) is 60–65 pS (Fig. 1*B*). The most striking features of this channel are shown in Fig. 1*C*. *1*) It closes within 2–3 min after addition of 6.5–10 mM glucose to the bath; closure coincides with the onset of repetitive action currents that are dependent on extracellular Ca^{2+} (i.e., action currents disappear when bath Ca^{2+} is reduced from 2.5 to 0.1 mM, data not shown). *2*) Reducing bath glucose to 3 mM results within minutes in the cessation of action currents and the return of channel activity. *3*) In the presence of 6.5 mM glucose, which is sufficient to nearly abolish channel activity, addition of 3 mM sodium azide (NaN_3), which inhibits mitochondrial cytochrome a_3, can rapidly increase channel activity to levels many times the level seen in a bath solution containing zero glucose. Because the gigaohm glass-to-membrane seal should prevent free diffusion of glucose to the outer surface of the patch, the action of glucose is presumed to be intracellular. Because either a glycolytic (hexokinase) inhibitor (mannoheptulose) or an oxidative respiration inhibitor (NaN_3) can reverse the effect of bath-applied glucose, the action of glucose is presumed to be indirect via cell metabolism.

This channel can be identified by its metabolic regulation in patches of membrane formed with ES in the pipette and IS in the bath; under these conditions, γ_s = 17 pS and E_{rev} = −85–90 mV. This recording condition nullifies the resting potential of the cell. E_{rev} closely approximates the calculated Nernst potential for K^+ across the membrane

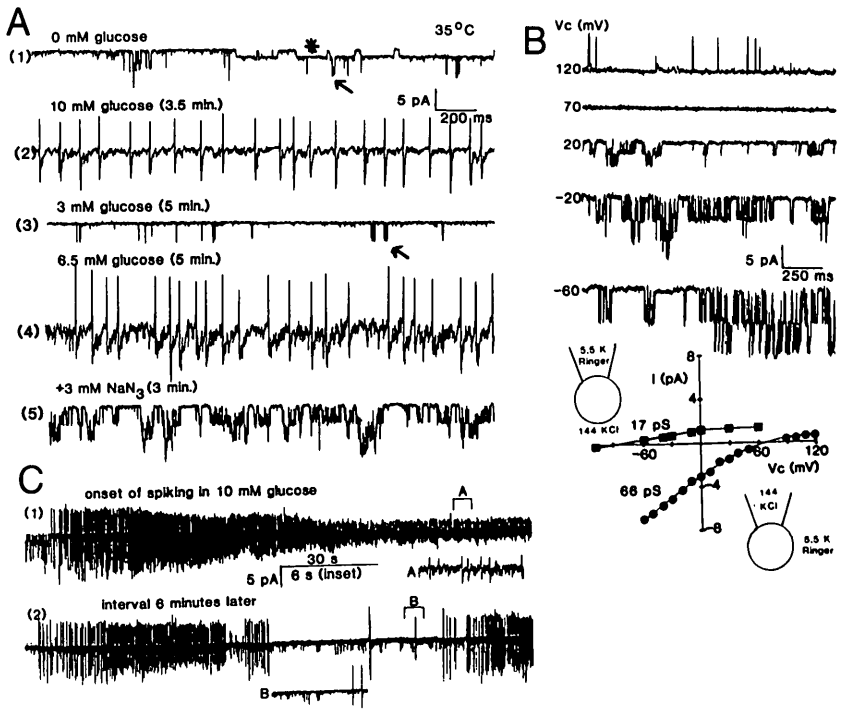

FIG. 1. Identification of metabolically regulated K^+ channel and depiction of glucose-induced electrical activity in cell-attached patches of surface cells of human islets. *A*: traces from continuous record of membrane current made at V_c = 0 with extracellularlike solution (ES, 5.5 mM K^+ Ringer) in bath and intracellularlike solution (IS, 144 mM KCl) in pipette. Responses to glucose are in *traces 1–4*, and response to NaN_3 is in *trace 5*. *Arrows* in *traces 1* and *3* point to metabolically regulated channel. *, Long-lasting 25- to 30-pS channel discussed below. *B*: current traces (IS pipette and ES bath) and current-voltage curves of cell-attached K^+(ATP) channel (in 2 ionic environments); note inward rectification of channel currents. *C*: closer look at pattern of glucose-induced action current activity at onset (*trace 1*) and during prolonged phase of near-periodic activity (*trace 2*). *Insets* depict records at expanded time scale for intervals A and B.

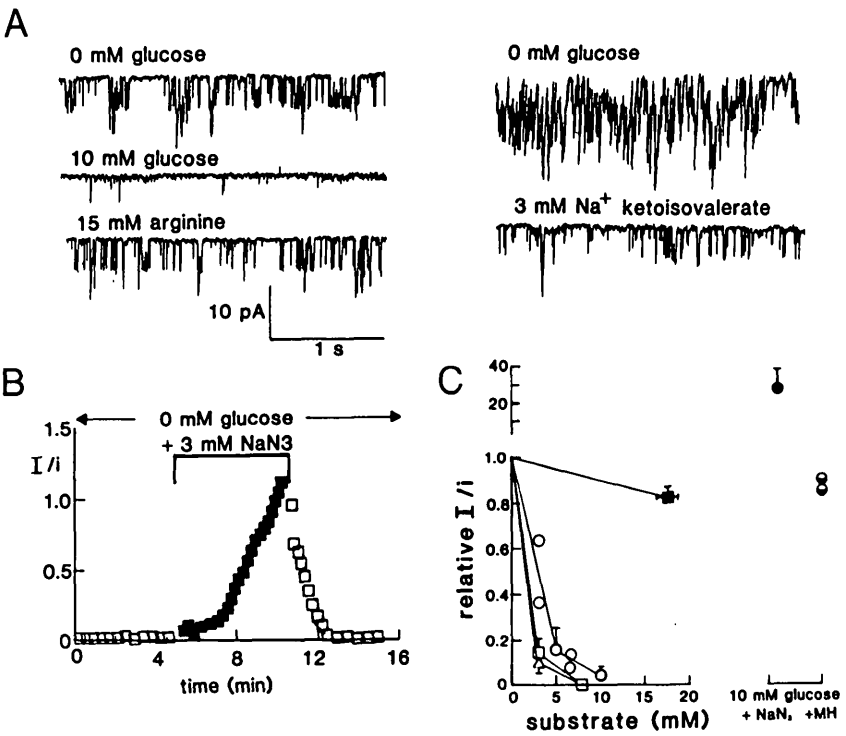

FIG. 2. Effects of fuel metabolites and metabolic inhibitors on K⁺(ATP) channel in cell-attached patch. *A*: traces depicting channel closure induced by glucose and α-ketoisovalerate (α-KIV) but not by arginine [intracellularlike solution (IS) pipette, extracellularlike solution (ES) bath, V_c = 0 mV at 37°C]. *B*: time course and reversibility of NaN_3-induced channel opening (IS pipette, ES bath, V_c = 0 mV at room temperature). *C*: normalized dose response of average channel activity (I/i) to metabolites and inhibitors (ES bath, IS pipette, V_c = 0 mV). Each determination based on analysis of 1- to 2-min record 10–12 min after solution change (n = 6 for 0 mM glucose, 10 mM glucose, and 10 mM glucose + NaN_3; n = 3 for other solutions with SD bars). ○, glucose; □, Na⁺ acetoacetate; △, Na⁺ α-KIV; ■, arginine; ●, 10 mM glucose; ◒, 10 mM glucose + 15 mM mannoheptulose. In each experiment, channel activity was determined in 0 and 10 mM glucose and then in 1 or more concentrations of test metabolite. NaN_3 and mannoheptulose were added to 10 mM glucose at end of experiment. Experiments were performed entirely at 35–37°C or at room temperature.

patch (assuming a normal $[K^+]_i$ of 100–120 mM), implying that the channel is highly selective for K^+ over Na^+.

The metabolically regulated K^+ channel is the most often encountered channel at or near the cell's resting potential; it should make a major contribution to the cell's resting P_{K^+} and resting voltage. Its closure should also provoke cell depolarization and action potential activity. Figure 1*C* depicts in more detail the time course of action currents recorded in the cell-attached patch mode after closure of this channel. As recorded here and in three other patches near body temperature (35°C), action current activity of moderate frequency persists for as long as 30 min after addition of 6.5–10 mM glucose. Spike frequency initially accelerates (up to 5 s^{-1}) and then decelerates to 1–2 s^{-1} (*trace 1*). Later, discrete minute-long volleys of activity separated by near-silent periods are seen. Some channellike activity is seen in the silent periods, but these consisted of very brief flickers rather than the clusters of openings that are more typical of the open-channel event for the channel under discussion. Spike activity was significantly more chaotic at room temperature and often occurred in zero glucose.

Several more detailed aspects of metabolic regulation of the resting K^+ channel are shown in Fig. 2. Bath-applied glucose is not unique in ability to promote channel closure over several minutes. Addition to the bath of sodium salts of α-ketoisovalerate or acetoacetate, two rapidly metabolized insulin secretagogues, at concentrations of 3–7 mM in the absence of glucose produced rapid channel closure; addition of arginine, which is poorly metabolized, at concentrations of 15–20 mM did not (Fig. 2, *A* and *C*). In single experiments, 3 mM glyceraldehyde and 10 mM leucine closed channels as potently as 5–6 mM glucose. Metabolic inhibitors, which enhance channel activity, also do so in a time-dependent manner. During exposure to NaN_3, I/i measured over 20-s intervals initially rises almost exponentially with time. By 10 min of exposure, >90% of all surviving patches, including most of those that previously exhibited action currents in zero-glucose ES, display the voltage-insensitive K^+ channel. The effects of NaN_3 are rapidly reversible even in the absence of an exogenous metabolite. This, together with the often observed sustained low channel activity in the prolonged absence of glucose, suggests that the cell might be able to rapidly and continuously oxidize a stored fuel over minutes to hours.

Figure 3 examines both the ionic selectivity and the gating of the metabolically regulated K^+ channel by ATP at the channel's cytoplasmic surface. Initially, the inwardly rectifying 65-pS channels were identified in the cell-attached patch by adding 3 mM NaN_3 to a modified IS bath (IS pipette). The patch was then excised inside out. When IS contained 10–15 mM NaCl and 2 mM $MgCl_2$, the inwardly rectifying current-voltage (I-V) characteristic of the channel seen while the cell attached was nearly reproduced; when IS contained no added Mg (and no NaCl), the I-V curve was nearly linear. When 104 mM KCl of IS was iso-osmotically replaced with NaCl, the E_{rev} of the channel was shifted positively by nearly 35 mV, confirming the overwhelming selectivity of the channel for K^+ over Na^+ previously implied by results from cell-attached patches. Application of ATP in micromolar concentrations to the solution in contact with the cytoplasmic surface of the patch has two effects on this channel. Acutely, it reduces the mean activity of the metabolically regulated K^+ channel; chronically, it helps to maintain the channel in a "gateable" state. In this patch, representative of four of six examined, channel activity rose dramatically after patch excision into IS containing 2 mM Mg^{2+} and 1 mM EGTA but then declined to steady state level. Addition of 25 μM ATP produced an immediate greater than twofold reduction in I/i; partial recovery was seen over the next 3 min. Increasing ATP to 200 μM nearly obliterated

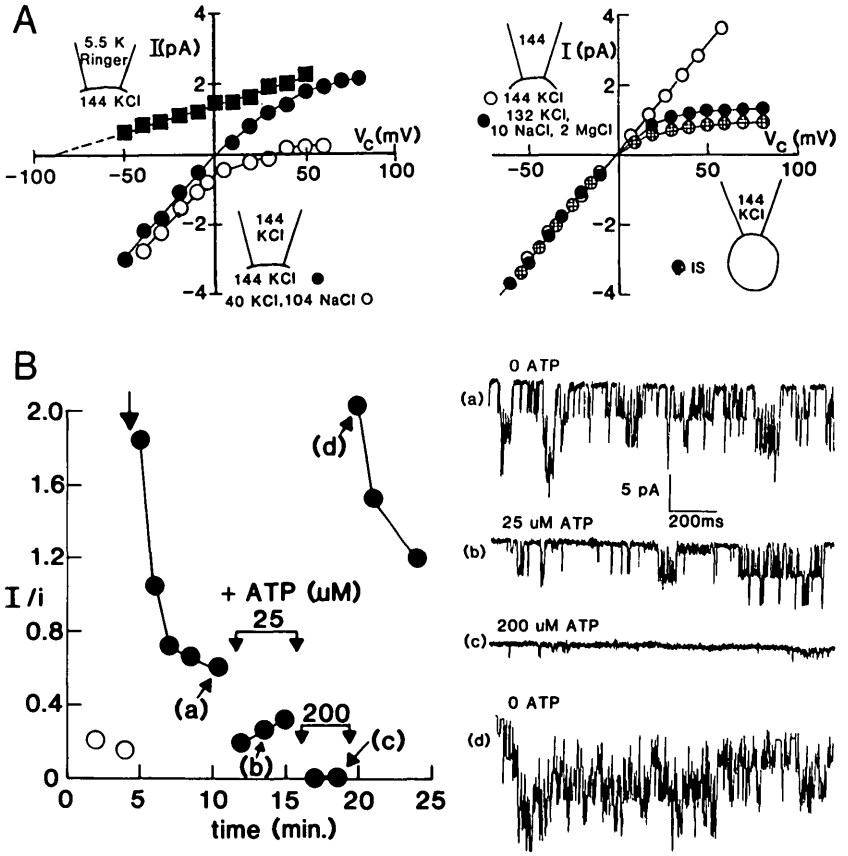

FIG. 3. ***A*: identification of metabolically regulated channel as K^+ selective in inside-out excised patch.** ***Left*, excision of patch, formed with extracellularlike solution (ES) pipette, into an intracellularlike solution (IS) bath reveals E_{rev} of about −80 mV or approximating calculated Nernst potential for K^+ (−86 mV). Excised patch formed with IS pipette and IS bath reveals E_{rev} of 0 mV, which is shifted to +35 mV on replacement of 104 mM KCl with NaCl.** ***Right*, demonstration that inward rectification of current flowing through channel in cell-attached path configuration can be mimicked in inside-out patch by addition of small and near-physiological concentration of NaCl and $MgCl_2$ to the cytoplasmic path.** ***B*: effects of ATP on K^+-channel gating in inside-out excised patch.** ***Left*, continuous time course of I/i before and after excision of patch (at *arrow*) into IS containing 1 mM EGTA (V_c = 0 mV when cell attached and −70 mV after excision; IS pipette).** ***Right*, sample traces from portion of experiment marked on *left*. Complex time course of events discussed in text. Each point represents 60–90 s of recording time. Record of "refreshed" channels (*trace d*) shows occasional opening of 30-pS channel, which appears with greater frequency after prolonged ATP exposure.**

channel activity; however, a dramatic rebound in I/i was seen on washout of ATP (i.e., "channel refreshment"). Activity of the refreshed channels then waned with time. [In rodent islets, channel closure occurs in the presence of nonhydrolyzable ATP analogues and the absence of Mg^{2+}, whereas channel refreshment requires the presence of at least micromolar concentrations of Mg_2ATP, suggesting the need for a phosphorylation reaction (4)]. In two other patches, acute inhibition of refreshed channels was less dramatic; 200–300 μM ATP was needed to reduce I/i to half. In these patches, addition of 500 μM ADP to 500 μM ATP nearly doubled I/i, suggesting that ADP competes with ATP at a channel-gating site as seen with rodent channels.

Pharmacology of K^+(ATP) channel in human islets. Given the striking similarity of metabolic regulation and intracellular ATP gating of the resting K^+ channel of human islet to that of rodent β-cell islets, it was reasonable to expect that this channel would be a site of action of sulfonamide secretagogue and antisecretagogue drugs as it is in rodents. Figure 4 demonstrates one experiment, typical of four others, in which tolbutamide at micromolar doses and glyburide at nanomolar doses nearly abolished NaN_3-augmented channel activity in the cell-attached patch. The effect of tolbutamide was rapidly reversible on washout; the effect of glyburide, although more potent, was much slower in onset and poorly reversible. From this series of experiments, the concentrations needed to reduce channel activity by half were estimated as ~5 μM for tolbutamide and ~50 nM for glyburide. Figure 5 shows that addition of diazoxide in micromolar doses to the bath reversibly increased channel activity

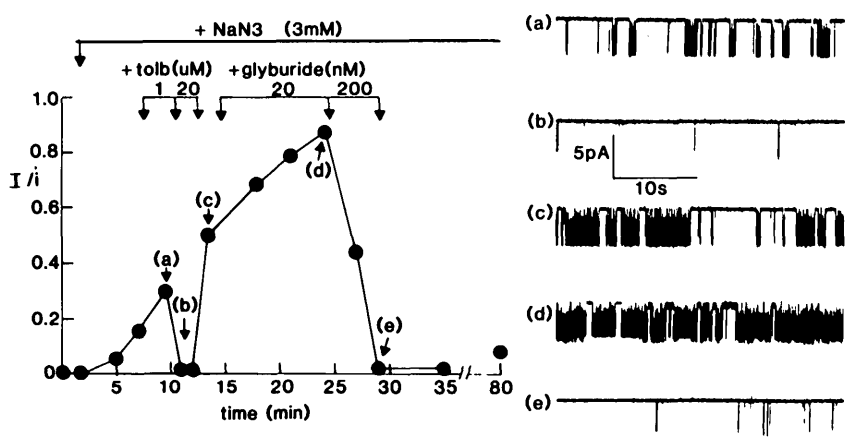

FIG. 4. ***Left*, time course of effects on K^+(ATP)-channel activity of varying concentrations of tolbutamide and glyburide applied to bath in presence of 3 mM NaN_3 (cell-attached patch, V_c = 0 mV; intracellularlike solution pipette, extracellularlike solution bath).** ***Right*, sample traces obtained at designated times.**

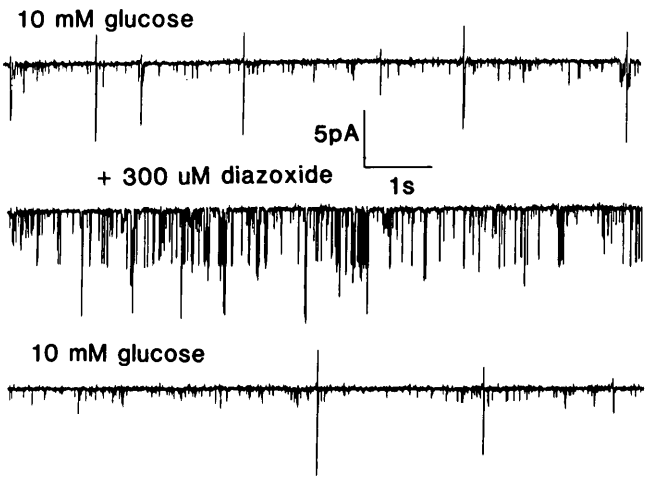

FIG. 5. Reversible effect of bath addition of 300 μM diazoxide to 10 mM glucose extracellularlike solution (cell-attached patch, V_c = 0 mV; intracellularlike solution pipette). Note disappearance of action currents and development of vigorous channel activity after addition of diazoxide.

in the cell-attached patch and blocked glucose-induced action currents. In three experiments performed in the absence of glucose, 50–100 μM diazoxide was sufficient to double channel activity.

Other ion channels active in human islet cell patches. Two other ion channels were readily discernible in cell-attached human islet patches (formed with IS pipettes and ES bath) that contained K⁺(ATP) channels (Fig. 6). Figure 6*A* presents a large-conductance voltage-dependent channel seen at large depolarizations from rest (which corresponds to V_c = 0 mV). γ_s approaches 200–250 pS, and I/i increases *e*-fold (~2.7-fold) with each 10- to 12-mV incremental depolarization. A large-conductance channel with similar voltage dependence of activity can be seen in patches formed with ES pipettes and IS bath. Here γ_s = 90–105 pS, but E_{rev} is nearly −70 mV. These features closely resemble those of a "maxiconductance," Ca^{2+}-activated and voltage-activated K^+ channel found in rodent islet cells. Figure 6*B* presents a moderate-conductance (~25–30 pS), long-lived, voltage-independent channel active over a wide range of V_c that was seen in several patches. The activity of this channel showed no obvious relationship to the metabolic state of the cell. A channel with identical γ_s and kinetic pattern but having an E_{rev} of 0 mV was also seen in patches formed with ES pipette and IS bath. Because the IS bath nullifies the resting potential of the cell membrane, the channel E_{rev} of 0 mV in the presence of a high-NaCl external solution and a high-K^+ intracellular solution is consistent with the channel being a nonselective cation-conductance pathway. Further characterization of these channels is in progress.

DISCUSSION

We present evidence that an ATP-inhibitable K^+ or K^+(ATP) channel, previously reported to exist in cell-attached and excised patches of surface cells of human islets (9) and human insulinoma cells (10), is the most consistently open ion channel at the resting membrane potential in cell-attached patches of plasma membrane of cultured human islets exposed to low glucose. Raising ambient glucose from a low normoglycemic range (3 mM) into the high normoglycemic range (6.5 mM) is sufficient to close the channel within 1–3 min. Small concentrations (<5 mM) of Na^+ acetoacetate, Na^+ α-ketoisovalerate, or glyceraldehyde, all of which are actively metabolized by islets, mimic this action of glucose; arginine, which is poorly metabolized, does not. Closure of the channel precedes the onset of action currents. The best

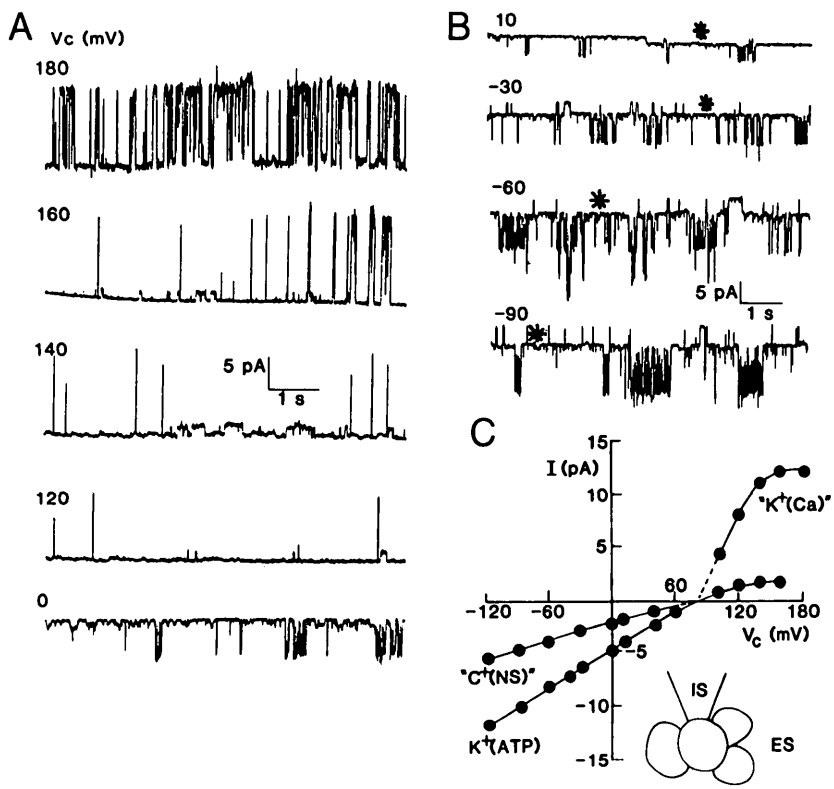

FIG. 6. *A*: sample traces of voltage-dependent, large-conductance K^+ channel seen at large depolarizing potentials and presumed to be "maxiconductance" Ca^{2+}-activated K^+ channel [$K^+(Ca^{2+})$]. *B*: sample traces depicting voltage-independent, persistently open, moderate-conductance channel (*) seen at membrane potentials around resting potential and presumed to be nonselective cation channel [C^+(NS)]. Larger-amplitude, more flickering channel currents are K^+(ATP) channels. *C*: current-voltage curves of $K^+(Ca^{2+})$ and C^+(NS) channels compared with K^+(ATP) channel. Intracellularlike solution pipette, extracellular solution bath in all cases.

evidence that the channel is physiologically gated by intracellular intermediate(s), e.g., ATP, generated by oxidative substrate metabolism is that *1*) metabolites with no access to the channel's outer surface are able to reduce channel activity, and *2*) inhibition of glucose phosphorylation or mitochondrial respiration reverses glucose-induced channel closure. In pilot experiments performed with sister aliquots from three of our islet batches, ATP content measured enzymatically with extracts of rapidly frozen cells clearly varied with cell metabolism and was 20% less after 20 min of incubation in zero-glucose ES compared with 20 min of incubation in 10-mM glucose ES and 60% less after addition of 3 mM NaN_3 (12). Suggested sources for the discrepancy between the presence of ATP in millimolar concentrations in the intact cell and the responsiveness of the excised patch to micromolar concentrations of bath-applied ATP include, among others, intracellular ATP compartmentalization, altered ATP responsiveness of the excised patch, and modulation of ATP sensitivity by other nucleotides (2–4).

The persistent and often cyclical nature of the trains of metabolite-induced action currents resembles the pattern of action potential activity recorded intracellularly from rodent islets during secretagogue stimulation. In rodent islets, pulses of Ca^{2+}-dependent insulin secretion are often time linked to individual trains of Ca^{2+}-dependent action potentials (13), suggesting a causal relationship between them. Studies are in progress to examine the roles of delayed rectifier K^+ channels, Ca^{2+}-activated K^+ channels and Ca^{2+} channels in generating the patterned activity in rat and human islets (14).

As in rodent β-cells, the K^+(ATP) channel in humans is also a clear locus of action of clinically useful sulfonamides (e.g., tolbutamide, glyburide, and diazoxide) at doses approximating therapeutic plasma concentrations (9,10). Glyburide has higher in vivo potency as an insulin secretagogue than tolbutamide and a longer duration of action; paralleling this, glyburide is shown to inhibit K^+(ATP) channel activity at ~1% the dose of tolbutamide and is much more slowly reversible. From companion studies in rodent islets, it appears that *1*) these sulfonamides specifically target K^+(ATP) channels and do not affect the activity of delayed rectifier or Ca^{2+}-activated K^+ channels (14), and *2*) in excised patches, the sulfonylureas directly close the K^+(ATP) channel even in the absence of ATP, whereas diazoxide disinhibits ATP-induced channel closure (6).

Our data suggest that the intact human islet is a useful preparation for electrophysiological studies of stimulus-secretion coupling in the β-cell. From this investigation, it appears that one link in that process, an ATP-sensitive K^+ channel, is very similar in rodents and humans. Further studies of human islets may help elucidate molecular mechanisms of action in humans of insulin secretagogue and antisecretagogue agents that may be species specific, including gut peptide hormones released during feeding and clinically useful drugs with antisecretagogue side effects (e.g., cyclosporin and diuretics).

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