Pflugers Arch - Eur J Physiol (2007) 453:703–718
DOI 10.1007/s00424-006-0116-z

INVITED REVIEW

ABCC8 and ABCC9: ABC transporters that regulate K^+ channels

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Received: 18 May 2006 / Accepted: 8 June 2006 / Published online: 8 August 2006
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Abstract The sulfonylurea receptors (SURs) *ABCC8*/SUR1 and *ABCC9*/SUR2 are members of the C-branch of the transport adenosine triphosphatase superfamily. Unlike their brethren, the SURs have no identified transport function; instead, evolution has matched these molecules with K^+ selective pores, either $K_{IR}6.1$/*KCNJ8* or $K_{IR}6.2$/*KCNJ11*, to assemble adenosine triphosphate (ATP)-sensitive K^+ channels found in endocrine cells, neurons, and both smooth and striated muscle. Adenine nucleotides, the major regulators of ATP-sensitive K^+ (K_{ATP}) channel activity, exert a dual action. Nucleotide binding to the pore reduces the activity or channel open probability, whereas Mg-nucleotide binding and/or hydrolysis in the nucleotide-binding domains of SUR antagonize this inhibitory action to stimulate channel openings. Mutations in either subunit can alter this balance and, in the case of the SUR1/KIR6.2 channels found in neurons and insulin-secreting pancreatic β cells, are the cause of monogenic forms of hyperinsulinemic hypoglycemia and neonatal diabetes. Additionally, the subtle dysregulation of K_{ATP} channel activity by a $K_{IR}6.2$ polymorphism has been suggested as a predisposing factor in type 2 diabetes mellitus. Studies on K_{ATP} channel null mice are clarifying the roles of these metabolically sensitive channels in a variety of tissues.

Keywords ABCC8 · ABCC9 · KCNJ8 · KCNJ11 · K_{ATP} channels · Diabetes · Hypoglycemia

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Introduction

The adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channel area has been widely, some would say over, reviewed during the past dozen years. Our intention here is to comment on recent studies with an emphasis on *ABCC8* and not reiterate material covered in recent extensive reviews on the muscle-type K_{ATP} channels [74, 92, 99, 101, 134, 144].

Background

Adenosine-triphosphate-sensitive K^+ channels are responsive to changes in ATP/adenosine diphosphate (ADP) and provide a means to couple movement of potassium ions and, thus, membrane potential to cellular energy status. Metabolic control of membrane potential is a key factor in the regulation of the Ca^{2+} triggering signals that underlie glucose homeostasis both in the endocrine pancreas and in the central nervous system (CNS). Genetic mutations that disrupt this control lead to a spectrum of changes, mild to severe, in blood glucose levels and energy balance, underscoring the importance of this dominant network.

Adenosine-triphosphate-sensitive K^+ channels are assembled from two different subunits: A $K_{IR}6.x$ subunit that forms the ion-conducting pore and a sulfonylurea receptor (SUR), a member of the ABCC subfamily, with affinity for hypoglycemic sulfonylureas (e.g., the channel antagonists

tolbutamide and glibenclamide) and hyperglycemic channel agonists (e.g., diazoxide, pinacidil, and cromakalim). K_{ATP} channels are obligate hetero-octamers $(SUR/K_{IR}6.x)_4$, whose subunit activities are highly integrated (34, 70, 138; see 2, 27 for review). Ordinarily, neither subunit will reach the cell surface in the absence of its partner. Trafficking from the endoplasmic reticulum to the cell surface is regulated by arginine-rich RKR motifs on both subunits [157] in combination with a C-terminal signal on SUR [136]. These motifs insure the correct assembly of full-length subunits necessary for channel surface expression. The quality control mechanism is not fully understood, but interaction(s) with 14-3-3 proteins are reported to play a role (156; see 96, 107 for review).

The SUR and $K_{IR}6.x$ subunits are the products of two pairs of genes: *ABCC8* [SUR1; Online Mendelian Inheritance in Man (OMIM) 600509] is paired with *KCNJ11* ($K_{IR}6.2$; OMIM 600937), which is approximately 5 kb downstream (3′ of *ABCC8*) on the short arm of human chromosome 11 (11p15.1). *ABCC9* (SUR2; OMIM 601439), on the short arm of chromosome 12 (12p12.1), is separated from *KCNJ8* ($K_{IR}6.1$; OMIM 600935) by approximately 26.2 kb. These *ABCC* genes specify three major SUR isoforms (see 1 for review). SUR1, the receptor with the highest affinity for sulfonylureas, is commonly assembled with $K_{IR}6.2$, and $(SUR1/K_{IR}6.2)_4$ channels are broadly distributed in the neuroendocrine system. Inhibition of pancreatic β-cell K_{ATP} channels by sulfonylurea and nonsulfonylurea hypoglycemic agents, which results in insulin secretion secondary to β-cell depolarization and increased intracellular Ca^{2+} levels, is the primary mechanism of action of these compounds. Differential splicing of the terminal exon of the *ABCC9* gene produces two SUR2 isoforms: SUR2A, paired with $K_{IR}6.2$ to assemble the K_{ATP} channels found in cardiac and skeletal muscle cells, and SUR2B, which assembles with $K_{IR}6.1$ to make K_{ATP} channels in smooth muscle, particularly in parts of the vasculature where they participate in maintenance of vascular tone (see 69 for brief review).

$K_{IR}6.x$ subunits are members of the inward rectifier superfamily

The $K_{IR}6.x$ pores are K^+ selective and conduct K^+ better into cells than out and are termed "inward rectifiers." Like other members of the K_{IR} superfamily, $K_{IR}6.2$ subunits assemble tetramers in which four M2 helices line the permeation pathway and converge to form a gate at the cytoplasmic face of the pore [42]. In crystallographic structures, the outward-facing M1 helices appear accessible for interaction. A submembrane helix termed "the slide helix" immediately precedes and forms approximately a right angle with the M1 helix (illustrated in Fig. 1). By analogy with a proposed mechanical mechanism for regulation of Kv channels [89], motions of this submembrane helix would reposition M1 and M2 to effect gating (see 5 for review).

Multiple studies have shown that engineered $K_{IR}6.x$ subunits can assemble functional pores in the absence of a SUR, and that their activity is sensitive to ATP [8, 43, 150]. Biochemical studies have demonstrated ATP binding to the large C-terminal domain [147, 148, 151]. Recent studies have used the coordinates of bacterial K^+ channels [42, 82, 110] to make homology models the $K_{IR}6.x$ pore and provide novel information on the adenine-selective, nucleotide-diphosphate-binding pocket, which is composed of residues from both the N- and C-termini (7, 29; reviewed in 5). Based on modeling and earlier analysis of a $K_{IR}6.2$ mutant channel with substitutions in both the K_{IR} N- and C-termini [9], we proposed a specific model where the amino and carboxy termini that comprise the nucleotide binding site are from adjacent K_{IR} subunits [7]. This model implies that inter-K_{IR} subunit coupling contributes to the concerted transitions characteristic of K_{ATP} channels.

Sulfonylurea receptors are typical ABC proteins

The SURs are multidomain proteins with a topology similar to other ABC proteins, including the classic ABC "core" consisting of two bundles of six transmembrane helices (TMD1 and 2) with nucleotide-binding domains (NBD1 and 2) C-terminal to each TMD (Fig. 1). The SURs, and several other ABCC proteins (i.e., ABCC1, 2, 3, 6, and 10), have an additional amino terminal module that consists of a bundle of five transmembrane helices (TMD0) connected to the core via an intracellular linker termed "L0." In ABCC8 and 9, TMD0-L0 is the principal domain interacting with the K_{IR} subunit as discussed below. The SUR NBDs contain the canonical phosphate-binding Walker A and B motifs, the Q-loop, the signature sequence, and the H-loop, hallmarks of the ABC family. The SURs were among the first ABC proteins recognized to have degenerate, nonsymmetric NBDs with a noncanonical signature sequence, FSQGQ vs LSGGQ, in NBD2 and an aspartate (D) in place of the usual glutamate (E) adjacent to the highly conserved D in the Walker B motif. Early studies on SUR1, without a K_{IR}, indicated tight binding of 8-azido ATP and affinity labeling of NBD1, irrespective of the presence of Mg^{2+}, with no indication of hydrolysis. Mg^{2+} potentiated nucleotide binding in NBD2 where hydrolysis is thought to occur (93, 94, 97; reviewed in 92). Although not yet explicitly demonstrated, by analogy with other ABC proteins reviewed in this issue of *Pflügers Archives*, ATP binding and hydrolysis are expected to drive dimerization

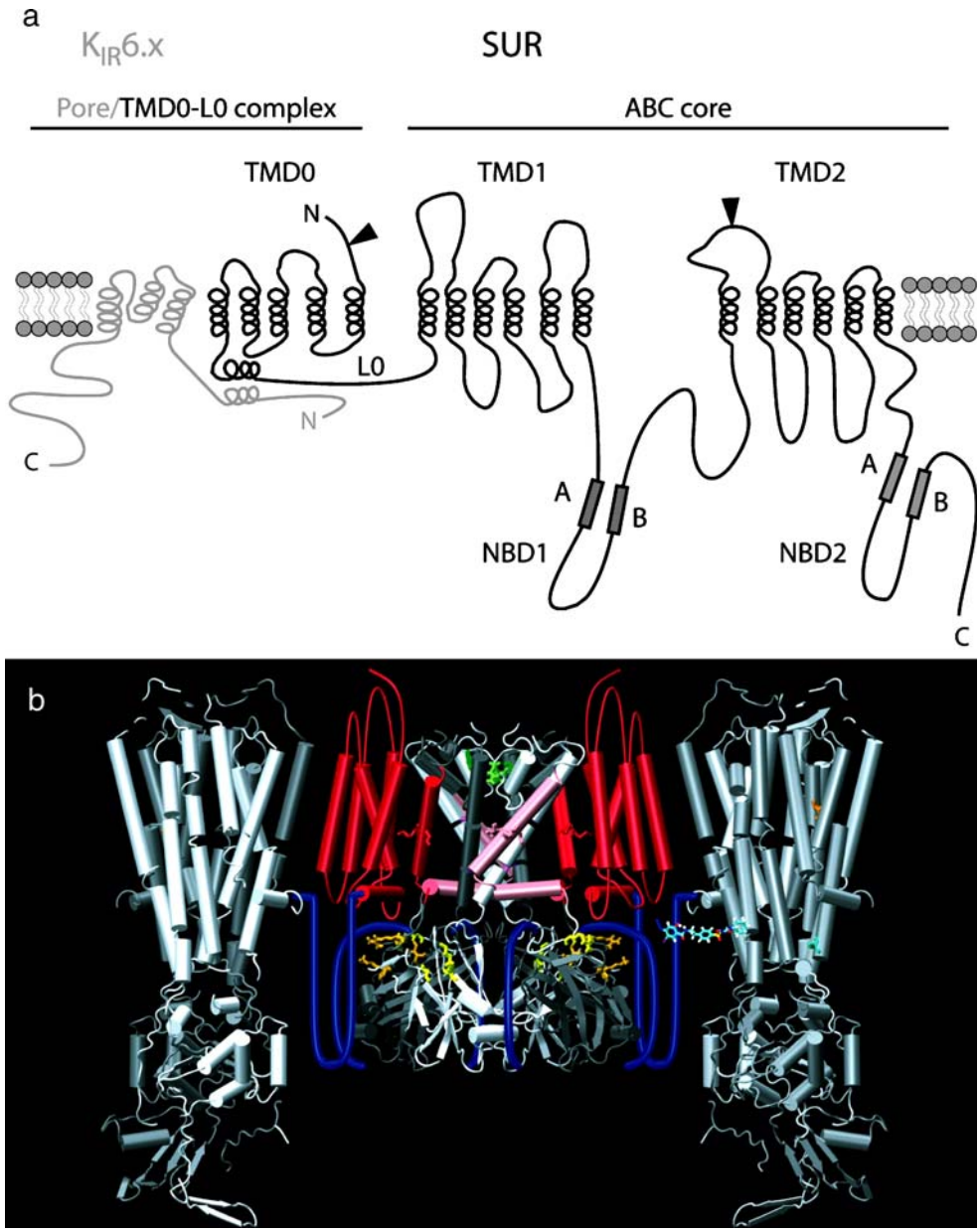

Fig. 1 Topology and homology model of K_{ATP} channels. (**a**) The $K_{IR}6.x$ and SUR topologies are illustrated schematically. The amino (*N*) and carboxyl (*C*) termini are marked. *A* and *B* symbolize the Walker A and B consensus motifs in the two NBDs, respectively. The *triangles* show the approximate positions of glycosylation sites required for correct trafficking. (**b**) A homology model for K_{ATP} channels. The $K_{IR}6.2$ model is based on the structures of KirBac1.1 [82] and the carboxy terminus of the $K_{IR}3.1$ subunit [110]; the model of the SUR core is based on the VC-MsbA-dimer [32]. A detailed description is given in Refs. [7, 26]. The GFG sequence (*green*) and ball identify the pore selectivity filter and a K^+ ion, respectively. TMS sequences in the K_{IR} outer helix, important for association with SUR [132], are shown in *red* or *pink* to distinguish neighboring subunits. The bundle of five *red cylinders* symbolizes TMD0 for which no structural template is available. L0 is illustrated by *horizontal red cylinders* and *connected blue loops*, and is positioned to interact with the distal residues of the K_{IR} amino termini in *blue*. Interactions between domains colored *red* or *pink* activate the pore, whereas interactions involving *blue* domains attenuate the P_{Omax}. *Gold* and *yellow* residues in the K_{IR} cytoplasmic domains identify ATP-binding sites in neighboring subunits. For the purpose of size comparison, iodo-azidoglibenclamide in an extended conformation is shown on the *right*. The cyan residue in the *lower left* is S1237, important for sulfonylurea binding [4]. Two side chains on TM 17 (T1286 and M1290), important for interactions of the channel with openers [103], are in *brown*. Panel (**b**) is modified from Ref. [26]

of the SUR NBDs and produce concomitant rearrangements of TMD1 and TMD2 [154]. In other ABC proteins, these rearrangements are associated with substrate transport, whereas in K_{ATP} channels, the challenge is to understand how they are coupled to the gating mechanism of the $K_{IR}6.x$ pore (see 104, 158 for discussion of specific models).

Drug binding sites

SURs are the targets for various compounds that bind and either stimulate or inhibit K_{ATP} channel activity. We [26] and others [72, 104, 118, 120] have reviewed this area recently. Therapeutic agents, like tolbutamide, glibenclamide, glipizide, glimeperide, nateglinide, repaglinide, etc., which antagonize the activity of the SUR1/K_{IR}6.2 β-cell channels, are perhaps best known because of their wide use as hypoglycemic agents that restore first phase of insulin secretion in patients with type 2 diabetes. Extensive effort has gone into understanding their pharmacophore structure and the mechanism of action of these compounds along with the location of the binding site. Current evidence suggests the binding site is an extended pocket on the cytoplasmic side of the receptor, which involves residues from TMD2 and L0 and the amino terminus of K_{IR}6.2. The binding of sulfonylureas to SUR1/K_{IR}6.2 channels has a dual effect, partially inhibiting channel activity in the absence of nucleotides and abolishing the stimulatory action of SUR1 on the pore in the presence of Mg nucleotides. Potassium channel openers (KCOs), like diazoxide, have been used to hyperpolarize β cells and reduce insulin release, whereas openers specific for SUR2 have long been sought in an effort to control the excitability of cardiac and vascular smooth muscle (see 120 for review). Amino acid residues in TMD2, in what appears to be a cavity in the homology models of the SUR ABC core, markedly affect KCO binding (Fig. 1b; 38, 102, 103; see 104 for review). Although the properties of these binding sites, and the effects of nucleotide binding and hydrolysis, are not as well studied as the classical ABC drug transporters, the structural parallels are clear.

Modulators

Various compounds have been shown to modulate K_{ATP} channel activity, particularly phosphoinositides (20, 52, 121, 130, 140; see 19 for review), long-chain acyl coenzyme As (CoAs) derived from fatty acids [23–25, 121], G proteins (127; but see 13), and phosphorylation (see 88 for review). The functions of these modulators are potentially important, but in most cases, their physiologic role(s) are only beginning to be firmly established. Lower pH has been reported to activate K_{ATP} channels by reducing their sensitivity to inhibitory ATP and may play a role in the regulation of vascular tone during hypercapnic acidosis [153]. Several recent studies [18, 22, 119] have shown that Zn^{2+}, cosecreted with insulin and present in high concentrations in areas of the CNS, can activate ATP-inhibited SUR1/K_{IR}6.2 K_{ATP} channels via binding to two histidines on the extracellular face of SUR1 [17]. In pancreatic islets, Zn^{2+} is coreleased with insulin, where it may play an autocrine role or serve to attenuate glucagon release from α cells [56, 71].

Assembly

The pathway(s) of K_{ATP} channel assembly are poorly understood. In studying the turnover of individual subunits expressed in COSm6 cells, we observed that SUR1 expressed alone appeared to be long-lived, whereas K_{IR}6.2 subunit turnover was biphasic [36]. We inferred that the slow phase represented assembly of stable K_{IR}6.2 tetramers, whereas the rapid phase was due to degradation. Coexpression with SUR1 eliminated the rapid phase, and SUR1/K_{IR}6.2 complexes were detectable at the earliest time points in pulse-chase experiments. The results are consistent with the hypothesis that during or shortly after their biogenesis, SUR1 and K_{IR}6.2 rapidly dimerize, protecting K_{IR}6.2 from degradation. The SUR1/K_{IR}6.2 dimers then assemble the octameric complex [36]. The results are summarized in Fig. 2.

The TMD0-L0 domain links the SUR ABC core with the pore

Recent studies have emphasized the role of the TMD0-L0 module in both the assembly and regulation of K_{ATP} channels. In some ABCC proteins TMD0 is required for correct trafficking [53, 91], whereas in MRP1, L0, but not TMD0, is required for transport activity [15] and is part of the glutathione binding site [75]. Coexpression of SUR1 TMD0 with poorly active $(K_{IR}6.2)_4$ pores demonstrated partial restoration of function, including an increase in their maximum channel open probability (P_{Omax}) and the restoration of bursting activity; immunoprecipitation experiments confirmed TMD0 forms complexes with K_{IR}6.2 [7, 31]. TMD0 consists primarily of transmembrane helices, and the idea that one or more TMD0 helices interact with the K_{IR} M1 helix is supported by experiments with chimeric K_{IR} subunits [132] and the observation that K_{IR}6.2 N-terminal fragments containing M1, but not M2 and the C-terminal domain, interact with SUR1 [27]. Because of their smaller size, we termed the TMD0/K_{IR}6.2 complexes "mini-K_{ATP}" channels and referred to the TMD0-L0 module as a "gatekeeper." These mini channels lack many of the defining characteristics of full channels and are not sensitive to sulfonylureas, are not stimulated by Mg nucleotides, and retain the reduced sensitivity to inhibitory ATP characteristic of $(K_{IR}6.2)_4$ pores. Additionally, TMD0 does not support the trafficking of K_{IR}6.2 with an intact ER retention motif to the cell

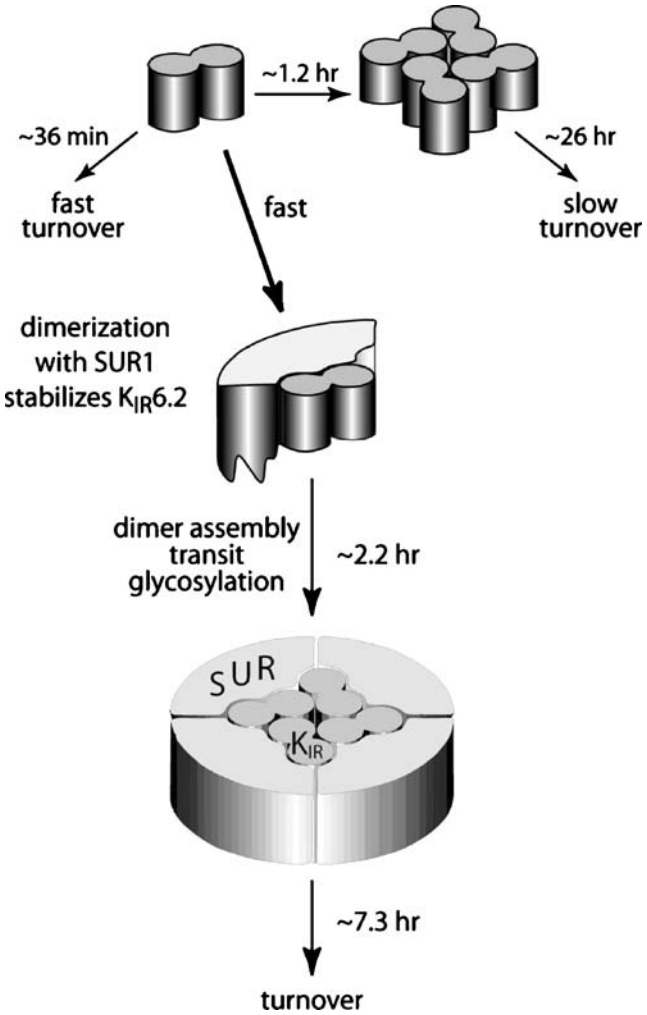

Fig. 2 Summary of K_{ATP} channel assembly. Based on turnover studies, K_{IR} monomers are hypothesized to assemble slowly into tetrameric pores. In the absence of SUR, the K_{IR} monomers are degraded rapidly, whereas tetramers are long-lived. When the subunits are coexpressed, the immature core glycosylated form of SUR1 assembles rapidly with $K_{IR}6.2$. Maturation to a functional channel has a half-time of approximatey 2.2 h and involves multiple steps, including completion of channel assembly, transit through the Golgi complex, and the addition of sialic acid residues. The estimated half-life for the complete, fully glycosylated channel is approximately 7.3 h. The figure is based on Ref. [36]

surface, implying that these properties of the full channel require interactions between the TMD0-K_{IR} pore complex and the ABC core [7].

L0 and the K_{IR} amino terminus are critical elements of the transduction mechanism

Early studies with chimeric receptors showed that L0 played a critical role in specifying gating differences between SUR1-based neuroendocrine vs SUR2-based muscle-type K_{ATP} channels [11]. Analysis of the mini-K_{ATP} channels underscored the importance of L0 in the control of gating. The progressive inclusion of L0 sequence into mini-K_{ATP} channels identified a proximal stimulatory segment that stabilized the pore in a continuous bursting mode [7]. This proximal segment contains a conserved, predicted amphipathic helix [5]; a similar sequence in MRP1 is important for transport [14]. The inclusion of more distal segments of L0 attenuated the strong stimulatory effect. The results implied that the TMD0-L0 pore complex had all of the structural elements necessary to affect bidirectional control of gating and dovetailed nicely with studies showing that the initial N-terminus of $K_{IR}6.2$ plays a critical role in limiting the length of time a K_{ATP} channel remains in an open bursting configuration. For example, the deletion of the $K_{IR}6.2$ amino terminus [9, 79] or the application of a synthetic N-terminal peptide [6] produced channels that burst continuously, suggesting that interaction (s) between the N terminus and a putative binding site on SUR limited burst length. We developed a model in which stimulatory interactions between the proximal helical segment of L0 and the $K_{IR}6.2$ slide helix are balanced by inhibitory interactions between the more distal half of L0 and the initial N terminus of $K_{IR}6.2$ (6, 7, 10; reviewed in 5, 27). In this quasimechanical model, the dimerization or reconfiguration of the ABC core as a consequence of ATP binding and hydrolysis is presumed to exert a force that repositions L0 to affect channel gating by moving the slide helix and, thus, M1 and M2. The movements are analogous to those proposed to affect gating in voltage-gated Kv1.2 channels, where changes in membrane potential produce a conformational change in the voltage sensor that moves the S4-S5 linker and repositions S5 and S6 to open or close the gate [89].

Dual regulation of K_{ATP} channel activity by adenine nucleotides

In most ABC proteins, hydrolysis of ATP is assumed to power substrate transport across the cell membrane. In K_{ATP} channels, adenine nucleotides can bind to both the K_{IR} and SUR subunits and exert inhibitory and stimulatory actions, respectively. The binding of ATP or ADP to $K_{IR}6.x$ subunits reduces channel activity. This binding and inhibitory action are Mg^{2+}-independent and do not require hydrolysis. The stimulatory action of SURs, on the other hand, is Mg-nucleotide-dependent, and nucleotide binding and hydrolysis increases the activity of the ATP-inhibited pore.

In pancreatic β cells, the glycolytic pathway is critically involved in signaling increases in glucose metabolism to K_{ATP} channels [46, 90, 95]. The nicotinamide adenine

dinucleotide (reduced form; NADH) equivalents derived from glycolysis are transferred into mitochondria via the glycerol-phosphate, dihydroxyacetone-phosphate, and malate-aspartate shuttles. Blockage of either shuttle alone has little effect on glucose-stimulated insulin secretion, whereas blockage of both pathways in mitochondrial glycerol-phosphate dehydrogenase null mice [50, 51] strongly inhibits first-phase insulin release and abolishes second-phase secretion in response to elevated glucose. How the NADH equivalents from glycolysis, via generation of ATP, inhibit K_{ATP} channels has not been established, but the results suggest that β-cell K_{ATP} channels are not sensing "bulk" cytosolic $[ATP]_i$. One idea is that specific respiratory chains couple the malate-aspartate and glycerol-phosphate NADH shuttles to a mitochondrial creatine kinase which transfers phosphate from matrix ATP to creatine to produce creatine phosphate [80]. The creatine phosphate is then converted to ATP at or near K_{ATP} channels. This hypothesis is supported by reports that SUR2A, the regulatory subunit of $K_{IR}6.2$/SUR2A K_{ATP} channels found in striated muscle, is physically associated with creatine kinase [37].

K_{ATP} channel pathologies

Multiple genetic disorders of glucose homeostasis and cardiovascular tone have been associated with mutations in K_{ATP} channel subunits. *KCNJ8* has been suggested as a candidate gene for Prinzmetal angina based on the phenotype of the $K_{IR}6.1$KO mouse [100], but human mutations have yet to be identified [49]. *ABCC9* has not been linked to single-gene disorders at this time, but it has been associated with dilated cardiomyopathy [21].

Hyperinsulinemic hypoglycemia

Mutations in SUR1 and $K_{IR}6.2$ are an established cause of hyperinsulinemic hypoglycemia of infancy (HI), characterized by excess insulin release for the degree of hypoglycemia (see 1 for review). More than 40 mutations in *KCNJ11* and more than 100 *ABCC8* mutations have been identified in patients with HI that lead to loss of channel function by affecting subunit assembly and channel trafficking [30, 36, 136, 149] or, in the case of some *ABCC8* missense mutations, by impairing the Mg-nucleotide-dependent stimulation of the pore by SUR1 (109, 139; reviewed in 55). The neuroendocrine SUR1/$K_{IR}6.2$-type K_{ATP} channels are a key regulator of membrane potential; thus, their loss in HI individuals abolishes the ability of pancreatic β cells to hyperpolarize when glucose is reduced and, thus, suppress insulin release. This uncoupling results in excess insulin release that produces hypoglycemia. There is no known therapeutic strategy to enhance folding, assembly, or trafficking of mutant subunits, and these cases often require surgical intervention. Many individuals with missense mutations are responsive to diazoxide, a K^+ channel opener, or to octreotide, a somatostatin analog, and can be treated pharmacologically.

Neonatal diabetes

Recent studies on the genetic basis of neonatal diabetes (ND) have confirmed the observation in transgenic mice [78] that expression of "overactive" K_{ATP} channels results in neonatal hyperglycemia secondary to reduced insulin secretion. Although ND is a rare genetic disorder (estimated at ~1/400,000 births) [117], these findings are important because they confirm the general ionic mechanism and how that increased K_{ATP} channel activity and, thus, more hyperpolarized β cells result in a decrease in insulin release. Multiple mutations in $K_{IR}6.2$ have been found to produce ND (59, 152; reviewed in 66, 143). Although various structural alterations can be anticipated that would result in more active channels, several of the reported $K_{IR}6.2$ mutations reduce the apparent affinity for inhibitory ATP, thus leading to more active channels at a given nucleotide level [59, 152]. Although these mutations are dominant, simulating heterozygosity by expression of 1:1 mixtures of mutant, for example, the R201H mutation, and wild-type K_{IR}s with SUR1 yielded a population whose inhibition by ATP was essentially indistinguishable from wild-type channels. The results suggest that the small percentage of homozygous mutant channels, expected to arise from random assortment during assembly of the pore, is sufficient to hyperpolarize β cells. Many of the ND-$K_{IR}6.2$ mutant channels retain their sensitivity to sulfonylureas, allowing patients to be switched from insulin to sulfonylurea therapy [126].

The dual action of nucleotides on K_{ATP} channels outlined above anticipated SUR "gain-of-function" mutations having an enhanced stimulatory action on the pore. Sequencing of the *ABCC8* gene in a small population of patients diagnosed with ND, from the French Network for the Study of Neonatal Diabetes Mellitus for Genetic Diagnosis, identified seven mutations that segregated with the disorder [12]. Analysis of two SUR1 mutant channels, I1424V or H1023Y, demonstrated they were more active than wild-type channels both in on-cell recordings from intact mammalian cells and in isolated patches exposed to a quasiphysiologic concentration of MgATP (1 mM). In the absence of Mg^{2+}, when the stimulatory action of SUR1 on the pore was abolished, there was no significant difference in the ATP inhibitory curves of mutant and wild-type channels, indicating the I1424V or H1023Y receptors exert an enhanced stimulatory action on the pore. The simulation

of heterozygosity by expression of 1:1 mixtures of ND-SUR1 H1023Y and wild-type SUR1 with $K_{IR}6.2$ produced average mean channel activities intermediate between the "homozygous" mutant and wild-type channels. The mutant ND-SUR1 channels are inhibited by sulfonylureas, allowing patients to substitute oral hypoglycemic agents for insulin therapy.

Type 2 diabetes

Hyperinsulinemic hypoglycemia and ND are clear examples of rare monogenic disorders of glucose homeostasis that provide insight into the regulation of insulin secretion. Genetic studies indicate K_{ATP} channels also may have a role in type 2 diabetes mellitus. Several studies (for example, 54, 60, 63; reviewed in 124) indicate a polymorphism, E32K, in the amino terminus of $K_{IR}6.2$ is a risk factor for type 2 diabetes. This $K_{IR}6.2$ polymorphism has a subtle activating effect on K_{ATP} channel activity and is reported to reduce sensitivity to inhibitory ATP [131] and increase the stimulatory action of long-chain acyl CoAs [122], particularly long-chain, saturated acyl CoAs [123].

Transgenic mouse models

All of the subunits of K_{ATP} channels, including SUR1, SUR2, $K_{IR}6.1$, and $K_{IR}6.2$, have been deleted in mice and their phenotypes studied. This area, particularly with respect to K_{ATP} channels in muscle, has been reviewed recently [99], and in the interest of space, we focus on the results with Sur1KO animals. Two independent SUR1 null mouse lines have been generated. Seghers et al. [133] replaced exon 2 with puromycin-*N*-acetyl-transferase, whereas Shiota et al. [137] used a cre recombinase strategy to delete exon 1, leaving a neomycin resistance cassette. Neither strain produces SUR1, and as expected, both strains lack SUR1/$K_{IR}6.2$-type K_{ATP} channels, with no studies showing upregulation of SUR2 subunits and compensatory ionic currents.

We initially developed Sur1KO mice as a potential animal model for the study of HI but unexpectedly found that the mice exhibited normal plasma glucose and insulin levels unless stressed [133], whereas in HI neonates, the loss of K_{ATP} channel activity can produce severe hypoglycemia secondary to excess insulin release. The early electrophysiological studies done on isolated β cells from HI neonates using the patch clamp technique demonstrated a loss of K_{ATP} channel activity and persistent Ca^{2+}-dependent action potentials consistent with their excessive insulin release [47, 73]. Similar analyses on isolated Sur1KO β cells identified a similar electrophysiological phenotype with loss of K_{ATP} channels, persistent Ca^{2+}-dependent action potentials, and elevated and slowly oscillating $[Ca^{2+}]_c$, although in contrast to HI neonates, the knockout animals have normal blood sugar and insulin levels [44, 133, 137]. Later membrane potential measurements on Sur1KO β cells with intracellular microelectrodes revealed an oscillatory pattern (Fig. 3; 44, 65). These papers introduce a cautionary note: membrane potential estimates derived from patch clamp measurements in isolated β cells can differ substantively from those made on β-cell clusters and islets. The results suggest that β cells in Sur1KO mice are probably not persistently depolarized but are rather oscillating, similar to the behavior of wild-type β cells.

Newborn Sur1KO mice were found to exhibit significant hypoglycemia secondary to hyperinsulinemia, but this resolved within several days [133], and the KO animals then remain normoglycemic [65, 108, 133]. Intraperitoneal glucose tolerance tests on adult mice showed that knockout animals fail to release insulin in response to a glucose challenge [133, 137], whereas fasted knockout animals are able to secrete insulin in response to feeding [137] consistent with stimulation via the CNS.

Secretion studies on isolated islets have produced divergent results, with some reports consistent with enhanced insulin release, whereas others were consistent with a defect in insulin secretion. Seghers et al. [133] showed a loss of first phase and an attenuated second phase of insulin secretion in response to a glucose challenge. Using animals from the same colony, Nenquin et al. [108] showed increased insulin release from isolated Sur1KO vs WT islets in low glucose (1 mM) consistent with the elevated Ca^{2+} triggering signal. This study confirmed the lack of first-phase response and showed further that increasing glucose metabolism stimulated insulin release, demonstrating the augmentation pathway (see 67, 68 for review) is intact in the Sur1KO animals. Similar glucose-stimulated insulin secretion was reported by Haspel et al. [65], and Muñoz et al. [105] showed increased insulin release from Sur1KO islets in low glucose plus amino acids. Studies on the Sur1KO animals generated by Shiota et al. [137] have usually failed to show insulin secretion under hypoglycemic conditions or a significant increase in secretion when glucose is elevated, thus leading to the conclusion that loss of SUR1 impairs insulin release [41, 87], although Eliasson et al. [48] reported glucose-stimulated insulin release using this strain. These divergent results with isolated islets, excessive insulin release in low glucose and increased secretion upon increasing glucose vs generally impaired insulin secretion, have suggested opposite compensatory mechanisms must operate to account for the normal insulin and blood sugar levels seen in the knockout animals. Nenquin et al. [108] suggested the need for a mechanism to suppress the excessive insulin release

seen in low glucose, whereas Doliba et al. [41] argue for an enhanced stimulation via a neural mechanism.

Role of K_{ATP} channels in the generation of Ca^{2+} and electrical oscillations

A signature feature of islets in elevated glucose is a tight coupling between oscillations of β-cell membrane potential and $[Ca^{2+}]_c$ that trigger pulsatile insulin release [58, 129]. Several mechanisms proposed to account for the generation of these oscillations involve the response of K_{ATP} channels to changes in ATP/ADP (see, for example, 40, 81). Using intracellular microelectrode recording techniques, Düfer et al. [44] showed that Sur1KO islets exhibit V_m and $[Ca^{2+}]_c$ oscillations in 15 mM glucose, which, in contrast to wild-type islets, persist in 0.5 mM glucose, implying K_{ATP} channels are not essential for oscillation. The microelectrode experiments showed that the electrical activity of Sur1KO β cells in islets was modulated by glucose as illustrated in Fig. 3. In contrast to wild-type β cells, the application of sodium azide did not result in hyperpolarization of Sur1KO β cells but did reduce the amplitude of Ca^{2+}-dependent action potentials by directly inhibiting Ca^{2+} channels [44, 45]. Neither tolbutamide nor diazoxide had any effect on V_m oscillations in K_{ATP} null islets. The activation of a low-conductance, Ca^{2+}-dependent K^+ current, termed "I_{Kslow}," has been implicated in the oscillatory activity of wild-type β cells [61, 62]. Haspel et al. [65] showed that Sur1KO β cells have a similar Ca^{2+}-dependent K^+ current that is inhibited when $[Ca^{2+}]_c$ is reduced using D600, an L-type Ca^{2+} channel blocker, and stimulated using BayK 8644, a Ca^{2+} channel opener. K_{ATP} channels control oscillations of V_m and $[Ca^{2+}]_c$ in wild-type β cells, but a secondary oscillatory mechanism must exist in Sur1KO cells. We presume the two mechanisms are not active in parallel because blocking K_{ATP} channels acutely with 100 μM tolbutamide does not induce oscillations in $[Ca^{2+}]_c$ [128].

Multiple compensatory mechanisms have been suggested to explain the large difference in glucose homeostasis between the HI neonates and the rodent models. Interestingly, several mouse models that exhibit partial loss of SUR1/K_{IR}6.2 channel activity exhibit hypoglycemic phenotypes, which more nearly approximate the human disorder [64, 85].

The incretin response is impaired in Sur1KO mice

Glucagon-like peptide 1 (GLP-1), secreted in response to feeding, is known to potentiate glucose-stimulated insulin secretion via an increase in cyclic adenosine monophosphate (cAMP). Shiota et al. [137] showed that Sur1KO mice failed to increase their plasma insulin in response to exogenous GLP-1, and Nakazaki et al. [106] demonstrated that, whereas GLP-1, gastric inhibitory peptide (GIP), and exendin 4 increased the cAMP level in isolated islets, their potentiation of glucose-stimulated insulin release was reduced. The impaired incretin response was secondary to a blunted response to elevated cAMP acting via a protein kinase A (PKA)-independent pathway [48, 106]. The impaired response was specific for cAMP, and Sur1KO islets were stimulated by carbachol, a nonhydrolyzable analog of acetylcholine, and by tissue plasminogen activator (TPA), a protein kinase C (PKC) activator. In low glucose, stimulation by carbachol and TPA was more pronounced in Sur1KO vs wild-type islets, presumably due to the elevated oscillating $[Ca^{2+}]_c$. Using a yeast two-hybrid approach, Ozaki et al. [114] demonstrated an interaction between a fragment of SUR1 containing NBD1 and Epac-2 (cAMP-GEFII), a cAMP-binding guanine-nucleotide exchange factor [39, 77] and showed that Epac-2 interacted with Rim2, a member of a family of proteins that promote priming of granules for release in neurons (see 135 for review). These findings, coupled with the observation that the membranes of insulin containing dense core vesicles are rich in K_{ATP} channels [57], has led to models in which interactions between SUR1, Epac-2, RIM2, and various other proteins serve bridging functions between the plasma membrane and dense core vesicles (for example, 48, 135). These models are attractive as a means to explain how cAMP can potentiate exocytosis and why there is a blunted response to cAMP in Sur1KO animals. We have attempted to extend these results and have confirmed the interaction between NBD1 and Epac-2 (Fig. 4). However, we have been unable to demonstrate an interaction between Epac-2 and full-length SUR1 or SUR1/K_{IR}6.2, suggesting either that the interaction with a single NBD is nonspecific or that other proteins are involved.

Catecholamine response in Sur1KO mice

Sieg et al. [141] explored the idea that elevated epinephrine might act to suppress insulin release in Sur1KO mice. Others have implied that the inhibitory action of epinephrine on insulin secretion might involve activation of K_{ATP} channels, but exogenous epinephrine hyperpolarized Sur1KO β cells via an α2-adrenoceptor mechanism, thus inhibiting insulin secretion from isolated islets and suppressing carbachol-induced insulin release in Sur1KO mice. The molecular nature of the low conductance, $BaCl_2$-sensitive K^+ channels regulated by pertussis-sensitive G proteins associated with β-cell hyperpolarization is not known [141]. Preliminary measurements of catecholamine levels in Sur1KO vs wild-type mice have not uncovered any significant differences

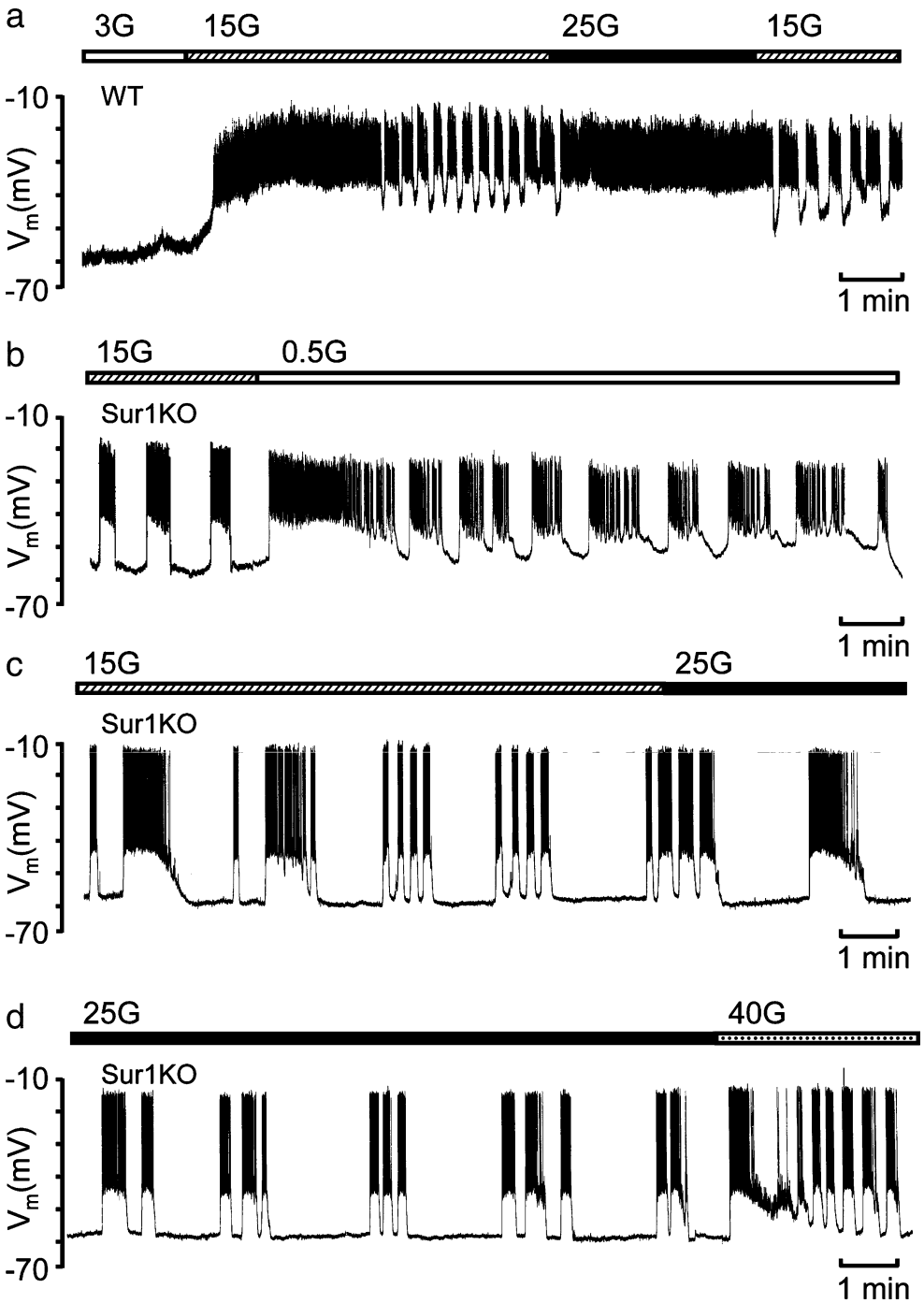

Fig. 3 Recording of plasma membrane potential using intracellular microelectrodes on intact islets. (**a**) Wild-type (*WT*) islets from C57Bl/6 mice in the presence of 3, 15, and 25 mmol/l glucose. (**b**–**d**) Continuous oscillations in Sur1KO islets perifused with 0.5, 15, 25, and 40 mmol/l glucose. Record (**d**) is the direct continuation of (**c**). The recordings are representative of five (**a**), nine (**b**), eight (**c**), and four (**d**) experiments. The figure is from Düfer et al. [44]

(unpublished data); therefore, we tentatively conclude that suppression of insulin release via elevated epinephrine does not tonically suppress insulin secretion in the knockout animals, but further study is warranted.

Acetylcholine and amino acids

Shiota et al. [137] showed that fasted Sur1KO mice increase their insulin level in response to feeding, suggesting that neural stimulation is an important factor. Doliba et al. [41] and Nakazaki et al. [106] reported that acetylcholine and carbachol stimulate insulin release from Sur1KO islets even in low glucose. Doliba et al. [41] argue secretion is impaired in the Sur1KO mice and suggest acetylcholine, released in response to feeding, enhances insulin secretion, thus contributing to their euglycemia. Amino acids are also known to potentiate insulin secretion, and several studies have reported amino acids stimulate insulin release from Sur1KO islets [65, 87, 105].

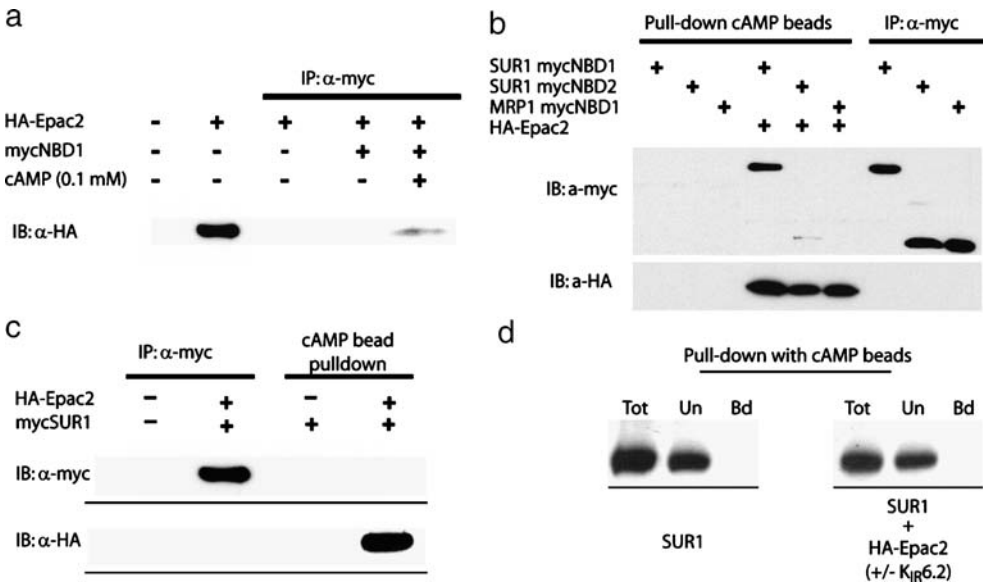

Fig. 4 Interaction of SUR1 NBD1, but not full-length SUR1, with Epac2. (**a**) Immunoprecipitation (*IP*) of myc-tagged SUR1 NBD1 with HA-tagged Epac2, a kind gift from Professor Johannes Bos. Constructs were expressed in COSm6 cells in combination as indicated, Triton X-100 (0.1%) cleared lysates were prepared and immunoprecipitated with an anti-myc antibody, solubilized in SDS, and blotted with anti-HA antibody. (**b**) Equivalent lysates were added to cAMP-agarose beads or precipitated with anti-myc antibodies. The beads or precipitates were washed, solubilized, separated by SDS–PAGE, then blotted with either anti-myc or anti-HA antibodies. NBD1 from mrp1 is given as a control. (**c**) COSm6 cells were transfected with HA-Epac2 and full-length myc-tagged SUR1. Cleared lysates were prepared as above and either precipitated with anti-myc antibodies or cAMP agarose beads. The beads or precipitates were washed, solubilized, separated by SDS–PAGE, then blotted with either anti-myc or anti-HA antibodies. (**d**) COSm6 cells were transfected with SUR1 or SUR1 plus HA-Epac2. SUR1 was specifically affinity-labeled with ^{125}I-azidoglibenclamide [34], and cleared lysates were prepared as above and incubated with cAMP agarose beads. The starting material (*Tot*), unbound fraction (*Un*), and bound material (*Bd*) were collected, separated by SDS–PAGE, and subject to autoradiography. There is a strong interaction with NBD1 (same fragment as 114), a weak interaction with NBD2, and no detectable interaction with NBD1 from MRP1 or with full-length SUR1

K_{ATP} channels are part of a brain–liver circuit that modulates hepatic glucose production

SUR1/K_{IR}6.2 channels are known to be present throughout the CNS and are implicated in neuroprotection during periods of anoxia (reviewed in 16). Here we focus on their role(s) in glucose homeostasis, particularly in the hypothalamus. Early electrophysiological studies identified a reciprocal response of hypothalamic neurons to applied glucose [3, 111, 112]. In the ventromedial hypothalamus (VMH), a majority of responding neurons increased their firing rate (glucose-responsive or glucose-stimulated), whereas in the lateral hypothalamus (LH), a majority reduced their activity (glucose-sensitive or glucose-inhibited). These results have been elegantly confirmed and extended by more recent studies, for example [142, 145]. Several reports and experiments on K_{IR}6.2KO mice (98; see 28, 86, 125 for review) indicate that glucose-stimulated neurons in the VMH underlie the counterregulatory response to hypoglycemia, although Yang et al. [155] have reported that glucose-inhibited neurons are involved. The behavior of glucose-stimulated neurons is consistent with a β-cell-type regulation of K_{ATP} channels in the sense that increased glucose metabolism reduces channel activity and, thus, increases the neuronal firing rate secondary to membrane depolarization. During hypoglycemia, the firing rate drops and is presumed to reduce an inhibitory effect on glucagon release.

Three recent articles delineate a novel brain–liver circuit involving neurons in the LH in which activation of K_{ATP} channels is implicated in the control of hepatic glucose production. The activity of these neurons is presumed to suppress hepatic glucose production and increased hypothalamic insulin [116], free fatty acids [84], and glucose [83] via intracerebroventricular (ICV) infusion, resulting in reduced blood glucose levels. These effects are mimicked by diazoxide alone and blocked by coinfusion of glibenclamide. Consistent with their lack of SUR1/K_{IR}6.2 K_{ATP} channels, Sur1KO mice maintained their hepatic glucose output when infused with fatty acids [84] or insulin [116].

It is not known whether the hypothalamic neurons involved in the brain–liver circuit are glucose-inhibited or glucose-stimulated, but based on the observation that the effect of increased glucose can be mimicked by diazoxide, a K_{ATP} channel activator, we tentatively conclude they are glucose-inhibited. In this case, the metabolic control of their membrane potential is distinctly at odds with the conventional β-cell paradigm in which increased fuel metabolism

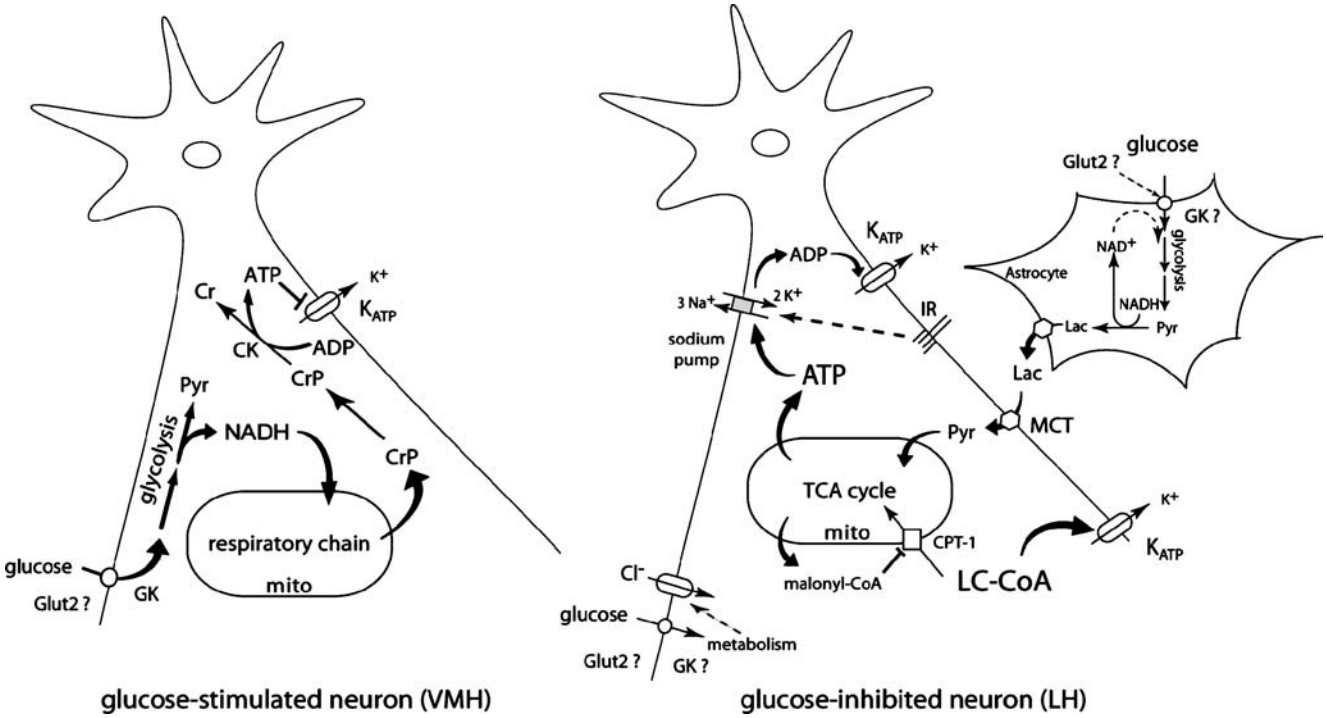

Fig. 5 Glucose-stimulated vs glucose-inhibited hypothalamic neurons. The *left panel* illustrates a β-cell-like mechanism of K_{ATP} channel regulation in a glucose-stimulated neuron in the VMH. Glucose metabolism increases the ATP/ADP ratio, reducing channel activity, thus depolarizing the neuron to increase its firing rate. The preferential role for NADH equivalents derived from glycolysis and hypothesized role for creatine phosphate (*CrP*) and creatine kinase (*CK*) described in the text are shown. The firing of glucose-stimulated VMH neurons is presumed to attenuate glucagon release from pancreatic α cells when blood glucose is elevated and reduced firing during periods of brain hypoglycemia leads to increased glucagon secretion as part of the counterregulatory response (reviewed in 28, 86, 125). The *right panel* illustrates three potential mechanisms whereby glucose metabolism is hypothesized to hyperpolarize glucose-inhibited neurons and decrease their firing rate. Song et al. [145] have suggested metabolic activation of an inward chloride (Cl^-) flux would result in hyperpolarization as diagramed in the *lower left side* of the *right panel*. Following the astrocyte-neuron lactate shuttle model [33, 76, 115] and Lam et al. [83], glucose metabolism in astrocytes leads to shuttling of lactate (*Lac*) into neurons via monocarboxylate transporters (*MCTs*), where it is converted to pyruvate (*Pyr*) and metabolized in mitochondria. The malonyl-CoA/LC-CoA model of glucose-stimulated insulin secretion holds that during glucose stimulation, increased TCA cycle activity in pancreatic β cells elevates malonyl-CoA via increased citrate production (reviewed in 35, 40). The inhibition of carnitine–palmitoyl transferase 1 (*CPT-1*) by malonyl–CoA subsequently leads to an increase in LC-CoAs that can activate K_{ATP} channels as illustrated in the *lower right*. Finally, early studies by Oomura and colleagues [113] implicated activation of the electrogenic sodium pump in the reduced firing rate of glucose-inhibited neurons. This hypothesis is supported by measurements of V_m, $[Na^+]_i$, and $[K^+]_i$ by Silver and Ereciñska [142], and the stimulation of pump activity by insulin via a multistep process involving insulin receptors (*IRs*) (reviewed in 146). Both glucokinase (*GK*) and the Glut2 glucose transporter have been implicated in regulation of VMH neurons (reviewed in 125)

reduces K_{ATP} channel activity and would be mimicked by sulfonylureas rather than diazoxide, which stimulates K_{ATP} channels. The metabolic control of firing rate in these neurons is poorly understood; three mechanisms, summarized schematically in Fig. 5, have been suggested: (1) Oomura and colleagues [113] proposed that increasing activity of the electrogenic sodium pump (Na^+-/K^+-ATPase), secondary to increased glucose metabolism, can hyperpolarize glucose-inhibited neurons. This would be consistent with the $[Na^+]_i$ and $[K^+]_i$ determinations of Silver and Erecińska [142] on glucose-inhibited neurons, and both insulin and long-chain acyl CoAs are reported to stimulate the sodium pump. (2) Song et al. [145] proposed metabolic activation of a Cl^- influx as the basis for hyperpolarization of glucose-inhibited (GI) neurons in the ventromedial nucleus. (3) The activation of K_{ATP} channels by LC-CoA is a potential mechanism. The cytosolic concentration of LC-CoA is expected to rise when fatty acids are elevated and with increased glucose metabolism due to a rise in malonyl-CoA, an inhibitor of CPT1 (carnitine-palmitoyl transferase 1), which transports LC-CoA into mitochondria (reviewed in 35, 40). Understanding metabolic control in these neurons and the role of K_{ATP} channels presents a clear challenge.

Summary

Adenosine-triphosphate-sensitive K^+ channels present a unique use of ABC proteins as regulators of ion channels rather than transporters in their own right. Continuing

analyses of the role of these channels in human genetic disease have provided better understanding of disorders of glucose homeostasis and their treatment and have validated the dual role nucleotides play in the regulation of channel activity. Understanding how HI and ND mutations inhibit and stimulate channel activity promises further insight into the molecular control of channel gating, whereas studies on K_{ATP} channel knockout mice continue to provide novel insights into their function.

Acknowledgement This work was supported by grants from the Deutsche Forschungsgemeinschaft (Dr225/6-1 and Du425/1-1) and the US National Institutes of Health (DK52771, DK44311, and JDRF 1-2005-950). There are no conflicts of interest in this study.

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