

# Channelopathies of inwardly rectifying potassium channels

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**ABSTRACT** Mutations in genes encoding ion channels have increasingly been identified to cause disease conditions collectively termed channelopathies. Recognizing the molecular basis of an ion channel disease has provided new opportunities for screening, early diagnosis, and therapy of such conditions. This synopsis provides an overview of progress in the identification of molecular defects in inwardly rectifying potassium (Kir) channels. Structurally and functionally distinct from other channel families, Kir channels are ubiquitously expressed and serve functions as diverse as regulation of resting membrane potential, maintenance of K<sup>+</sup> homeostasis, control of heart rate, and hormone secretion. In humans, persistent hyperinsulinemic hypoglycemia of infancy, a disorder affecting the function of pancreatic  $\beta$  cells, and Bartter's syndrome, characterized by hypokalemic alkalosis, hypercalciuria, increased serum aldosterone, and plasma renin activity, are the two major diseases linked so far to mutations in a Kir channel or associated protein. In addition, the weaver phenotype, a neurological disorder in mice, has also been associated with mutations in a Kir channel subtype. Further genetic linkage analysis and full understanding of the consequence that a defect in a Kir channel would have on disease pathogenesis are among the priorities in this emerging field of molecular medicine.—Abraham, M. R., Jahangir, A., Alekseev, A. E., Terzic, A. Channelopathies of inwardly rectifying potassium channels. *FASEB J.* 13, 1901–1910 (1999)

*Key Words:* ion channel disease • persistent hyperinsulinemic hypoglycemia of infancy • Bartter's syndrome • weaver phenotype

MALFUNCTIONS IN ION channels, due to mutations in genes encoding channel proteins, have been implicated in the pathogenesis of a growing number of diseases termed channelopathies (1–4). This is the case with cystic fibrosis, which represents a common hereditary disease in Caucasians. This channelopathy is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) and is associated with defective chloride conductance, which leads to

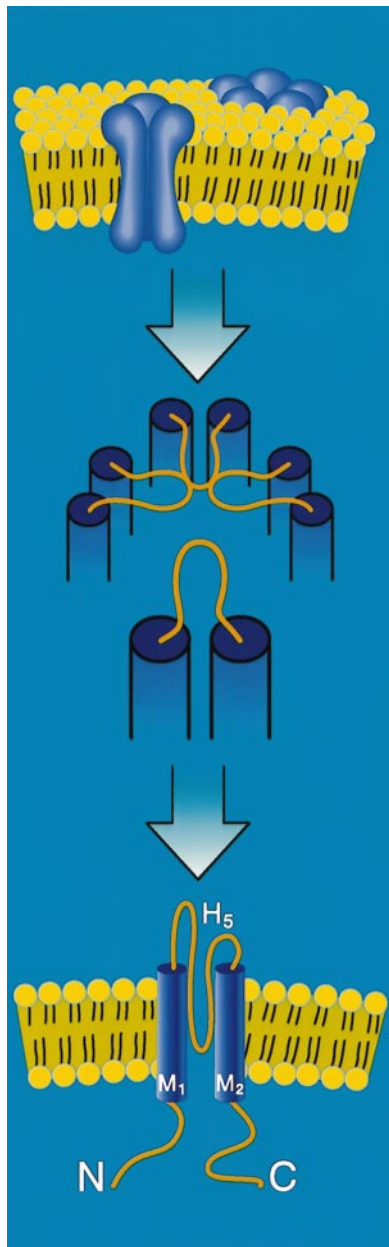
pulmonary and pancreatic insufficiency (5–8). Another well-characterized channelopathy is congenital long QT syndrome associated with sudden cardiac death in otherwise healthy young individuals. This condition is due to mutations in Na<sup>+</sup> channels or voltage-dependent K<sup>+</sup> channels (9–13). Recognizing the molecular basis of an ion channel disease has provided new opportunities for screening, early diagnosis, and therapy of these conditions (1–18).

We provide an overview of progress made in the identification of molecular defects in inwardly rectifying K<sup>+</sup> (Kir) channels. This is a distinct family of ion channels that regroups seven channel subfamilies that have been recently cloned (19–21). A description of fundamental properties of this channel family is provided, along with molecular defects causing specific disease conditions. In humans, persistent hyperinsulinemic hypoglycemia of infancy and Bartter's syndrome are the two diseases that have been linked to mutations in Kir channel or associated proteins. In addition, the weaver phenotype, a neurological disorder in mice, has also been associated with Kir channel defects. As Kir channels serve multiple roles throughout the body, it is conceivable that additional clinical conditions will be found related to dysfunctions in one or several members of this channel family.

## Kir CHANNELS

The existence of Kir channels was first recognized half a century ago (22), but only recently have genes encoding Kir proteins been cloned (23–28). This family of potassium channel genes encodes proteins in the range of ~360–500 amino acids (19–21, 27). In accordance with an early place in evolution, Kir channels have a structure that is simpler than that of other ion channel families (19–21, 27, 29, 30). The general structure of a Kir channel consists of two

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**Figure 1.** Inwardly rectifying  $K^+$  channel structure. An inwardly rectifying  $K^+$  channel complex spans the plasma membrane (top panel) and is a tetramer (middle panel) of individual subunits that consist of two transmembrane-spanning domains (M1 and M2) flanking the pore region (H5), in addition to the amino (N) and carboxy (C) terminus of the channel protein (lower panel).

membrane-spanning domains (M1 and M2) that flank a highly conserved pore (P) region containing the conserved H5 segment (Fig. 1). The H5 and M2 segments, in conjunction with the carboxyl terminus hydrophilic domain, are critical for potassium permeation. Four channel subunits presumably assemble to form functional Kir channels (Fig. 1). A tetrameric channel complex can be formed by physical association of identical ('homomers') or different ('heteromers') subunits. The amino acid sequences of various Kir channels diverge at the distal

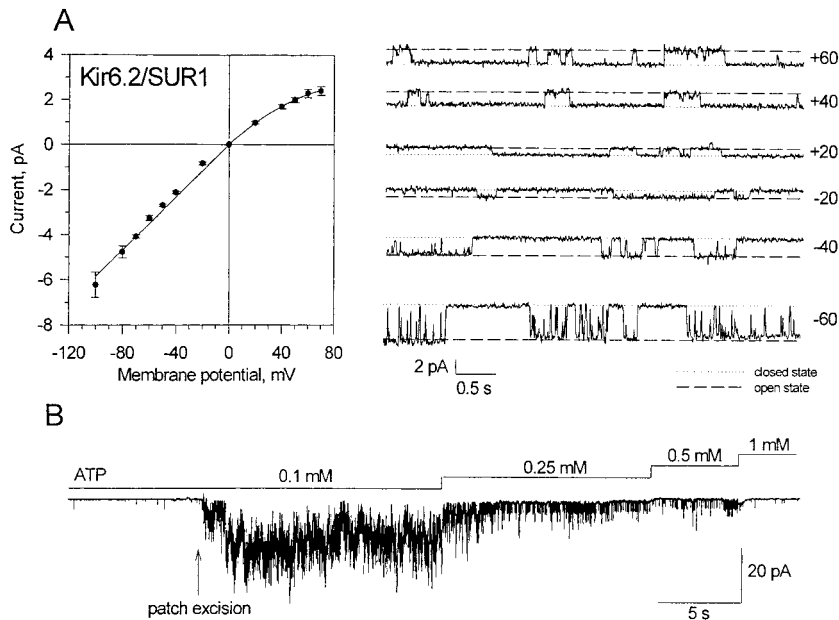
TABLE 1. Kir channels: nomenclature and function

Channel	Function
Kir1.0 (ROMK)	Maintenance of $K^+$ homeostasis and renal $K^+$ secretion
Kir2.0 (IRK)	Maintenance of resting membrane potential and modulation of action potential waveforms
Kir3.0 (GIRK)	Modulation of heart rate and neuronal excitability
Kir4.0	Maintenance of $K^+$ homeostasis in kidney and glia
Kir5.0	Unknown
Kir6.0 ( $K_{ATP}$ )	Links metabolic state of a cell to membrane excitability, insulin secretion, cytoprotection, and maintenance of vascular tone
Kir7.0	Maintenance of resting membrane potential

carboxyl and amino terminus, as well as in the extracellular loop linking the M1 and P regions. Comparisons among the remaining core sequences reveal the existence of at least seven subfamilies (Table 1), designated Kir1.0 to Kir7.0 (21, 28). Further diversity is achieved through association of Kir subunits with additional, structurally unrelated protein(s) that play important roles in the expression, distribution, or regulation of channel activity (19–21, 27). The biophysical fingerprint of Kir channels is inward rectification in the current-voltage relationship (Fig. 2), which limits potassium efflux at depolarizing membrane potentials (20). By virtue of their properties, Kir channels are essential in the control of resting membrane potential, coupling of the metabolic cellular state with membrane excitability, and maintenance of potassium homeostasis (19–21). The properties of the seven major subfamilies of Kir channels are summarized in Table 1.

Kir1.1, also known as ROMK1, was the first Kir channel to be cloned (23). This channel is predominantly expressed in the kidney, where it plays a major role in the maintenance of potassium homeostasis. The biophysical properties of this channel, including a single channel conductance in the range of 35–45 pS, enable efficient flux of large amounts of potassium into collecting tubules of the distal nephron (23, 27, 31). A number of ROMK channel isoforms have been cloned and are differentially expressed among different segments of renal tubules, suggesting distinctive functional roles in controlling potassium secretion in the kidney (27, 31).

Kir2.0 channels, also known as IRK channels, play a significant role in setting the resting membrane potential, buffering extracellular potassium, and modulating the action potential waveform (19–21, 27, 29). The first Kir2.0 channel cloned was Kir2.1 (IRK1), which has a single channel conductance of



**Figure 2.** Inwardly rectifying  $K^+$  current. Current, recorded at equimolar  $K^+$  concentration, through the recombinant ATP-sensitive  $K^+$  channel after coexpression of the inwardly rectifying  $K^+$  channel subunit, Kir6.2, with the regulatory SUR1 subunit. *A*) Current-voltage relationship (left panel) and actual single channel tracings (right panel) show smaller outward than inward currents at positive vs. equivalent negative membrane potentials, a characteristic of inwardly rectifying  $K^+$  channels. *B*) Single channel recording showing channel activity before and high channel activity after excision of a membrane patch from a cell coexpressing Kir6.2 and SUR1. Addition of higher concentrations of ATP to the intracellular side of the excised patch suppressed channel activity, a characteristic of ATP-sensitive  $K^+$  channels.

$\sim 22$  pS (24) and is expressed in the forebrain, heart, and skeletal muscle. Kir2.2 (IRK2), which produces current with a conductance of  $\sim 34$  pS, is believed to govern the resting phase of the action potential in cardiomyocytes (27). Kir2.3 (IRK3) predominates in the forebrain (27).

The Kir3.0 subfamily, designated as GIRK channels, regroups Kir channels that are gated by GTP binding proteins (G-proteins). These channels are expressed primarily in the brain and heart. The first member to have been cloned was GIRK1 (Kir3.1), which is predominantly expressed in the cardiac atrium (25). It is a strong inward rectifier with a single channel conductance of  $\sim 42$  pS. Coassembly of Kir3.1 (GIRK1) with Kir3.4 (GIRK4 or CIR) forms the receptor-gated Kir channel, also known as the  $K_{ACh}$  channel (32). This channel helps to slow down heart rate during vagal stimulation of muscarinic M2 receptors through activation of  $\beta\gamma$  subunits of the G-proteins (33–36). This channel is also responsible for the bradycardic action of adenosine through activation of A1-adenosine receptors (35). Knockout mice lacking GIRK4 are unable to adjust heart rate on a rapid time scale, indicating a critical role for  $K_{ACh}$  in the regulation of heart rate variability (37). In the central nervous system, activation of GIRK channels is involved in the inhibitory actions of GABA, acetylcholine, adenosine, somatostatin, and opioid peptides. Mice lacking GIRK2 are more susceptible to develop seizures induced by GABA antagonists (38).

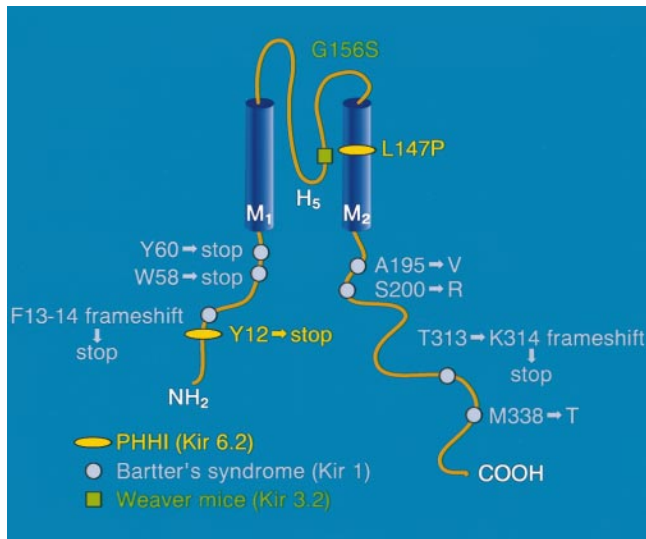
Kir4.0 is also a strong inward rectifier expressed in the kidney and brain. In the kidney it is located mainly in the basolateral membrane of the distal tubular epithelia, suggesting it may contribute to supplying potassium to the  $Na^+-K^+$  pump. In the brain, it is expressed mainly in glia, where it may be responsible for potassium buffering (39, 40).

Kir5.1 apparently does not produce functional Kir channels when expressed by itself. It may serve a role in Kir channel diversity by coassembly with other Kir channel subunits (21).

Kir6.1 and 6.2 assemble with a structurally unrelated ATP binding cassette protein, known as the sulfonylurea-receptor or SUR (26, 41–44). Kir6.2 and SUR1 form the pancreatic ATP-sensitive potassium ( $K_{ATP}$ ) channel (Fig. 2) responsible for glucose-mediated insulin secretion (26, 45–51). Transgenic animals with targeted disruption of pancreatic Kir6.2 exhibit hypoglycemia after birth due to abnormal insulin secretion, but develop hyperglycemia with age due to calcium overload and loss of pancreatic  $\beta$  cells (50). Overexpression of Kir6.2 and SUR1 prevents calcium overload conferring protection against injury (52). Kir6.2 and SUR2A form the cardiac  $K_{ATP}$  channel phenotype (53, 54), which mediates action potential shortening in ischemic cardiomyocytes (55, 56) and confers resistance to hypoxia-reoxygenation (57). SUR2B is believed to associate with either Kir6.2 or Kir6.1 to generate a vascular  $K_{ATP}$  channel type (43, 58). Through ATP/ADP-dependent gating,  $K_{ATP}$  channels sense the metabolic state of a cell and accordingly regulate membrane excitability (59–67).  $K_{ATP}$  channels are targets for neurohormones (68, 69) as well as pharmacological agents, including the clinically used sulfonylureas (70) and potassium channel openers (71, 72).

Kir7.1 is the newest addition to the family of inward rectifiers (28). Widely expressed in the brain, but also present in kidney and intestine, this channel appears to be responsible for setting the resting membrane potential in these tissues (28).

Among the seven Kir subfamilies, disease-causing mutations in humans have been found in Kir6.2 and



**Figure 3.** Mutations in inwardly rectifying  $K^+$  channels associated with disease conditions. These include two mutations in Kir6.2 (the pore-forming subunit of the  $K_{ATP}$  channel) related to persistent hyperinsulinemic hypoglycemia of infancy (PHHI), seven mutations in ROMK2 (Kir 1) in Bartter's syndrome, and a mutation in Kir3.2 (GIRK2) causing the weaver phenotype.

Kir1 genes (**Fig. 3; Table 2**). In addition, the weaver phenotype, a neurological disorder in mice, has been linked to mutations in the GIRK2 gene (Fig. 3; Table 2).

## Kir-ASSOCIATED CHANNELOPATHIES

### Persistent hyperinsulinemic hypoglycemia of infancy

Mutations in Kir6.2 and the associated protein SUR1 have been linked to the syndrome of persistent hyperinsulinemic hypoglycemia of infancy (PHHI),

also known as nesidioblastosis or familial hyperinsulinism (73–78). This is the most common cause of persistent hypoglycemia in young children. Estimates for the incidence of this disease vary from 1 in 40,000 live births in Northern Europe to 1 in 2500 live births in Saudi Arabia, where there is a high degree of consanguinity. Both autosomal dominant and recessive forms of PHHI have been described. The autosomal recessive forms are more common, and the locus for PHHI has been assigned to chromosome 11p14–15.1 by genetic linkage analysis (76). Both SUR1 and Kir6.2 are clustered on chromosome 11p15.1 (26).

More than 20 distinct mutations have been described in the SUR1 gene, which encodes the regulatory subunit of the pancreatic  $K_{ATP}$  channel (77). Among these, one mutation occurred in the first nucleotide binding fold (NBF-1) of SUR1 and eight were located in the second nucleotide binding fold (NBF-2); the remaining mutations were found throughout putative transmembrane domains of SUR1 (77–80). Frequent mutations in patients with Ashkenazi Jewish descent affect the NBF-2 of the SUR1 gene and include a glycine to alanine transition in intron 32 (3993–9G→A), as well as the deletion of the codon for phenylalanine at position 1388 ( $\Delta F1388$ ), associated with loss of normal  $K_{ATP}$  channel activity (81). Other mutations in NBF-2 include, for example, a point mutation G1479R, where glycine is replaced by arginine at position 1479, which gives rise to an insensitivity of the  $K_{ATP}$  channel toward the endogenous channel activator, ADP (61).

Mutations within Kir6.2, the pore-forming core of the  $K_{ATP}$  channel, have also been implicated in the pathogenesis of the disease (Fig. 3). These include a point, missense mutation in Kir6.2 (Fig. 3) that is predicted to disrupt the conserved  $\alpha$ -helical second transmembrane (M2) domain of this inward-rectify-

TABLE 2. Kir channelopathies

Channelopathy	Chromosome location	Channel	Mutations	Functional effect	Mode of inheritance	Clinical manifestations
Persistent hyperinsulinemic hypoglycemia of infancy	11p14-15.1 (human)	Kir6.2 (subunit of $K_{ATP}$ )	Y12→stop L147P	Loss of function	Autosomal recessive	Hyperinsulinemic hypoglycemia, macrosomia, seizures, coma
Bartter's syndrome	11q24 (human)	Kir1 (ROMK)	F13-14→stop W58→stop Y60→stop A195V; S200R T313-K314→stop M338T	Loss of function	Autosomal recessive	Polyhydramnios, premature birth, dehydration, hypokalemia, alkalosis, hypercalciuria
Weaver phenotype	16 (mouse)	Kir3.2 (GIRK2)	G156S	Loss of function and gain of new function	Autosomal recessive	Severe ataxia, male sterility, seizures

ing channel by substitution of a proline for a leucine (L147P) residue (82). Also, a nonsense mutation in Kir6.2 at codon 12 (Y12X, tyrosine→Stop) has been identified (Fig. 3) in patients with familial hyperinsulinism (83). This latter mutation is expected to produce a truncated Kir6.2 polypeptide, lacking the putative potassium selective pore region, and domains that are proposed to confer gating and inward rectification properties (83).

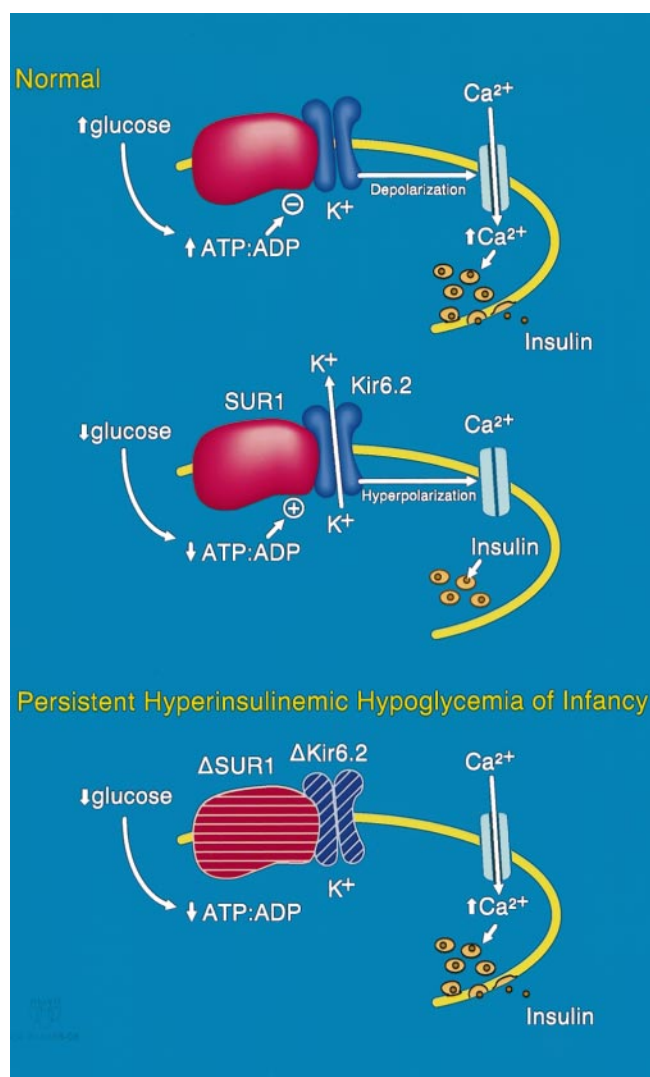
Normal pancreatic  $K_{ATP}$  channels close in response to hyperglycemia, leading to membrane depolarization, influx of  $Ca^{2+}$ , and insulin release (Fig. 4). During hypoglycemia, opening of pancreatic  $K_{ATP}$  channels hyperpolarizes the membrane, preventing insulin release (Fig. 4). Mutated Kir6.2 and/or SUR1 genes generate defective  $K_{ATP}$  channels in pancreatic  $\beta$  cells, which leads to loss in the ability to regulate insulin release in response to changes in blood glucose concentration (Fig. 4). Although mutations have been associated with specific changes in  $K_{ATP}$  channel behavior, the precise mechanism that translates a specific mutation into a disease phenotype is not entirely characterized (78, 84). Moreover, a number of patients with the autosomal dominant variant of hyperinsulinism have no identifiable mutations in Kir6.2 or SUR1 genes, and the disease condition may be associated with disruption of other protein functions (85, 86).

Despite a heterogeneity in the underlying pathology and clinical presentation, the characteristic feature of PHHI is a persistent hyperinsulinism in the presence of severe hypoglycemia. In fact, familial hyperinsulinism is commonly defined as a disorder characterized by inadequate suppression of insulin secretion in the presence of severe, recurrent fasting hypoglycemia (73–75). PHHI usually presents within a few hours or days after birth with macrosomia, seizures, and/or coma. Occasionally it can present in adulthood with fasting hypoglycemia.

Treatment involves glucose infusion and a high carbohydrate diet. In addition, certain patients respond to pharmacotherapy with openers of pancreatic  $K_{ATP}$  channels that inhibit insulin secretion such as diazoxide or somatostatin analogs. The mechanism underlying the beneficial action of potassium channel openers in patients with mutations in the  $K_{ATP}$  channel is not fully understood (87). Patients with mild disease can be managed with diet alone. Patients with severe disease, who fail diet and drug therapy, require a partial or subtotal pancreatectomy to prevent recurrent hypoglycemia. In the absence of treatment, PHHI can be lethal or result in irreversible neurological sequelae (73–75).

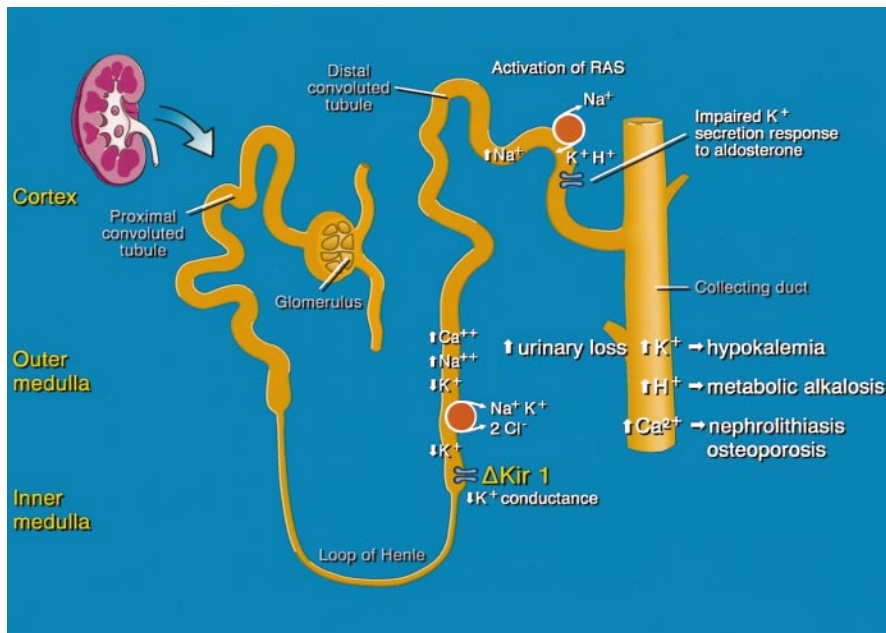
### Barter's syndrome

Barter's syndrome is an autosomal recessive disease characterized by hypokalemia, salt wasting, metabolic



**Figure 4.** Normal or mutated pancreatic Kir6.2/SUR1 channels and glucose-regulated insulin secretion. In normal individuals, hyperglycemia increases the intracellular ATP/ADP ratio, causing ATP-sensitive  $K^+$  channels (composed of Kir6.2 and SUR1 subunits) to close, which depolarizes the plasma membrane and promotes  $Ca^{2+}$  influx leading to insulin release. Hypoglycemia decreases the intracellular ATP/ADP ratio, causing ATP-sensitive  $K^+$  channels to open, which hyperpolarizes the plasma membrane and inhibits  $Ca^{2+}$  influx, preventing insulin release. Persistent hyperinsulinemic hypoglycemia of infancy may result from mutations in Kir6.2 ( $\Delta$ Kir6.2) or SUR1 ( $\Delta$ SUR1). This could lead to defective ATP-sensitive  $K^+$  channel behavior with loss of normal response to hypoglycemia, resulting in persistent insulin secretion despite low glucose levels.

alkalosis, hypercalciuria, hyperreninism, hyperaldosteronism, and normal blood pressure (88, 89). Infants with Barter's syndrome are usually born prematurely with polyhydramnios and show marked dehydration in the neonatal period. The molecular basis of the Barter's syndrome is genetically heterogeneous (88, 89). Originally, mutations in gene encoding the bumetanide-sensitive  $Na^+-K^+-2Cl^-$  transporter (NKCC2) (90, 91) and the chloride channel gene, CLCNKB (92, 93), had been associated with the disease. More recently, in



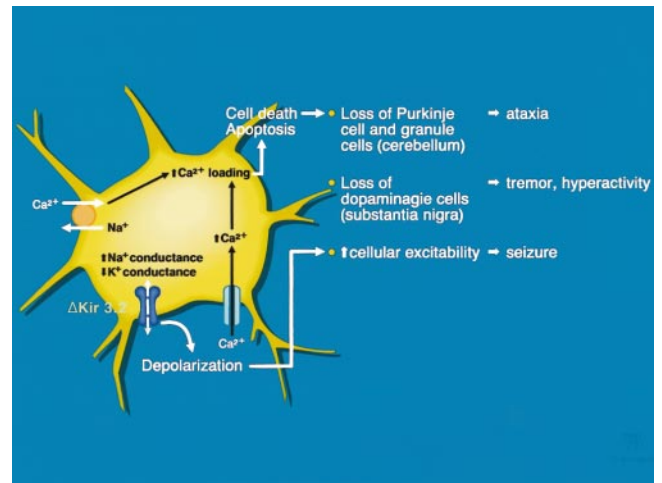
**Figure 5.** Bartter's syndrome due to mutations in Kir1 (ROMK) channels expressed in the renal tubule. Defective  $K^+$  channels in the ascending loop of Henle result in decreased  $K^+$  in the lumen. This prevents reabsorption of  $NaCl$  through the  $Na^+/K^+/2Cl^-$  exchanger, leading to salt wasting from this segment. Increased  $Na^+$  delivery to distal tubules promotes  $Na^+$  reabsorption in exchange for  $K^+$  and  $H^+$ . In addition, decreased  $Na^+$  absorption in the thick ascending limb produces decreased  $Ca^{2+}$  reabsorption. Mutated  $K^+$  channels further cause impaired  $K^+$  secretion in response to aldosterone. This results in loss of urinary salt,  $H^+$ , and  $Ca^{2+}$  causing hypokalemia, metabolic alkalosis, nephrolithiasis, and/or osteoporosis.

a subset of patients with Bartter's syndrome, mutations in the ROMK subfamily of Kir channels have also been implicated in the pathogenesis of this disease (94–96).

ROMK channels regulate  $K^+$  recycling and mediate net  $K^+$  secretion in the thick ascending loop of Henle and distal nephron (Fig. 5), respectively (23, 31). Multiple ROMK isoforms are generated by alternative splicing of a gene located on chromosome 11q24 (31). Defects associated with the Bartter's syndrome include mutations (94) occurring at codon 58 (W58→STOP) or codon 60 (Y60→STOP), which lead to truncation of the protein prior to the first transmembrane domain, or a frameshift mutation (F13–14→Frameshift) resulting in premature termination of the ROMK protein (Fig. 3). A missense mutation, substituting arginine for serine at codon 200 (S200→R), was also identified (94) in another Bartter's kindred (Fig. 3). This serine is a conserved protein kinase A phosphorylation site in the carboxyl terminus domain of ROMK channels required for optimal channel activity (94). Other mutations (Fig. 3) include a valine for alanine (A→V) mutation at a conserved site (position 195) in the carboxyl terminus as well as a frameshift mutation (T313-K314→Frameshift) altering the encoded protein from amino acid 315 onward, ending at a new stop codon (94). Finally, a single ROMK variant substituting threonine for methionine at amino acid M338 (Fig. 3) was also identified in one outbred kindred (94).

Loss of ROMK function results in the inability to recycle potassium from cells of the thick ascending loop of Henle back into the renal tubule, resulting in low luminal potassium levels that prevent continued  $Na^+-K^+-2Cl^-$  cotransporter activity (Fig. 5). This results in salt wasting from this segment of the

nephron (94). Increased delivery and reabsorption of sodium occur in the distal tubule in exchange for potassium and hydrogen, leading to hypokalemic alkalosis (Fig. 5). In addition, hypercalciuria, nephrolithiasis, and/or osteoporosis can occur as a consequence of increased urinary calcium loss (Fig. 5). Loss of ROMK activity in the distal tubule would also be expected to result in impaired potassium secretion in response to aldosterone (94–96).



**Figure 6.** Mutation in Kir3.2 (GIRK2) and weaver mice pathophysiology. Mutation in the pore region of Kir3.2 leads to an aberrant increase in  $Na^+$  conductance (with decrease in  $K^+$  conductance), promoting membrane depolarization, and neuronal  $Ca^{2+}$  loading through  $Ca^{2+}$  channels and the  $Na^+/Ca^{2+}$  exchanger. This may lead to cell death, with loss of Purkinje and granule cells in the cerebellum, resulting in ataxia. In addition, loss of dopaminergic cells in substantia nigra results in tremor and hyperactivity. Membrane depolarization leads to increase in neuronal excitability and seizures.

## Weaver phenotype

The weaver phenotype in mice is inherited as an autosomal recessive disease and results in severe ataxia within 2 wk of birth (97). The weaver mutation causes a defect in neuronal differentiation: precursor granule cells in the external germinal layer of the cerebellar cortex fail to extend neurites or migrate, resulting in neuronal degeneration (17). The homozygous weaver genotype results in a decreased cerebellar size, death of dopaminergic cells in the substantia nigra, male sterility, and sporadic tonic-clonic seizures (Fig. 6).

The weaver mutation (Fig. 3) is a missense mutation resulting in a single amino acid substitution (G156S) within the highly conserved H5 pore region of the Kir3.2 (GIRK2) channel (97). This mutation leads to loss of potassium selectivity of homomeric GIRK2 channels and strongly reduces heteromeric GIRK1/GIRK2 function (98–100). Moreover, channels containing mutated GIRK2 exhibit weaker inward rectification and impaired G-protein activation (98, 100). Overall, mutated GIRK2 causes both a new function (increased Na<sup>+</sup> conductance) and a loss of function (reduction in the expression of GIRK-2 containing channels). Thus, the mutated GIRK2 allele is neomorphic for some phenotypes and hypomorphic for others (101). An increase in Na<sup>+</sup> conductance (and decrease in K<sup>+</sup> conductance) would promote membrane depolarization and activate voltage-gated Ca<sup>2+</sup> channels and NMDA-glutamate receptors (Fig. 6). This might lead to intracellular Ca<sup>2+</sup> loading and cell death (102). Unlike homozygous weaver mutants, transgenic animals lacking the GIRK2 gene are morphologically indistinguishable from wild-type mice and exhibit milder cerebellar abnormalities than the weaver mice, although they are susceptible to seizures (38, 103). These results would indicate that the weaver phenotype results most likely from a gain-of-function mutation of GIRK2 (38, 103). Further elucidation of the primary defect in weaver mice may provide insight into human degenerative neural diseases. It is conceivable that conditions associated with loss of substantia nigra dopaminergic neurons, such as Parkinson disease, may result from dysfunction of potassium channels.

## CONCLUSION

After the most recent cloning of genes encoding Kir channels (Table 1), major progress has been made in identifying disease states associated with mutations in inwardly rectifying potassium channels or associated proteins (Table 2). In humans, mutations in the Kir6.2 gene and associated SUR1 protein have

already been linked to persistent hyperinsulinemic hypoglycemia of infancy, whereas mutations in ROMK channels have been related to certain forms of Bartter's syndrome. Since Kir channels serve diverse and important roles throughout the human body (19, 20, 23, 37, 51, 104), the search for clinical conditions associated with aberrant Kir channels has only begun. The major challenge for the future will be to recognize the molecular basis of a Kir-mediated channelopathy in order to screen, diagnose, and treat these ion channel diseases. FJ

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