

The molecular mechanisms and pharmacotherapy of ATP-sensitive potassium channel gene mutations underlying neonatal diabetes

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Abstract: Neonatal diabetes mellitus (NDM) is a monogenic disorder caused by mutations in genes involved in regulation of insulin secretion from pancreatic β -cells. Mutations in the *KCNJ11* and *ABCC8* genes, encoding the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel Kir6.2 and SUR1 subunits, respectively, are found in ~50% of NDM patients. In the pancreatic β -cell, K_{ATP} channel activity couples glucose metabolism to insulin secretion via cellular excitability and mutations in either *KCNJ11* or *ABCC8* genes alter K_{ATP} channel activity, leading to faulty insulin secretion. Inactivation mutations decrease K_{ATP} channel activity and stimulate excessive insulin secretion, leading to hyperinsulinism of infancy. In direct contrast, activation mutations increase K_{ATP} channel activity, resulting in impaired insulin secretion, NDM, and in severe cases, developmental delay and epilepsy. Many NDM patients with *KCNJ11* and *ABCC8* mutations can be successfully treated with sulfonylureas (SUs) that inhibit the K_{ATP} channel, thus replacing the need for daily insulin injections. There is also strong evidence indicating that SU therapy ameliorates some of the neurological defects observed in patients with more severe forms of NDM. This review focuses on the molecular and cellular mechanisms of mutations in the K_{ATP} channel that underlie NDM. SU pharmacogenomics is also discussed with respect to evaluating whether patients with certain K_{ATP} channel activation mutations can be successfully switched to SU therapy.

Keywords: neonatal diabetes, *KCNJ11*, *ABCC8*, ATP-sensitive potassium channels

Introduction

Neonatal diabetes mellitus (NDM), either transient or permanent, is characterized by the occurrence of insulin-requiring diabetes in the first 6 months of life. The incidence of NDM is estimated to be 1 in ~200,000 live births.^{1,2} The diabetes in 50%–60% of NDM is transient in nature, resolving within 18 months of birth and is thus termed TNDM.³ The remaining 40%–50% of NDM cases are permanent (PNDM) and require insulin treatment throughout life.³ In the most severe cases of NDM, the diabetes may be accompanied by marked developmental delay, muscle weakness, and epilepsy, termed DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome.⁴ A form of NDM, between PNDM and DEND in severity, is known as intermediate DEND (iDEND), in which patients with PNDM show developmental delay or muscle weakness but not epilepsy.⁴

The evidence to date indicates that NDM is a monogenic disorder. Although mutations in multiple genes can cause NDM, such as *INS* (insulin gene) mutations^{5,6} and *GCK* (glucokinase gene) mutations,^{7,8} much attention has focused on the most common forms of NDM caused by heterozygous activation mutations in the *KCNJ11*^{9–12} and

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ABCC8^{13–15} genes that encode the two subunits Kir6.2 and SUR1, respectively, of the adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel that couples cellular metabolism to cellular excitability.¹⁶ K_{ATP} channels composed of Kir6.2 and SUR1 subunits are predominately expressed in endocrine tissues such as the pancreatic islet and nervous system. Therefore, the diabetic phenotype of NDM is believed to arise from K_{ATP} channel activation mutations in pancreatic β -cells,^{10,16} whereas neurological features associated with the more severe iDEND/DEND syndromes are likely the result of K_{ATP} channel activation mutations deleteriously affecting the nervous system.^{4,17}

The physiological role of K_{ATP} channels in pancreatic β -cells

K_{ATP} channels sense changes in the cytosolic ATP/ADP ratio as a result of cellular metabolism and are a major regulator of the β -cell membrane potential. As glucose-stimulated insulin secretion is primarily controlled by the β -cell membrane potential, K_{ATP} channels serve to couple glucose metabolism to insulin secretion.^{16,18} When plasma glucose levels are low, the cytosolic ATP/ADP ratio is reduced, leading to a basal efflux of potassium ions from the cell via K_{ATP} channel activity that maintains the membrane potential of the β -cell at approximately -70 mV. This polarized membrane potential prevents calcium entry through voltage-gated calcium channels. As elevations in cytosolic calcium are the primary trigger for insulin granule

exocytosis, insulin secretion is suppressed when plasma glucose levels are low (Figure 1A).^{19,20} When plasma glucose levels rise, glucose enters the β -cells via the glucose transporter 2. Subsequent glucose metabolism leads to an increase in the ratio of cytosolic ATP/ADP ratio, promoting K_{ATP} channel closure. The resultant decrease in potassium ion efflux depolarizes the β -cell membrane potential, leading to activation of voltage-gated calcium channels, calcium influx, and calcium-stimulated insulin granule exocytosis (Figure 1B).²¹ Graded increases in plasma glucose and subsequent metabolism lead to proportional decreases in K_{ATP} channel activity, resulting in an appropriate insulin secretory response that is tightly coupled to the plasma glucose concentration.

As the electrical resistance of β -cell is high,²² only small changes in K_{ATP} channel activity are required to change β -cell excitability (and hence insulin secretion) via alterations in the β -cell membrane potential.²³ Mutations within the K_{ATP} channel complex that change their intrinsic activity and/or ability to sense changes in either ATP or ADP will result in altered K_{ATP} channel activity that is correlated to the specific effects of the individual mutation on K_{ATP} channel activity.

K_{ATP} channels encoded by the *KCNJ11* and *ABCC8* genes are also expressed in other excitable tissues such as the nervous system. As K_{ATP} channels are involved in the control of neuronal excitability, mutations may also cause neuronal abnormalities, again dependent on the severity of the individual mutation.^{24–27}

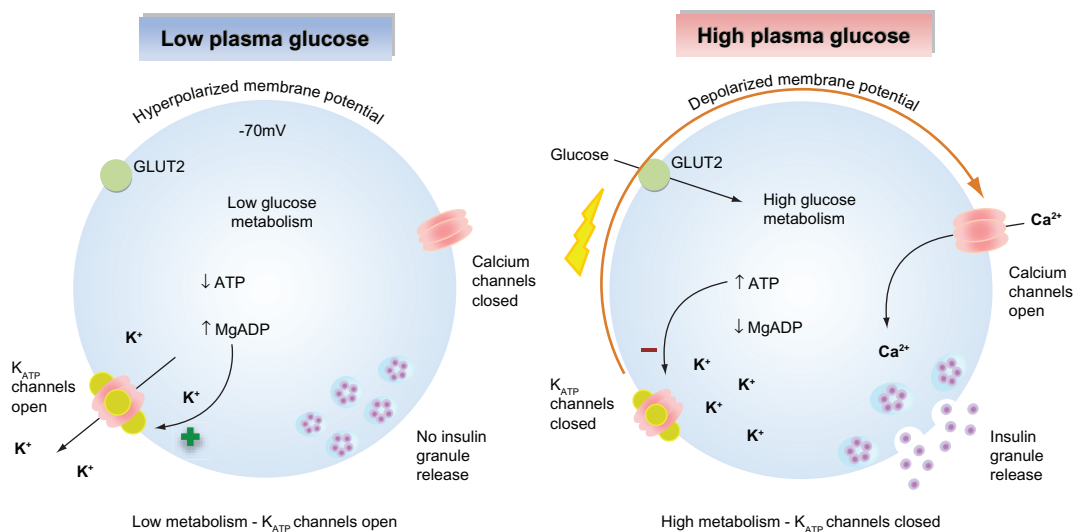


Figure 1 Glucose-stimulated insulin secretion in pancreatic β -cells. (Left) When plasma glucose is low, the decreased ratio of ATP/Mg-ADP will increase K_{ATP} channel opening. Consequently, the cell membrane is hyperpolarized, preventing voltage-gated calcium channel opening, Ca^{2+} influx, and insulin secretion. (Right) When plasma glucose is high, glucose is transported into the cell via GLUT2. Glucose metabolism leads to an increased ratio of ATP/Mg-ADP, resulting in K_{ATP} channel closure, membrane depolarization, opening of voltage-gated calcium channels, Ca^{2+} influx, and insulin secretion.

Molecular structure of pancreatic K_{ATP} channels

The K_{ATP} channel is a hetero-octameric membrane protein complex^{28,29} composed of four pore-forming inwardly rectifying potassium channel (Kir6.x) subunits and four regulatory sulfonylurea receptor (SURx) subunits (Figure 2A).³⁰ There are two isoforms of the Kir6.x subunit, Kir6.1 and Kir6.2. Kir6.2 is more widely expressed than Kir6.1, which is predominantly expressed in vascular smooth muscle.^{31,32} There are two isoforms of the SUR subunit (SUR1 and SUR2), and the subunit composition of K_{ATP} channel differs between tissue types.³³ In pancreatic β -cells and neurons, K_{ATP} channels are assembled from Kir6.2 and SUR1 subunits.³⁴ In cardiac tissue and skeletal muscle, K_{ATP} channels are composed of Kir6.2 and the SUR2A splice variant subunits,³⁵ whereas in smooth muscle, K_{ATP} channels contain Kir6.1/Kir6.2 and SUR2A/SUR2B splice variant subunits.^{36,37}

The Kir6.2 subunit contains ~390 amino acid and is encoded by *KCNJ11* gene, while ~1,580 amino acid SUR1 subunits are encoded by *ABCC8* gene. Both *KCNJ11* and *ABCC8* genes are located at the same chromosomal locus (11p15.1) and are only 4.5 kb apart.³⁰ Each Kir6.2 subunit consists of two transmembrane (TM) helices connected by a pore-forming loop that confers potassium selectivity to the channel.³⁸ The α -helix linking TM helix 1 (TM1) and intracellular N-terminus, termed as the “slide helix,” plays an important role in channel gating.³⁹ Extensive interactions are found between the cytosolic N- and C-termini of adjacent Kir6.2 subunits that contribute to the formation of binding pocket for the inhibitory ATP molecule.⁴⁰ Each SUR1 subunit consists of three TM domains (TMD) with

a total of 17 TM segments.⁴¹ Each SUR1 subunit contains two nucleotide-binding domains (NBD1 and NBD2) that dimerize to form catalytic sites for the intrinsic Mg-ATPase activity of the channel complex, regulating channel activity through binding and hydrolysis of magnesium-bound ATP and the formation of stimulatory Mg-ADP.^{42,43} Each NBD contains two amino acid sequence nucleotide hydrolysis “Walker A” and “Walker B” motifs (Figure 2B).^{44,45} TMD0 and the cytosolic loop linking TMD0 and TMD1 of the SUR1 subunit are responsible for the interaction between Kir6.2 subunit.⁴⁶ The Kir6.2 and SUR1 subunits each possess an endoplasmic reticulum retention motif that requires masking via subunit co-assembly to enable correct trafficking of the assembled hetero-octameric channel complex to the cell membrane.⁴⁷

K_{ATP} channels are inhibited by ATP binding to the Kir6.2 subunits but are activated by the binding and hydrolysis of Mg-ATP in the NBD1/NBD2 dimers on SUR1 subunit, the resulting Mg-ADP generated antagonizes the inhibitory action of ATP on the Kir6.2 subunits. Therefore, the overall activity of the K_{ATP} channel complex, and hence the excitability of pancreatic β -cells, is primarily governed by the ratio of cytosolic ATP/ADP^{45,48} in the close vicinity of the K_{ATP} channel complex.

Mutations in either subunit that alter 1) the correct ATP/ADP-sensing machinery within the K_{ATP} channel complex, 2) subunit assembly, or 3) trafficking to the cell membrane may adversely affect the appropriate insulin secretion in response to plasma glucose. Inactivation mutations in the K_{ATP} channel complex decrease channel activity, causing over-secretion of insulin that is poorly coupled to plasma

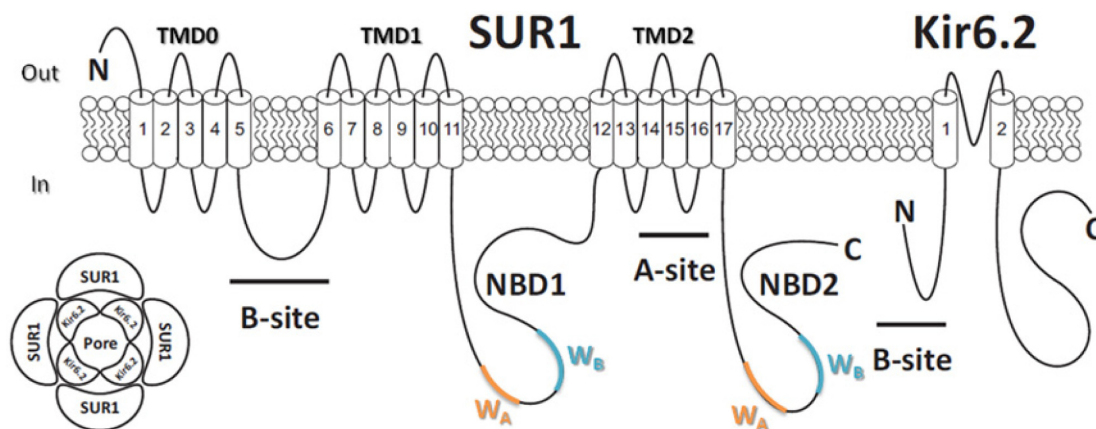


Figure 2 Molecular make-up of the K_{ATP} channel complex. (Lower left) K_{ATP} channel is a hetero-octameric complex composed of four pore Kir6.2 subunits and four regulatory SUR1 subunits. (Right) Membrane topology of SUR1 and Kir6.2 subunits of the K_{ATP} channel. ATP binds to the Kir6.2 subunit, inhibiting K_{ATP} channels. Hydrolysis of MgATP within the SUR1 subunit nucleotide-binding domains (NBDs) leads to generation of stimulatory MgADP. The A and B sites for sulfonylurea drug binding on both subunits are labeled as indicated.

glucose levels. Indeed, mutations in SUR1 subunit that 1) reduce the stimulatory effect of Mg-ADP or 2) prevent correct trafficking of the channel complex to the cell membrane cause persistent hyperinsulinemia that presents as hypoglycemia in infancy (HI).^{49,50}

Conversely, activation mutations in the K_{ATP} channel complex lead to increased channel opening, resulting in a suppression of insulin secretion and subsequent hyperglycemia. Consistent with the cellular regulation of K_{ATP} channel activity are the findings that mutations 1) in the Kir6.2 subunit that reduce sensitivity to inhibitory ATP and 2) in the SUR1 subunit that enhance the stimulatory effects of Mg-ADP may precipitate DEND,¹⁷ iDEND,⁴ PNDM,⁵¹ TNDM,⁵² MODY (maturity onset diabetes of the young),⁵³ and type II diabetes (T2D).^{54,55}

K_{ATP} channel inactivation mutations underlie HI

Inactivation mutations in both K_{ATP} channel subunits can cause HI, which is characterized by severe hypoglycemia.⁵⁶ Mutant K_{ATP} channels with reduced or completely abolished channel activity lead to persistent depolarization of cell membrane, which results in continuous calcium influx and excessive insulin secretion that is uncoupled from the plasma glucose level, producing the hyperinsulinemic hypoglycemia phenotype.^{12,57,58} Compared to inactivation mutations in the *KCNJ11* gene (Kir6.2 subunit), more inactivation mutations have been reported in the *ABCC8* gene encoding the SUR1 subunit. Table 1 lists the reported inactivation mutations causing HI in both *KCNJ11* and *ABCC8* genes and their corresponding locations on each subunit.^{59,60} Inactivation mutations in the K_{ATP} channel complex can be divided into two functional classes: class I, a reduced number of functional K_{ATP} channels inserted into the cell membrane, and class II, mutant K_{ATP} channels that are correctly inserted but remain refractory to opening regardless of the cellular metabolic state of the cell.²² Class I mutations in either SUR1 or Kir6.2 subunits lead to reduced surface expression of K_{ATP} channels, which may result from a total loss of protein, defective channel assembly, or faulty trafficking to the cell membrane.^{61–63} Class II mutations impair the ability of Mg-ADP to stimulate channel activity,^{64–66} such that ATP inhibition becomes dominant and the K_{ATP} channel is permanently closed even at low glucose concentrations. The majority of class II mutations are located in the NBDs of SUR1 subunit, where the binding and hydrolysis of Mg-ATP occurs. In general, class I mutations produce a more severe phenotype, often requiring

near-total or total pancreatectomy, whereas a number of class II mutations result in a milder phenotype as some residual response to stimulatory Mg-ADP may remain. However, there is no strict genotype–phenotype correlation as the same mutation in different patients can produce HI with differing degrees of severity. As HI class II mutations lead to cell membrane expression of dysfunctional K_{ATP} channels, less severe forms of HI can often be treated with K_{ATP} channel opener diazoxide.⁶⁷

K_{ATP} channel activation mutations underlie NDM

Monogenic activation mutations in the *KCNJ11* and *ABCC8* genes can be found in all forms of NDM (DEND,^{4,17} PNDM,⁵¹ TNDM,⁵² and MODY).⁵³ Activation mutations result in a reduced coupling of channel activity to plasma glucose levels via glucose metabolism. In general, the more stimulatory the mutation, the greater the suppression of insulin secretion and the resulting level of hyperglycemia (Figure 3A).^{68–71} The underlying molecular mechanisms for the majority of activation mutations can be tested experimentally and correlated well with their specific locations within the K_{ATP} channel subunits as follows.

Activation mutations in the Kir6.2 subunit

Heterozygous activation mutations in Kir6.2 subunit have been identified in ~50% of PNDM cases and also have been found in a large number of TNDM cases.³ To date, >40 activation mutations in Kir6.2 subunit have been reported at 30 distinct residues (Table 2).⁶⁰ The locations of these mutations are clustered into three common regions in the Kir6.2 subunit. One cluster of mutations line the putative ATP-binding pocket (eg, R50, R201, and Y330) and reduce channel ATP inhibition by decreasing ATP-binding affinity.^{69,72–74} Another cluster of mutations reside in subunit regions involved in channel gating such as the slide helix (eg, V59), the cytosolic mouth of the channel (eg, I296), or gating loops (eg, C166) between ATP-binding site and the slide helix. These mutations decrease ATP inhibition by stabilizing the open conformation of the channel in both the absence and the presence of ATP, leading to increases in channel activity.^{75–77} The third cluster of mutations is located at the interface between the subunits such as the interface between adjacent Kir6.2 subunits (eg, F35 and E322) and the interface between Kir6.2 and SUR1 subunits (eg, Q52 and G53). These mutations likely alter channel activity by affecting the interactions between adjacent Kir6.2

Table 1 Mutations in K_{ATP} channel genes *KCNJ11* and *ABCC8* causing hyperinsulinism of infancy

Genotype	Position in structure	Molecular mechanism	Phenotype
Kir6.2 subunit <i>KCNJ11</i>			
Y12Δ	N terminus	Immature Kir6.2 subunits	HI
R34H	Interface between Kir6.2 subunits		HI
F55L	Interface with SUR1 subunits		HI
K67N	Slide helix		HI
W91R	Linker between TM1 and pore region		HI
A101D	Linker between TM1 and pore region		HI
S116P	Pore region		HI
G134A	Linker between pore region and TM2		HI
R136L	Linker between pore region and TM2		HI
L147P	TM2		HI
A187V	ATP-binding site		HI
P254L	ATP-binding site		HI
H259R	ATP-binding site	Reduced trafficking of the channel	HI
P266L	C terminus		HI
E282 K	C terminus		HI
T294M	Gating	Reduced channel Po	HI
R301H	Gating		HI
C344Δ	C terminus	Immature Kir6.2 subunits	HI
SUR1 subunit <i>ABCC8</i>			
G70E	Linker between TM1 and TM2	Immature SUR1 subunits	HI
R74Q/W	Linker between TM1 and TM2		HI
G111R	TM3		HI
A116P	TM3		HI
H125Q	Linker between TM3 and TM4		HI
V167L	TM5		HI
V187D	TM5		HI
N188S	TM5		HI
Q219Δ	Linker between TM5 and TM6		HI
R248Δ	Linker between TM5 and TM6		HI
N406D	Linker between TM7 and TM8		HI
N418R	Linker between TM7 and TM8		HI
L508P	Linker between TM9 and TM10		HI
F591L	NBD1		HI
R598Δ	NBD1	Immature SUR1 subunits	HI
R620C	NBD1		HI
G716V	Walker A in NBD1		HI
C717Δ	Walker A in NBD1	Immature SUR1 subunits	HI
R837Δ	NBD1		HI
R842G	NBD1	Immature SUR1 subunits	HI
K890T	NBD1		HI
Q954Δ	NBD1		HI
S957F	NBD1	Immature SUR1 subunits	HI
R999Δ	NBD1		HI
T1139M	Linker between TM13 and TM14		HI
R1215Q/W	Linker between TM15 and TM16	Immature SUR1 subunits	HI
K1337N	NBD2		HI
W1339Δ	NBD2		HI
G1343E	NBD2	Immature SUR1 subunits	HI
R1353P/H	NBD2		HI
V1361M	NBD2		HI
G1379R	Walker A in NBD2	Reduced Mg-nucleotide binding	HI
G1382S	Walker A in NBD2	Reduced Mg-nucleotide binding	HI
S1387F	NBD2	Immature SUR1 subunits	HI
F1388Δ	NBD2		HI
R1394H	NBD2		HI
G1401D	NBD2	Impaired trafficking of SUR1 subunits	HI

(Continued)

Table 1 (Continued)

Genotype	Position in structure	Molecular mechanism	Phenotype
R1419H	NBD2	Reduced Mg–nucleotide binding	HI
R1421C	NBD2		HI
R1437Q	NBD2		HI
A1458T	NBD2		HI
G1479R	NBD2	Reduced Mg–nucleotide binding	HI
A1493T	NBD2		HI
R1494Q/W	NBD2		HI
E1507K	Walker B in NBD2	Reduced Mg–nucleotide binding	HI
L1544P	NBD2	Impaired trafficking of SUR1 subunits	HI
V1551D	NBD2	Reduced Mg–nucleotide binding	HI
L1552V	NBD2	Reduced Mg–nucleotide binding	HI
G1555S	C terminus		HI

Abbreviations: HI, hyperinsulinism of infancy; SUR1, sulfonylurea receptor 1.

and SUR1 subunits that are important for correct channel gating.^{78–82}

To directly study the ability of ATP to inhibit the K_{ATP} channel via the Kir6.2 subunit, Mg-free experimental conditions can be used to eliminate the channel stimulatory effect of Mg-ATP on the SUR1 subunit of the channel.⁸³ In Mg-free conditions, homomeric channels containing Kir6.2 activation mutations are less sensitive to ATP inhibition compared to wild-type channels. There are two major molecular mechanisms by which Kir6.2 activation mutations elicit a reduction in ATP sensitivity. 1) An increase in the maximal open probability (P_o) of the channel in the absence of ATP.^{17,84} In the ATP-unbound state of channels (ATP absent), mutations in the region involved in channel gating (eg, V59G)⁴ exhibit a higher maximal channel P_o compared to wild-type channels. (In the absence of Mg^{2+} , IC_{50} was $7.0 \pm 1.1 \mu\text{mol/L}$ and $7.4 \pm 1.5 \text{ mmol/L}$ for wild-type channels and homomeric V59G channels, respectively; $P < 0.001$. Channel P_o was 0.53 ± 0.02 and 0.83 ± 0.01 for wild-type channels and homomeric V59G channels, respectively; $P < 0.001$.)⁴ 2) A decrease in ATP-binding affinity.^{51,85,86} Homomeric channels containing mutations in the ATP-binding region (eg, R201C)⁴ display altered ATP inhibition, yet their maximal P_o in the absence of ATP is not significantly different compared to wild-type channels. (In the absence of Mg^{2+} , IC_{50} was 7.0 ± 1.1 and $106 \pm 12 \mu\text{mol/L}$ for wild-type channels and homomeric R201C channels, respectively; $P < 0.001$. Channel P_o was 0.53 ± 0.02 and 0.6 ± 0.03 for wild-type channels and homomeric R201C channels, respectively; P is not significant.)⁴

Activation mutations in the SUR1 subunit

There are more than 30 individual activation mutations in SUR1 subunit that have been reported to cause NDM

(Table 2).⁶⁰ Many of these mutations are dispersed throughout the SUR1 subunit sequence, although a large number of mutations reside in two specific regions of the SUR1 subunit. One cluster of mutations is concentrated in TMD0 and the cytosolic loop linking TMD0 and TMD1.^{14,87–91} As this region is known to interact with adjacent Kir6.2 subunit, mutations in this region are believed to reduce ATP inhibition via the Kir6.2 subunit.^{92,93} The second cluster of mutations resides in the NBD2 of the SUR1 subunit, where stimulatory Mg–nucleotide diphosphates such as Mg-ADP bind.^{94–96} Therefore, NBD2 mutations are thought to either increase direct Mg-ADP stimulation or enhance MgATPase activity in NBD2, leading to increased Mg-ADP stimulation. (For example, R1380L, V_{max} of ATPase activity was 60.8 ± 1.8 and $104.3 \pm 9.9 \text{ nmol/min/mg}$ for wild-type NBD2 and R1380L NBD2, respectively; $P < 0.01$. K_m of ATPase activity was 0.41 ± 0.04 and $0.55 \pm 0.09 \text{ mmol/L}$ for wild-type NBD2 and R1380L NBD2, respectively. P is not significant.)⁹⁴

Genotype–phenotype correlation in NDM caused by mutations in K_{ATP} channels

There is a wide spectrum of NDM severity associated with different degrees of insulin secretion deficiency and neuronal defects caused by activation mutations in K_{ATP} channels (Figure 4). The severity of these clinical phenotypes increases in the order of T2D < MODY/TNDM < PNDM < iDEND/DEND.²² In general, the greater the activation of K_{ATP} channels, the more severe the phenotype; however, several factors need to be considered when attempting to predict the clinical severity caused by a specific mutation.

Heterozygosity is an important factor affecting the clinical phenotype of a mutation. NDM patients with activation mutations in either Kir6.2 or SUR1 subunits are heterozygous⁷⁷ for

Table 2 Mutations in K_{ATP} channel genes *KCNJ11* and *ABCC8* causing diabetes in terms of DEND, PNDM, TNDM, MODY, and T2D

Genotype	Position in structure	Molecular mechanism	Phenotype	Sensitivity to SU
Kir6.2 subunit <i>KCNJ11</i>				
E23K	N terminus		T2D	Normal sensitivity
R34C	Interface between Kir6.2 subunits		TNDM	
F35L/V	Interface between Kir6.2 subunits	Increased channel Po	PNDM	Normal sensitivity
C42R	Interface between Kir6.2 subunits	Increased channel Po	PNDM/TNDM/MODY	
H46Y	Slide helix	Increased channel Po	PNDM	Normal sensitivity
H46 L	Slide helix	Increased channel Po	iDEND	Normal sensitivity
N48D	ATP-binding site	Decreased ATP-binding affinity	PNDM	
R50P/Q	ATP-binding site	Decreased ATP-binding affinity	PNDM	Normal sensitivity
Q52R	Interface with SUR1 subunits	Increased channel Po	DEND	Reduced sensitivity
G53R/S	Interface with SUR1 subunits	Decreased ATP-binding affinity	TNDM	Normal sensitivity
G53N/D	Interface with SUR1 subunits	Decreased ATP-binding affinity	PNDM	Normal sensitivity
V59G	Slide helix	Increased channel Po	DEND	Reduced sensitivity
V59M	Slide helix	Increased channel Po	iDEND	Normal sensitivity
F60Y	Slide helix		DEND	
V64L	Slide helix		DEND	
L164P	Gating		PNDM	Reduced sensitivity
C166F/Y	Gating		DEND	Reduced sensitivity
I167L	Gating	Increased channel Po	iDEND	Normal sensitivity
K170N/R/T	ATP-binding site	Decreased ATP-binding affinity	PNDM	Normal sensitivity
A174G	ATP-binding site		TNDM	
R176C	ATP-binding site		PNDM	
E179A	ATP-binding site		TNDM	
I182V	ATP-binding site	Decreased ATP-binding affinity	TNDM	
K185E	ATP-binding site	Decreased ATP-binding affinity	DEND	
R201C	ATP-binding site	Decreased ATP-binding affinity	PNDM/DEND	Normal sensitivity
R201H/L	ATP-binding site	Decreased ATP-binding affinity	PNDM	Normal sensitivity
E227K/L	Gating	Increased channel Po	PNDM	Normal sensitivity
E229K	Gating	Increased channel Po	TNDM	
V252A	ATP-binding site	Decreased ATP-binding affinity	TNDM	
E292G	Gating	Increased channel Po	PNDM	
T293N	Gating	Increased channel Po	DEND	Reduced sensitivity
I296L	Pore	Increased channel Po	DEND	Reduced sensitivity
E322K	Interface between Kir6.2 subunits	Decreased ATP-binding affinity	PNDM	Normal sensitivity
Y330C/S	ATP-binding site	Decreased ATP-binding affinity	PNDM/DEND	Normal sensitivity
F333I	Interface with SUR1 subunits	Increased Mg-ATP hydrolysis by NBD2 in SUR1 subunits	PNDM	Normal sensitivity
G334D	ATP-binding site	Decreased ATP-binding affinity	DEND	Reduced sensitivity
I337V	ATP-binding site		T2D	
R365H	C terminus		TNDM	
SUR1 subunit <i>ABCC8</i>				
P45L	TM1		PNDM	Normal sensitivity
N72S	Linker between TM1 and TM2		PNDM	
V86A/G	TM2		PNDM	Normal sensitivity
A90V	TM2		PNDM	
F132L/V	Linker between TM3 and TM4	Reduced ATP inhibitory effect in Kir6.2 subunits	DEND	
L135P	TM4		iDEND	
R176C	TM5		PNDM	
P207S	Linker between TM5 and TM6	Reduced ATP inhibitory effect in Kir6.2 subunits	PNDM	
E208K	Linker between TM5 and TM6	Reduced ATP inhibitory effect in Kir6.2 subunits	PNDM	Normal sensitivity
D209E	Linker between TM5 and TM6	Reduced ATP inhibitory effect in Kir6.2 subunits	PNDM/TNDM	Normal sensitivity
Q211K	Linker between TM5 and TM6	Reduced ATP inhibitory effect in Kir6.2 subunits	PNDM	Normal sensitivity

(Continued)

Table 2 (Continued)

Genotype	Position in structure	Molecular mechanism	Phenotype	Sensitivity to SU
D212I/N	Linker between TM5 and TM6	Reduced ATP inhibitory effect in Kir6.2 subunits	TNDM	
L213R	Linker between TM5 and TM6	Reduced ATP inhibitory effect in Kir6.2 subunits	DEND	Normal sensitivity
L225P	Linker between TM5 and TM6		PNDM	Normal sensitivity
T229I	Linker between TM5 and TM6		TNDM	Normal sensitivity
Y263D	Linker between TM5 and TM6		PNDM	Normal sensitivity
A269D	Linker between TM5 and TM6		PNDM	
R306H	TM6		TNDM	
V324M	TM6		TNDM	
Y356C	TM7		T2D	
E382K	Linker between TM7 and TM8		PNDM	
C435R	TM8		TNDM	
L438F	TM8		PNDM	
L451P	TM9		TNDM	
L582V	TM11		TNDM	
R826W	NBD1	Increased channel activation by Mg-nucleotide	TNDM	
H1024Y	TM12		TNDM	Normal sensitivity
R1183Q/W	Linker between TM15 and TM16		TNDM	
A1185E	Linker between TM15 and TM16		PNDM	
M1290V	TM17		PNDM	
R1314H	NBD2		TNDM	Normal sensitivity
E1327K	NBD2		PNDM	
S1369A	NBD2		T2D	
R1380C/H/L	Walker A in NBD2	Increased ATPase activity in NBD2	TNDM	Normal sensitivity
G1401R	NBD2		PNDM	Normal sensitivity
I1425V	NBD2	Increased channel activation by Mg-nucleotide	PNDM	Normal sensitivity
V1524L/M	NBD2		PNDM	Normal sensitivity

Abbreviations: DEND, developmental delay, epilepsy, and neonatal diabetes; PNDM, permanent neonatal diabetes mellitus; TNDM, transient neonatal diabetes mellitus; MODY, maturity onset diabetes of the young; T2D, type II diabetes; iDEND, intermediate developmental delay, epilepsy, and neonatal diabetes; Po, open probability; SUR1, sulfonylurea receptor 1.

the mutation; thus, both wild-type and mutant subunits are expressed in the same cell. The assembly of Kir6.2 subunits can be used to explain the nature of heterozygosity in NDM patients. In a heterozygous NDM patient carrying one copy of normal (wild type) and one copy of mutant *KCNJ11* gene,²⁸ there will be a mixed population of channels, each of which carries from 0 to 4 mutant Kir6.2 subunits (Figure 5).^{4,22} Two factors determine the inhibitory ATP sensitivity of any individual channel in this population. One is the number of mutant subunits that an individual channel contains and the other is the contribution of mutant subunits to overall channel ATP sensitivity. This contribution is also linked to the molecular mechanism of each activation mutation in Kir6.2 subunit.

If the mutation impairs ATP-binding affinity alone, there will be only a small reduction in ATP sensitivity in heterozygous population compared to wild-type population. (For example, R201H of Kir6.2 subunit. In the absence of Mg²⁺, IC₅₀

were 7.0 ± 1.1 , 12.5 ± 1.1 , and 298 ± 25 $\mu\text{mol/L}$ for wild type, heterozygous, and homomeric R201H channels, respectively; $P < 0.05$ and $P < 0.001$ vs wild-type, respectively.)⁴ This is because binding of a single ATP molecule to 1 of 4 ATP-binding sites is sufficient to inhibit the K_{ATP} channel.⁹⁷ The ATP sensitivity of the channel will only be substantially impaired when all four subunits contain the mutation; otherwise, the mutant Kir6.2 subunit's effects will be largely compensated for by the presence of the other wild-type subunits. This can be explained by using a simple statistical probability model. If the co-assembly of wild-type and mutant Kir6.2 subunits is independent and random and follows a binomial distribution, as a single channel is made of 4 Kir6.2 subunits, then only 1 out of 16 channels in the heterozygous population will contain all 4 mutant Kir6.2 subunits that display a significant decrease in ATP sensitivity (Figure 5).⁴ The other 15 channels (4/16 with 3 mutant subunits; 6/16 with 2 mutant subunits; 4/16 with 1 mutant subunit, and 1/16 with 0 mutant subunits)

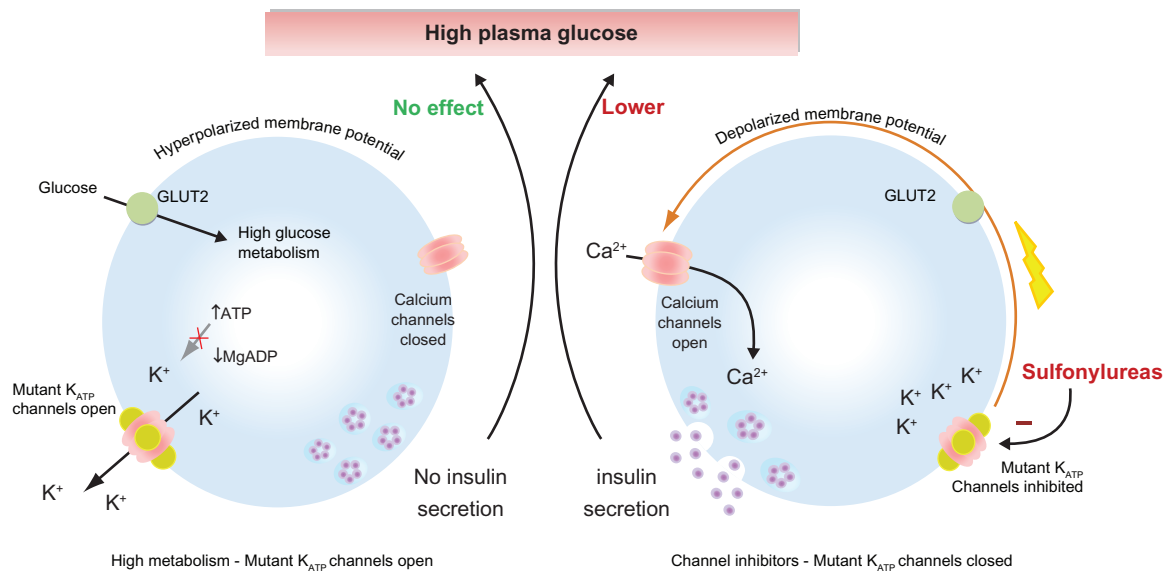


Figure 3 Sulfonylureas stimulate insulin secretion in neonatal diabetes caused by K_{ATP} channel mutations. (Left) Activation mutations in the K_{ATP} channel prevent channel closure in response to high plasma glucose. Consequently, the membrane potential remains hyperpolarized even, thereby preventing insulin secretion. (Right) Sulfonylureas bind directly to K_{ATP} channels causing channel inhibition that triggers membrane potential and insulin secretion resulting in a lowering of plasma glucose.

will have comparable ATP sensitivity to the channel containing all wild-type subunits, so the resulting ATP sensitivity of heterozygous population is very close, but not identical, to that of a pure wild-type channel population. However, this small shift of ATP sensitivity in the heterozygous channel population leads to NDM for the following reasons. Under physiological conditions, intracellular concentration of ATP is in the range of 1–5 mM, such that K_{ATP} channels exhibit very low activity. Additionally, the β -cell membrane possesses a high electrical resistance such that only a small reduction in ATP sensitivity to the channel results in a small increase in K_{ATP} channel activity that holds the β -cell membrane potential in a more polarized state and suppresses insulin secretion.²³ Therefore, even a very modest reduction in heterozygous K_{ATP} channel ATP sensitivity can lead to significantly impaired insulin secretion resulting in NDM.

In direct contrast, if the mutation in question increases intrinsic K_{ATP} channel P_o (in the absence of ATP), there will be a significant reduction in ATP sensitivity in heterozygous population compared to wild-type population, as the presence of one single mutant subunit will increase the intrinsic P_o of K_{ATP} channels. (For example, Q52R of Kir6.2 subunit. Channel P_o were 0.53 ± 0.02 , 0.70 ± 0.03 , and 0.83 ± 0.01 for wild type, heterozygous, and homomeric Q52R channels, respectively. $P < 0.001$ and $P < 0.001$, vs wild-type, respectively.)⁴ This can be explained by using the same statistical model described in detail earlier. Fifteen out of 16 channels will contain at least one mutant subunit in a heterozygous channel population (Figure 5) and exhibit a marked decrease in ATP sensitivity. Thus, the ATP sensitivity of heterozygous population is significantly reduced compared to that of wild-type population and is associated with a more

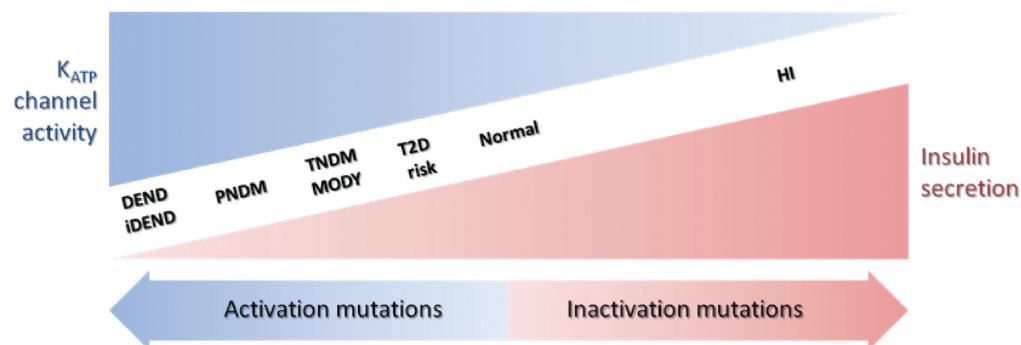


Figure 4 Relationship between insulin secretion and K_{ATP} channel activity in a spectrum of clinical presentations of hypo- and hyperglycemia. The clinical severity of the disease is correlated with the extent of K_{ATP} channel activity caused by the mutations.

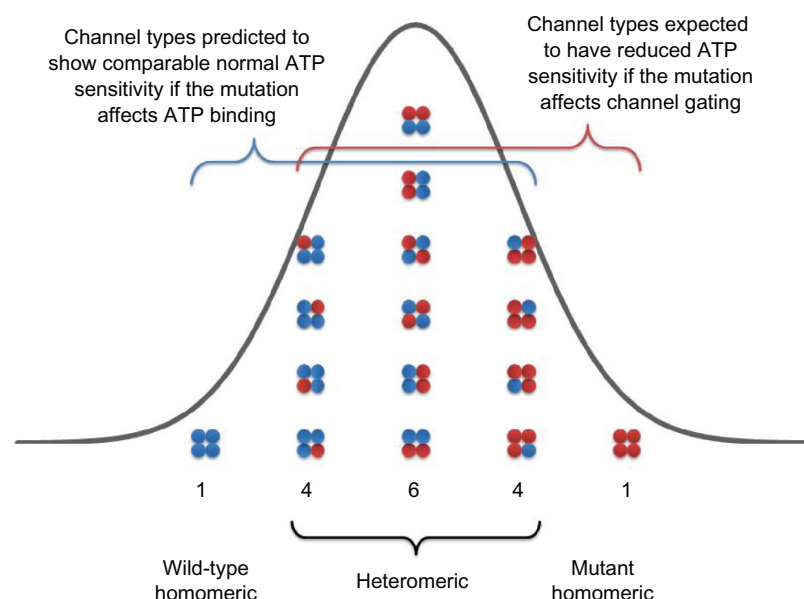


Figure 5 Schematic of the K_{ATP} channel Kir6.2 subunit compositions expected when wild-type (blue) and mutant (red) Kir6.2 are co-expressed in the heterozygous state. If the co-assembly wild-type (blue) and mutant (red) Kir6.2 subunits is independent and random and follows a binomial distribution, as a single K_{ATP} channel is made of 4 Kir6.2 subunits, there will be 1/16 channel with 0 mutant subunit, 4/16 channel with 1 mutant subunit, 6/16 channel with 2 mutant subunits, 4/16 channel with 3 mutant subunits, and 1/16 channel with all 4 mutant subunits.

severe DEND syndrome phenotype.¹⁷ This provides a rational explanation as to why mutations that increase the intrinsic P_o produce a more severe clinical phenotype, such as DEND, whereas mutations that decrease ATP-binding affinity lead to a milder clinical phenotype such as PNDM.

The specific location of mutations within either subunit also correlates well with the severity of the clinical phenotype. In general, mutations in Kir6.2 subunit are typically associated with PNDM, iDEND, and DEND, whereas mutations in SUR1 subunit are more frequently associated with TNDM. This may be accounted for by the overriding ability of ATP to inhibit channel activity within wild-type Kir6.2 subunits even when there is an enhanced stimulatory effect of Mg-ADP via the effects of a SUR1 subunit activation mutation causing TNDM.⁷⁴ Furthermore, although some activation K_{ATP} channel mutations lead to transient diabetes, these patients are at increased risk of developing T2D later in life. Interestingly, the common genetic variants E23K in *KCNJ11* and S1369A in *ABCC8* form a haplotype and are associated with an increased risk to T2D.^{98–100} The precise molecular mechanisms that underlie this increased risk likely result from even subtler alterations of ATP/ADP sensitivity¹⁰¹ than those described for the monogenic mutations that cause overt forms of NDM.

While there is good evidence for a clear genotype–phenotype relationship with several activation mutations in K_{ATP} channels, the association between phenotype and

genotype is not absolute, as there is often a different severity of clinical phenotype among patients carrying the same mutation. This strongly implies that there are other factors (such as underlying polygenic diabetes risk, diet, or environment) that influence the development of clinical phenotype besides the presence of a single *KCNJ11* or *ABCC8* mutation in NDM patients.^{102,103}

Pharmacotherapy for NDM patients carrying *KCNJ11* and *ABCC8* mutations

Before the discovery that mutations in a number of genes underlie NDM, daily insulin therapy was the only effective treatment for patients. As mentioned earlier, NDM can be the result of mutations in multiple genes (eg, *KCNJ11*, *ABCC8*, *GCK*, *INS*, *FOXP3*, *EIF2AK3*, and *ZAC/HYMAI*).¹⁰⁴ Since 2004, many NDM patients with either *KCNJ11* or *ABCC8* mutations have been successfully treated with a pharmacological approach, removing the requirement for insulin injections.^{105,106} The SU drugs, a class of K_{ATP} channel inhibitor, have been widely used as a treatment of T2D for over 50 years. SUs bind directly to the K_{ATP} channel complex, leading to channel closure and subsequent stimulation of insulin secretion (Figure 3B). Recent studies now demonstrate that glycemic control in NDM patients with K_{ATP} channel activation mutations can be managed with SU therapy alone.^{107,108} Therefore, SUs should be considered as an

attractive alternative therapy to treat NDM patients carrying mutations in *KCNJ11* and *ABCC8* genes. As mutations in a number of genes can cause NDM and the causal mutation in each patient may differ greatly, a pharmacogenomic approach to treatment may be possible to “tailor” SU therapy based on specific NDM genotype.

SUs can be classified according to their historical discovery with first generation SUs, including tolazamide, tolbutamide, and chlorpropamide, and second generation SUs, including glyburide, glipizide, and glimepiride (Figure 6). Compared to the first generation SUs, the second generation SUs are now

more commonly used in the treatment of NDM as they are more potent and tend to have a longer duration of action.

There are two SU-binding sites within the K_{ATP} channel complex¹⁰⁹ that have been identified to date. The “A-site” is located in the intracellular loops connecting TM segments 14–16 on SUR1 subunit. The “B-site” is composed of the intracellular loop between TM segments 5–6 in the SUR1 subunit and the N-terminus in Kir6.2 subunit (Figure 2B). Therefore, SUR1 subunit possesses a bipartite pocket with distinct A- and B-binding sites. Furthermore, SUs can be classified as A-site or AB-site drugs based on

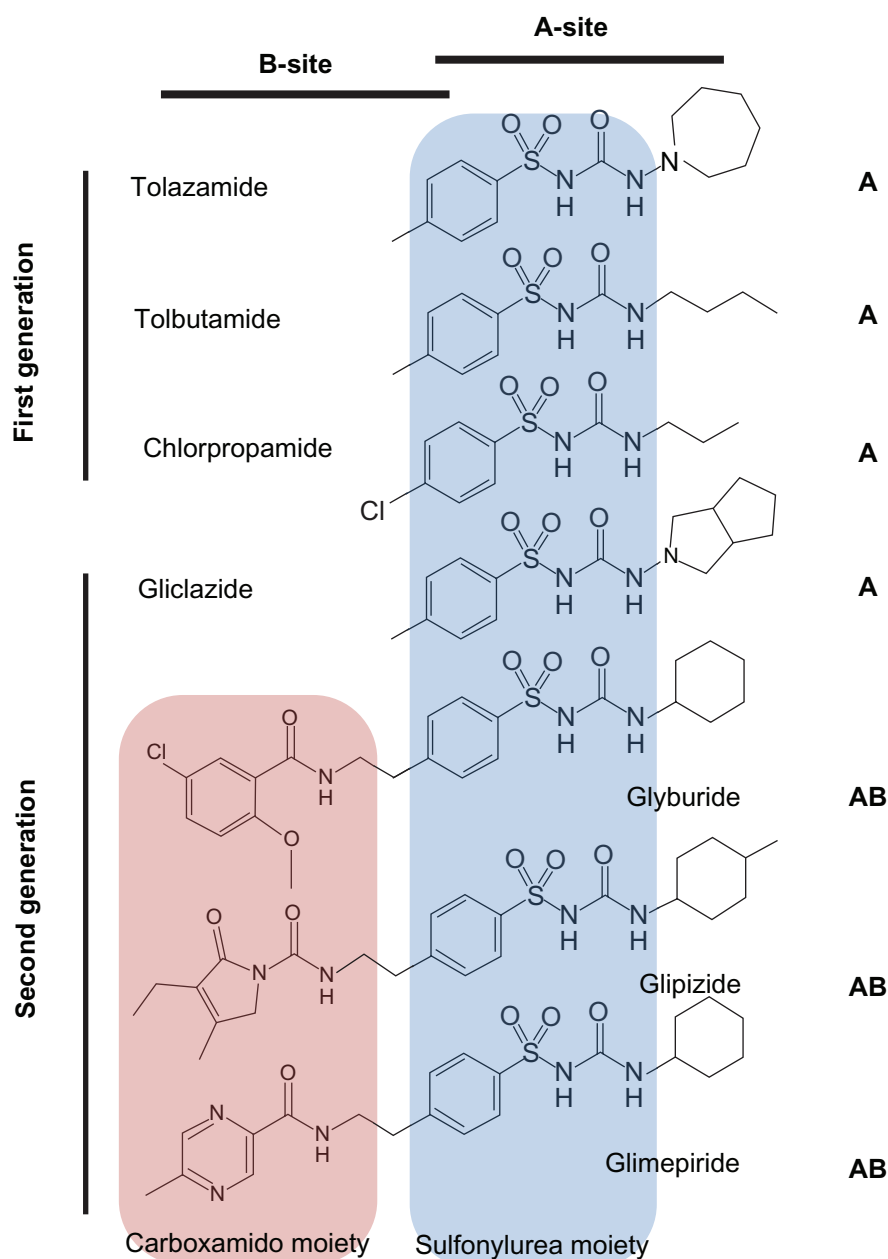


Figure 6 Structures and binding-site classification of clinically used sulfonylurea drugs.

where they bind to the channel (Figure 6). The A site within SUR1 subunit binds the SU moiety, whereas the B site binds the non-SU carboxamido moiety of the molecule.¹⁰⁹ Most of the first generation SUs (eg, tolbutamide and chlorpropamide) are A-site drugs, whereas the majority of the second generation SUs (eg, glyburide, glipizide, and glimepiride) are AB-site drugs, which also accounts for the higher potency of the second generation SUs. An exception to this is gliclazide, which is an A-site SU with potency comparable to the AB-site SUs.

A key issue in the optimization of SU therapy in NDM is whether mutant K_{ATP} channels can be inhibited by SUs in a similar concentration range to wild-type channels. For NDM patients with SUR1 subunit mutations, there are no reports of mutations in the *ABCC8* altering SU inhibition. This may be because NDM patients with mutant SUR1 subunits often exhibit a milder clinical NDM phenotype. Therefore, SU therapy should be effective for most NDM patients with SUR1 subunit mutations.

In contrast, several studies suggest that NDM patients with Kir6.2 subunit mutations respond differently to SU therapy,^{110–112} which is likely related to the underlying molecular mechanisms of mutations that alter K_{ATP} channel function. Mutations that reduce binding affinity of inhibitory ATP causing TNDM or PNDM show adequate efficacy of SUs.¹¹³ However, mutations that enhance intrinsic channel P_o causing DEND or iDEND have a reduced inhibitory efficacy of SUs.¹¹⁴ In general, the greater the ability of a specific mutation to increase the intrinsic channel P_o , the higher the SU dosage required to achieve the same level of channel inhibition seen in with mutations causing PNDM and TNDM.^{115,116} As SUs are unable to sufficiently inhibit K_{ATP} channels with mutations that cause a greatly enhanced intrinsic channel P_o , DEND patients with activation mutations in Kir6.2 subunit often require a combination of SU and insulin therapy rather than SU therapy alone. SU dosage for NDM patients can be quite high (up to 2.5 mg/kg/day of glyburide) compared with the dosage for patients with T2D (~0.2 mg/kg/day).

SUs are extensively metabolized in the liver, primarily by the cytochrome P450 2C9 enzyme encoded by the *CYP2C9* gene. To date, several pharmacogenomic studies have focused on the influence of common gene variants in the *CYP2C9* gene on SU pharmacokinetics.^{117–119} As the activity of cytochrome P450 2C9 variants correlates well with serum levels of SUs, patients carrying *CYP2C9* variants that reduce cytochrome P450 2C9 enzymatic activity possess elevated serum levels of SUs.¹²⁰ Therefore, screening for these common *CYP2C9* variants may provide additional information

as to whether a NDM patient carrying a *KCNJ11* or *ABCC8* gene mutation may respond better to SU therapy.

Although insulin therapy may control glucose homeostasis in NDM patients with mutant K_{ATP} channels, it does not restore the normal K_{ATP} channel activity in nonpancreatic tissues such as the brain and skeletal muscle. On the other hand, SUs can inhibit K_{ATP} channels in many tissues such as the central nervous system (CNS), ameliorating the neurological dysfunction observed in iDEND/DEND.^{121–123}

One potential concern is that the dosage for SUs needed to adequately control glucose homeostasis may not be enough to resolve neurological symptoms, as SUs have to cross the blood–brain barrier to exert inhibitory effect on CNS K_{ATP} channels. However, several studies showed that improvements in mental and motor function were found in patients carrying mutant K_{ATP} channels with DEND syndrome treated with SUs.^{121–123} These observations suggest that SUs are able to cross the blood–brain barrier at concentrations sufficient to inhibit K_{ATP} channels in the CNS.

Several recent studies now show that early diagnosis and treatment of DEND patients carrying *KCNJ11* or *ABCC8* gene mutations with SU therapy could reduce or even prevent the neurological dysfunction in addition to dramatically improving glycemic control.^{121–123} Most DEND patients who have successfully transferred to SU therapy were children at the time of transfer. Therefore, if the causal mutation is on either *KCNJ11* or *ABCC8* genes, then an early switch to SU therapy may minimize the extent of neurological problems. This also emphasizes the importance of early screening for mutations in *KCNJ11* and *ABCC8* genes in those NDM patients with neurological features.

Traditionally, PNDM patients with mutations in other genes such as *GCK* gene encoding glucokinase are treated with insulin therapy. A recent study reported that a PNDM patient with the T168A mutation in glucokinase exhibited modest responsiveness to SU therapy.¹²⁴ Furthermore, MODY patients with mutations in *HNF1 α* (hepatocyte nuclear factor) are very sensitive to SU therapy and many of them have been successfully transferred to SU therapy from insulin therapy.^{125,126} Therefore, the use of SU therapy should also be considered in NDM patients with mutations in genes other than *KCNJ11* and *ABCC8*. These findings also highlight the central role that K_{ATP} channels play in regulating insulin secretion.

SUs exhibit differential potencies on K_{ATP} channels with different subunit compositions that are often expressed in a variety of tissues.^{127–130} The majority of first generation SUs and gliclazide (A site) are more selective for K_{ATP}

channels containing the SUR1 subunit as found in the pancreas and CNS (IC_{50} was 50 nmol/L for gliclazide on K_{ATP} channels containing SUR1 subunits).¹³¹ Thus, K_{ATP} channels containing either SUR2A or SUR2B subunits (heart/skeletal/smooth muscle) would not be inhibited by these SUs at the same concentration (IC_{50} was 0.8 mmol/L for gliclazide on K_{ATP} channels containing SUR2A subunits).¹³¹ As second generation SUs (AB site) are nonselective, they will inhibit all K_{ATP} channels with similar potency (IC_{50} s were 3, 5.4, and 7.3 nmol/L for glimepiride on K_{ATP} channels containing SUR1, SUR2A, and SUR2B subunits, respectively).¹³²

Recent studies implicate a role for skeletal muscle (Kir6.2 and SUR2A) K_{ATP} channels in peripheral insulin sensitivity.^{133,134} In NDM patients with Kir6.2 activation mutations, overactive K_{ATP} channels in skeletal muscle (Kir6.2 and SUR2A) may reduce insulin sensitivity in addition to decreasing insulin secretion, further contributing to the development of NDM.¹³⁵ Inhibition of skeletal muscle K_{ATP} channels with Kir6.2 activation mutations with SUs may increase peripheral insulin sensitivity.¹³⁶ This notion is supported by studies showing that better glycemic control is achieved with AB-site SUs, compared with A-site SUs.^{116,123,128,137} This is because skeletal muscle and β -cell are inhibited by AB-site SUs as both insulin secretion and insulin sensitivity are achieved. Therefore, AB-site SUs may be the better choice for NDM patients with Kir6.2 activation mutations.

In clinical practice, the two major treatments for NDM patients are insulin therapy and oral SUs and treatment for individual patient varies depending on the genetic cause of NDM.¹³⁸ For 50% of PNDM patients and 10% of TNDM patients carrying mutant K_{ATP} channels, SU therapy is an attractive alternative to insulin therapy. However, for other PNDM patients carrying mutations in *PTF1A*, *EIF2AK3*, *FOXP3* and 80% of TNDM patients carrying mutations in chromosome 6q24 (eg, *ZAC/HYMAI*), SU responsiveness is minimal and the patients' only option is insulin therapy.³ Therefore, it is important to diagnose the underlying genetic cause of NDM to fully optimize treatment.¹³⁹ Genetic testing is not only important for the correct diagnosis but may now also be used in the optimization of treatment in a large number of PNDM and TNDM patients with K_{ATP} channel mutations.¹⁴⁰

Conclusion

K_{ATP} channels play a central physiological role in pancreatic β -cells, where they act as key regulators of insulin secretion

in response to changes in plasma glucose. Inactivation or activation mutations in K_{ATP} channels lead to altered K_{ATP} channel activity, producing a phenotype of either HI or NDM. With respect to K_{ATP} channel mutations in NDM, the severity of the clinical phenotype correlates well with the magnitude of K_{ATP} channel activation.

To date, it is estimated that ~90% of NDM patients carrying K_{ATP} channel activation mutations can discontinue daily insulin injections and show improved glycemic control when they are switched to a high-dose SU therapy. Besides improving the quality of life for NDM patients, switching from insulin injection to SU therapy can also reduce neurological symptoms associated with patients with more severe forms of NDM (iDEND/DEND).

Furthermore, genetic information, coupled with clinical factors, may help to improve the treatment of NDM by aiding in the appropriate selection of therapeutic strategies (insulin injection, or SU therapy, or a combination of both) and a more accurate adjustment of SU dosage. Future research will likely lead to improved glycemic control by the development of a rational pharmacogenomic approach to "tailor" SU therapy based on an NDM patient's individual genotype.

Disclosure

The authors report no conflicts of interest in this work.

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