1521-0111/102/5/234–239$35.00
MOLECULAR PHARMACOLOGY

dx.doi.org/10.1124/molpharm.122.000570
Mol Pharmacol 102:234–239, November 2022

Emerging Concepts

The Emerging Structural Pharmacology of ATP-Sensitive Potassium Channels

Jing-Xiang Wu,[1] Dian Ding,[1] and Lei Chen

State Key Laboratory of Membrane Biology, College of Future Technology, Institute of Molecular Medicine, Beijing Key Laboratory of Cardiometabolic Molecular Medicine (J.-X.W., D.D., L.C.), Peking-Tsinghua Center for Life Sciences (D.D., L.C.), Academy for Advanced Interdisciplinary Studies (D.D., L.C.), and National Biomedical Imaging Center, Peking University, Beijing, China (J.-X.W., D.D., L.C.)

Received May 31, 2022; accepted August 29, 2022

ABSTRACT

ATP-sensitive potassium channels (K_{ATP}) are energy sensors that participate in a range of physiologic processes. These channels are also clinically validated drug targets. For decades, K_{ATP} inhibitors have been prescribed for diabetes and K_{ATP} activators have been used for the treatment of hypoglycemia, hypertension, and hair loss. In this Emerging Concepts article, we highlight our current knowledge about the drug binding modes observed using cryogenic electron microscopy techniques. The inhibitors and activators bind to two distinct sites in the transmembrane domain of the sulfonylurea receptor (SUR) subunit. We also discuss the possible mechanism of how these drugs allosterically modulate the dimerization of SUR nucleotide-binding domains (NBDs) and thus K_{ATP} channel activity.

SIGNIFICANCE STATEMENT

ATP-sensitive potassium channels (K_{ATP}) are fundamental to energy homeostasis, and they participate in many vital physiological processes. K_{ATP} channels are important drug targets. Both K_{ATP} inhibitors (insulin secretagogues) and K_{ATP} activators are broadly used clinically for the treatment of related diseases. Recent cryogenic electron microscopy studies allow us to understand the emerging concept of K_{ATP} structural pharmacology.

The Emerging Concept of ATP-Sensitive Potassium Channel Structural Pharmacology

The potassium currents passing through ATP-sensitive potassium channels (K_{ATP}) are inhibited by intracellular ATP and activated by intracellular Mg-ADP (Nichols, 2006). As such, K_{ATP} channels tune their potassium conductance according to changes in the intracellular ATP/ADP ratio of the cell. K_{ATP} channels play essential roles in several important physiologic processes, including insulin secretion and vasodilation (Ashcroft, 2006; Flagg et al., 2010). The genetic mutations of K_{ATP} channels lead to human diseases such as neonatal diabetes and cardiovascular diseases (Ashcroft, 2006; Flagg et al., 2010).

K_{ATP} channels are assembled from four pore-forming inward-rectifier potassium channel 6 (Kir6) subunits and four regulatory sulfonylurea receptor (SUR) subunits (Fig. 1, A–C). The Kir6 subunit in the center has the inhibitory nucleotide-binding site, whereas the SUR subunit in the peripheral harbors the activating Mg-nucleotide-binding site (Fig. 1, A–C). The interplay of these nucleotide-binding sites during the fluctuation of intracellular nucleotide concentrations shapes the overall K_{ATP} channel activities. In the past several decades, fruitful medicinal research on K_{ATP} channels has established that SUR proteins, either SUR1 or SUR2, are validated drug targets (Li et al., 2021). SUR proteins belong to the subfamily C of the ATP-binding cassette transporter (ABCC) subfamily of the ATP binding cassette (ABC) transporters and have a transmembrane domain 0 (TMD0), which is unique to certain ABCC family members. SUR proteins have a canonical structural core formed by TMD1-NBD1-TMD2-NBD2 (Aittoniemi et al., 2009; ter Beek et al., 2014) (Fig. 1D). The helices from transmembrane domain 1 (TMD1) and TMD2 are intertwined to form two structural halves. The first half consists of TM6–8, TM11 of TMD1, and TM15–16 of TMD2; and the remaining

The work is supported by grants from the National Natural Science Foundation of China [Grant 91957201], [Grant 31870833], and [Grant 31821091] (to L.C.) and Center for Life Sciences.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

[1]J.-X.W. and D.D. contributed equally to this work.

dx.doi.org/10.1124/molpharm.122.000570.

ABBREVIATIONS: cryo-EM, cryogenic electron microscopy; CTD, cytoplasmic domain; GBM, glibenclamide; IS, insulin secretagogue; ISBS, insulin secretagogue binding site; K_{ATP}, ATP-sensitive potassium channel; KCO, K_{ATP} opener; KCOS, K_{ATP} opener binding site; Kir, inward-rectifier potassium channel; KNtp, Kir6 N-terminal peptide; MTG, mitiglinide; NBD, nucleotide-binding domain; RPG, repaglinide; SUR, sulfonylurea receptor; TMD, transmembrane domain.

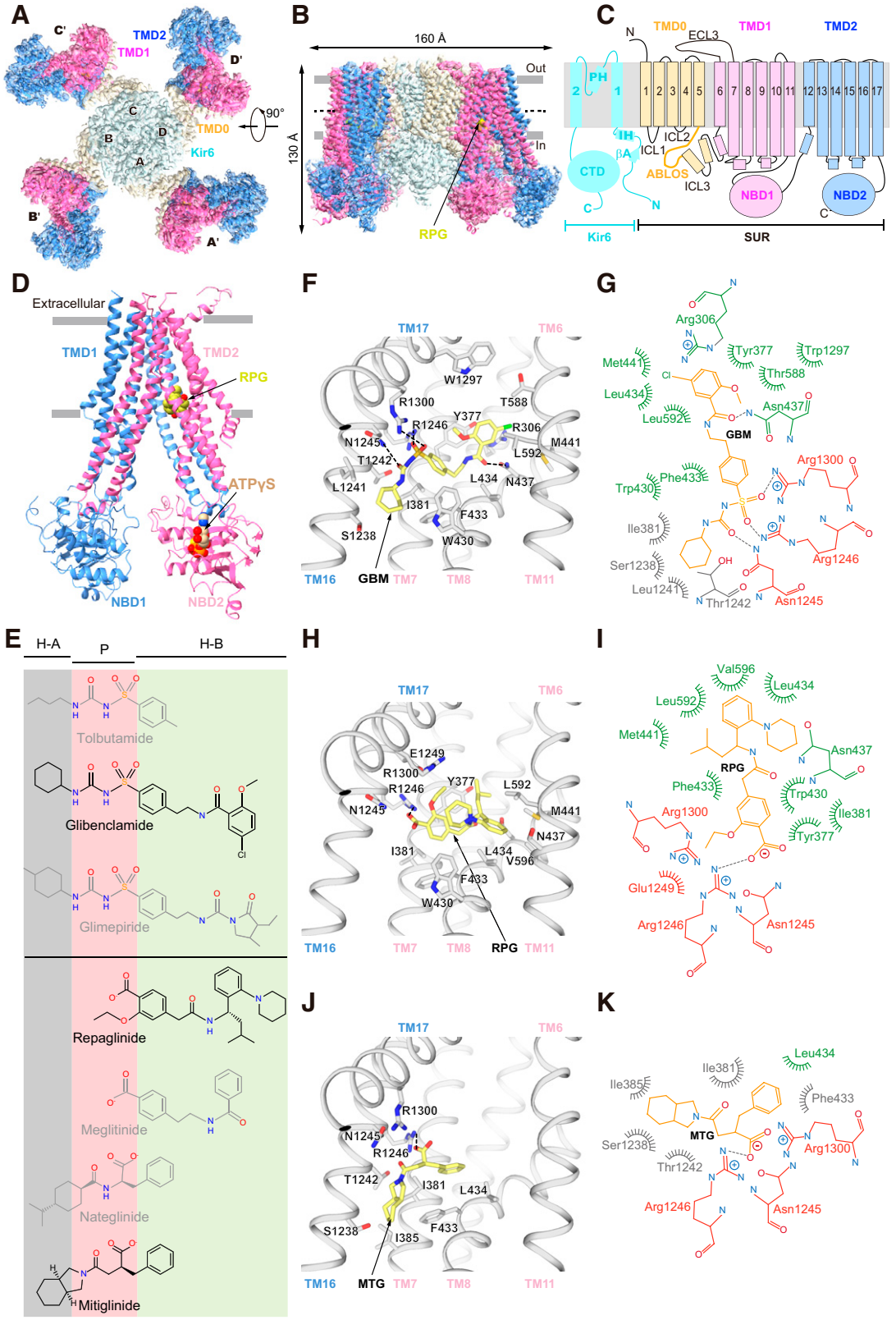

Fig. 1. The insulin secretagogue binding site of SUR (A) and (B). Bottom view (from the intracellular side) and side view of the K_{ATP} hetero-octamer in complex with RPG (PDB code: 6JB1; EMDB code: 9787). The Kir6, SUR TMD0, TMD1-NBD1 (nucleotide binding domain 1), TMD2-NBD2, RPG, and ATP are colored in cyan, orange, pink, blue, yellow, and brown, respectively. TMD (transmembrane domain) and NBD (nucleotide binding domain). (C) The cartoon topology of Kir6 and SUR. PH (pore helix), IH (interfacial helix), CTD (cytoplasmic domain), ABLOS (ATP binding loop of SUR), ICL (intracellular loop), ECL (extracellular loop). (D) Side view of the SUR1 ABC transporter module in the presence of RPG and ATPγS (PDB code: 6JB1). (E) The chemical structures of IS. The hydrophobic A (H-A) and hydrophobic B (H-B) sites are in the gray background and the polar site (P) is in pink background, respectively. The IS without available K_{ATP} complex structure are colored in gray. (F–K) Close-up view of the binding site of (F) GBM (PDB code: 5YW7), (H) RPG (PDB code: 6JB3), and (J) MTG (PDB code: 7WIT). SUR1 and ISs are colored in gray and yellow, respectively. Residues of SUR1 that interact with IS are shown as sticks and colored as Fig. 1E according to the binding sites. The SUR1-IS interactions analyzed by LigPlot. (G) GBM, (I) RPG, and (K) MTG.

helices in the transporter core form the second half. SUR proteins were found to have two major conformations: the NBD-separated inward-facing conformation represents an inactive state, whereas the NBD-dimerized occluded conformation is associated with K_{ATP} activation (Wu et al., 2020). SUR subunits also dominate the pharmacological profile of K_{ATP} channels. K_{ATP} channels in pancreatic cells are mainly formed by the SUR1-Kir6.2 combination. SUR1 inhibitors can trigger depolarization of β cells and thus insulin secretion. They are used for the treatment of diabetes (Li et al., 2021) and are therefore named "insulin secretagogues" (designated IS). Conversely, SUR1 activators can inhibit insulin secretion and thus can treat certain hypoglycemia (Li et al., 2021). SUR2 is expressed in blood vessels, heart, and skeletal muscles. SUR2 activators are used for the treatment of hypertension and hair loss (Li et al., 2021). SUR activators are called "K_{ATP} openers" (designated KCO). Recent revolutionary advances in single particle cryogenic electron microscopy (cryo-EM) allowed the visualization of membrane protein structures at near-atomic resolution (Kühlbrandt, 2014). Using this technique, we and others have experimentally determined the binding sites and poses of not only K_{ATP} inhibitors but also K_{ATP} activators inside the SUR proteins.

The IS Binding Site of K_{ATP} Channel

Structurally, IS are classified into sulfonylureas (Sus) [such as glibenclamide (GBM)] and glinides [such as repaglinide (RPG) and mitiglinide (MTG)] (Gribble and Reimann, 2003; Winkler et al., 2007; Wu et al., 2020). Based on the structure-activity relationship of IS, researchers guessed that there were the "A" site and "B" site on SUR long before the structure determination of K_{ATP} (Rufer et al., 1974; Brown and Foubister, 1984; Winkler et al., 2007). Up to today, high-resolution structures of K_{ATP} have revealed the binding sites of three IS inside the central vestibule of SUR, including GBM, RPG, and MTG (Li et al., 2017; Martin et al., 2017a,b, 2019; Wu et al., 2018; Ding et al., 2019; Sung et al., 2021; Wang et al., 2022a) (Fig. 1). The binding of IS stabilizes SUR in the inward-facing state with two NBDs separated (Fig. 1D). These structures have depicted the IS binding site (ISBS) at near-atomic resolution and allowed us to analyze IS-SUR interactions in detail (Fig. 1, F–K). We conceptually divide the ISBS into three connecting regions according to the structures: the hydrophobic A site (H-A), the polar site (P), and the hydrophobic B site (H-B) (Fig. 1E). Based on the common pharmacophores, we also tentatively list and align several representative IS, the structures of which in complex with K_{ATP} are not available yet (Grell et al., 1998; Hu et al., 1999; Reimann et al., 2001b; Vila-Carriles et al., 2007; Winkler et al., 2007; Basit et al., 2012) (Fig. 1B).

Intriguingly, all of these IS interact with the P site and the H-B site (Fig. 1E). The P site is formed by positively charged R1246, R1300, and polar N1245 of SUR1 and interacts with the electrostatically negative group of IS, such as the sulfonyl group of GBM, and the carboxyl group of RPG and MTG (Fig. 1, E–K). Mutations at the P site abolished the inhibition of GBM, RPG, and MTG (Ding et al., 2019; Wang et al., 2022a).

IS have diverse chemical groups at the H-A site, which is one of the key determinants for the subtype selectivity of IS. S1238 of SUR1 at the H-A site is replaced by a much larger tyrosine in SUR2. Therefore, IS with a bulkier group at the H-A site could be accommodated by SUR1 but might not bind SUR2 favorably, in agreement with the order of SUR1/SUR2 selectivity: MTG > GBM > RPG (Quast et al., 2004; Wang et al., 2022a).

The common hydrophobic phenyl group of IS is bound in the hydrophobic pocket formed by residues on the H-B site, including F433 and I381 (Fig. 1, E–K). A large hydrophobic cavity formed by residues from helices TM6–8 and TM11 (Y377, F433, L434, M441, L592, V596, and W1297) accommodates the chlorobenzamide group of GBM or the large hydrophobic group including the piperidinylphenyl moiety and the butyl carbamoyl-methyl moiety of RPG (Fig. 1). GBM and RPG make differential interactions with the H-B site. R306 on TM8 of the H-B site of SUR1 only forms polar interactions with the chloride atom of GBM but not with RPG (Fig. 1, E–K), which is consistent with the decreased potency of GBM but not RPG to the R306A mutant of SUR1 (Ding et al., 2019). It was initially found that Kir6 N-terminal peptide (KNtp) is close to the H-B site according to the map of SUR1/Kir6.2 K_{ATP} in the presence of GBM (Wu et al., 2018). This was later confirmed in SUR1/Kir6.2 K_{ATP} in the presence of RPG and even SUR2B/Kir6.1 K_{ATP} in the presence of GBM (Ding et al., 2019; Martin et al., 2019; Sung et al., 2021). Therefore, the H-B site is formed not only by the SUR subunits but also by the KNtp, providing a plausible mechanism for the IS-enhanced inhibitory coupling between SUR and Kir6. However, due to the flexibility of KNtp, the exact residues that interact with IS remain poorly defined.

The KCO Binding Site of K_{ATP} Channel

KCO are chemically diverse and comprise distinct classes, including cyanoguanidines (such as pinacidil and P1075), benzopyrans (such as levcromakalim, abbreviated as Lev), thiadiazines (such as diazoxide and NN414), and others (Tusnády et al., 1997; Gilbert et al., 2000; Mannhold, 2004, 2006). Their exact binding sites on the SUR subunit were elusive despite the enlightening work on chimeric SUR and mutagenesis (D'hahan et al., 1999a,b; Uhde et al., 1999; Ashcroft and Gribble, 2000; Babenko et al., 2000; Moreau et al., 2000; Reimann et al., 2001a). To experimentally determine the KCO binding site, our laboratory has solved the structure of SUR2 in complex with SUR2-selective P1075 and Lev (Ding et al., 2022) and SUR1/Kir6.2 K_{ATP} with SUR1-selective NN414 (Wang et al., 2022b), providing comprehensive views of KCO binding sites (KCOS) at near-atomic resolutions (Fig. 2). The binding of KCO synergizes with Mg-nucleotides to stabilize the SUR in the NBD-dimerized occluded conformation (Fig. 2A) in agreement with the fact that KCO bind to SUR with slower off-rates in the presence of Mg-nucleotides (Gribble et al., 2000). Despite the distinct chemical structures and selectivities of these three KCO, they all bind at a common KCOS in the middle of the transmembrane domain of SUR (Fig. 2A) in agreement with the competitive binding behavior of KCO (Bray and Quast, 1992). KCOS is embraced by TM10, TM11, TM12, TM13, TM14, and TM17 helices (Fig. 2, C, E, and G) and is about 20 Å away from the aforementioned ISBS (Ding et al., 2022). Based on the structures, we define the KCOS as three connecting regions on SUR: the A site, the polar site (P site), and the B site (Fig. 2B).

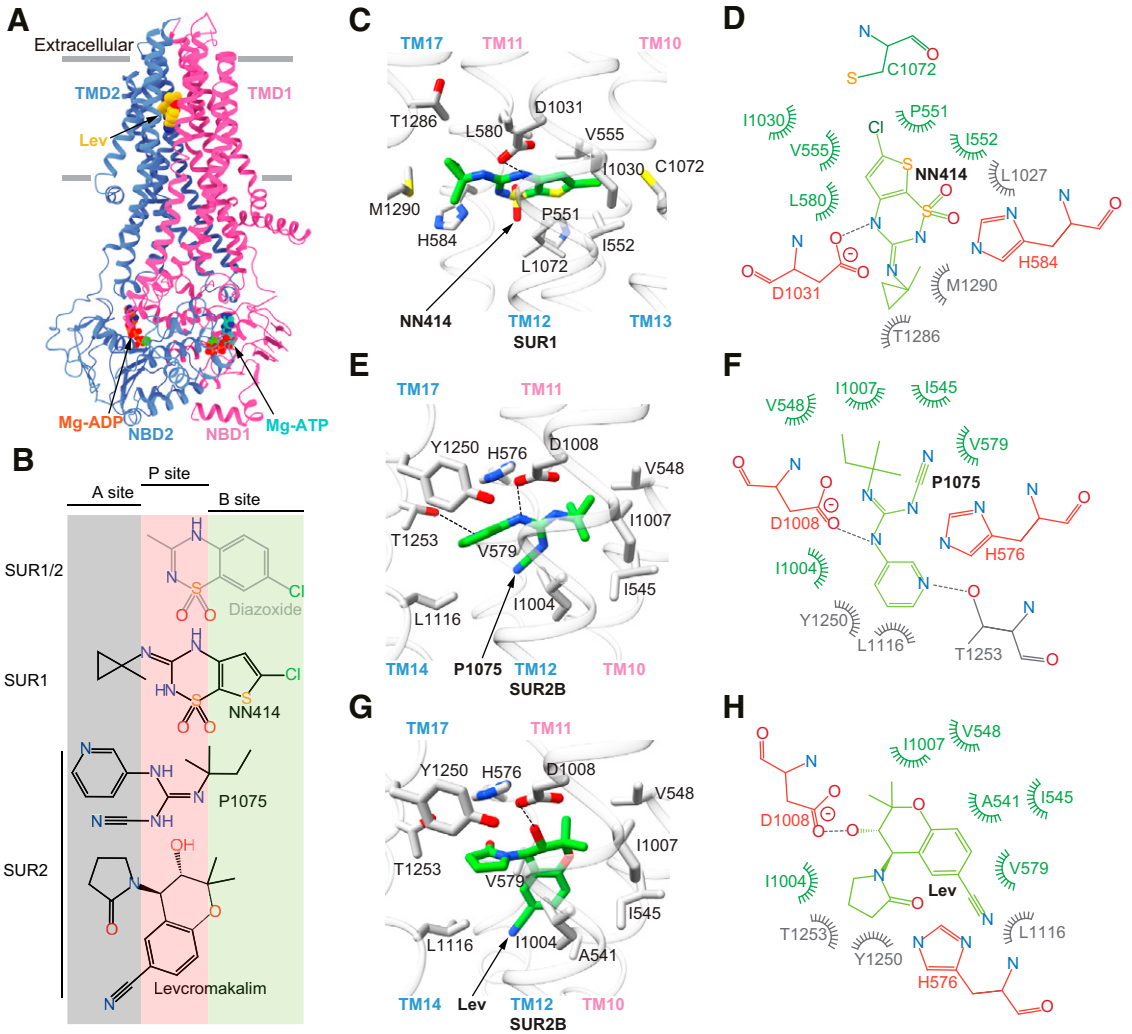

Fig. 2. The KCO binding sites of SUR. (A) Structure of SUR2B in complex with levcromakalim (Lev) and Mg-nucleotides. TMD1-NBD1, TMD2-NBD2, Lev, Mg-ATP, and Mg-ADP are colored in pink, blue, yellow, cyan, and orange, respectively. (B) Chemical structures of KCO. A site, P site, and B site are in gray, pink, and green background, respectively. KCO without available K_{ATP} complex structure are colored in gray. C-D. Close-up view of NN414 binding site. SUR1 and NN414 are colored in gray and green, respectively. Residues of SUR1 interacting with NN414 are shown as sticks and are colored as Fig. 1E according to the binding sites. (E and F) Close-up view of P1075 binding site. SUR2B and P1075 are colored in gray and green, respectively. Residues of SUR2B interacting with P1075 are shown as sticks. (G and H) Close-up view of Lev binding site. SUR2B and Lev are colored in gray and green, respectively. Residues of SUR2B interacting with Lev are shown as sticks.

Two residues in the P site, a His (H584 in SUR1 and H576 in SUR2) and an Asp (D1031 in SUR1 and D1008 in SUR2), play critical roles in interacting with the central polar groups of KCO. H584 of SUR1 interacts with the sulfonylurea group on the thiadiazine ring of NN414, and D1031 forms hydrogen bonds between its carboxyl group and the thiadiazine ring of NN414 (Fig. 2, C and D). H576 on TM11 interacts with the guanidine group of P1075. D1008 on TM12 forms hydrogen bonds between its carboxyl group and guanidine group of P1075 (Fig. 2, E and F). D1008 interacts with the hydroxyl group on the chiral carbon of Lev and H576 interacts with the hydroxyl group and pyrrolidinone ring on the other chiral carbon of Lev (Fig. 2, G and H). Structural information is consistent with previous studies showing that NH groups of pyridylamino group of P1075 can act as a hydrogen-bond donor and make a crucial contribution toward K_{ATP} activation (Manley and Quast, 1992); the substitution of pyrrolidinone of Lev changed drug potency significantly (Mannhold, 2006); the substitution of the methyl group on the thiadiazine rings by alkylamino group enhanced the potency of dioxide derivatives (Hansen, 2006). Mutation of these two residues greatly decreased the activation effect of both SUR1-selective opener NN414 (Wang et al., 2022b) and SUR2-selective KCO, including P1075 and Lev (Ding et al., 2022), emphasizing that the polar interactions between the P site of SUR and KCO are essential for channel activation.

The A site is formed by residues in TMD2, and these residues are not identical between SUR1 and SUR2 (Ding et al., 2022). I1004 and T1253 in SUR2 are L1027 and M1290 in SUR1, respectively. I1004 of TM12 and T1253 of TM17 of SUR2 are close to the cyano group and pyridine ring of P1075. Mutations of I1004L and T1253M introduce steric hindrance to the binding of P1075 (Ding et al., 2022). Rb^+ efflux assay showed that I1004L in SUR2B reduced the activating effect of P1075 significantly and that T1253M in SUR2B had a more profound effect (Ding et al., 2022). In the structure of SUR2B in complex with Lev, I1004, and T1253 are located close to the benzonitrile group and pyrrolidinone ring of Lev, respectively (Fig. 2 G and

H). I1004L and T1253M mutations in SUR2B reduced the activating effect of Lev to a similar extent (Ding et al., 2022). M1290 at the A site of SUR1 interacts with the hydrophobic methyl cyclopropane group of NN414 (Fig. 2, C and D). This group is replaced by a smaller methyl group in diazoxide (Fig. 2B), which could not efficiently make hydrophobic interactions with M1290, partially explaining the higher potency of NN414 than diazoxide in the activation of the SUR1-containing K_{ATP} channel (Dabrowski et al., 2003).

The B site is mainly formed by TMD1. P551, I552, and V555 on TM10, L580 on TM11, I1030 on TM12, and C1072 on TM13 of SUR1 form a hydrophobic pocket and embrace the chlorothiophene ring of NN414 (Fig. 2, C and D). The hydrophobic pocket of SUR2 is formed by I545 and V548 of TM10, V579 of TM11, and I1004 and I1007 of TM12. Dimethylpropyl group of P1075 and benzopyran group of Lev are inserted into the hydrophobic pocket of SUR2 (Fig. 2, E–H). Although residues that form the B and P sites are conserved between SUR1 and SUR2 subunits, the B and P sites of KCOS in SUR1 is enlarged compared with SUR2. The Cα distance between H576 and D1008 is increased from 10.2 Å in SUR2 (Ding et al., 2022) (PDB ID: 7VLS) to 12.4 Å in SUR1 (Wang et al., 2022b) (PDB ID: 7W4O) due to the conformational difference of their transmembrane helices.

Future Efforts

As described above, the currently available structures have uncovered the ISBS and KCOS on the SUR subunits, but the exact mechanisms of how IS and KCO work remain incompletely understood. Based on previous functional studies and available structures, IS likely inhibit K_{ATP} through two interdependent mechanisms. First, IS wedge in the TMD to allosterically inhibit the dimerization of two NBDs. Second, IS facilitate the recruitment of Kir6 N-terminal peptide (KNtp) to the central vestibule of SUR1, and KNtp further restrains the rotation of Kir6.2 cytoplasmic domain (CTD) to inhibit channel opening (Wu et al., 2018, 2020). Despite recent progress in the cryo-EM studies of K_{ATP} with intact KNtp (Li et al., 2017; Martin et al., 2017a, 2019; Sung et al., 2021) or KNtp-SUR1 chimera (Ding et al., 2019), the exact residues on KNtp that make interactions with IS and SUR1 could not be explicitly identified in currently available maps because of their poor local map qualities due to the flexibility of KNtp. Similarly, the pharmacophores on IS that are responsible for KNtp binding are also poorly defined, although it is obvious that different IS use distinct chemical groups at H-B site for KNtp recruitment (Fig. 1E). These fundamental questions about the structural pharmacology of IS await further structural and functional investigation. This allosteric model for IS inhibition is also in agreement with the shortcoming of IS: some neonatal diabetes patients with Kir6.2 mutations are resistant to the sulfonylurea therapy (SU-insensitive mutants) (Pipatpolkai et al., 2020). This is likely because the Kir6.2 CTDs of these SU-insensitive mutants seldom sample the closed conformation that allows the insertion of KNtp into the SUR1 central vestibule. Therefore, drugs that directly inhibit the Kir6.2 channel would be a better choice to suppress the activity of these mutants. However, available small-molecule inhibitors of Kir6.2 such as imidazoline-type compound phentolamine are low affinity, and their binding sites are unknown yet (Cui et al., 2021). Recently, a centipede toxin, SpTx-1, has been reported to inhibit the Kir6.2 channel with high potency (Ramu et al., 2018), and SpTx-1 could trigger insulin secretion and lower blood glucose levels in the diabetic mice model (Ramu et al., 2022). We believe further elucidation of the structural mechanism of Kir6.2-specific small molecules or SpTx-1 toxins might shed light on the development of novel antidiabetic drugs targeting SU-insensitive K_{ATP} mutants.

The structures of SUR in complex with KCO reveal that KCO activate the channel by promoting SUR to adopt the occluded state, which is in synergy with Mg-ADP (Ding et al., 2022; Wang et al., 2022b). Recent structures of the pancreatic K_{ATP} channel in the activated nonconductive state (radii of the ion permeation pathway at the constriction are smaller than the hydrated potassium ion 3.3 Å) provide hints of how the occluded SUR activates K_{ATP} (Zhao and MacKinnon, 2021; Wang et al., 2022b): first, the KNtp is released from the central vestibule of SUR, alleviating its allosteric effects on the inhibition of Kir6; and second, the ATP binding loop of SUR (ABLOS) is away from Kir6, which decreases the affinity of K_{ATP} for the inhibitory nucleotides. However, the exact activation mechanism of K_{ATP} by the occluded SUR awaits the determination of K_{ATP} structure in the fully open conformation.

Taken together, recent progress on the structural determination of K_{ATP}-drug complexes shed lights on the concept of K_{ATP} pharmacology at near-atomic resolution and sets the foundation for future structure-based drug design and optimization. However, a complete mechanistic understanding of the K_{ATP} pharmacology awaits further investigation.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Wu, Ding, Chen.

References

Aittoniemi J, Fotinou C, Craig TJ, de Wet H, Proks P, and Ashcroft FM (2009) Review. SUR1: a unique ATP-binding cassette protein that functions as an ion channel regulator. *Philos Trans R Soc Lond B Biol Sci* **364**:257–267.

Ashcroft FM (2006) K(ATP) channels and insulin secretion: a key role in health and disease. *Biochem Soc Trans* **34**:243–246.

Ashcroft FM and Gribble FM (2000) New windows on the mechanism of action of K(ATP) channel openers. *Trends Pharmacol Sci* **21**:439–445.

Babenko AP, Gonzalez G, and Bryan J (2000) Pharmaco-topology of sulfonylurea receptors. Separate domains of the regulatory subunits of K(ATP) channel isoforms are required for selective interaction with K(+) channel openers. *J Biol Chem* **275**: 717–720.

Basit A, Riaz M, and Fawwad A (2012) Glimepiride: evidence-based facts, trends, and observations (GIFTS). [corrected]. *Vasc Health Risk Manag* **8**:463–472.

Bray KM and Quast U (1992) A specific binding site for K+ channel openers in rat aorta. *J Biol Chem* **267**:11689–11692.

Brown GR and Foubister AJ (1984) Receptor binding sites of hypoglycemic sulfonylureas and related [(acylamino)alkyl]benzoic acids. *J Med Chem* **27**:79–81.

Cui M, Cantwell L, Zorn A, and Logothetis DE (2021) Kir channel molecular physiology, pharmacology, and therapeutic implications. *Handb Exp Pharmacol* **267**:277–356.

Dabrowski M, Larsen T, Ashcroft FM, Bondo Hansen J, and Wahl P (2003) Potent and selective activation of the pancreatic beta-cell type K(ATP) channel by two novel diazoxide analogues. *Diabetologia* **46**:1375–1382.

D'hahan N, Jacquet H, Moreau C, Catty P, and Vivaudou M (1999a) A transmembrane domain of the sulfonylurea receptor mediates activation of ATP-sensitive K(+) channels by K(+) channel openers. *Mol Pharmacol* **56**:308–315.

D'hahan N, Moreau C, Prost AL, Jacquet H, Alekseev AE, Terzic A, and Vivaudou M (1999b) Pharmacological plasticity of cardiac ATP-sensitive potassium channels toward diazoxide revealed by ADP. *Proc Natl Acad Sci USA* **96**:12162–12167.

Ding D, Wang M, Wu, J-X, Kang Y, and Chen L (2019) The structural basis for the binding of repaglinide to the pancreatic K_{ATP} channel. *Cell Rep* **27**:1848–1857.e4.

Ding D, Wu JX, Duan X, Ma S, Lai L, and Chen L (2022) Structural identification of vasodilator binding sites on the SUR2 subunit. *Nat Commun* **13**:2675.

Flagg TP, Enkvetchakul D, Koster JC, and Nichols CG (2010) Muscle KATP channels: recent insights to energy sensing and myoprotection. *Physiol Rev* **90**:799–829.

Gilbert AM, Antane MM, Argentieri TM, Butera JA, Francisco GD, Freeden C, Gundersen EG, Graceffa RF, Herbst D, Hirth BH, et al. (2000) Design and SAR of novel potassium channel openers targeted for urge urinary incontinence. 2. Selective and potent benzylamino cyclobutenediones. *J Med Chem* **43**:1203–1214.

Grell W, Hurnaus R, Griss G, Sauter R, Rupprecht E, Mark M, Luger P, Nar H, Wittneben H, and Müller P (1998) Repaglinide and related hypoglycemic benzoic acid derivatives. *J Med Chem* **41**:5219–5246.
Gribble FM and Reimann F (2003) Differential selectivity of insulin secretagogues: mechanisms, clinical implications, and drug interactions. *J Diabetes Complications* **17**(2, Suppl)11–15.
Gribble FM, Reimann F, Ashfield R, and Ashcroft FM (2000) Nucleotide modulation of pinacidil stimulation of the cloned K(ATP) channel Kir6.2/SUR2A. *Mol Pharmacol* **57**:1256–1261.
Hansen JB (2006) Towards selective Kir6.2/SUR1 potassium channel openers, medicinal chemistry and therapeutic perspectives. *Curr Med Chem* **13**:361–376.
Hu S, Wang S, and Dunning BE (1999) Tissue selectivity of antidiabetic agent nateglinide: study on cardiovascular and beta-cell K(ATP) channels. *J Pharmacol Exp Ther* **291**: 1372–1379.
Kühlbrandt W (2014) Biochemistry. The resolution revolution. *Science* **343**:1443–1444.
Li N, Wu JX, Ding D, Cheng J, Gao N, and Chen L (2017) Structure of a pancreatic ATP-sensitive potassium channel. *Cell* **168**:101–110.e10.
Li Y, Aziz Q, and Tinker A (2021) The pharmacology of ATP-sensitive K^+ channels (K_{ATP}). *Handb Exp Pharmacol* **267**:357–378.
Manley PW and Quast U (1992) Structure-activity studies of potassium channel opening in pinacidil-type cyanoguanidines, nitroethenediamines, thioureas, and ureas. *J Med Chem* **35**:2327–2340.
Mannhold R (2004) KATP channel openers: structure-activity relationships and therapeutic potential. *Med Res Rev* **24**:213–266.
Mannhold R (2006) Structure-activity relationships of K(ATP) channel openers. *Curr Top Med Chem* **6**:1031–1047.
Martin GM, Kandasamy B, DiMaio F, Yoshioka C, and Shyng SL (2017a) Anti-diabetic drug binding site in a mammalian K_{ATP} channel revealed by cryo-EM. *eLife* **6**:e31054.
Martin GM, Sung MW, Yang Z, Innes LM, Kandasamy B, David LL, Yoshioka C, and Shyng SL (2019) Mechanism of pharmacochaperoning in a mammalian K_{ATP} channel revealed by cryo-EM. *eLife* **8**:e46417.
Martin GM, Yoshioka C, Rex EA, Fay JF, Xie Q, Whorton MR, Chen JZ, and Shyng SL (2017b) Cryo-EM structure of the ATP-sensitive potassium channel illuminates mechanisms of assembly and gating. *eLife* **6**:e24149.
Moreau C, Jacquet H, Prost AL, D'hahan N, and Vivaudou M (2000) The molecular basis of the specificity of action of K(ATP) channel openers. *EMBO J* **19**: 6644–6651.
Nichols CG (2006) KATP channels as molecular sensors of cellular metabolism. *Nature* **440**:470–476.
Pipatpolkai T, Usher S, Stansfeld PJ, and Ashcroft FM (2020) New insights into K_{ATP} channel gene mutations and neonatal diabetes mellitus. *Nat Rev Endocrinol* **16**: 378–393.
Quast U, Stephan D, Bieger S, and Russ U (2004) The impact of ATP-sensitive K+ channel subtype selectivity of insulin secretagogues for the coronary vasculature and the myocardium. *Diabetes* **53** (Suppl 3):S156–S164.
Ramu Y, Xu Y, and Lu Z (2018) A novel high-affinity inhibitor against the human ATP-sensitive Kir6.2 channel. *J Gen Physiol* **150**:969–976.
Ramu Y, Yamakaze J, Zhou Y, Hoshi T, and Lu Z (2022) Blocking Kir6.2 channels with SpTx1 potentiates glucose-stimulated insulin secretion from murine pancreatic β cells and lowers blood glucose in diabetic mice. *Elife* **11**:e77026.
Reimann F, Ashcroft FM, and Gribble FM (2001a) Structural basis for the interference between nicorandil and sulfonylurea action. *Diabetes* **50**:2253–2259.
Reimann F, Proks P, and Ashcroft FM (2001b) Effects of mitiglinide (S 21403) on Kir6.2/SUR1, Kir6.2/SUR2A and Kir6.2/SUR2B types of ATP-sensitive potassium channel. *Br J Pharmacol* **132**:1542–1548.
Rufer C, Biere H, Ahrens H, Loge O, and Schröder E (1974) Blood glucose lowering sulfonamides with asymmetric carbon atoms. *J Med Chem* **17**:708–715.
Sung MW, Yang Z, Driggers CM, Patton BL, Mostofian B, Russo JD, Zuckerman DM, and Shyng SL (2021) Vascular K_{ATP} channel structural dynamics reveal regulatory mechanism by Mg-nucleotides. *Proc Natl Acad Sci USA* **118**:e2109441118.
ter Beek J, Guskov A, and Slotboom DJ (2014) Structural diversity of ABC transporters. *J Gen Physiol* **143**:419–435.
Tusnády GE, Bakos E, Váradi A, and Sarkadi B (1997) Membrane topology distinguishes a subfamily of the ATP-binding cassette (ABC) transporters. *FEBS Lett* **402**:1–3.
Uhde I, Toman A, Gross I, Schwanstecher C, and Schwanstecher M (1999) Identification of the potassium channel opener site on sulfonylurea receptors. *J Biol Chem* **274**: 28079–28082.
Vila-Carriles WH, Zhao G, and Bryan J (2007) Defining a binding pocket for sulfonylureas in ATP-sensitive potassium channels. *FASEB J* **21**:18–25.
Wang M, Wu J-X, and Chen L (2022a) Structural insights into the high selectivity of the anti-diabetic drug mitiglinide. *Front Pharmacol* **13**:929684.
Wang M, Wu J-X, Ding D, and Chen L (2022b) Structural insights into the mechanism of pancreatic K_{ATP} channel regulation by nucleotides. *Nat Commun* **13**:2770.
Winkler M, Stephan D, Bieger S, Kühner P, Wolff F, and Quast U (2007) Testing the bipartite model of the sulfonylurea receptor binding site: binding of A-, B-, and A + B-site ligands. *J Pharmacol Exp Ther* **322**:701–708.
Wu JX, Ding D, Wang M, and Chen L (2020) Structural insights into the inhibitory mechanism of insulin secretagogues on the pancreatic ATP-sensitive potassium channel. *Biochemistry* **59**:18–25.
Wu JX, Ding D, Wang M, Kang Y, Zeng X, and Chen L (2018) Ligand binding and conformational changes of SUR1 subunit in pancreatic ATP-sensitive potassium channels. *Protein Cell* **9**:553–567.
Zhao C and MacKinnon R (2021) Molecular structure of an open human K_{ATP} channel. *Proc Natl Acad Sci USA* **118**:e2112267118.

Address correspondence to: Lei Chen, Room 218, Research Building No. 2, Peking University, Yiheyuan Road No.5, Beijing, China 100871. E-mail: chenlei2016@pku.edu.cn