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REVIEW
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Functional Regulation of K_{ATP} Channels and Mutant Insight Into Clinical Therapeutic Strategies in Cardiovascular Diseases

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ATP-sensitive potassium channels (K_{ATP} channels) play pivotal roles in excitable cells and link cellular metabolism with membrane excitability. The action potential converts electricity into dynamics by ion channel-mediated ion exchange to generate systole, involved in every heartbeat. Activation of the K_{ATP} channel repolarizes the membrane potential and decreases early afterdepolarization (EAD)-mediated arrhythmias. K_{ATP} channels in cardiomyocytes have less function under physiological conditions but they open during severe and prolonged anoxia due to a reduced ATP/ADP ratio, lessening cellular excitability and thus preventing action potential generation and cell contraction. Small active molecules activate and enhance the opening of the K_{ATP} channel, which induces the repolarization of the membrane and decreases the occurrence of malignant arrhythmia. Accumulated evidence indicates that mutation of K_{ATP} channels deteriorates the regulatory roles in mutation-related diseases. However, patients with mutations in K_{ATP} channels still have no efficient treatment. Hence, in this study, we describe the role of K_{ATP} channels and subunits in angiocardiopathy, summarize the mutations of the K_{ATP} channels and the functional regulation of small active molecules in K_{ATP} channels, elucidate the potential mechanisms of mutant K_{ATP} channels and provide insight into clinical therapeutic strategies.

Keywords: K_{ATP} channels, mitoK_{ATP} channels, myocardial ischemia, channelopathy, small active molecules, mutation

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INTRODUCTION

The aging of the population and improved survival after acute myocardial infarction have resulted in high morbidity and mortality, a poor clinical prognosis and high expenses due to heart failure (HF) (Savarese et al., 2022). The prevalence of HF is predicted to increase by 46% from 2012 to 2030. After several years of therapeutic exploration, the prognosis of HF remains poor, with a 5-years mortality of ≈40%–50%, and the projections suggest that the total costs for HF in 2030 will be close to $38.99 billion in the United States (Kaneko et al., 2021; Yu et al., 2021; Savarese et al., 2022). Sudden cardiac death (SCD) is the leading cause of death in HF, and malignant arrhythmia is regarded as the overriding risk within SCD (Akhtar et al., 2021; Grune et al., 2021; Mulder et al., 2021). HF involves numerous physiological and pathological processes, among which calcium (Ca^{2+}) overload is a typical representative. Ca^{2+} overload destroys membranes, organelles and DNA, leading to structural

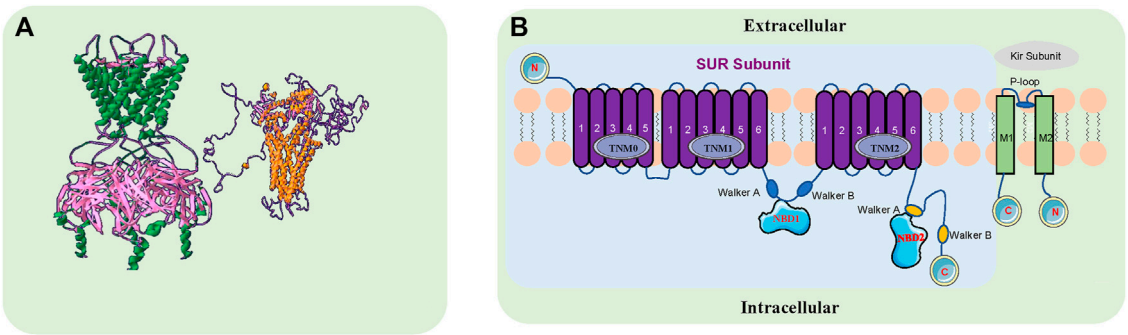

FIGURE 1 | The Structure of the K_{ATP} Channel. **(A)**. K_{ATP} channels are comprised of four sulfonylurea receptors (SURx) and four K^+ inward rectifiers (Kir6. x) that assemble to form hetero-octameric protein complexes. The green and pink sections on the left represent the side view of the Kir6. x subunit, and the gold and purple sections on the right represent the side view of the SURx subunit. FASTA comes from NCBI, designed by www.swissmodel.com, Image designed by Swiss-Pdbviewer software. **(B)**. The pore-forming subunit Kir6. x (Kir6.1 and Kir6.2) has intracellular N- and C-termini and two transmembrane segments M1 and M2, encoded by KCNJ8 and KCNJ11, respectively. The modulatory subunit SURX (SUR1, SUR2A, SUR2B) consists of three groups of transmembrane domains (TMD0, TMD1 and TMD2) and extracellular N- and intracellular C-termini, encoded by ABCC8 and ABCC9. There are two intracellular nucleotide binding folds (NBD1 and NBD2) within the SUR subunit. ABCC8 and KCNJ11 are adjacent to each other on chromosome 11p15.1, with ABCC9 and KCNJ8 on chromosome 12P12.1.

TABLE 1 | Distribution of K_{ATP} channels.

System	Organ/Tissue/Cell	Subunit Types	Disease Contributory
Circulatory System	Atrium Ventricle	Kir6.2/SUR2B, Kir6.2/SUR1 (Zhang et al., 2013)	Atrial Fibrillation, Hypertension
	Vascular smooth muscle	Kir6.2/SUR2A (Yang et al., 2020b)	Dilated Cardiomyopathy, Myocardial Ischemia, Endothelium
	Endothelial cell	Kir6.1/SUR2B (Zhang et al., 2021a)	Dysfunction, Vasculature Atherosclerosis (Zhang et al., 2013; Wang et al., 2019b; Yang et al., 2020b; Zhang et al., 2021a)
	Capillary endothelial cell	Kir6.1/Kir6.2/SUR2B (Wang et al., 2019b)	
Respiratory System	Alveolar epithelial cells	Kir6.1/SUR2B (Leroy et al., 2006)	Pulmonary Hypertension (Leroy et al., 2006; Rieg et al., 2020)
Digestive System	Mesenteri artery	Kir6.1 (Li et al., 2020b; Jin et al., 2020)	Regulation of Blood Pressure, Excessive Atherosclerotic (Li et al., 2020b)
	Gastric smooth muscle	Kir6.1/SUR2B (Sim et al., 2002)	
	Liver	Kir6.1/Kir6.2/SUR1/SUR2A/SUR2B (Zhou et al., 2019b)	

and functional disruption of cells and tissues, eventually promoting cardiomyopathy, ventricular fibrillation and sudden death (Yang et al., 2021).

ATP-sensitive potassium channels (K_{ATP} channels) were first discovered in cardiac muscle in 1983 by Noma (Noma, 1983) and were successively found in skeletal muscle, the digestive system, urinary system, integumentary system, reproductive system, and central nervous system (Huang et al., 2019; Zhao et al., 2020) (**Figure 1**). Activating K_{ATP} channels shorten the action potential duration, reduce intracellular Ca^{2+} entry to suppress calcium overload, inhibit contractility, and prevent arrhythmias and cardiac insufficiency caused by calcium overload; however, completely opening K_{ATP} channels in the heart may result in complete cessation of cardiac electrical activity and contractile failure (Huang et al., 2019). Hence, K_{ATP} channels play an irreplaceable role in HF, whether from myocardial ischemia or arrhythmia.

K_{ATP} channels are widely distributed in various organs, but the assembly of their subunits varies depending upon the tissue and they may confer different functional and pharmacological properties depending on which subunits are present (Li et al., 2021; Stewart and Turner, 2021) (**Table 1**). K_{ATP} channels are comprised of four sulfonylurea receptors (SURx) and four K^+ inward rectifiers (Kir6. x) that assemble to form hetero-octameric protein complexes. The pore-forming subunit Kir6. x (Kir6.1 and Kir6.2) has intracellular N- and C-termini and two transmembrane segments M1 and M2, encoded by KCNJ8 and KCNJ11, respectively. The modulatory subunit SURx (SUR1, SUR2A, SUR2B) consists of three groups of transmembrane domains (TMD0, TMD1 and TMD2) and extracellular N- and intracellular C-termini, encoded by ABCC8 and ABCC9. There are two intracellular nucleotide binding folds (NBD1 and NBD2) within the SUR subunit. ABCC8 and KCNJ11 are adjacent to each

other on chromosome 11p15.1, with ABCC9 and KCNJ8 on chromosome 12P12.1.

Cardiac K_{ATP} channels provide cardioprotection against ischemia/reperfusion injury; in contrast, overexpressed cardiac K_{ATP} channels have proarrhythmic effects, which associates them with profound value for clinical applications and exploration. There are three subtypes of K_{ATP} channels found within the cardiovascular system: two widely accepted channels, mitoK_{ATP} and sarcolemma K_{ATP}, and a controversial K_{ATP} channel, plasma membrane K_{ATP} (Iguchi et al., 2019; Pertiwi et al., 2019; Aziz et al., 2020; Jiang et al., 2021). Different cardiac K_{ATP} channels play different roles in the cardiovascular system, which will be explained here. Recent evidence has shown that several refractory diseases are closely related to mutations in K_{ATP} channel subunits. Disease-related clinical symptoms and high medical costs will burden the patient, the family, and society. Most encouraging, some K_{ATP} channel activators and antagonists have shown good results for treating K_{ATP} channel subunit mutation-related diseases, such as Cantú syndrome, congenital hyperinsulinism (CHI), neonatal diabetes mellitus (NDM), developmental delay epilepsy and neonatal diabetes (DEND) and ABCC9-related intellectual disability myopathy Syndrome (AIMS) (Demirbilek et al., 2019; Martin et al., 2020; McClenaghan et al., 2020).

In this review, we focus on the regulatory mechanism of K_{ATP} channels during angiocardiopathy and provide insights into how mutations in K_{ATP} channelopathies lead to some incurable diseases. Furthermore, we will explore the therapeutic strategy of targeting K_{ATP} channel drugs in clinical practice.

K_{ATP} CHANNELS IN CARDIOVASCULAR DISEASES

Mitochondrial ATP-Sensitive Potassium Channels (mitoK_{ATP} Channels)

As an independent factor associated with high mortality, acute myocardial infarction is an irreversible process characterized by glycogen depletion, margination of nuclear chromatin, mitochondrial swelling and sarcolemmal breaks. Myocardial infarct size and the duration of ischemia are the main determinants of the prognosis (Heusch, 2020). Rapidly restoring blood flow is the key to successful salvage of ischemic myocardium; however, reperfusion not only salvages ischemic myocardium from infarction but also induces an increased risk of additional complications and further cardiomyocyte death, a process called myocardial ischemia reperfusion injury (MIRI) (Griffiths et al., 2021). In myocardial ischemia, the mitochondrial matrix is damaged and extensively broken, and it dissolves the mitochondrial crest, ruptures and vacuolates the mitochondrial membrane, significantly decreases glycogen granules, increases intracellular Ca^{2+}, diminishes ATP production, and induces myocardial cell apoptosis (Paggio et al., 2019; Basalay et al., 2020; Wang et al., 2020; Bai et al., 2021; Wang et al., 2021). A novel autologous mitochondrial transplantation therapy, in which respiration-competent mitochondria are isolated from autologous nonischemic tissue and transplanted into ischemic myocardium, improves the contractile function and tissue viability of the injured myocardium, proving that mitochondrial injury is the main pathogenesis of MIRI (Shin et al., 2019).

mitoK_{ATP} channels are involved in a series of physiological and pathophysiological changes to mitigate cardiomyocyte injury and apoptosis. mitoK_{ATP} channels have been described as being located in the inner mitochondrial membrane and they have protective properties for ischemic myocardium; moreover, their existence has been the subject of heated debate (Bezerra Palácio et al., 2021). Recently, the molecular composition of mitoK_{ATP} was shown by Paggio et al., and they are comprised of pore-forming (MITOK, encoded by the CCDC51 gene (NCBI ID 79714)) and regulatory (MITOSUR, tissue expression correlates with ABCB8) subunits (Paggio et al., 2019) (**Figure 2**). The opening of mitoK_{ATP} channels promotes mitochondrial K^+ inward flow into the deeply negative polarized matrix (mitochondrial membrane potential (Ψ_m)), decreases the transmembrane potential discrepancy, depolarizes the Ψ_m, reduces Ca^{2+} inward flow dynamics, inhibits Ca^{2+} inward flow, and prevents mitochondrial calcium overload, leading to mitochondrial relaxation, enhanced fatty acid oxidation, oxidative phosphorylation, respiratory function, and ATP production, thus improving myocardial cell survival (Sakamoto and Kurokawa, 2019; Jiang et al., 2021).

During the process of MIRI, the activation of mitochondrial K_{ATP} channels depolarizes the mitochondrial membrane, reduces the driving force of mitochondrial calcium uptake, and prevents Ca^{2+} accumulation in the mitochondrial matrix, thus preventing the formation of the mitochondrial permeability transition pore (MPTP) (Testai et al., 2021). Currently, the main components of MPTP are as follows: adenine nucleotide translocator (ANT) and mitochondrial phosphate carrier (PiC) on the inner mitochondrial membrane (IMM), mammalian F1Fo(F)-ATP synthase (the Fo subunit consists of a, e, f, g and A6 L; the F1 subunit α, β, and the ε and γ subunits needed for ATP synthase dimer formation, the peripheral stem consists of b, d, and the F6 subunit and oligomycin sensitivity conferring protein (OSCP)) (Kent et al., 2021) (**Figure 2**). MPTP is the point at which reactive oxygen species (ROS), Ca^{2+}, cytochrome C (Cyt C), and other small molecule modulators escape from the mitochondrial matrix, and its opening leads to the loss of oxidative phosphorylation capacity as well as the release of pro-death mitochondrial proteins (mitochondrial swelling and membrane rupture), increased Bax expression and decreased Bcl_2 expression, ultimately activating the apoptotic cascade in the mitochondria in ischemia–reperfusion heart tissues (Jiang et al., 2021; Kent et al., 2021; Pereira and Kowaltowski, 2021). Mitochondrial ROS spreading from the electron transport chain damages the mitochondrial DNA, which can cause mitochondrial dysfunction and affect nuclear gene expression, ion handling, and mitochondrial metabolism, finally causing the activation of an inflammatory response, apoptotic signaling, and endoplasmic reticulum stress in the cardiovascular system (Bou-Teen et al., 2021). Indeed, MIRI triggers a cascade involving increased NO production (NO function; anti-inflammatory and antioxidant

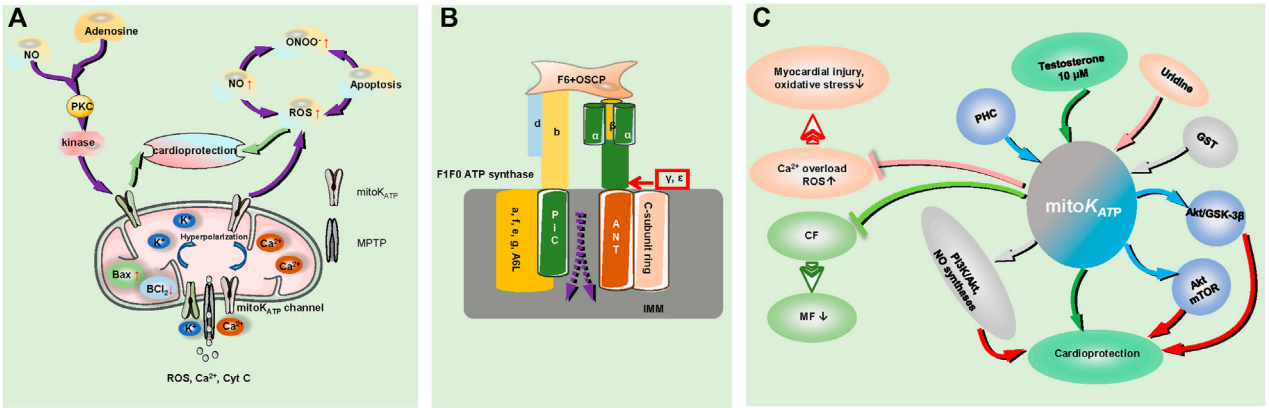

FIGURE 2 | The role of mitoK$_{ATP}$ in myocardial ischemia and the regulation of the signaling pathways involved. **(A)**. Mitochondrial injury and mitoK$_{ATP}$ play a role in cardiac protection during the process of MIRI; MIRI increased Bax expression and decreased BCL_2 expression, triggering a cascade involving increased NO production and leading to the superficial formation of $ONOO^-$ with increased production of ROS. Activation of mitoK$_{ATP}$ stimulates the anti-inflammatory and antioxidant effects of NO on ischemic myocardium by inhibiting the overproduction of ROS. Ischemic postadaptation activates protein kinase C and the reperfusion injury salvage kinase pathway through the intracellular concentration of adenosine and NO, and it acts on the mitoK$_{ATP}$ channel to protect the myocardium; activation of the mitoK$_{ATP}$ channel leads to cell hyperpolarization, resulting in reduced Ca^{2+} entry, and a reduced driving force of mitochondrial calcium uptake, prevent Ca^{2+} accumulation in the matrix and MPTP formation. The MPTP is the escape pore of ROS, Cyt C, Ca^{2+} and other signaling molecules. CF indicates cardiac fibroblasts; MF, myofibroblasts; MIRI, myocardial ischaemia reperfusion injury; and $ONOO^-$, peroxynitrite. **(B)**. The structure of MPTP; F1Fo ATP synthase: The Fo subunit consists of a, e, f, g and A6 L, the F1 component consists of α and *β* subunits, labeled in bottle green and yellow, respectively, and the γ, ε subunits. The F1 peripheral stalk is comprised of subunits b, d, F6, and OSCP. The C cyclic subunit, ANT and PiC are overlaid by IMM; the dotted line represents the MPTP signal molecule outflow position. OSCP indicates oligomycin sensitivity conferring protein; IMM, inner mitochondrial membrane; ANT, adenine nucleotide translocase; and PiC, phosphate carrier. **(C)**. mitoK$_{ATP}$ channels prevent transdifferentiation of CF to MF to reduce MF maturation. Testosterone (10 μM) increases the opening probability of mitoK$_{ATP}$ channels, PHC regulates the mitochondrial K$_{ATP}$ channel, Akt/GSK-3β, and Akt/mTOR signaling pathways, GST depends on protein-kinase C and mitoK$_{ATP}$ channel pathway activation by some typical pathways such as PI3K/Akt and NO synthases, and plays roles in cardioprotection. Uridine attenuates myocardial injury and oxidative stress by activating the mitoK$_{ATP}$ channel to reduce excessive ROS production and prevent calcium overload. PHC indicates penehyclidine hydrochloride; GST, genistein.

effects) and leads to the superfluous formation of peroxynitrite ($ONOO^-$) with increased production of ROS, which mediates the pernicious impact of NO (Liu et al., 2021a). The activation of mitoK$_{ATP}$ during ischemia plays a role in the cardioprotective function by inhibiting the overproduction of ROS and stimulating the NO effects on anti-inflammatory and antioxidant activities in the ischemic myocardium (Liu et al., 2021a; Rameshrad et al., 2021). Ischemic postconditioning activates protein kinase C and reperfusion injury salvage kinase pathways through modulating the intracellular concentrations of adenosine and NO, ultimately acting on the mitoK$_{ATP}$ pathway to protect the myocardium (Li et al., 2020a).

mitoK$_{ATP}$ channels also affect other cardiac components. Within rat cardiac fibroblasts (CFs), mitoK$_{ATP}$ channels prevent the transdifferentiation of CFs to myofibroblasts (MFs) to reduce MF maturation and antagonize cardiac pathological remodeling following simulated ischemia-reperfusion injury (Stewart and Turner, 2021). ROMK (a kidney mRNA detectable in the thick ascending limb and the distal nephron) participates in K^+ reabsorption and secretion. An experiment performed by Irina B. Krylova et al. implicated ROMK in Ca^{2+}-induced MPTP opening but did not play a role in mitoK$_{ATP}$ activity in the mouse heart (Papanicolaou et al., 2020). Electrophysiological analysis revealed that 10 μM testosterone increased the open probability of mitoK$_{ATP}$ channels, which offered cytoprotection against MIRI (Sakamoto and Kurokawa, 2019).

The recently discovered signal-regulated pathways involved in mitoK$_{ATP}$ channels are as follows. Penehyclidine hydrochloride (PHC) preconditioning plays a cardioprotective role by regulating the mitochondrial K$_{ATP}$ channel and Akt/GSK-3β and Akt/mTOR signaling pathways (Zi et al., 2020). Uridine attenuates myocardial injury and oxidative stress in MIRI, which may be mediated by activation of the mitoK$_{ATP}$ channel, achieved by reducing excessive ROS production and preventing the appearance of calcium overload (Krylova et al., 2021). GST (genistein, a phytoestrogen) provides a cardioprotective function that depends on protein kinase C and activates mitoK$_{ATP}$ channels via a typical pathway, such as PI3K/Akt and NO synthases (Colareda et al., 2020).

Sarcolemma ATP-Sensitive Potassium Channels

Early evidence indicated that sarcolemma ATP-sensitive potassium (sarcK$_{ATP}$) channels play a crucial role in ischemic preconditioning and myocardial resistance to ischemia, which close during general conditions and open in response to increased [ADP]/[ATP], linking membrane excitability to the balance of ATP production and shortening action potential (AP) duration (APD) via the efflux of K^+ (Garrott et al., 2017; Sudhir et al., 2020). SarcK$_{ATP}$ channels improve adaptation to physical stress and profoundly alter membrane excitability and other membrane

potential-related functions, such as Ca^{2+} overload, thus helping to maintain cellular homeostasis during cardiac challenge (i.v. adenosine) (Zhang et al., 2016). The partial opening of sarcK_{ATP} channels plays a crucial role in the regional depolarization of Ψm, which can transform cellular electrical excitability and increase the propensity for reentry arrhythmogenesis (Solhjoo and O'Rourke, 2015). An unstable or oscillating Ψm can expose cardiomyocytes to ROS or result in glutathione depletion, activate sarcK_{ATP} channels and abate the cellular ATP/ADP ratio, which has been deemed to be a dominant factor in arrhythmogenesis during MIRI (Solhjoo and O'Rourke, 2015).

Increased activation of the sarcK_{ATP} channel (a role in cardioprotection) does not participate in the protection provided by ordinary cardioprotective stimulation. sarcK_{ATP} opening actually occurs later during metabolic inhibition (after cardioprotection), cardioprotective stimuli prolong normal mitochondrial function during ischemia, and the delay in the opening of sarcK_{ATP} channels is a consequence of the continuation of ATP production, so sarcK_{ATP} channel opening is the last defense of cardiomyocytes to preserve ATP and limit the Ca^{2+} overload during ischemia (Brennan et al., 2015). The density of sarcK_{ATP} channels under physiological conditions plays a significant role in cardioprotection; however, certain pathophysiologic circumstances give rise to a declining density of sarcK_{ATP} channels, including hyperinsulinemia and cardiac ischemia (Yang et al., 2018). The lower basal expression level of sarcK_{ATP} channels in hESCs (human embryonic stem cells)-VCMs (ventricular cardiomyocytes) (~1/8 of adults) means they were partially activated and sufficient to cause APD shortening and accelerate AP firing; when fully activated, sarcK_{ATP} channels silenced automaticity without compromising intrinsic cellular excitability (Keung et al., 2016).

Studies on the cardiac sarcK_{ATP} channel regulatory subunit SUR2A/SUR2B are ongoing. The activation of β_1-adrenoceptors upregulates SUR2B/Kir6.2, in which SUR2B physically associates with Kir6.2 to act as a regulatory subunit in sarcK_{ATP} channels to offer cardioprotection (Jovanovic et al., 2016). With an increasing number of sarcK_{ATP} channels, increased expression of SUR2A regulates cardiac physiology and improves the adaptation to physical stress by shortening the action potential and improving cardiac Ca^{2+} homeostasis (Zhang et al., 2016).

The recently discovered signal-regulated pathways and regulatory proteins involved in sarcK_{ATP} channels are as follows. Eps15 homology domain-containing protein (EHD)-2 affects the sarcK_{ATP} channel by stabilizing sarcK_{ATP} channel-containing caveolar structures to increase its surface density, which results in a reduced rate of endocytosis. Pathophysiologically, EHD-2 mutant-activated cardiomyocytes may be cardioprotective against ischemic damage (Yang et al., 2018). In rat cardiomyocytes, the sarcK_{ATP} channel exerts a cardioprotective effect against lipopolysaccharide (LPS)-induced apoptosis and it is mediated by mitochondrial Ca^{2+} (Zhang et al., 2016). The cardioprotective effect of BNP is related to sarcK_{ATP} channel opening. Additionally, the cardioprotective effects of ANP and cANP4-23 are mediated via sarcK_{ATP} channel opening (Krylatov et al., 2021). ANP (atrial natriuretic peptide) positively regulates the function of the sarcK_{ATP} channel in adult rabbit ventricular cardiomyocytes by activating NPR-A (natriuretic peptide receptor type A), an effect mediated by intracellular signaling mechanisms that cover PKG (cGMP-dependent protein kinase), ROS, ERK (extracellular signal-regulated protein kinase)1/2, CaMK II (calcium/calmodulin-dependent protein kinase II), and RyR (ryanodine receptor)-2; meanwhile, RyR2 (activation) is feasibly situated downstream of ROS/H_2O_2, which process enhances the opening frequency whereas it labilizes the long closures of the channel, thereby heightening channel activity (Zhang and Lin, 2020).

MUTATION OF K_{ATP} CHANNELS

Kir 6.1

Endothelium-expressed Kir6.1 is located on human chromosome 12p, and via elevated endothelin-1 release it controls vascular tone. Smooth muscle Kir6.1 gain-of-function mutation causes overt hypertension and hypotension; notably, autosomal dominant hypertension is related to chromosome 12p recombination, and postural hypotension is related to chromosome 12 (Li et al., 2013) (**Table 2**). In gain-of-function mutation Kir6.1 [GD-QR] (point mutations in two C-terminal residues of Kir6.1; Gly343Asp and Gln53Arg), lymphatic smooth muscle and vascular dysfunction are present, and lymphatic smooth muscle-specific expression subunit mutations result in profound lymphatic contractile dysfunction and lymphatic smooth muscle hyperpolarization rather than lymphatic endothelial cells (Davis et al., 2020). In a CS animal model, the $Kir6.1^{wt/VM}$ mutation directly and/or indirectly affects the skeletal muscle through vascular dysfunction, resulting in reduced limb strength, skeletal muscle atrophy, autophagy, and myofiber connective tissue replacement (Scala et al., 2020). The S422 L mutation, a missense mutation in the KCNJ8 gene, leads to a gain-of-function Kir6.1 channel, which leads to shortened repolarization in ventricular tissue; nevertheless, it could shorten repolarization in the atrium to increase atrial fibrillation susceptibility (Delaney et al., 2012).

Kir 6.2

Approximately 38.5% of mutations in the KCNJ11 gene, which encodes Kir 6.2 and consists of a single exon containing 390 amino acids, have been identified, which is associated with clinical diseases including but not limited to neonatal diabetes mellitus, maturity-onset diabetes of the young, type 2 diabetes mellitus, and even persistent hyperinsulinemic hypoglycemia of infancy (He et al., 2021). Patients with the E227K mutation in the KCNJ11 gene typically manifest with transient neonatal diabetes, which remits spontaneously, usually within 4–60 weeks of onset; however, more than half of these patients relapse into permanent diabetes in adolescence or early adulthood (Devaraja et al., 2020). rs5215 G/G (nucleotide change; G-A, amino acid change; Val337Ile) of the KCNJ11 gene, located at 11p15.1 and encoding the Kir6.2 subunit, causes valine-isoleucine substitution in exon 1,009 (ATC-GTC), and it is associated

TABLE 2 | Monosubunit mutation and their locus and consequence.

Mutant Subunit	Mutant Locus	Consequence
Kir 6.1	Smooth muscle	Hypertension/hypotension
	Lymphatic smooth muscle	Lymphatic contractile dysfunction lymphatic smooth muscle hyperpolarization
	Skeletal muscle	Reduced limb strength, skeletal muscle atrophy, autophagy, and myofibers connective tissue replacement
	S422L	Shortened repolarization in ventricular tissue Increase atrial fibrillation susceptibility
Kir 6.2	Pancreatic islet cell	Neonatal diabetes mellitus, maturity-onset diabetes of the young 13, type 2 diabetes mellitus, and even persistent hyperinsulinemic hypoglycemia of infancy
	rs5215 G/G	Vasodilation augment and shear stress reduction
	Hypertension mouse model	Heart failure and death, myocardial incommensurate remodeling
	p.V59M	Intellectual disability
SUR1	Pancreas	Neonatal diabetes
	V187D	Higher insulin secretion in hypoglycemia and make K_{ATP} channel acting pharmaceuticals out of action
	p.H1401Tfs	Clinical heterogeneity congenital hyperinsulinemia
	Unstated	Increased channel activity in MgATP/MgADP, reduced the K_{ATP} channel surface expression
SUR2A	Fs1524 and A1513T	Severely dilated hearts with impaired systolic function and arrhythmia
SUR2B	R659C	Heart disease and early repolarization syndrome
	C24S and C1455S	Prevent the detrimental effects of sulfhydration and NaHS-induced tyrosine nitration

with a gain of function of the K_{ATP} channel, leading to vasodilation augmentation and shear stress reduction, which protects humans from lower coronary microvascular dysfunction, reducing the risk of ischemic heart disease in women (Severino et al., 2020). In a hypertension mouse model, the Kir6.2 mutation led to heart failure and death, involving knockout mutation-induced myocardial incommensurate remodeling (Liu et al., 2021b). In neurons, Kir6.2 has critical roles in glucose sensing and neuronal excitability in response to metabolic demands, and the KCNJ11 p. V59 M mutation was strongly associated with intellectual disability (Moriguchi et al., 2018; Svalastoga et al., 2020).

SUR1

SUR1 is mainly expressed in the pancreas, and its mutations may lead to neonatal diabetes by disrupting inhibitory binding/gating or enhancing nucleotide stimulation. Some SUR1 mutant models in mice did not recapitulate the human phenotype (Sachse et al., 2020; Usher et al., 2020). SUR1-mutant (a homozygous c.560T > A (V187D) mutation in exon four of the ABCC8 gene encoding the SUR1 protein) stem cell-derived islet-like clusters (SC islets) leads to increased beta-cell proliferation and mass, higher insulin secretion in hypoglycemia and makes K_{ATP} channels-acting pharmaceuticals ineffective (Lithovius et al., 2021). The homozygous p. H1401Tfs ABCC8 mutation could cause significant clinical heterogeneity congenital hyperinsulinemia, ranging from a late-onset and diazoxide-responsive mild form to an extremely early-onset severe form requiring multimodality treatment with a full-course assessment of neurodevelopment and glycometabolism (Takasawa et al., 2021). Some SUR1 mutations resulted in increased channel activity in MgATP/MgADP and drastically reduced K_{ATP} channel surface expression, which suggests that the overactive defects due to altered nucleotide sensitivities outweigh their biogenesis and surface expression defects and lead to an overall gain-of-channel-function effect and the neonatal diabetes mellitus disease phenotype (Balamurugan et al., 2019).

SUR2A

Due to the strong difficulties and inferior feasibility of single subunit mutation research, we mainly noted several common cases herein. In individuals with idiopathic dilated cardiomyopathy, two heterozygous mutations in exon 38 of ABCC9 encode at the C-terminal domain of SUR2A, Fs1524 (a frameshift at Leu1524, which introduces four anomalous terminal residues followed by a premature stop codon) and A1513T (a missense mutation (4537G→A) causing the amino acid substitution), substantially diminishing the maximal rate of the NBD2 ATPase reaction without altering the Michaelis-Menten constant of catalysis, resulting in abnormal hydrolytic dynamics of the regulatory channel subunits, disrupting catalysis-dependent gating and impairing metabolic decoding, resulting in severely dilated hearts with impaired systolic function and arrhythmia (Bienengraeber et al., 2004).

SUR2B

The SUR2B mutation R659C located in the secondary structure region in the L1 linker (it has the greatest α-helical propensity) most stably interacts with NBD1, which could cause heart disease and even lead to early repolarization syndrome, a life-threatening condition (Sooklal et al., 2018). During colonic inflammation, two specific mutations within SUR2B (C24S and C1455S) prevent the detrimental effects of sulfhydration and NaHS-induced tyrosine nitration from reducing the pore-forming subunit (Kir6.1) (Kang et al., 2015).

Multiple Subunits Mutations of K_{ATP} Channels

Cantú syndrome (CS) is an ultrarare autosomal dominant inherited disorder caused by dominant gain-of-function mutations in both the SUR2A and Kir6.1 subunits of the K_{ATP} channel, which is also characterized by multiple cardiovascular abnormalities, including edema, pericardial effusion, pulmonary hypertension, dilated and tortuous blood vessels with decreased

TABLE 3 | Multiple subunit mutation-related disease and clinical manifestations.

Mutant Subunit	Diseases	Clinical Features
SUR2A and Kir6.1	Cantú syndrome	Edema, pericardial effusion, pulmonary hypertension, dilated and tortuous blood vessels with decreased systemic vascular resistance, and patent ductus arteriosus and cerebrovascular defects, patent ductus arteriosus, and marked cardiac hypertrophy
SUR1 and Kir6.2	Congenital hyperinsulinism	Persistent hypoglycemia in infants and children High risk of permanent brain damage
KCNJ11 and/or ABCC8 subunits	Neonatal diabetes	The first 6 months of life, beta-cell destruction, pancreatic hypoplasia or aplasia, impaired beta-cell function or severe insulin resistance
Kir 6.2 and SUR1	DEND syndrome	Neonatal diabetes with developmental delay, muscle weakness, and epilepsy
SUR2A and/or SUR2B	ABCC9-related intellectual disability myopathy syndrome	Intellectual disability, anxiety, muscle weakness and fatigability, and some shared dysmorphic features

systemic vascular resistance, cerebrovascular defects, patent ductus arteriosus, and marked cardiac hypertrophy (Chen et al., 2019; Chihara et al., 2020; McClenaghan et al., 2020; Zhang et al., 2021a) (**Table 3**). CHI is a rare genetically heterogeneous disorder caused by inactivating mutations in the SUR1 and Kir6.2 subunits of the K_{ATP} channel and it is characterized by persistent hypoglycemia in infants and children, which may increase the risk of permanent brain damage (Boodhansingh et al., 2019; Rosenfeld et al., 2019; Männistö et al., 2020; Rosenfeld et al., 2021). NDM is characterized by the development of hyperglycemia within the first 6 months of life, beta-cell destruction, pancreatic hypoplasia or aplasia, impaired beta-cell function or severe insulin resistance resulting from impaired insulin secretion caused by gain-of-function mutations in KCNJ11 and/or ABCC8 subunits of the K_{ATP} channel, which can be divided into two transient diabetes mellitus (TNDM) and perma-nent diabetes mellitus (PNDM) clinical subtypes, depending on the length of the disease course (Cao et al., 2020; Dahl and Kumar, 2020; Pipatpolkai et al., 2020; Horita et al., 2021). DEND syndrome is a severe pathological condition of neonatal diabetes with developmental delay, muscle weakness, and epilepsy caused by gain-of-function mutations in Kir 6.2 and SUR1 (Dahl and Kumar, 2020; Pipatpolkai et al., 2020; Gopi et al., 2021). AIMS is characterized by delayed psychomotor development with intellectual disability, anxiety, muscle weakness and fatigability and some shared dysmorphic features caused by loss-of-function mutations in ABCC9 (SUR2A and/or SUR2B) (Smeland et al., 2019).

REGULATION OF K_{ATP} CHANNELS BY SMALL ACTIVE MOLECULES

Hydrogen Sulfide

Hydrogen sulfide (H_2S), as a gaseous signaling molecule, has a wide range of biological functions, including vasodilatation, anti-endoplasmic reticulum stress, anti-apoptotic and anti-inflammatory functions, and it contributes to ameliorating ventricular structural remodeling and cardiac function (Li et al., 2021). In cardiac tissue, the most important enzyme for the synthesis of H_2S is cystathionine γ-lyase (CSE), which has reduced activity in atherosclerotic patients connected with angina and atrial fibrillation (Bibli et al., 2021) (**Figure 3**). H_2S has many significant bioactivities, including cytoprotective, antioxidant, anti-inflammatory, anti-apoptotic, and smooth muscle relaxing effects, in part because it acts as a K_{ATP} channel opener (Fouad et al., 2020). H_2S partially inhibits phosphodiesterase-5 through the activation of K_{ATP} channels and increases intracellular cGMP to evoke direct vasorelaxing responses (Citi et al., 2020). H_2S activates the K_{ATP} channel and inhibits insulin secretion in INS-1E cells (a pancreatic *β*-cell line), but the function of hyperpolarizing the plasma membrane and closing voltage-gated Ca^{2+} channels is not mediated by the K_{ATP} channel (Lu et al., 2019; Shoji et al., 2019). H_2S modulates K_{ATP} channel activity, promotes protective effects against pulmonary hypertension and increases uterine blood flow by antagonizing vasoconstriction (Guerra and Hurt, 2019; Roubenne et al., 2021). H_2S protects the embryonic heart from I/R injury by opening the K_{ATP} channel rather than increasing coronary artery flow, demonstrating that H_2S treatment of the embryonic heart is independent of the mother and the underdeveloped placenta (Hess et al., 2020). NaHS, a rapid-releasing H_2S donor, stimulates ANP secretion via the K_{ATP} channel under hypoxic conditions, resulting in decreased blood pressure, ECF volume and antiproliferation of vascular smooth muscle cells in the cardiovascular system (Yu et al., 2019). Briefly, the interaction between H_2S and K_{ATP} plays an irreplaceable role in cardiovascular disease.

Nitric Oxide (NO)

The NO-cyclic guanosine monophosphate (cGMP) signaling pathway is a potential therapeutic target for heart failure, and a reduction in NO bioavailability may result in the decreased production of cGMP, which could lead to decreased protection against myocardial injury, vascular and ventricular sclerosis, fibrosis, hypertrophy, and cardiorenal syndrome (Udelson et al., 2020). K_{ATP} channels can activate the L-arginine/NO/cGMP cascade pathway to induce membrane hyperpolarization, which results in shortening the action potential and restricting Ca^{2+} entry through Ca^{2+} channels, thus contributing to cardioprotection and vasodilatation (Wang et al., 2019a; Iguchi et al., 2019). Reductions in the arterial blood pressure effect of white mulberry fruit polysaccharides, the vascular relaxation effect of tetrahydropalmatine on rat aortae, and the vasodilatory effect of formaldehyde, either partially or completely, are all mediated by the NO/cGMP/K_{ATP} pathway (Wang et al., 2019a; Zhou et al.,

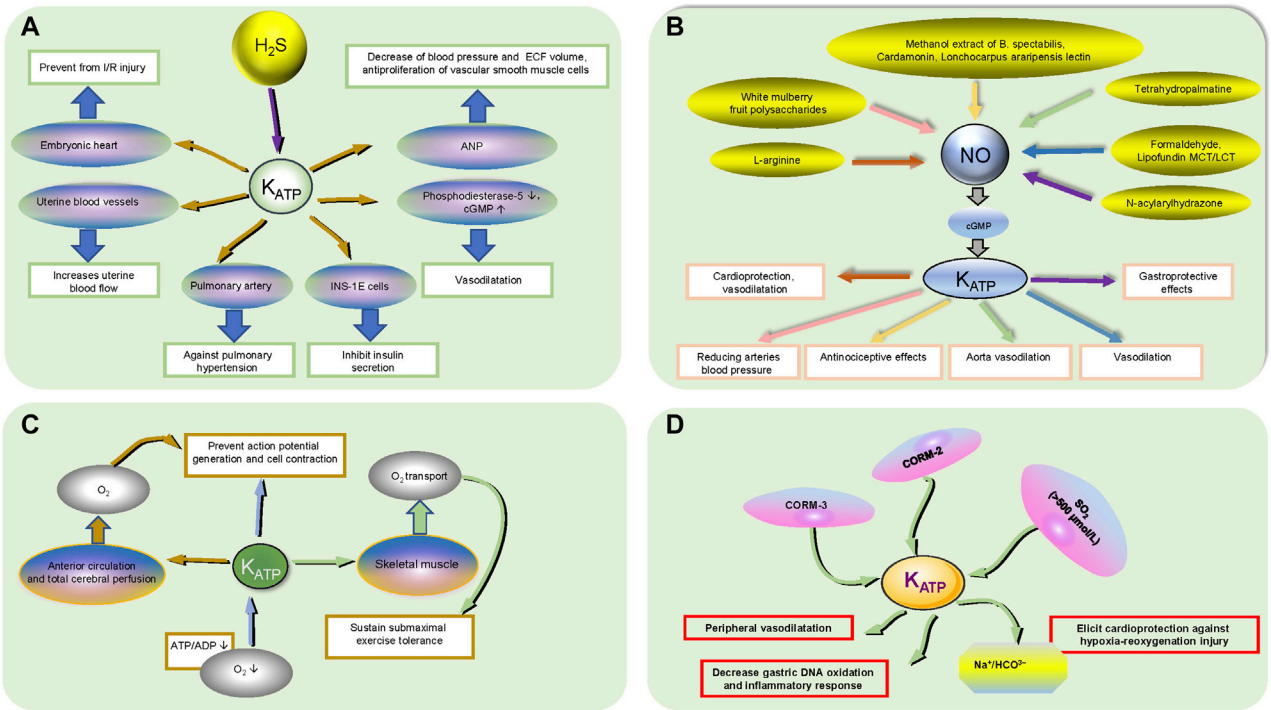

FIGURE 3 | The functional regulation of active small molecules on K_{ATP} channels. **(A)** H_2S participates in K_{ATP} channel regulation. H_2S acts on the corresponding organ/tissues/cytochemical small molecules in the oval through K_{ATP} channels to produce physiological effects in a rectangular box. The black up and down arrows inside the ellipse represent increasing and decreasing, respectively. **(B)**. NO participates in K_{ATP} channel regulation. The relative drugs in the ellipses produce physiological effects in the rectangular boxes through the K_{ATP} channels and NO/CGMP signaling pathways, which the reaction goes in the direction of the arrows in the same color. **(C)**. O_2 participates in K_{ATP} channel regulation. Hypoxia results in a decrease in ATP/ADP acting on K_{ATP} channels to prevent action potential generation and cell contraction; The K_{ATP} channel acts on skeletal muscle and affects O_2 transport to sustain submaximal exercise tolerance; The K_{ATP} channel affects anterior cerebral circulation and total cerebral perfusion through O_2 transport to prevent action potential generation and cell contraction. The black up and down arrows inside the ellipse represent increasing and decreasing, respectively. **(D)**. Other small active molecules. CORM-3 can mimic the HO-1/CO pathway, activate mitoK_{ATP} channels and elicit cardioprotection against hypoxia-reoxygenation injury by inhibiting the Na^+/HCO_3^- transporter; CORM-2 alleviates gastric lesions at the systemic level *via* K_{ATP} channels, reducing gastric DNA oxidation and inflammatory responses; SO_2 plays a vasodilatory role through K_{ATP} channel activation in the peripheral cardiovascular system at high concentrations (>500 μmol/L).

2019a; Zhao et al., 2019). Lipofundin MCT/LCT is involved in attenuating K_{ATP} channel-induced vasodilation by inhibiting basally released endothelial NO and/or cGMP (Lee et al., 2020). The antinociceptive effects of methanol extracts of B. spectabilis, cardamonin and Lonchocarpus araripensis lectin ether are partially or completely mediated by the NO/cGMP/K_{ATP} pathways (Assreuy et al., 2020; Ferdous et al., 2020; Pui Ping et al., 2020). The K_{ATP} channel, a gastroprotective factor, is involved in the gastroprotective effects of N-acylarylhydrazone derivatives on ethanol-induced gastric lesions in mice via the NO/cGMP pathway (da Silva Monteiro et al., 2019). Therefore, the NO/cGMP/K_{ATP} pathway is involved in a variety of organoprotective and vasodilative pharmacological processes.

Oxygen(O_2)

The heart operates exclusively under aerobic metabolism and three factors, heart rate, contractility, and ventricular wall tension, require myocardial mitochondria for maintaining sufficient O_2 to sustain oxidative phosphorylation. Hypoxia causes the opening of the K_{ATP} channel due to a decline in the ATP:ADP ratio, which couples cellular metabolism to excitability to prevent action potential generation and cell contraction, ultimately leading to coronary artery smooth muscle cell hyperpolarization and the closure of voltage-dependent Ca^{2+} channels and relaxation (Yang et al., 2020a). Vascular K_{ATP} channels supporting skeletal muscle convective and diffusive O_2 transport and oxidative phosphorylation sustain submaximal exercise tolerance; conversely, K_{ATP} channel inhibitors may exacerbate exercise intolerance in healthy rats (Colburn et al., 2020). Additionally, K_{ATP} channel activation modulates the anterior circulation and total cerebral perfusion, contributing to cerebral blood flow and oxygen delivery responses to hypoxia, maintaining a constant cerebral blood supply, avoiding disturbances in the precise regulation of cerebral perfusion and oxygen delivery, and preventing severe tissue damage and even death (Smith et al., 2020).

Regulated by Other Factors

CORM-3, a water-soluble CO-releasing molecule that can mimic the HO-1/CO (heme oxygenase-1/carbon monoxide) pathway by

liberating CO under appropriate conditions in biological systems, activates mitoK_{ATP} channels and elicits cardioprotection against hypoxia-reoxygenation injury by inhibiting a bicarbonate transporter (most likely $Na^+/HCO3^-$) during reoxygenation (Portal et al., 2019). CORM-2 increases the gastric mucosal CO content and blood carboxyhemoglobin concentration, resulting in gastroprotection, alleviation of gastric lesions, decreased gastric DNA oxidation and the inflammatory response at the systemic level, which is partly mediated by K_{ATP} channels (Li et al., 2019). Sulfur dioxide (SO_2), a major toxic gas and environmental pollutant, plays a vasodilatory role through K_{ATP} channel activation in the peripheral cardiovascular system at high concentrations (>500 μmol/L) (Magierowska et al., 2019). The search for signaling molecular regulatory pathways related to K_{ATP} channels is still in progress.

Highly specific HCN 2 (hyperpolarization-activated, cyclic-nucleotide gated channels 2) in ventricular myocytes, an integral part of ventricular electric remodeling, and the reduced expression of its mRNA, leads to the downregulation of the K_{ATP} channel current, which is one of the partial causes of arrhythmia in diabetic rats (Hadova et al., 2021; White et al., 2021). Exogenous cholesterol eliminated the increase in SUR2, suggesting that cholesterol may regulate K_{ATP} channel expression and explain why patients with hypercholesterolemia were also able to cope with ischemic events (Geiger et al., 2021). Low-density lipoprotein (LDL)5, the most negatively charged subfraction of circulating LDL, which has been considered a novel factor for predicting coronary vascular disease and stroke, prolongs the APD and increases the current density of K_{ATP} channels, and may induce arrhythmias (Ma et al., 2020). Under 5-Hz pacing conditions, the ATP-sensitive potassium current of ZFHX3 knockdown (zinc finger homeobox three gene) cells was increased compared with that under other conditions, confirming that ZFHX3 knockdown and tachypacing are related to increased stress (Lkhagva et al., 2021). Statins increased the ADP/ATP ratio and activated K_{ATP} channels to dedifferentiate myofibroblasts, while inhibition of K_{ATP} channels weakened the role of statin-induced myofibroblast dedifferentiation (Emelyanova et al., 2019). K_{ATP} channels participate in the cardiomyocyte-specific expression of photoinduced proton pump inhibitors, hyperpolarizing the intact heart to terminate ventricular arrhythmias (Funken et al., 2019). Resistin, secreted by PVAT (the fat reserve surrounding blood vessels consisting of fat cells, immune cells, fibroblasts, and endothelial cells), did not alter K_{ATP} channel-mediated relaxation in males, while K_{ATP} channel-mediated relaxation was significantly reduced in females (Small et al., 2019).

CLINICAL THERAPY OF TARGETED K_{ATP} CHANNELS

The functional regulation of small active molecules on K_{ATP} channels and the potential mechanisms of mutant K_{ATP} channels have been introduced in the previous content, and the relevant clinical effects and pharmacological mechanisms of some irre-placeable K_{ATP} channel openers and inhibitors will be introduced.

Nicorandil is a renowned cardioprotective drug that is characterized by opening K_{ATP} channels. It participates in the regulation of multiple signaling pathways and can be used to treat arrhythmias, chronic heart failure, stable angina, and acute coronary syndromes, including post-PCI (percutaneous coronary intervention). Nicorandil regulates coronary blood flow, protects cardiomyocytes from ischemia-reperfusion injury, alleviates endothelial dysfunction and reduces myocardial necrosis due to its K_{ATP} channel-opening effects, thereby relieving angina symptoms and limiting infarct size and subsequent severe ischemic insult (Jiang et al., 2021). A systematic review and meta-analysis demonstrated that nicorandil could effectively improve microvascular perfusion, alleviate microvascular spasms, reduce platelet aggregation, open K_{ATP} channels, reduce the excessive production of oxygen free radicals and myocardial ischemia, improve myocardial antioxidant capacity, and inhibit myocardial apoptosis and inflammatory reactions after ischemia to treat unstable angina pectoris and related microvascular complications (Zhang et al., 2021b).

Levosimendan is a calcium sensitization agent and K_{ATP} channel opener that is clinically used for the treatment of decompensated heart failure, which is characterized by inducing vasodilation of the pulmonary, coronary, and peripheral arteries and venous circulation, anti-inflammatory and antioxidant effects, and then it exerts a cardioprotective effect in various settings (Herpain et al., 2019; Efentakis et al., 2020). Levosimendan may be considered for the prevention of overt acute heart failure and cardiogenic shock due to its hemodynamic and anti-ischemia effects and its pharmacodynamic properties (Cosentino et al., 2020).

Sulfonamides, as an antibacterial drug, Marcel Janbon discovered its hypoglycemic side effects, and A. Loubatières proved that its hypoglycemic mechanism is to promote insulin secretion, so they were widely used in clinic as hypoglycemic drugs (Zhang et al., 2013). In pancreatic ß cells, when blood glucose concentration increases, intracellular ATP concentration increases with active glucose uptake and metabolism and inhibits K_{ATP} channels, leading to cell plasma membrane depolarization, activation of voltage-gated calcium channels, and calcium influx triggering insulin release (Yang et al., 2020b). Sulfonamides bind to K_{ATP} channel sulfonylurea receptors, inhibit the opening of K_{ATP} channel, promote the release of insulin, and reduce blood glucose and the risk of microvascular complications associated with diabetes (Wang et al., 2019b). Sulfonylureas might increase the risk of adverse cardiovascular events, due to K_{ATP} channel closure in the heart, in Neil Dhopeshwarkar et al. cohort included 268,094 glipizide users and 124,354 glimepiride users in Medicaid, they found that glimepiride (as opposed to glipizide) was associated with an elevated risk of sudden cardiac death/fatal ventricular arrhythmia, in Abdelmoneim et al. cohort included 7,441 gliclazide and 13 884 glyburide users, and they observed that statistically significant 14% higher risk of acute coronary syndrome was observed in patients taking glyburide compared with those taking gliclazide (Leroy et al., 2006; Rieg et al., 2020). In conclusion, the exploration of pancreatic specific K_{ATP} channel inhibitors can

help control patients' blood glucose, reduce microvascular complications.

At present, there is no specific pharmacotherapeutic treatment options are currently suitable for the diseases of K_{ATP} channels mutation (Rosenfeld et al., 2019). Glibenclamide inhibited K_{ATP} and slightly improved sensorimotor performance in DEND patients, but did not improve cognitive deficits caused by neuronal K_{ATP} gain-of-function expression (Jin et al., 2020). Glibenclamide directly act on SUR1, leading to the closure of K_{ATP} channel and the normal release of insulin, improving the growth imbalance, nervous system disorders and muscle strength of some PNDM children, but may cause hypoglycemia, temporary diarrhea, tooth staining, long Q-T syndrome and other adverse reactions (Cao et al., 2020). Chen et al. verified that Cantú Mutations C166S (Kir6.2) and S1020P (SUR2A) are inhibited by travoprost, betaxolol, and ritodrine, meanwhile, these compounds are not known to cause cardiac side effects or hypoglycemia (Chen et al., 2019). Scala et al. 's animal experiments demonstrated that glibenclamide treatment may help to reverse or avoid muscle weakness and atrophy in CS (Li et al., 2020b). In addition, in partially effective treatment regimens for patients with CHI, diazoxide opens the sarcK_{ATP} channel and inhibits insulin secretion, octreopeptide and long-acting somatostatin analogues act downstream of the K_{ATP} channel, inhibition of insulin secretion, subtotal pancreatectomy is used to reduce insulin production in focal and medically responsive non-focal cases (Rosenfeld et al., 2019). K_{ATP} openers may indeed prove beneficial in some AIMS patients (Bibli et al., 2021). K_{ATP} channel activator tifenazoxide, VU0071063 can be unlocked by opening the K_{ATP} channel, providing CHI patients with a new pharmacological option for CHI therapy to maintain normal blood glucose and reduce drug side effects and postoperative complications (Sim et al., 2002). Interestingly, CRISPR-based genome editing techniques were found to detect changes in ABCC8 and SUR1 expression levels in type 2 diabetes, suggesting that gene editing could be useful in diagnosing and treating K_{ATP} channel mutations in the future (Zhou et al., 2019b).

CONCLUSION

At present, no specific pharmacotherapeutic treatment options are currently suitable for CS, but glibenclamide can partially reverse the vascular symptoms of CS by inhibiting the overactivity of the K_{ATP} channel (McClenaghan et al., 2020; Laimon et al., 2021). Sulfonylureas can inhibit the effect of ABCC8 and KCNJ11 activation mutations that prevent the closure of K_{ATP} channels leading to insulin deficiency, reversing a condition that has historically been treated only with insulin (Laimon et al., 2021). The early ascertainment of a genetic diagnosis help us find the underlying cause which is the optimal treatment of the diseases of mutations in K_{ATP} channels. These facts support the hypothesis that the study of K_{ATP} channels may improve the prognosis, alleviate pain, and reduce the economic burden on patients. In the short run, Patients with cardiovascular disease and refractory K_{ATP} channel subunit mutations will have more treatment options, more promising outcomes, and acceptable medical costs.

AUTHOR CONTRIBUTIONS

ZW contributed to literature search, and drafted the manuscript; WB, YY contributed to literature search; D-MZ contributed to review design, wrote and revised the manuscript. All authors reviewed the manuscript.

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GLOSSARY

ADP adenosine diphosphate

AIMS ABCC9-related intellectual disability myopathy Syndrome

ANP atrial natriuretic peptide

ANT adenine nucleotide translocator

AP action potential

APD action potential duration

ATP adenosine triphosphate

BCL2 B-cell lymphoma-2

CaMK calcium/calmodulin-dependent protein kinase

CF cardiac fibroblasts

cGMP cyclic guanosine monophosphate

CHI congenital hyperinsulinism

CO carbon monoxide

CORM-3 CO-releasing molecule-3

CS cantú syndrome

CSE cystathionine γ-lyase

Cyt C cytochrome C

DEND syndrome developmental delay epilepsy and neonatal diabetes syndrome

EAD early afterdepolarization

EHD-2 Eps15 homology domain-containing protein-2

ERK extracellular signal-regulated protein kinase

GST genistein

H_2S hydrogen sulfide

HCN hyperpolarization-activated cyclic-nucleotide gated channels

hESC human embryonic stem cell

HF heart failure

HO-1/CO heme oxygenase-1/carbon monoxide

IMM inner mitochondrial membrane

INS-1E cells a pancreatic β cell line

K^+ potassium

KATP channels ATP-sensitive potassium channels;

Kir K^+ inward rectifiers

LDL low-density lipoprotein

LPS lipopolysaccharide

MF myofibroblasts

MIRI myocardial ischaemia reperfusion injury

mitoKATP mitochondrial ATP-sensitive potassium

MPTP permeability transition pore

NBF nucleotide binding folds

NDM neonatal diabetes mellitus

NO nitric oxide

NPR-A natriuretic peptide receptor type A

O_2 oxygen

ONOO- peroxynitrite

PCI percutaneous coronary intervention

PHC penehyclidine hydrochloride

PNDM permanent neonatal diabetes mellitus

PiC phosphate carrier

PKG cGMP-dependent protein kinase

PLN phospholamban

ROS reactive oxygen species

RyR ryanodine receptor

sarcKATP sarcolemma ATP-sensitive potassium

SCD sudden cardiac death

SO_2 sulfur dioxide

SUR sulfonylurea receptors

TMD transmembrane domains

TNDM transient neonatal diabetes mellitus

VCMs ventricular cardiomyocytes

ZFHX3 zinc finger homeobox three gene