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K_{ATP} channels and cardioprotection

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Abstract

This review discusses ATP-sensitive potassium (K_{ATP}) channels, which connect intracellular energy metabolism to cellular electrical activity and play crucial roles in various physiological processes, particularly in the pancreas and cardiovascular system. K_{ATP} channels open when ATP levels decrease during metabolic stress, such as ischemia, helping to protect the heart from injury by maintaining membrane potential and preventing calcium overload. These channels are found in multiple cell types across the cardiovascular system, influencing vascular tone and cardiac excitability. The review highlights the need for further research into the specific expression of K_{ATP} channel subunits in humans and the consequences of ischemic events on their functionality. Additionally, it explores the interplay between glycolysis and K_{ATP} channels, suggesting that glycolytic ATP can modulate K_{ATP} channel activity while emphasizing the cardioprotective effects during ischemic events. The potential for K_{ATP} channel openers (KCOs) as therapeutic agents for ischemic heart disease is noted, particularly in improving outcomes in patients undergoing cardiac procedures. Challenges remain in developing specific KCOs with minimal side effects, but advances in precision medicine may enhance targeted therapies in the future. Overall, K_{ATP} channels represent promising targets for enhancing cardiovascular health.

Key words: K_{ATP} channels, potassium channel openers, cardiac protection, ischemia, reperfusion, preconditioning

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Preface

There are several relatively recent overviews on ATP-sensitive K^+ (K_{ATP}) channels, including general reviews (1, 2), their structural aspects (3), their roles in metabolic regulation of insulin secretion and neonatal diabetes (4-6), decline during advanced aging (7), their subcellular trafficking mechanisms (8), genetic disorders such as Cantú syndrome (9), and their roles in the microvascular system, including cells as diverse as smooth muscle, endothelium, capillary pericytes, and the lymphatic system (10-13). This treatise focuses on K_{ATP} channels and cardioprotection, but even this topic has been reviewed (1, 14, 15). Rather than simply repeating well-reviewed concepts, this text will briefly review the current state of affairs of pertinent topics, but also ask (sometimes provocative) questions to highlight unexplored research areas – some of which are based on data yet to be published. The hope is that the text will highlight new areas for research to stimulate growth in the field.

The K_{ATP} channel

The ATP-sensitive potassium channel, also called the K_{ATP} channel, is a type of potassium ion channel that couples intracellular energy metabolism to cellular electrical events. The K_{ATP} channel opens when intracellular ATP levels fall, and correspondingly, when intracellular ADP and AMP levels rise (1, 2).

K_{ATP} channels are expressed relatively ubiquitously, with pronounced roles in tissues such as the pancreas, vascular smooth muscle, the heart, and the nervous system. They have key roles in diverse processes ranging from regulating insulin secretion to vascular smooth muscle contractility, the regulation of blood flow, and neuronal excitability (please refer to the reviews cited above for more information).

Role of K_{ATP} channels in the pancreas

In the pancreas, K_{ATP} channels are located on the surface of β cells in the islets of Langerhans. With rising plasma glucose levels (such as after a meal), the canonical view is that glucose is metabolized by mitochondrial oxidative phosphorylation, which in turn leads to elevated cytosolic ATP levels and lower cytosolic ADP levels. This sets off a cascade of events that starts with K_{ATP} channel blockade, depolarization of the membrane potential into the threshold for initiating bursting action potentials, which in turn opens voltage-gated channels such as Ca^{2+} channels. The resulting Ca^{2+} entry (and concomitant Ca^{2+} release from intracellular stores) elevates cytosolic Ca^{2+} levels that are responsible for triggering insulin-containing vesicles to dock to the plasma membrane and release their content from the β cells (4).

Roles in neurons, astrocytes, microglia and cerebral circulation

K_{ATP} channels have significant roles in regulating neuronal excitability and neurotransmitter release. This may include the regulation of membrane potential, where K_{ATP} channel opening hyperpolarizes the membrane potential to inhibit neuronal firing, thereby reducing excitability. K_{ATP} channels are widely expressed throughout

different brain regions, including cortical and hippocampal pyramidal- and interneurons, striatal neurons, the hypothalamus, GABAergic and dopaminergic substantia nigra neurons, vagal neurons, the brain stem, and others (16). In addition to regulating firing frequency, K_{ATP} channels act to sense glucose levels in the hypothalamus, regulate synaptic plasticity, learning and memory, as well as having a neuroprotective role against hypoxia and ischemia, and featuring in several neurodegenerative diseases, epilepsy and stroke (16-20). K_{ATP} channels in astrocytes have a protective effect against neurodegenerative diseases such as Parkinson's disease, Huntington's disease, and Alzheimer's disease–related pathologies (21-23). Microglia, the resident immune cells of the central nervous system, also express K_{ATP} channels, although their roles in these cells are not as extensively studied as in neurons and astrocytes. Finally, K_{ATP} channels are also expressed in brain blood vessels, where they regulate blood flow in the cerebral circulation (24).

Roles in the vascular system

K_{ATP} channels are widely expressed in various cell types of the cardiovascular system, including cardiomyocytes, smooth muscle cells, endothelial cells and pericytes. The reader is referred to a relatively recent publication for a comprehensive review of these channels (1). In short, these channels play crucial roles in regulating vascular tone, cardiac excitability under metabolically impaired conditions, and cardiovascular homeostasis. K_{ATP} channels in vascular smooth muscle cells contribute to the regulation of vascular tone and blood flow, where activation of K_{ATP} channels leads to membrane hyperpolarization and relaxation of smooth muscle cells, resulting in vasodilation. Conversely, inhibition of K_{ATP} channels causes membrane depolarization and vasoconstriction. Thus, K_{ATP} channels play a central role in modulating vascular resistance, blood flow and blood pressure. Some studies suggested that K_{ATP} channels in the endothelium may also participate in the regulation of vascular tone by participating in the release of vasoactive factors such as endothelin-1 (25). Endothelial K_{ATP} channels can also protect against the development of hypertension and atherosclerosis (26). Blood flow is predominantly regulated by the microvasculature, and indeed, K_{ATP} channels are highly expressed in microvascular complexes consisting of small arterioles (< 20 μm diameter), feeder vessels, capillaries and pericytes (27). A major role of K_{ATP} channels in vascular pericytes to regulate blood flow has recently become apparent (11, 28-30).

Roles in the heart

The K_{ATP} channel was first identified in a ventricular cardiac myocyte (31), but arguably, it is the least well characterized functionally in cardiac muscle. K_{ATP} channels are not open in the basal state under patch clamp conditions (1). An argument can be made that the basal metabolic demand is low in an isolated cardiac myocyte and that the oxygen and nutrients supply is abundant, which might be a reason that K_{ATP} channels are not functional. In the intact heart, there is evidence that K_{ATP} channels can operate under physiological conditions. In mice, for example, the progressive

action potential duration shortening that is associated with a sudden increase in heart rate (e.g. during exercise) appears to be mediated by K_{ATP} channel activation (32). Most of the cardiac literature regarding the role of K_{ATP} channels in the heart originates from pathophysiological states, such as cardiac ischemia, and will be discussed later in this text.

Overall, K_{ATP} channels serve as metabolic sensors in the cardiovascular system, integrating signals related to cellular energy status with vascular and cardiac function. Changes in cytosolic high-energy phosphate molecules directly influence K_{ATP} channel activity, leading to adjustments in vascular tone, myocardial contractility, and cardiac output.

K_{ATP} channel subunits

A significant advance in our understanding of K_{ATP} channel function came with the molecular identification of the subunits that comprise the K_{ATP} channel protein complex. These findings also advanced our understanding that there is not a single type of K_{ATP} channel, but instead, that there is significant diversity of K_{ATP} channel subtypes in different tissues, in terms of their biophysical properties, regulation and pharmacological sensitivities (33). The reader is referred to other reviews for a detailed description of K_{ATP} channel subunits and genes (1, 2). In short, K_{ATP} channel subunits are encoded by four genes. *KCNJ8* encodes the Kir6.1 subunit, *KCNJ11* encodes Kir6.2, *ABCC8* encodes SUR1 and *ABCC9* encodes SUR2. Although there are several splice variants for both SUR1 and SUR2 (34), the two variants most commonly considered are SUR2A and SUR2B. In the cardiovascular system, the major functional subunits are Kir6.1, Kir6.2, SUR2A and SUR2B (Table I). The dogma is that K_{ATP} channel in cardiac muscle is comprised of Kir6.2/SUR2A subunits, whereas those in the vasculature are comprised of Kir6.1/SUR2B subunits.

Table I Diversity of K_{ATP} channel subunits and genes

Tabela I Raznolikost podjedinica K_{ATP} kanala i gena

Tissue	K_{ATP} channel subunits
Pancreatic β-cells	Kir6.2 and SUR1
Cardiac and skeletal myocytes	Kir6.2 and SUR2A
Vascular smooth muscle cells	Kir6.1 and SUR2B
Vascular endothelial cells	Kir6.1 and SUR2B
Vascular pericytes	Kir6.1 and SUR2B

K_{ATP} channel subunits in the mouse heart

Several lines of evidence demonstrate that the mouse ventricular K_{ATP} channel is composed of Kir6.2/SUR2A subunits. Evidence supporting this contention is that the mRNA and protein of both Kir6.2 and SUR2A are expressed in the mouse ventricle, and that compounds that affect these two subunits modulate the mouse cardiac K_{ATP} channel measured with patch clamp techniques (1, 35). Moreover, mice deficient of Kir6.2 or SUR2A lack functional K_{ATP} channels in the heart. Other than the possibility that SUR1 has a role in the mouse atrium (36), the concept that "the cardiac K_{ATP} channel" is composed of a Kir6.2/SUR2A subunit combination appears to be firmly grounded.

K_{ATP} channel subunits in the human heart

Most of the molecular data regarding K_{ATP} channels come from rodents and other animal models. We know that human ventricular myocytes have functional K_{ATP} channels since the opener, lemakalim, shortens the human cardiac action potential, and this effect can be prevented by the K_{ATP} channel blocker glibenclamide (37). A K_{ATP} channel with a unitary conductance of ~75 pS can be directly recorded in myocytes isolated from human right atrium, and these channels are blocked by 'intracellular' ATP (with an IC_{50} value of 39 μM) and activated by cromakalim (38). Action potentials are significantly shortened by diazoxide and pinacidil in both atria and ventricles of coronary-perfused preparations from explanted human heart (39). Support for the concept that human ventricular K_{ATP} channels are composed of Kir6.2 and SUR2A subunits comes from the observation that heterologously expressed Kir6.2/SUR2A channels recapitulate the biophysical properties of channels recorded from ventricular myocytes isolated from human myocardium (40). Semi-quantitative RT-PCR measurements of human heart, however, show that all of the K_{ATP} channels (Kir6.1, Kir6.2, SUR1 and SUR2) may be expressed in human heart (39). Likely differences in primer efficiencies, however, complicate comparative expression of the K_{ATP} channels genes in this study. Human genetic studies have linked *ABCC9* variants to dilated cardiomyopathy, acute myocardial infarction, Brugada syndrome, and sudden infant death syndrome (41-44), which strongly suggests a role for SUR2. By contrast, there is a multitude of *KCNJ11* (Kir6.2) variants mutations associated with insulin disorders such as familial hyperinsulinemic hypoglycemia, and permanent neonatal diabetes mellitus (see OMIM entry 600937), but few (if any) of these are linked to cardiac defects. A common E23K *KCNJ11* variant has been suggested to be associated with human heart failure (45). However, the allelic frequency of this polymorphism is 64% in the "normal" population (according to the gnomAD database) and the involvement of this polymorphism in insulin disorders is questioned (46). It seems unlikely, therefore, that this polymorphism has a key role in heart disease. Thus, although human genetic evidence strongly links Kir6.2 to pancreatic β cell function, the genetic evidence for an involvement of Kir6.2 in heart function is scant at best.

Curious about these apparent discrepancies, we turned to human heart RNA-seq data deposited in the Gene Expression Omnibus (GEO) database. We used data (GEO #GSE226283) from a study that investigated transcriptome alterations in different parts of the human heart of ten patients (47). Heart samples were collected from the sino-atrial node (SAN), right atrium (RA), pulmonary vein (PV), left atrium (LA), left atrial appendage (LAA), left ventricle (LV), and right ventricle (RV). We used the DESeq2 package and the R statistical language to analyze the mRNA reads of GSE226283 data. Normalized RNA-seq copy numbers for the K_{ATP} channel subunit genes are shown in Figure 1. Not surprisingly, SUR1 (*ABCC8*) was expressed at very low levels in the human heart. The K_{ATP} channel gene with the highest mRNA copy number was SUR2 (*ABCC9*), which is consistent with the genetic evidence linking *ABCC9* variants to human heart disease. The SUR2 mRNA copy number was higher in ventricles than in the other heart regions. The surprising result was that the expression of Kir6.2 (*KCNJ11*) mRNA was an order of magnitude lower compared to SUR2. Moreover, Kir6.1 (*KCNJ8*) mRNA copy number was 3-6 times higher in the human ventricles compared to Kir6.2. One would expect Kir6.1 mRNA to be present since it is expressed in the coronary microvasculature (Table I), but it is puzzling that the Kir6.1 copy numbers are so high relative to Kir6.2 in each of the heart regions. This is not the case in the mouse heart (see later). This analysis points to the urgent need to better characterize the human cardiac K_{ATP} channel, and may give credence to the observations that *KCNJ8* variants were described to be associated with certain forms of inherited arrhythmias such as Brugada syndrome (48) and sudden infant death syndrome (49).

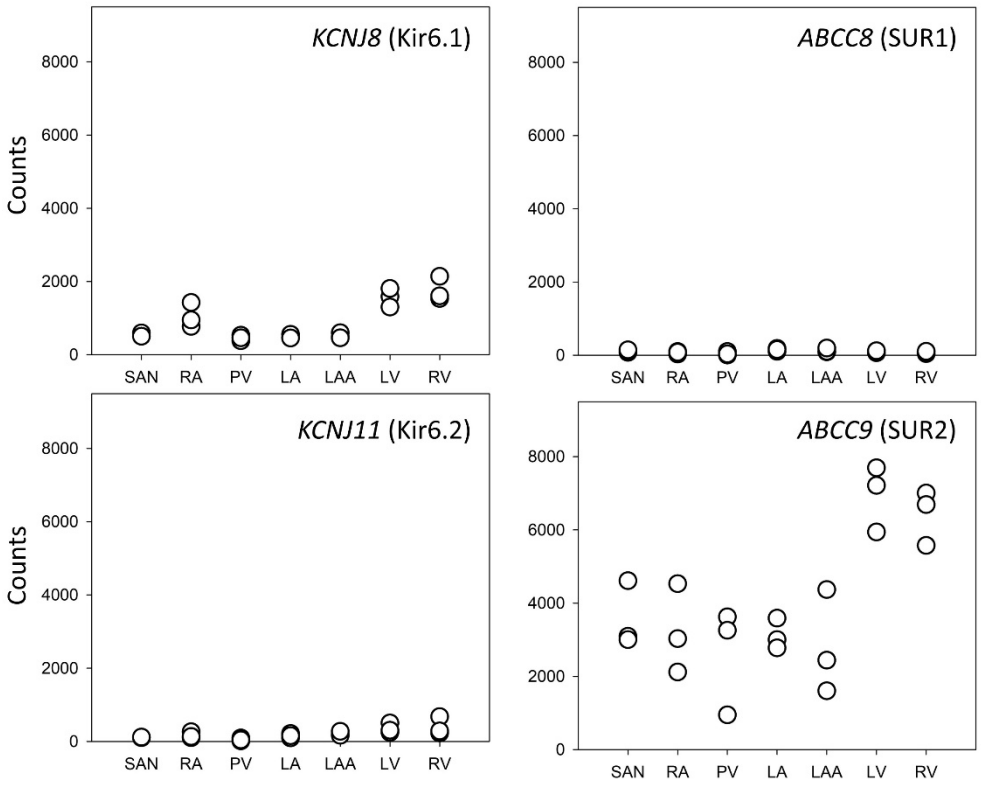

Figure 1. KATP channel subunit mRNA copy number in the human heart.
We analyzed RNA-seq data (dataset GSE226283) deposited in the Gene Expression Omnibus (GEO). The study design was a comparison between sinus rhythm and atrial fibrillation samples from different cardiac regions. We focused on the samples from patients in normal rhythm. Sequencing was performed with Illumina NovaSeq 6000, FASTP was used for read quality control and adapter removal, and reads were aligned using STAR. We used the DESeq2 package and the R statistical language to analyze the normalized reads of these data. Shown are the mRNA copy numbers for each of the KATP channel genes in seven heart regions: sino-atrial node (SAN), right atrium (RA), pulmonary vein (PV), left atrium (LA), left atrial appendage (LAA), left ventricle (LV), and right ventricle (RV).

Slika 1. Broj kopija mRNA podjedinica K_{ATP} kanala u ljudskom srcu.
Analizirali smo RNA-seq podatke (dataset GSE226283) deponovane u Gene Expression Omnibus (GEO). Dizajn studije bio je zasnovan na poređenju uzoraka iz sinusnog ritma i atrijalne fibrilacije iz različitih regiona srca. Fokusirali smo se na uzorke pacijenata u normalnom ritmu. Sekvenciranje je izvedeno pomoću Illumina NovaSeq 6000, za kontrolu kvaliteta očitavanja i uklanjanje adaptera je korišćen FASTP, a očitavanja su poravnata koristeći STAR. Koristili smo paket DESeq2 i statistički jezik R za analizu normalizovanih očitavanja ovih podataka. Prikazan je broj kopija mRNA za svaki od gena K_{ATP} kanala u sedam regiona srca: sinoatrijalni čvor (SAN), desna pretkomora (RA), plućna vena (PV), leva pretkomora (LA), levi atrijalni dodatak (LAA), leva komora (LV) i desna komora (RV).

A historical perspective on the cardioprotective role of sarcolemmal K_{ATP} channels

Much of the early work that links K^+ fluxes to metabolic impairment in the heart came from the laboratory of the late Edward Carmeliet. In 1973 (half a century ago), they found that the cardiac action potential was drastically shortened by hypoxia (50). With radioisotope flux experiments, they subsequently found that the hypoxia-induced action potential shortening was correlated with K^+ efflux from the myocardial cells (51). A few years later, their voltage clamp approaches with multicellular heart preparations revealed that hypoxia directly causes the activation of a time-independent outward K^+ current (52, 53). They confirmed these findings when it became possible to perform voltage clamp experiments with isolated Ca^{2+} tolerant cardiac myocytes (54). At around the same time, Noma used single channel patch clamp recordings from isolated cardiac myocytes and directly identified the K^+ channel as having a weakly inward rectifying characteristic with a high conductance of ~80 pS that is blocked by intracellular ATP (31, 55). Akinori Noma's finding led to a major paradigm shift in our understanding of the role of K_{ATP} channels, for example in the response of a pancreatic β cell to elevated blood glucose levels (4). The discovery also revealed the mechanism of action of a class of anti-diabetic drugs (sulphonylureas), which directly block K_{ATP} channels. Glibenclamide, for example, was found not only to block the activity of the pancreatic β cell K_{ATP} channel (56, 57), but also to act as a blocker of cardiac K_{ATP} channels (58). One of the earliest descriptions of a protective role of K_{ATP} channels against myocardial ischemia came with the use of glibenclamide, which, in the late 1980s, we and others found not only to mitigate K^+ loss from the ischemic heart, but also to decrease the arrhythmia burden during ischemia (59, 60).

Pharmacological evidence linking K_{ATP} channels to cardioprotection

In the early 1990s, the K_{ATP} channel openers cromakalim and nicorandil were found to significantly improve post-ischemic cardiac function in isolated rodent hearts and intact dogs (61-63). These observations led to a slew of studies demonstrating that, in general, a diverse range of K_{ATP} channel openers (nicorandil, cromakalim, aprikalim, pinacidil, P-1075, Y-26763, diazoxide and others) improve post-ischemic functional recovery and infarct size, while K_{ATP} channel blockers (such as glibenclamide, tolbutamide, BMS-180448, HMR 1098 and others) have the opposite effect (1). K_{ATP} channels also strongly feature in the mechanism(s) of ischemic and pharmacological preconditioning, defined as cardioprotection paradoxically induced by a prior short period of ischemia, or transient pre-ischemic application of a pharmacological compound (such as a K_{ATP} channel opener) (1).

The relative roles of mitochondrial and sarcolemmal K_{ATP} channels

Diazoxide is an antihypertensive, nondiuretic benzothiadiazine (64) that also has hypoglycemic effects (65) and regulates coronary blood flow (66). Following the finding that mitochondrial K_{ATP} channels are activated by nanomolar concentrations of

EMD60480 and EMD57970, as well as by diazoxide and cromakalim in the submicromolar range (67), the literature became somewhat confusing when it became common to use diazoxide (mostly at concentrations over 10-60 μM) to assign a specific role for mitochondrial K_{ATP} channels in cardioprotection. At these concentrations, the multiplicity of effectors of the cardioprotective agent diazoxide was reviewed (68). Given the large overlap in the sensitivities of K_{ATP} channels to pharmacological intervention, it remains a challenge to assign cardioprotective roles to specific isotypes of K_{ATP} channels. Until more isotype-specific K_{ATP} channel pharmacology becomes feasible, the best evidence to date comes from genetic data and mouse models.

Genetic and molecular evidence linking sarcolemmal K_{ATP} channels to cardioprotection

There is little doubt that sarcolemmal K_{ATP} channels mediate cardioprotection – at least in the mouse. Post-ischemic functional recovery, for example, is severely depressed in hearts of mice that lack Kir6.2 subunits (i.e., cardiac K_{ATP} channels) (69, 70). Likewise, diazoxide is no longer cardioprotective in Kir6.2$^{-/-}$ mice (70, 71). Pharmacological preconditioning induced by A_3 receptor stimulation also fails in hearts of Kir6.2$^{-/-}$ mice (72). Moreover, the infarct-limiting effect of ischemic preconditioning is absent in hearts of mice with a cardiac-specific knockout of Kir6.2 subunits (73). Other genetic studies that link cardiac sarcolemmal K_{ATP} channels to cardioprotection and arrhythmogenesis have been reviewed (1). A recent study has identified MITOK (a product of the *CCDC51* gene) and MITOSUR (a gene product of *ABCB8*) as the molecular components of the mitochondrial K_{ATP} channel (74). Cardiac infarct size after ischemia, however, is unaffected in MITOK knockout mice (35% infarct size in WT and 34% infarct size in MITOK knockout) (74). Other roles for these proteins exist since *CCDC51* and *ABCB8* may be involved in autosomal recessive rod-cone dystrophy and mitochondrial iron and glutathione export (75, 76). On balance, the genetic evidence is strong that sarcolemmal K_{ATP} channels composed of Kir6.2 and SUR2A are linked to cardioprotection in mice.

Current concepts

Although there is significant pharmacological and molecular support for a protective role of K_{ATP} channels in cardioprotection as discussed above, the underlying mechanisms of protective role(s) remain largely unresolved.

Events during ischemia

Consider the consequences of myocardial ischemia, which occurs when myocardial metabolic demand is unmet due to the inadequate supply of metabolites and oxygen, typically caused by occlusion of the coronary arterial blood flow. Ischemia leads to immediate biochemical and functional abnormalities, which include severe impairment of energy production, accompanied by a metabolic switch from fatty acid to glucose as a fuel (77). K^+ loss occurs from cardiomyocytes and K^+ accumulates in the extracellular space within the first few minutes after the ischemic insult (78).

These processes coincide with depolarization of the "resting" membrane potential, action potential duration shortening (79, 80), and loss of myocardial contractility (81) within the first few minutes of ischemia. In studies performed with isolated rat, guinea-pig and rabbit hearts, the extracellular K^+ accumulation during global ischemia is mitigated by K_{ATP} channel block with glibenclamide or 5-hydroxydecanoate (59, 82-84). It should be noted that other mechanisms contribute to K^+ loss from ischemic myocytes since the effect of K_{ATP} channel blockers is incomplete [a caveat to this statement is that K channel blockers become ineffective during metabolic impairment (85)]. Moreover, ischemic K^+ loss is not completely prevented in hearts from Kir6.2$^{-/-}$ mice (86). Since membrane potential depolarization and action potential shortening during ischemia is due predominantly to the elevated extracellular K^+ concentration, K_{ATP} channel opening also contributes to these electrophysiological parameters (1).

In general, blocking K_{ATP} channels is detrimental during ischemia, whereas K_{ATP} channel opening is beneficial (1). K_{ATP} channel opening is linked to protection against contractile failure during ischemia, protection against infarct development, and it prevents deficits in coronary blood flow and the "no reflow" phenomenon. Arrhythmias that occur during ischemia and during reperfusion after an ischemic event are the exception, where both pro- and antiarrhythmic effects of K_{ATP} channel opening have been described (1).

Intracellular effectors of the protection afforded by K_{ATP} channels

The intracellular mechanisms that participate in K_{ATP} channel-mediated cardioprotection are not fully understood. Overall, the hypothesis initially proposed by Noma (31) has largely withstood the test of time; namely that "*activation of the ATP-sensitive channel may prevent further depletion of ATP and protect the cell from irreversible impairment of its energy metabolism*". An expanded version of this "energy sparing" hypothesis is depicted in Figure 2. Key to this hypothesis is the concept that action potential duration shortening during ischemia, caused in part by K_{ATP} channel activation and extracellular K^+ accumulation, leads to less Ca^{2+} influx and hence a negative inotropic response. Less ATP being consumed by the hypocontractile cardiomyocyte presumably makes more energy available for repair processes. Indeed, a number of studies have shown that K_{ATP} channel opening promotes APD shortening, protects against the decline in high energy phosphates and preserves mitochondrial function early during the ischemic event (1). The K_{ATP} channel-mediated APD shortening may also mitigate the rise in cytosolic Ca^{2+} levels during ischemia, which by itself can be detrimental, for example by causing mitochondrial damage. There is also evidence that a loss of surface membrane K_{ATP} channel expression directly alters energetics and mitochondrial function (87). For further details regarding the relationship between K_{ATP} channels and Ca^{2+} overload, protection against contractile dysfunction, protection against infarct development, and the decline in high-energy phosphates during ischemia, please refer to Foster and Coetzee, 2016 (1). Not surprisingly, the overall mechanism is more complex and other processes are involved.

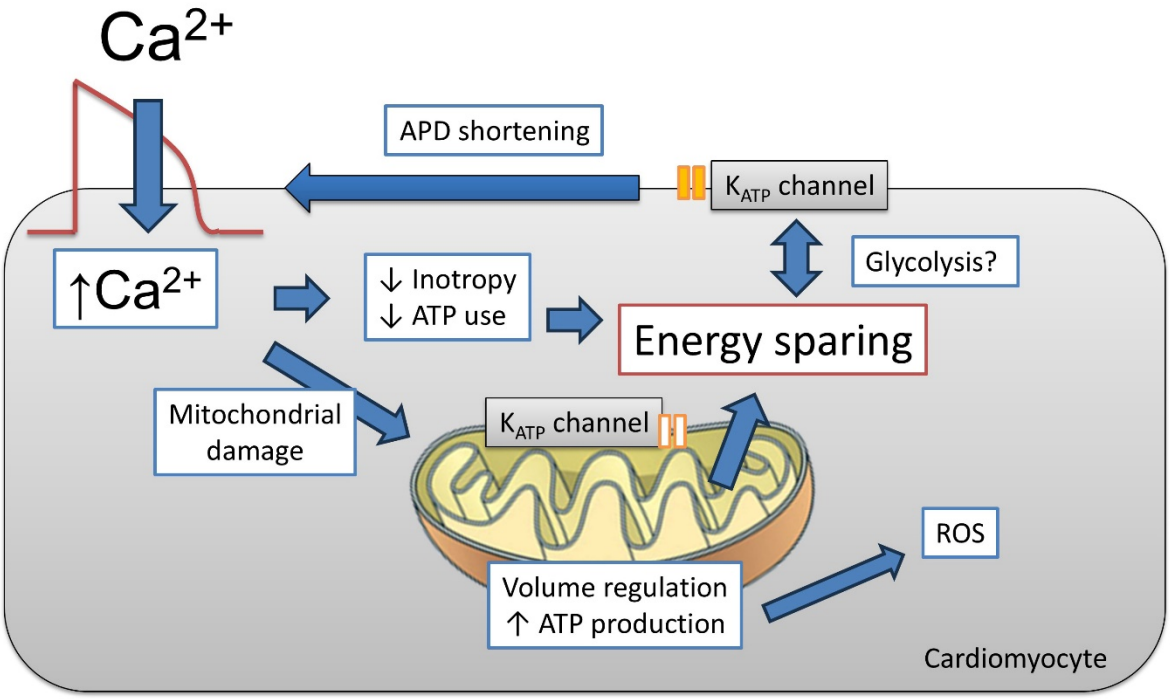

Figure 2. The *"energy-sparing"* hypothesis of possible mechanisms by which K_{ATP} channels may mediate cardioprotection.
Data from pharmacological and genetic approaches point to a role for sarcolemmal K_{ATP} channels to mediate K^+ loss from ischemic cells, and to mediate electrophysiological alterations during ischemia such as action potential shortening and membrane potential depolarization. The resulting decreased Ca^{2+} influx and negative inotropic state leads to less ATP consumption, thereby "sparing" energy for repair processes. There is also evidence for improved mitochondrial function and diminished production of damaging reactive oxygen species.

Slika 2. Hipoteza „očuvanja energije" o mogućim mehanizmima kojim K_{ATP} kanali mogu posredovati u kardioprotekciji.
Podaci iz farmakoloških i genetskih pristupa ukazuju na ulogu sarkolemalnih K_{ATP} kanala u posredovanju gubitka K+ iz ishemijskih ćelija, kao i u posredovanju elektrofizioloških promena tokom ishemije, kao što su skraćivanje akcionog potencijala i depolarizacija membranskog potencijala. Smanjen ulazak Ca^{2+} i negativno inotropno stanje dovode do manje potrošnje ATP-a, čime se „štedi" energija za procese popravke. Takođe postoje dokazi o poboljšanoj funkciji mitohondrija i smanjenoj proizvodnji štetnih reaktivnih kiseoničnih vrsta.

Receptor and molecular signaling converge on K_{ATP} channels

Several receptor and molecular signaling mechanisms are involved in the genesis of ischemic damage and in cardioprotection (88). A key player is protein kinase C (PKC), which mediates the protective mechanisms of several forms of preconditioning.

The downstream targets of PKC may include preservation of mitochondrial function, diminished ROS generation and improved cardiac function (89). K_{ATP} channels are also effectors of PKC signaling, which may both upregulate the channel's open probability and its surface expression (90-98). Indeed, the K_{ATP} channel may have a causative role in the PKC signaling axis, as suggested by the observations that Kir6.2 knockdown can prevent ischemic preconditioning (73, 99) and that pharmacological preconditioning with phenylephrine, a mediator of preconditioning that signals through a PKC signaling pathway, act in a K_{ATP} channel-dependent manner (98, 100). There is, however, a paucity of studies to investigate the cardioprotective role of PKC activation using Kir6.2$^{-/-}$ mice. This remains a challenge for future studies.

PKC activation likely regulates many target proteins. One of the downstream effectors, however, is AMP-activated protein kinase (AMPK), which is cardioprotective in its own right by reducing post-ischemic infract size (101). Cellular processes affected include altered glucose metabolism (102) and enhanced glucose uptake during ischemia (103). K_{ATP} channels are necessary AMPK effectors since cardioprotection elicited by AMPK activation is not present in hearts from Kir6.2 knockout mice (104). Moreover, the protection afforded by AMPK activation against hypoxia in a cellular assay is prevented by the K_{ATP} channel blocker HMR 1098 (105). K_{ATP} channels are positively regulated by AMPK (98), both by an increase of the channel's open probability (106) and an increase in surface expression (105). Interestingly, AMPK was also identified as a key regulator of translocating K_{ATP} channels to the membrane surface in pancreatic β cells upon glucose deprivation (107).

Subcellular endosomal trafficking of K_{ATP} channels as a mechanism of preconditioning

The fate of a membrane protein is determined by many quality control and trafficking proteins. In most mammalian cells, many membrane proteins are internalized by endocytosis and are recycled back to the surface membrane – thus being reused many times (108). This process of endocytic recycling is a powerful mechanism to control the surface density and function of membrane proteins such as ion channels (109). Somewhat surprisingly, the mechanisms that regulate this important modality of channel function are typically understudied. We recently summarized the available literature related to trafficking mechanisms of K_{ATP} channels (8). The following text is based on Figure 3. Pertinent to this review, there is strong evidence that sarcolemmal K_{ATP} channels stabilized on the surface by proteins such as EHD proteins (110), but that they internalized during ischemia (73). A key player in the internalization process appears to be the Ca^{2+}-dependent calmodulin kinase II (CaMKII) (111), since blocking CaMKII with KN-93 mitigates internalization (73) and genetic inhibition of CaMKII with AC3-I promotes ischemic preconditioning by enhancing the surface K_{ATP} channel density (112). One of the major effects of ischemic preconditioning appears to enhance the recycling of internalized K_{ATP} channels back to the surface membrane (73), thus maintaining the protective cardioprotective role of K_{ATP} channels. Some of the key players in the receptor

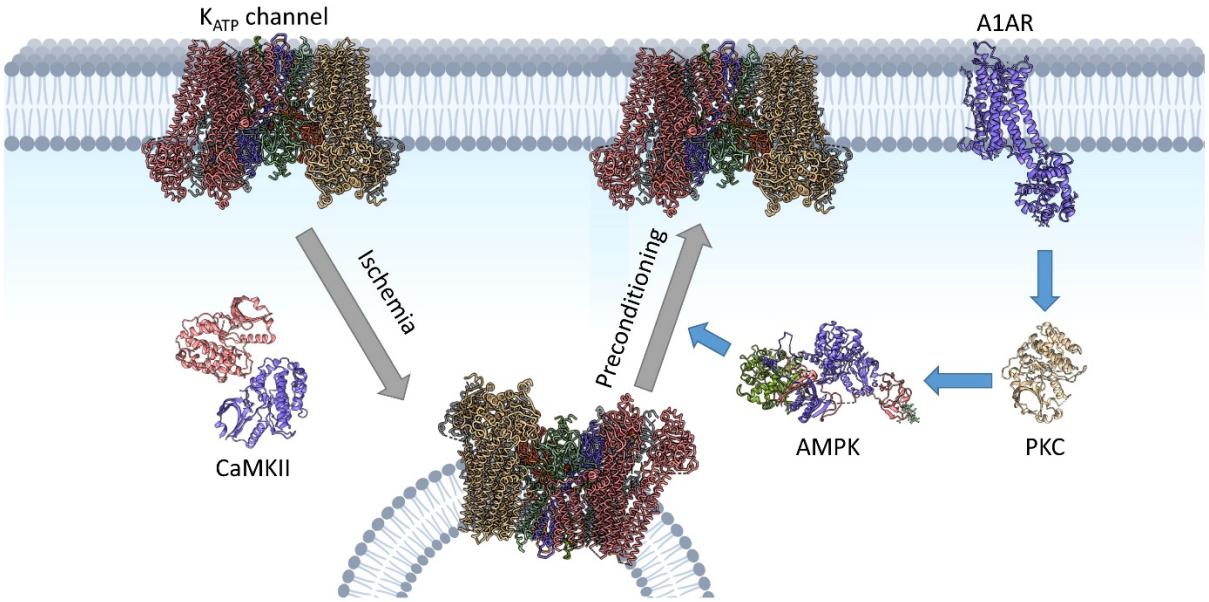

Figure 3. **Endocytic recycling of K_{ATP} channels during ischemia and ischemic preconditioning.**
This model holds that K_{ATP} channels are internalized during cardiac ischemia by the process of endocytosis driven by Ca^{2+} and CamKII. Rescue of the loss of K_{ATP} channels from the surface is accomplished during ischemic preconditioning, with key roles of known cardioprotective receptor signaling cascades, including PKC and AMPK. A better understanding of the mechanisms underlying these trafficking events may have therapeutic benefits. A part of the figure was created with BioRender.com.

Slika 3. **Endocitna reciklaža K_{ATP} kanala tokom ishemije i ishemijske prekondicije. Ovaj model pretpostavlja da se K_{ATP} kanali internalizuju tokom srčane ishemije procesom endocitoze koju pokreću Ca^{2+} i CamKII. Spasavanje gubitka K_{ATP} kanala sa površine ostvaruje se tokom ishemijske prekondicije, uz ključne uloge poznatih kardioprotektivnih signalnih kaskada receptora, uključujući PKC i AMPK. Bolje razumevanje mehanizama koji leže u osnovi ovih procesa transporta može biti od koristi u terapiji. Deo slike je kreiran pomoću BioRender.com.**

and molecular signaling pathways discussed above appears to be causative in the restoration of K_{ATP} channel surface expression during preconditioning and the initiation of cardioprotection. Indeed, PKC inhibition with chelerythrine does not affect internalization, but mitigates both reexpression of surface K_{ATP} channels and the protective effect of ischemic preconditioning (73). Other receptor signaling proteins appear to be involved in the same process. AMPK, for example, was found to mediate hypoxic preconditioning in isolated cardiomyocytes by regulating surface expression of sarcolemmal K_{ATP} channels (105). A similar conclusion was reached by others, which not only implicated PKC and AMPK, but also p38 MAPK in promoting K_{ATP} channel surface

expression as a means to mediate pharmacological preconditioning with phenylephrine (98). A major gap in our knowledge is the understanding of how K_{ATP} channel surface trafficking is conferred by these receptor signaling pathways. Identification of the biological processes and proteins involved may offer major therapeutic benefits. We may learn from the pancreatic β cell field, where K_{ATP} surface expression induced by low glucose and leptin is mediated by a cascade of events that involve (amongst others) AMPK, Rac proteins and actin cytoskeleton remodeling (8).

K_{ATP} channel expression post-ischemia

There is significant evidence that sarcolemmal K_{ATP} channels contribute to stress adaptation responses and protection of the heart against ischemic injury (1, 113). The previous paragraph describes how K_{ATP} channels can be internalized during ischemia and how the surface expression can be maintained by preconditioning events. These are relatively short-term events that occur over a time scale of minutes. It is not clear, however, whether (and how) K_{ATP} channels are changed in the long term by the ischemic event itself. There are indications in the literature that K_{ATP} channels are remodeled following stress events. For example, structural remodeling occurs after infarction in the rat heart after long periods (8-20 weeks), and this remodeling is associated with upregulation of Kir6.1, SUR1 and SUR2 mRNA expression (114). In another study, where rat hearts were subjected to 60 min of coronary artery occlusion, followed by reperfusion for 3, 6, 24, or 72 h, there was little change in mRNA expression levels of Kir6.2 and SUR2A, whereas Kir6.1 mRNA was upregulated (115).

In an attempt to get more clarity on expression levels of K_{ATP} channel genes post-ischemia, we turned to public databases. Specifically, we analyzed reads of an RNA-seq dataset that was obtained with C57BL/6JR mice, in which hearts were rendered ischemic by left anterior descending coronary artery ligation (116, 117). The caveat of this analysis is that mRNA expression may not represent functional channels. Nevertheless, in this study, RNA-seq analysis was performed with a sham-operated group, and in groups at different time points (10 min, 1 h, 6 h, 24 h and 72 h) after the onset of myocardial ischemia. Figure 4 depicts the normalized RNA-seq reads after the ischemic event. As expected, the number of RNA copies was higher for Kir6.2 (*Kcnj11*) and SUR2 (*Abcc9*) compared to the other K_{ATP} channel subunits. The low expression of Kir6.1 (*Kcnj8*) is expected since this subunit is expressed in the coronary vasculature (smooth muscle, endothelium and pericytes). Again, as expected, SUR1 (*Abcc8*) expression is very low in the mouse heart. Expression of each of the subunits declined over the 3 days following cardiac ischemia (Figure 4). The profile of SUR2 mRNA copy number is interesting for two reasons. First, it is the only one of the four subunits that exhibited an early (albeit transient) upregulation of copy number, which might be consistent with a regulatory role of this subunit (15). Second, as in the human heart, SUR2 mRNA copies were by far the most abundant of all the K_{ATP} channel subunits. The physiological relevance of the high SUR2 mRNA expression in both mouse and human heart needs to be explored in future studies.

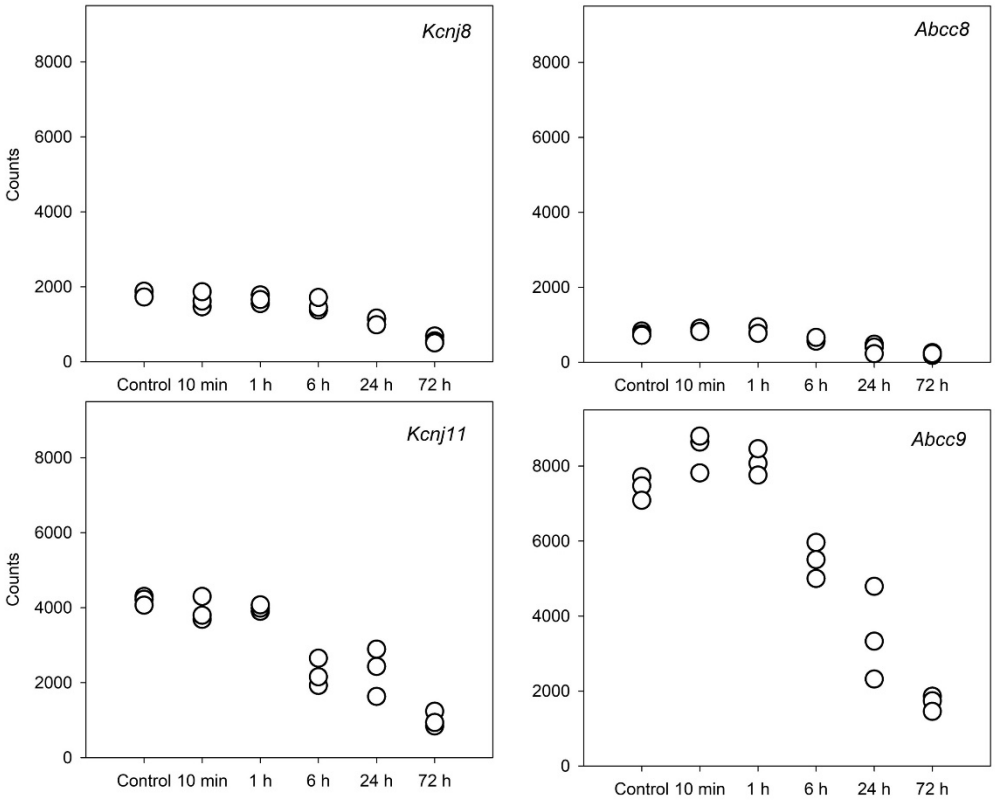

Figure 4. Expression of K_{ATP} channel genes in mouse heart following ischemia and reperfusion injury.

Dataset GSE206281, deposited in the Gene Expression Omnibus (GEO), summarizes the transcriptome obtained by RNA-seq data (Illumina NovaSeq 6000) in eighteen 12-week-old male C57BL/6JR mice. The control group denotes a sham-ischemic group. Tissue was harvested at different time points (10 min, 1 h, 6 h, 24 h and 72 h) after the onset of myocardial ischemia. We used the DESeq2 package and the R statistical language to analyze the normalized reads of GSE206281 data. Shown are normalized RNA-seq reads of *Kcnj8* (ENSMUSG00000030247), *Kcnj11* (ENSMUSG00000096146), *Abcc8* (ENSMUSG00000040136) and *Abcc9* (ENSMUSG00000030249) as a function of the post-ischemic time.

Slika 4. Ekspresija gena KATP kanala u srcu miša nakon ishemijske i reperfuzione povrede.

Dataset GSE206281, deponovan u Gene Expression Omnibus (GEO), sumira transkriptom dobijen putem RNA-seq podataka (Illumina NovaSeq 6000) kod osamnaest mužjaka C57BL/6JR miševa starih 12 nedelja. Kontrolna grupa je grupa sa lažno izazvanom ishemijom. Tkivo je uzeto u različitim intervalima (10 minuta, 1 sat, 6 sati, 24 sata i 72 sata) nakon početka miokardne ishemije. Koristili smo paket DESeq2 i statistički jezik R za analizu normalizovanih očitavanja podataka GSE206281. Prikazana su normalizovana očitavanja RNA-seq za *Kcnj8* (ENSMUSG00000030247), *Kcnj11* (ENSMUSG00000096146), *Abcc8* (ENSMUSG00000040136) i *Abcc9* (ENSMUSG00000030249) kao funkcija vremena nakon ishemije.

The preliminary findings in Figure 4 may be important therapeutically if they are reproducible. Currently, reperfusion therapy is the only and most effective anti-infarct intervention. Although reperfusion therapy reduces mortality, clinical trials report a 2 to 6% incidence of reinfarction during the post-MI period (118-120). Patients with reinfarction have significantly higher death rates, with an elevated incidence of arrhythmias and heart failure compared to those without recurrent myocardial ischemia (RMI) (121). The 30-day mortality rate is more than 3x higher, with a median time to death within 2 days after an ischemic event (120). Earlier reinfarction is associated with worse survival (120). In order to develop rational therapies against RMI, it is essential to understand the biochemical and electrical alterations in the heart following ischemia, and further research into expression and function of K_{ATP} channels in the days following an ischemic event is encouraged.

Is there a preferential role for glycolysis?

Metabolic-electrical coupling mediated by glycolysis

Also known as the Embden-Meyerhof pathway, glycolysis is an evolutionary ancient metabolic process comprising ten enzymes, where glucose is converted to two moles of pyruvate and NADH with the concomitant generation of two moles of ATP. Some of the glycolytic products (pyruvate and NADH) can enter the mitochondria, where they are subject to oxidative phosphorylation reactions to produce larger amounts of ATP, which is responsible for sustaining the majority of high-ATP consuming cellular functions (such as contraction, etc.) in mammalian cells. However, it has become increasingly clear that glycolytic intermediates and end-products are by themselves capable of regulating the activity of specific proteins, including some membrane ion translocators that couple cellular energy metabolism with cellular excitability and/or the regulation of ion homeostasis (122). Glycolytic enzymes are associated with membranes - both at the cell surface and with membranes of intracellular compartments such as the sarcoplasmic reticulum (123-129), possibly in association with subcortical f-actin network. As a result, the production of glycolytic intermediates and end-products (e.g. NADH and ATP) is compartmentalized. This concept of functional compartmentalization is not new (130) and has been described for a variety of tissues, including cardiac, skeletal and smooth muscle myocytes, neuronal cells, and the pancreatic insulin-secreting β-cell (131-138). The model that has evolved, therefore, is that glycolysis preferentially regulates physiological processes located in the microenvironment of the cell boundary (122), thereby accomplishing metabolic-electrical coupling.

K_{ATP} channel activity is modulated by glycolysis

The K_{ATP} channel directly couples intracellular energy metabolism with membrane excitability and secretion (1). It does so by its unique ability to sense intracellular ATP, ADP, and AMP levels. Work from the Weiss group has demonstrated that glycolysis is more effective than oxidative phosphorylation in preventing the cardiac K_{ATP} channel from opening (139, 140). Interestingly, even though the canonical view has been that the

pancreatic β cell K_{ATP} channel is regulated by ATP generated by oxidative phosphorylation (see "*Role of K_{ATP} channels in the pancreas*"), there have been hints in the literature indicating a preferential role of glycolysis in regulating K_{ATP} channels in pancreatic β cells as well (141, 142). Recent studies now show that plasma membrane-localized glycolytic enzymes (pyruvate kinase in particular) are sufficient to close pancreatic K_{ATP} channels, initiate calcium influx and trigger insulin secretion (143, 144). A similar observation has previously been made in cardiac tissue. Mass spectrometry of proteins in the cardiac K_{ATP} channel complex has identified glycolytic enzymes to be overrepresented relative to other proteins (145, 146). In patch clamp experiments, it was found that phosphoenolpyruvate, a substrate for pyruvate kinase, is more effective to regulate the cardiac K_{ATP} channel activity than substrates that act upstream in glycolysis, such as fructose 1,6-bisphosphate (145). Thus, the consensus appears to be that ATP being produced by the distal (or late) steps in glycolysis preferentially regulate K_{ATP} channel activity.

Glycolysis is stimulated during cardiac ischemia

Under physiological conditions, the heart preferentially utilizes fatty acids and lactate as the preferred fuels for energy production (131, 147). During energy-delimited situations such as myocardial ischemia, however, a metabolic switch occurs and glucose becomes the preferred source of energy (148). This increased glucose flux via glycolysis is protective against ischemic insults (149-152). The protective mechanism was proposed to be that the availability of glycolytically produced ATP promotes the maintenance of the action potential and membrane integrity (131, 147). This "glucose hypothesis" holds that the enhanced glucose metabolism by glycolysis exerts anti-ischemic cardioprotective effects. This hypothesis is supported by the subcellular link that exists between key glycolytic enzymes and the activity of survival-promoting membrane-bound channel and pumps (122).

What is the significance of K_{ATP} channels in the cardioprotective effects of glycolysis?

K_{ATP} channel opening is associated with cardioprotection, and so is elevated glycolytic flux. An apparent conundrum exists, however, since the ATP produced during elevated glycolysis is expected to block K_{ATP} channels, thereby limiting the cardioprotective effects of K_{ATP} channel opening during ischemia.

We will show unpublished data from an experiment designed to examine this complex interaction between glycolysis and K_{ATP} channel opening during cardiac ischemia. A previous study has defined conditions using isolated rat hearts to either stimulate glycolysis (perfusion with 30 mM glucose and 1000 μU/mL insulin) or to stimulate non-glycolytic carbohydrate oxidation with 5 mM glucose plus 50 μU/mL insulin in the presence of dichloroacetate (DCA; Figure 5A), which removes the inhibitory effect of pyruvate dehydrogenase (PDH) by inhibiting its upstream regulator, pyruvate dehydrogenase kinase (153, 154). The substrates were ^{13}C-labeled, which

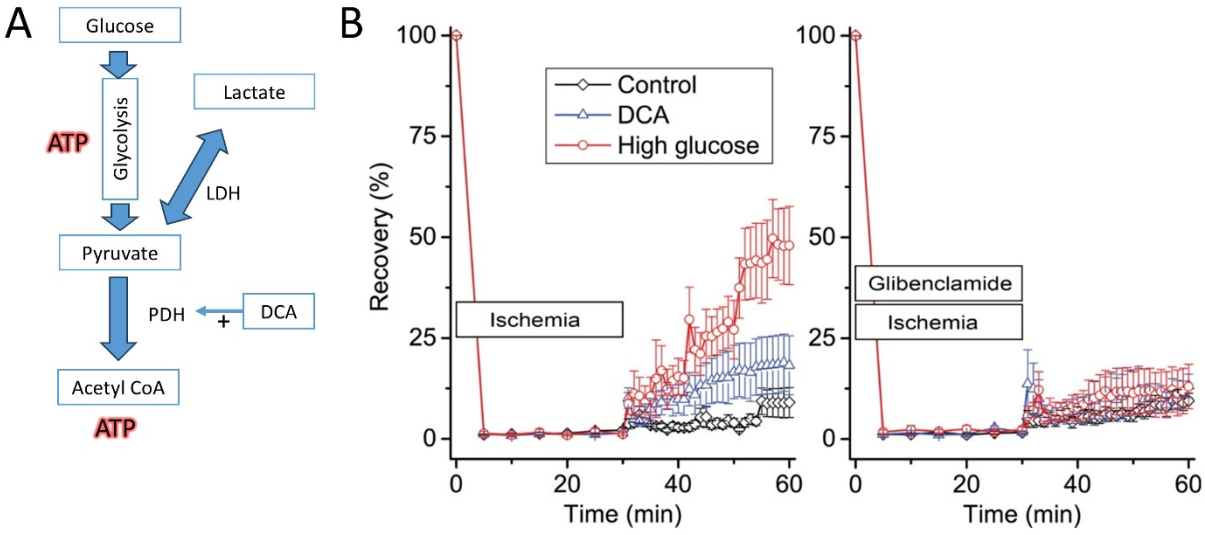

Figure 5. **Elevated glycolytic flux is cardioprotective during cardiac ischemia and active K_{ATP} channels are needed for cardioprotection.**
A) Experimental paradigm to study myocardial carbohydrate metabolism. Glycolysis is stimulated with high glucose plus insulin. Energy production from mitochondrial metabolism is stimulated by fatty acids in the presence of dichloroacetate (DCA), which stimulates pyruvate dehydrogenase (PDH) by inhibiting its upstream negative regulator, pyruvate dehydrogenase kinase. B) Rat hearts were rendered ischemic by low-flow ischemia for 30 min, followed by normoxic reperfusion. Recovery of left ventricular developed pressure during reperfusion was improved by stimulating glycolysis; this improvement was prevented by blocking K_{ATP} channels with glibenclamide.

Slika 5. **Povećan glikolitički protok pruža kardioprotekciju tokom srčane ishemije, a aktivni KATP kanali su potrebni za kardioprotekciju.**
A) Eksperimentalni model za proučavanje metabolizma ugljenih hidrata u miokardu. Glikoliza je stimulisana visokim nivoom glukoze uz dodatak insulina. Proizvodnja energije iz mitohondrijskog metabolizma je stimulisana masnim kiselinama u prisustvu dihloracetata (DCA), koji stimuliše piruvat dehidrogenazu (PDH) inhibirajući njen uzvodni negativni regulator, kinazu piruvat dehidrogenaze. B) Srca pacova su dovedena u stanje ishemije primenom ishemije sa niskim protokom u trajanju od 30 minuta, praćene normoksičnom reperfuzijom. Vraćanje pritiska razvijenog u levoj komori tokom reperfuzije bilo je pospešeno stimulacijom glikolize; ovo pospešivanje je sprečeno blokiranjem KATP kanala glibenklamidom.

showed that the total carbohydrate metabolism and total ATP production was equivalent in the two groups, but that ATP was primarily derived respectively from glycolysis or oxidative phosphorylation. Supportive of the "glucose hypothesis", hearts perfused with high glucose were better protected from ischemic insults compared to the DCA-perfused hearts (154). We adopted a similar approach to directly investigate the role of carbohydrate metabolism on K_{ATP} channels and cardioprotection during ischemia. Isolated rat hearts were Langendorff-perfused with Krebs-Henseleit buffer containing 3% BSA, 0.32 mM palmitate, 1 mM lactate, 0.1 mM pyruvate, 5 mM glucose, and 50 µU/mL insulin (control group). In two other groups, we either stimulated carbohydrate flux via glycolysis with high glucose (30 mM glucose with 1000 µU/mL insulin) or activated non-glycolytic carbohydrate oxidation with DCA. Hearts were subjected to 30 min low-flow (0.3 ml/min) ischemia and 30 min reperfusion, while monitoring coronary flow, heart rate and contractile activity (with an intraventricular balloon). Similar to data from the previous study (154), post-ischemic recovery of ventricular function was improved by both interventions, but was significantly better when stimulating glycolysis (Figure 5B). The glycolysis-induced protection was completely prevented by blocking K_{ATP} channels with glibenclamide. This experiment demonstrates a tight link between elevated glycolysis and K_{ATP} channel opening during ischemia to elicit cardioprotection. A key question that needs further investigation is whether the glycolyic ATP production actually blocked the K_{ATP} channels during ischemia, or whether other mechanisms come into play. It might be possible, for example, that detrimental K_{ATP} channel internalization that occurs during ischemia (73) might be mitigated by glycolysis.

Do K_{ATP} channels regulate energy metabolism?

There is plenty of evidence to show that K_{ATP} channels are subject to control by glycolytically derived ATP (139, 140, 143-145). Might it be possible that a reciprocal regulation occurs (e.g., does K_{ATP} channel opening regulate glycolysis or other steps in cardiac energy metabolism)? This seemingly provocative question has merit. It has been known for some time, for example, that K_{ATP} channel block with sulfonylureas (glibenclamide and tolbutamide) stimulates glycolysis (155, 156). We recapitulated these data. Figure 6A shows values of lactate, measured in the effluent of normoxic Langendorff-perfused rat hearts using a colorimetric/fluorometric assay (MAK064, Sigma Aldrich) before and 10 min after perfusing the heart with glibenclamide (1 µM). Consistent with the published data, glibenclamide led to a significant increase in lactate production by the heart, which is consistent with elevated glycolytic flux or inhibition of oxidative phosphorylation. Since glibenclamide (up to 10 µM) does not decrease oxygen uptake or oxidative phosphorylation (157-159), the most parsimonious explanation is that blocking K_{ATP} channels with glibenclamide stimulates glycolysis.

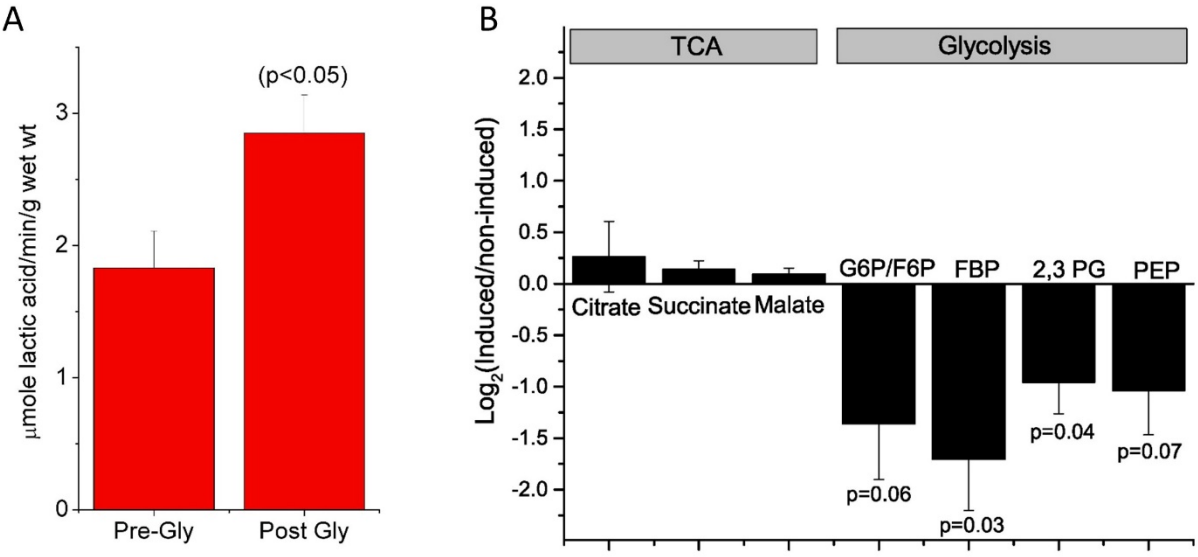

Figure 6. Is there a possibility that K_{ATP} channels regulate energetics?
A) The effluent of isolated hearts, perfused via the aorta, was collected and lactate was measured using a colormetic assay. Measurements were made before (Pre-Gly), and 10 min after (Post-Gly) perfusion with glibenclamide (1 μM). B) Metabolomics changes in the hearts of mice with cardiac-specific deficiency of the K_{ATP} channel subunit, Kir6.2. Aqueous metabolites from hearts were extracted using chloroform-methanol buffer as published (162) and subjected to analysis using the Agilent 6456 quadrupole time-of-flight mass spectrometer coupled to Agilent 1290 liquid chromatography.

Slika 6. Postoji li mogućnost da K_{ATP} kanali regulišu energetiku?
A) Sakupljen je efluent izolovanih srca, perfundiranih preko aorte, a koncentracija laktata je izmerena pomoću kolorimetrijskog testa. Merenja su izvršena pre (Pre-Gly) i 10 minuta nakon (Post-Gly) perfuzije sa glibenklamidom (1 μM). B) Metabolomske promene u srcima miševa sa specifičnim nedostatkom podjedinice K_{ATP} kanala Kir6.2 u srcu. Vodeni metaboliti iz srca su ekstrahovani pomoću hlorofor-metanolnog pufera, kako je objavljeno (162), te su podvrgnuti analizi korišćenjem Agilent 6456 kvadrupolnog TOF masenog spektrometra povezanog sa Agilent 1290 tečnom hromatografijom.

Energy metabolism has also been studied in mice deficient of K_{ATP} channels. Members of the Light laboratory, for example, measured the rates of glycolysis, fatty acid oxidation, and glucose oxidation in the hearts of wild-type mice, or mice that lack K_{ATP} channels (Kir6.2 deficient mice) (87). In their study, the glycolytic rate was 45% lower in the Kir6.2$^{-/-}$ hearts, with no change in the glucose oxidation rate. We have similar unpublished findings. We performed a metabolomics experiment in a mouse model with cardiac-specific deletion of Kir6.2 (Figure 6B). There was a decrease in the amounts of glycolytic intermediates G6P/F6P ratio, FBP, 2,3 PG and PEP, without changes in the

intermediates of the tricarboxylic acid (TCA or Krebs) cycle, citrate, succinate or malate. Moreover, there were no changes in fatty acid as reflected by unchanged levels of CoA and carnitine (not shown). It is noteworthy that metabolomics data from the Terzic lab did not support our findings or those of the Light lab, which suggested wide-ranging effects on cardiac metabolism in the Kir6.2 knockout mice (160). Future studies are needed to elucidate the effects of cardiac metabolomics alterations in K_{ATP} channel deficient mice, and to explore possible study differences (e.g. possible differences in mouse models used, etc.).

Evidence has recently emerged for a role of K_{ATP} channels in the central nervous system to regulate glycolytic flux. It was, for example, shown that K_{ATP} channels couple elevated glucose levels with lactate levels in the brain interstitial fluid to sustain neuronal firing, suggesting that K_{ATP} channels stimulate glycolysis in neurons. Moreover, the glucose to lactate metabolism was uncoupled in Kir6.2$^{-/-}$ mice (23). More direct evidence was recently obtained by the same group to demonstrate that K_{ATP} channels do in fact stimulate glycolytic flux, thereby controlling cortical EEG activity, arousal, and the sleep/wake homeostasis (161). The latter study used ^{13}C-labeled glucose incorporation into different metabolic pathways and showed that glucose was shunted into glycolysis, without changes in the TCA cycle or fatty acid metabolism.

The published studies are not entirely consistent with each other. Overall, K_{ATP} channel blockers stimulate lactate production, which suggests that K_{ATP} channels inhibit glycolysis (or conversely, that blocking K_{ATP} channels stimulates glycolysis). Most studies in hearts and neurons, however, suggest the possibility that K_{ATP} channels stimulate glycolysis. At present, it is unclear whether there are differences when a study is performed acutely (e.g., with a blocker) or whether long-term adaptive responses are involved (e.g., with a knockout mouse). Off-target effects of drugs also need to be considered. These are early days and the relationship between K_{ATP} channels and glycolytic flux needs to be further explored – particularly in the pancreatic β-cell, where glycolysis is gaining a strong foothold as a regulator of K_{ATP} channels and insulin secretion (143, 144).

Conclusion

This review pointed out the crucial role of K_{ATP} channels in cardioprotection, particularly during ischemic events. These channels are unique in that they link the metabolic state of the cell to its electrical activity by sensing intracellular nucleotide levels. With metabolic stress, such as cardiac ischemia, the decreased intracellular ATP and increased intracellular ADP cause the K_{ATP} channels to open. Their opening helps to maintain the cellular membrane potential and reduce Ca^{2+} overload by shortening the action potential duration. The reduced Ca^{2+} influx minimizes mitochondrial dysfunction and prevents activation of apoptotic pathways. These combined actions play a pivotal role in protecting the myocardium from injury and improving overall cardiac function during and after ischemic events. We highlight key areas where further investigation is needed, including the relative expression of K_{ATP} channel subunits (particularly Kir6.1) in mouse

and human heart, and the importance of evaluating K_{ATP} channel expression in the days following an ischemic insult, when cardiac mortality after a second infarct is at its highest. We delved briefly into the complicated relationship that exists between the cardioprotective effects of elevated glycolytic energy production during ischemia and K_{ATP} channel opening and the intriguing possibility that K_{ATP} channels may regulate cardiac energetics. The potential of K_{ATP} channels as therapeutic targets in clinical practice is promising, particularly for conditions involving ischemic heart disease. K_{ATP} channel openers (KCOs) can mimic the protective mechanisms activated during ischemic preconditioning, which can help to maintain cellular homeostasis, Ca^{2+} overload, and prevent cell death, thus improving cardiac function during ischemic events. As such, KCOs could be developed as treatments to reduce myocardial infarction size, protect against reperfusion injury, and improve outcomes in patients undergoing procedures like coronary artery bypass grafting or angioplasty. Moreover, targeting K_{ATP} channels might benefit patients with chronic conditions such as heart failure by enhancing the heart's resilience to metabolic stress. The challenge lies in developing KCOs with high specificity and minimal side effects, as these channels are also present in other tissues. Moreover, some KCOs are proarrhythmic. Developing compounds that retain cardioprotective properties without having these side effects would be advantageous. Advances in precision medicine and drug delivery systems could aid in overcoming these hurdles, enabling targeted therapy with fewer off-target effects. As research progresses, the therapeutic modulation of K_{ATP} channels holds significant promise for improving cardiovascular health and patient outcomes in clinical settings.

Declaration of Competing Interest

S. F. is a scientific cofounder and consultant of CalciMedica. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Eylem Taskin: Data curation, Investigation, Methodology, Writing - review & editing

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Hua-Qian Yang: Conceptualization, Data curation, Writing - review & editing

Tomoe Y. Nakamura: Writing - review & editing

Ravichandran Ramasamy: Formal analysis, Investigation, Methodology, Resources, Supervision, Validation

William A. Coetzee: Conceptualization, Formal analysis, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing - original draft

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K_{ATP} kanali i kardioprotekcija

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Kratak sadržaj

U ovom preglednom radu razmatraju se ATP-osetljivi kalijumski (K_{ATP}) kanali, koji povezuju unutarćelijski energetski metabolizam sa ćelijskom električnom aktivnošću i igraju ključnu ulogu u različitim fiziološkim procesima, posebno u pankreasu i kardiovaskularnom sistemu. K_{ATP} kanali se otvaraju kada se nivo ATP smanji tokom metaboličkog stresa, kao što je ishemija, pomažući tako u zaštiti srca od oštećenja održavanjem membranskog potencijala i sprečavanjem preopterećenja kalcijumom. Ovi kanali se nalaze u različitim tipovima ćelija širom kardiovaskularnog sistema, utičući na vaskularni tonus i ekscitabilnost srca. U radu se naglašava potreba za daljim istraživanjem specifične ekspresije podjedinica K_{ATP} kanala kod ljudi i posledica ishemijskih događaja na njihovu funkcionalnost. Takođe, istražuje se međusobni odnos glikolize i K_{ATP} kanala i sugeriše se da glikolitički ATP može modulisati aktivnost K_{ATP} kanala, pri čemu se naglašavaju kardioprotektivni efekti tokom ishemijskih događaja. Uočen je potencijal otvarača K_{ATP} kanala (KCOs) kao terapijskih agenasa za ishemijsku bolest srca, posebno u poboljšanju ishoda kod pacijenata podvrgnutim kardiološkim zahvatima. I dalje postoje izazovi u razvoju specifičnih KCOs sa minimalnim nuspojavama, ali napredak u preciznoj medicini može u budućnosti poboljšati ciljane terapije. Imajući sve ovo u vidu, K_{ATP} kanali predstavljaju obećavajuće mete za unapređenje kardiovaskularnog zdravlja.

Ključne reči: KATP kanali, otvarači kalijumskih kanala, kardioprotekcija, ishemija, reperfuzija, prekondicija