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Mitochondrial ATP-Sensitive Potassium Channels and Cardioprotection

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Abstract

Coronary artery disease is the leading causes of morbidity and mortality in man worldwide. Substantial efforts have been dedicated toward improvement of functional recovery and reduction of the extent of infarction after ischemic states. The mitochondrial adenosine triphosphate (ATP)-sensitive potassium channels (mito K_{ATP}) is the receptor for K_{ATP} channel openers (KCOs) that have been reported to possess protective role against various cardiovascular complications. Several experimental studies have shown a wide range of possible clinical uses of KCOs as bronchodilators, vasodilators and bladder relaxants. In addition, KCOs show various cardioprotective effects against arrhythmias, angina and heart failure. The present article highlights on the physiologic properties and functions of mito K_{ATP} channels in the cardiovascular system and on the role of the KCOs in the treatment of various cardiovascular complications.

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INTRODUCTION

An ATP-sensitive potassium channel is a type of potassium channel that is gated by ATP which can be divided on the basis of their position in the cell as being either sarcolemma (sarc K_{ATP}) or mitochondrial (mito K_{ATP}) [1, 2]. The K_{ATP} activity has been initially detected at the level of sarc K_{ATP} and mito K_{ATP} [3, 4, 5]. The mito K_{ATP} is the receptor for K_{ATP} channel openers (KCOs) that possesses cardioprotection

against various complications [6,7]. The KCOs are a class of chemically diverse agents sharing K_{ATP} as their common target. Pharmacological studies starting in 1989 showed that KCOs exert profound cardioprotective effects in numerous mammalian species [6, 7, 8]. Consequently, pharmacological activation of K_{ATP} would be expected to mimic an endogenous cardioprotective mechanism that also seems to be operative clinically [9, 10]. It has been comprehensively shown that the heart is significantly protected against myocardial injury by administering KCOs. Moreover, this pivotal role was mediated by the mito K_{ATP} channels. Numbers of experimental and clinical studies have reported beneficial clinical uses of KCOs in cardiac arrhythmias, angina, myocardial infarction and heart failure [11, 12, 13, 14, 15]. The present article chats about the mechanisms by which mito K_{ATP} opening affords cardioprotection. Moreover, the review article provides an overview of the most recent literature in the field and discusses about the use of KCOs in the treatment of myocardial and vascular dysfunctions.

STRUCTURE AND SUBTYPES OF K_{ATP}

The K_{ATP} channels belong to ATP-binding cassette transporter superfamily and are comprised of two subunits, i.e., a pore-forming inward rectifying potassium channel subunit (Kir); and a regulatory sulfonylurea receptor (SUR) [4]. Both Kir and SUR subunits have been required to form fully functional channels in which the SUR subunit cooperates with the Kir subunit to act as ATP-dependent potassium channel complex. The mitochondrial Kir subunit has a molecular mass of 55 kD, whereas mitochondrial SUR subunit has a molecular mass of 63 kD [16]. Moreover, the two subunits coassemble with a 4:4 stoichiometry in order to form a hetero-octameric K_{ATP} channel [4, 9].

Two subtypes of ATP-sensitive potassium channels have been noted to coexist in the myocardium, with one subtype located in the sarcolemma (sarc K_{ATP}) membrane, while other in the inner membrane of the mitochondria (mito K_{ATP}) [4, 5]. Several observations with respect to the pharmacological profile suggests that the mito K_{ATP} belongs to the inward rectifier K^+ channel family. The cardiac sarc K_{ATP} channels are shown to exist in a variety of tissues. They have been molecularly characterized as SUR2A/Kir6.2, in which Kir 6.2 subunit has a molecular mass of 51 kD and SUR2A subunit with amolecular mass of 140 kD [17, 18]. Mito K_{ATP} channels were first identified in 1991 by single-channel recordings of the inner mitochondrial membrane [19]. Further, the mito K_{ATP} channels were firstly identified in liver and later in the heart. In addition, they have been shown to be located in the inner membrane of the mitochondria [20, 21].

ROLE OF KCOS IN CARDIOVASCULAR SYSTEM

Numbers of experimental data provides an evidence for the wide range of possible clinical uses of KCOs that include roles as bronchodilators, vasodilators and bladder relaxants [11, 12, 13]. In addition, mito K_{ATP} channels play important role in the ischemic reperfusion (I/R) injury and cell apoptosis [4]. The KCOs have been noted to cause efflux of K^+ ions and hyperpolarize the cardiac membrane by activating sarc K_{ATP} present on vascular smooth muscles cells, which ultimately produces a negative iontropic effect in cardiomyocytes and further results in the dilatation of the blood vessels [12, 22, 23]. Moreover, when KCOs were studied *in vitro* in the heart, they showed similar pharmacological profile with respect to their vasodialatory effects as shown on other organs. In addition, the *in vivo* activities of KCOs have also been significantly reviewed [24, 25]. Levosimendan, an inodilator has been significantly used in the treatment of congestive heart failure by opening sarc K_{ATP} channels in vascular smooth muscle cells. The drug has been shown to be an active vasodilator in arteries,

arterioles and veins by opening sarc K_{ATP} and hence exerted an effect on systemic vascular resistance and organ microcirculation [12, 26, 27]. The potential of KCOs as an antiarrhythmic agent in I/R is still under investigation. However, it has been shown that opening of sarc K_{ATP} triggers some potential hazards for ventricular arrhythmia whereas no such harm has been seen in the mito K_{ATP} opening providing evidence of mito K_{ATP} in arrhythmias [14, 28]. Administration of Nicorandil, a potent K_{ATP} channel opener, has been reported to provide protection against ventricular arrythmias in conscious rats with myocardial
infarction [29]. Moreover, in patients undergoing coronary angioplasty, treatment of Nicorandil decreased the chances of ventricular fibrillation and QT dispersion in patients. Additionally, both short and long term treatment with Levosimendan, showed protective effects on the ventricular arrhythmias after occlusion of the coronary arteries in conscious rats that further proved the potential of KCOs in cardiac arrhythmias [15, 30] (Fig. 1).

Further, it can be suggested that the KCOs possess protective effects in various pathological conditions such as angina and acute myocardial infarction (AMI) [31, 32]. Furthermore, KCOs might also be used in cardiology and heart surgery to gain cardioprotection of organs from ischemic injury [33, 34]. The potential of KCOs in various cardiovascular diseases is further evidenced by the fact that treatment with Nicorandil reduced the prevalence of primary state of coronary heart disease, myocardial infarction alongwith secondary state of coronary arteries disease, acute myocardial infarction, stable and unstable angina [35, 36]. The preclinical studies have shown that KCOs induce late preconditioning against myocardial infarction in conscious rabbits evidencing the role in ischemic heart diseases (IHD) [37]. It has also been demonstrated that early administration of Nicorandil as an adjunct to reperfusion showed cardioprotection in patients presented with AMI [35, 38]. Furthermore, administration of inodilator Levosimendan has been shown to reduce the risk of heart failure and death in patients with AMI that further evidenced the role of KCOs in IHD [39]. Further, KCOs have been documented to prevent constriction of the pulmonary blood vessel caused by hypoxia which showed the potential of KCOs in the management of lung hypertension [40, 41]. Levosimendan has been shown to significantly reduce the pulmonary hypertension and showed no adverse effect on the exchange of oxygen and carbon dioxide in a porcine model of endotoximia [42]. It has been reported that the infants with AMI caused by congential stenosis of left coronary artery and subsequent dysfunctioning of left ventrical and mitral rigrugitation, show repeated refractory pulmonary hypertension [43]. In such cases, treatment with Levosimendan overemphasized the left ventricular dysfunction, enhanced cardiac index and reduced the resistance of pulmonary vessels. Thus, it can be comprehensively suggested that KCOs might be used for long term dilatation of pulmonary vessels in patients with improper cardiac function (Fig. 1). Further, the potential of KCOs in perioperative cardiprotection has been studied. Results from various experimental and clinical studies suggest that KCOs possess important roles in relieving the pain occurred during the first inflation of an intra-aortic balloon in coronary angioplasty. Moreover, the KCOs has also been noted to result in the reduction of the ischemic condition after performing surgical treatments like artery bypass grafting of heart [44, 45]. In addition, KCOs have been shown to possess potential role in organ perfusion and preservation of transplants. Experimental study in a canine model showed that administration of Levosimendan increased blood flow to renal medulla, decreased renal medullary and cortical vascular resistance and increased blood flow to small intestine and liver. Moreover, it has been shown to reduce vascular resistance in these organs, increased hepatic

blood flow, reduced cerebral vascular resistance and skeletal muscle vascular resistance, confirming the potential of KCOs in organ perfusion [11, 13, 26]. Furthermore, it has been reported that addition of Pinacidil, an opener of potassium channels, to the cardioplegic solution in a heart preservation study, showed improvement in donor heart preservation when administered in a histidine-buffered lactobionate-enriched vehicle, which further evidenced the potential of KCOs in organ preservation for transplant [12, 46].

FUTURE DIRECTIONS

Recent years have seen an explosive growth of interest in the role of mito K_{ATP} channel activation and the use of KCOs in the pathogenesis of myocardial dysfunction. However, sufficient bodies of matter are available regarding the role of mito K_{ATP} channel activation and KCOs in the protection of various cardiovascular diseases, but there are many future directions for this rich area of investigation. Firstly, the determination of the subunit composition for cardiac mito K_{ATP} channels and evaluation of differences between various populations of cardiomyocytes need to be addressed. Moreover, the determination of cellular and molecular mechanisms directing appropriate Kir and SUR subunits to the mitochondria and evaluation of factors determining mito K_{ATP} channel density and subunit composition needs attention. The investigation of developmental regulation of mito K_{ATP} channel composition and function should be taken into consideration. Further, the discovery of additional naturally occurring openers and blockers of mito K_{ATP} under physiological and pathological conditions must be clearly understood. The discovery of new drugs that are tissue or cell-specific activators and inhibitors of mito K_{ATP} channels should be performed. Furthermore, the determination of protective effects of mito K_{ATP} activators against other types of acute myocardial injury and occlusive events during cardiac surgery must be comprehensively done. In addition, the elucidation of the complete signaling mechanisms of cardioprotection by mito K_{ATP} channel activation must be taken into account for the successful implementation of this class in various cardiovascular complications.

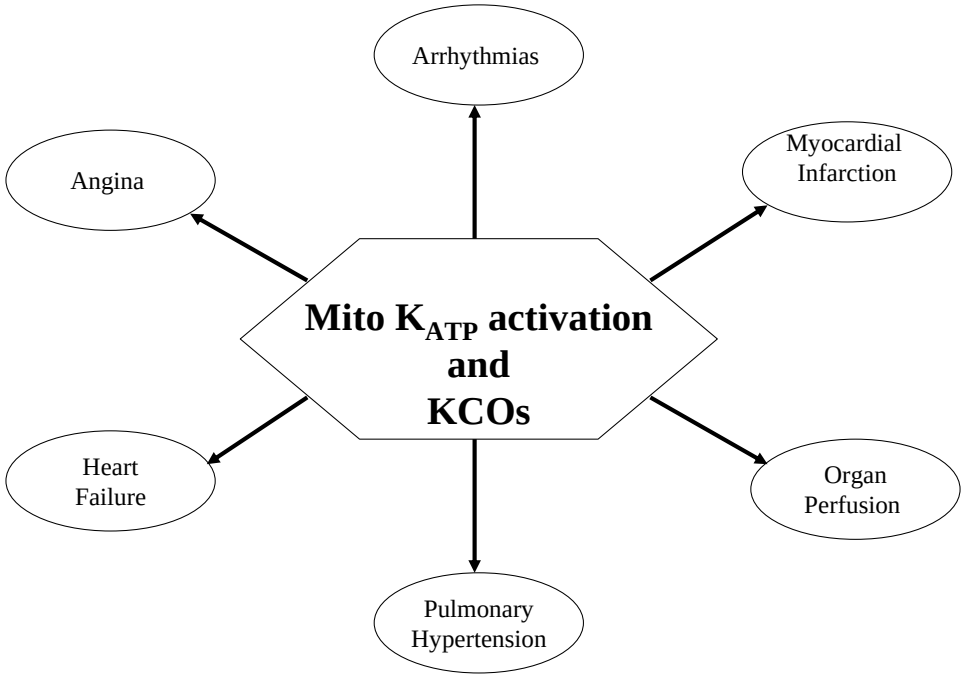

Figure 1: Modulatory role of mito K_{ATP} channel activation and KCOs in various cardiovascular diseases

CONCLUSION

The K_{ATP} have shown wide-range of therapeutic interest as potential targets in a range of cardiovascular conditions like arrhythmias, angina and heart failure. The materialization of new-fangled chemical entities with enhanced tissue selectivity and better pharmacokinetic and pharmacodynamic profiles has created supplementary clinical applications for this class of agents. However, potent KCOs have been reported till date possessing various beneficial effects in cardiovascular complications but further studies are demanded in order to improve the quality of life with KCOs in various pathological disorders.

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