

Cardiac Arrhythmias Associated to Abnormalities in the Functionality of K⁺ ATP-Sensitive Channels

Editorial

Knowledge of the pathophysiology of ion channel abnormalities is essential to understand the development and management of cardiac arrhythmias. Ion channels are transmembrane proteins mediating ion fluxes across cell membranes. They are being expressed in all cell types, and are involved in almost all physiological processes, including neurotransmission, muscle contraction or relaxation, secretion, immune response, cell proliferation, and differentiation [1-4]. ATP-sensitive K⁺ (KATP) channels were first discovered in cardiac muscle more than two decades ago. It has been also found in a variety of tissues including pancreatic beta-cells, skeletal muscle, smooth muscle, renal tubule cells, and in the central nervous system [1,2]. Due to the presence of these channels in various organs it is understandable the implication of the exact knowledge of the functionality of KATP in internal medicine. This knowledge could determine an important therapeutic potential for the adequate management of several diseases. These KATP channels have been associated with diverse cellular functions, such as insulin secretion from pancreatic beta-cells, smooth muscle relaxation, Cardiac contractility and function, regulation of skeletal muscle excitability, and neurotransmitter release [3,4].

Despite the large number of ion channels causing cardiac arrhythmias, the therapeutic options are very limited, and are based mostly on symptomatic treatments. Therefore, investigation should aim at improving measures in this context. The K⁺ ATP-sensitive channels play an important role in the cardiovascular system and have a potential importance in the treatment of several diseases, like cardiac arrhythmias, cardiac ischemic disease, and hypertension. The KATP channels are inhibited by intracellular ATP and activated by nucleoside diphosphates (NDPs) and thus, provide a link between cellular metabolism and excitability. Patch-clamp experiments have demonstrated electrophysiological and pharmacological features of the KATP channels in a variety of tissues. In addition, studies using molecular biological techniques have shown that the KATP channels are heteromeric proteins composed of at least two subunits, a member of the inwardly rectifying K⁺ (Kir) channel subfamily and a sulfonylurea receptor, which belongs to the ATP-binding cassette transporter family [5,6].

The cardiac KATP channel also has a physiological role in modulating cardiac function particularly under conditions of metabolic stress such as hypoxia, ischemia and metabolic inhibition when ATP is reduced. The channel may be involved in increase of K⁺ efflux and shortening of the action potential duration in the ischemic heart [7,8]. These findings contribute to the electrophysiological abnormalities, which predispose the heart to the development of reentrant arrhythmias [1].

A positive aspect, on the other hand, is the fact that opening of the cardiac KATP channel has also been implicated as a cardio-protective mechanism underlying ischemia-related preconditioning [2]. In the coronary arteries, the KATP channel

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is believed to mediate vasodilation particularly during ischemia. The vasodilation induced by ischemia, hypoxia and metabolic inhibition can be prevented by sulfonylureas, blockers of KATP channels, and can be mimicked by K⁺ channel openers [3,4]. The K⁺ channel openers have also been shown to relax vascular smooth muscle in other organs than heart. Thus, KATP channels in the cardiovascular system play important roles, and thus may have potential importance in the treatment of several diseases.

As mentioned before, the KATP channels are regulated by various intracellular factors, such as ATP and NDPs. ATP is the main regulator of KATP channels and has mainly two functions; 1) closure of the KATP channels, and 2) maintaining the channel activity in the presence of magnesium (Mg²⁺) [1,11]. The first action of ATP is referred as the "ligand action", because it is assumed to require the binding of ATP to the KATP channel and persists as long as ATP is bound to the channel. Typically, KATP channels have a very low probability of being opened at physiological concentrations of ATP. The second action of ATP is referred to as the "hydrolysis-dependent" action of ATP, because it apparently requires the hydrolysis of ATP in the presence of Mg²⁺, and can last for several-tens of minutes after removal of ATP. The effect of ATP on KATP channels depends on the state of the channel protein. When the channels are operative, ATP inhibits channel opening. When the channels are not operative, treatment with MgATP restores channel opening [1,9-13].

In the therapeutic management in internal medicine, KATP channels are the targets of two important classes of drugs, which are the anti-diabetic sulfonylureas which block the channels, and K⁺ channel openers which tend to maintain the channels in an open conformation. Sulfonylureas including glybenclamide and tolbutamide are hypoglycemic drug agents that stimulate insulin secretion by blocking the KATP channel with consequent

depolarization and Ca²⁺ influx. As a collateral effect, these hypoglycemic drugs can also block the KATP channels in cardiac and smooth muscle cells though require higher concentrations than in the pancreatic beta-cells [14].

Likewise, K⁺ channel blockers including certain antiarrhythmic drugs block the channels [15]. K⁺ channel openers include divergent chemical compounds, such as cromakalim, pinacidil, levromakalim, nicorandil, diazoxide and minoxidil sulphate. These agents may possess high therapeutic potential in treating various clinical conditions including hypertension, acute and chronic myocardial ischemia, or congestive heart failure, as well as in managing bronchial asthma, urinary incontinence, and certain skeletal muscle myopathies [1]. These effects are ascribed to an increase probability in the opening of KATP channels. KATP channels in different tissues exhibit considerable variations in response to K⁺ channel openers. The cardiac KATP channel is activated by pinacidil, but not by diazoxide. Most of the smooth muscle type KATP channels are activated by both of these agents. Thus, the properties of KATP channels vary among tissues leading to the premise that these channels may be composed of heterogeneous channel proteins [16-18].

Several studies with various genetically engineered mice have developed considerably our understanding of the molecular structure and function of KATP channels in the cardiovascular system. The availability of the knockout mice of KATP channel subunits may provide excellent model of vasospastic angina. It is likely that in the next several years, molecular biological and molecular genetic studies would enable us to clarify the roles of KATP channels in physiology and pathophysiology, which may allow further development of strategies and pharmacological agents to treat various cardiovascular diseases. These diseases can range from common to very rare disorders and their variability in severity can be mild, disabling, or life-threatening. In spite of this, ion channels are the primary target of only about 5% of the marketed drugs suggesting their potential in drug discovery and therapeutic management.

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