Risk of Ventricular Proarrhythmia with Selective Opening of the Myocardial Sarcolemmal versus Mitochondrial ATP-Gated Potassium Channel

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ABSTRACT

Myocardial ATP-gated potassium channels (K-ATPs) are critical in the intracellular signaling cascade resulting in ischemic preconditioning (IP). Mitochondrial K-ATP channels seem to be responsible for IP, whereas the functions of K-ATP channels in the sarcolemmal membrane are less well understood. The proarrhythmic potential of specific versus nonspecific opening of K-ATP channels has not been investigated. In this study, Langendorff-perfused rabbit hearts were exposed to either pinacidil (1.25 μM), a nonselective K-ATP channel agonist, or selective mitochondrial or sarcolemmal K-ATP channel agonists or antagonists. The hearts were then subjected to 12 min of hypoxic perfusion and 40 min of reoxygenation. Hearts were monitored for the induction of ventricular fibrillation (VF). No heart subjected to hypoxia-reoxygenation without drug treatment developed VF (0 of 5). Pinacidil pretreatment induced VF (12 of 14; p = 0.004 versus control). Pinacidil’s effect was blocked by HMR-1098 [1-5-[2-(5-chloro-o-anisamide)ethyl]-2-methoxyphenyl][sulfonfonyl]-3-methylthiourea] (1 μM), a selective sarcolemmal K-ATP channel antagonist (1 of 7; p = 0.007 versus pinacidil; N.S. versus control). Hearts pretreated with 5-hydroxydecanoate (5-HD) (100 μM), a putatively selective mitochondrial K-ATP channel blocker developed VF in one of eight trials (N.S. versus control). 5-HD did not alter the effects of pinacidil (6 of 8; p < 0.05 versus control; N.S. versus pinacidil alone). Selective mitochondrial K-ATP channel activation with [(3R)-trans-4-[(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)dimethyl-2H-1-benzopyran-6-carbonitril monohydrochloride] (BMS-191095) (6 μM) resulted in zero of five hearts developing VF (N.S. versus control). Our data suggest that selective opening of the sarcolemmal K-ATP channel during hypoxia-reoxygenation induced VF, whereas opening of the mitochondrial channel was not associated with VF. The findings suggest that caution should be exercised when developing compounds aimed at inducing IP, and nonspecific opening of the K-ATP channel should be avoided.

Ischemic preconditioning (IP) describes a physiological adaptation to short episodes of nonlethal myocardial ischemia that results in tissue resistant to ensuing further myocardial ischemia. IP, initially described by Murry et al. (1986) has been demonstrated in every experimental animal studied, including human (Nakano et al., 2000). IP may be mimicked pharmacologically by several different endogenous and exogenously administered agents, including adenosine (Liu et al., 1997; Cope et al., 1997). IP results from a cascade of intracellular events with the opening of ATP-gated potassium (K-ATP) channels as a major component.

Myocardial K-ATP channels may be divided into two distinct populations. One channel type resides in the sarcolemmal membrane (sarcK-ATP), whereas the other is localized in the mitochondrial inner membrane (mitoK-ATP). The mitoK-ATP and sarcK-ATP channels may be differentiated based on their pharmacological sensitivities. The mitoK-ATP channel is purported to be responsible for IP (Garlid et al., 1997; Liu et al., 1998). Although the sarcK-ATP channel may also participate in IP, the exact role that the channel serves remains unclear (Flagg and Nichols, 2001). Although opening of the mitoK-ATP does not affect the electrophysiological properties of the myocyte, sarcK-ATP channel opening leads to a large outward repolarizing current, shortening the action potential of the individual cell.

ABBREVIATIONS: IP, ischemic preconditioning; K-ATP, ATP-gated potassium channel; sarcK-ATP, sarcolemmal ATP-gated potassium channel; mitoK-ATP, mitochondrial ATP-gated potassium channel; DMSO, dimethyl sulfoxide; SUR, sulfonylurea; HMR-1098, 1-[5-[2-(5-chloro-o-anisamide)ethyl]-2-methoxyphenyl][sulfonfonyl]-3-methylthiourea; 5-HD, 5-hydroxydecanoate; BMS-191095, (3R)-trans-4-[(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)dimethyl-2H-1-benzopyran-6-carbonitril monohydrochloride.
and decreasing the refractory period of the tissue as a whole. The shortening of the refractory period forms a myocardial substrate potentially susceptible to reentrant arrhythmias. The potential for proarrhythmia generated via K-ATP channel opening is important because the ability to pharmacologically precondition the heart and protect it from a future ischemic insult represents an attractive therapeutic target. Patients undergoing cardiac surgery requiring circulatory arrest, donor organs and patients with myocardial ischemia would stand to benefit significantly. This study, therefore, was designed to examine the effects of selective and nonselective opening of the K-ATP channel on the incidence of ventricular arrhythmias in isolated hearts exposed to hypoxia and reoxygenation.

Materials and Methods

The procedures used in this study were in accordance with the guidelines of the University of Michigan Committee on the Use and Care of Animals and conforms to the standards in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication number 86-23). The University of Michigan Unit for Laboratory Animal Medicine provided veterinary care.

Isolated Heart Preparation. Rabbit hearts were prepared as described previously (Fischbach et al., 2003). Male New Zealand White rabbits (1.9–2.5 kg) were rendered unconscious using cervical dislocation. The heart was removed rapidly via a median sternotomy and placed in iced buffered saline. The hearts were mounted on a Langendorff apparatus and perfused with a modified Krebs-Henseleit solution at a constant flow rate to achieve a coronary perfusion pressure of 50 to 60 mm Hg.

The composition of the perfusion buffer was 117 mM NaCl, 1.9 mM KCl, 2.6 mM CaCl₂, 1.2 mM MgCl₂, 25 mM NaHCO₃, 1.1 mM KH₂PO₄, 5 mM glucose, 5 mM Na-glutamate, and 2 mM Na-pyruvate. The final K⁺ concentration was 3 mM. The pH of the solution was adjusted to 7.4 using HCl. The buffer was gassed continuously with 95% O₂, 5% CO₂ as it passed through an “artificial membrane-lung” (Silastic tubing; Dow Corning, Midland, MI) and maintained at 37°C using a circulating water bath. Pacing leads were attached to the right atrial appendage, and the hearts were paced at twice the normal atrial rate to keep the ventricles beating in unison. A polyethylene tube also was advanced across the mitral valve. A polyethylene tube also was advanced across the mitral valve and served as a vent for the left ventricle. Coronary perfusion pressure, a volume conducted ECG, left ventricular end diastolic pressure and left ventricular developed pressure were monitored continuously and recorded on a Grass Instrumets model 7 polygraph (AstroMed, Warwick, RI) interfaced to a MacLab (Castle Hill, Australia) data acquisition system. The data were archived on a Macintosh computer (Apple Computer, Inc., Cupertino, CA) for subsequent off-line analysis.

Experimental Protocol. After a 20-min stabilization period, the hearts were treated for an additional 15 min (Fig. 1). In the drug-treated hearts, the test agents were added to the buffer at the conclusion of the stabilization period. For those experiments with both a K-ATP channel opener and blocker, the blocker was added to the buffer 5 min before the activator. Perfusion with the test agent was continued for the length of the experiment. The buffer was then made hypoxic by changing the gas content in the “membrane-lung” to 95% N₂/5% CO₂. The pO₂ of the solution was checked using a gas analyzer to ensure appropriate hypoxemia. Hearts were perfused with the hypoxic perfusion medium for 12 min and then reoxygenated for 40 min. In those experiments using a pharmacological intervention, the drugs were perfused throughout the entire experiment. Electrocardiographic and hemodynamic monitoring was performed for the duration of the experiment. The occurrence of VF and the time of onset of the VF were recorded.

A total of seven groups were included in the first portion of the study. The groups were control, 1.25 μM pinacidil (a nonselective K-ATP channel opener), 100 μM 5-hydroxydecanoate (a selective mitoK-ATP channel blocker), 100 μM 5-hydroxydecanoate + 1.25 μM pinacidil, 6 μM BMS-191095 (in DMSO, a selective mitoK-ATP opener), 1 μM HMR-1098 (a selective sarK-ATP channel blocker) and 1 μM HMR-1098 + 1.25 μM pinacidil, the concentration of each agent was based upon published studies. An additional group of three hearts (not included in data) were perfused with DMSO alone was subjected to the hypoxia-reoxygenation protocol to ensure no proarrhythmic effects. To demonstrate that these effects were due to opening of the K-ATP channel, a limited number of rabbit hearts were treated with 5 μM cromakalim, like pinacidil a nonspecific opener of the K-ATP channel. Four groups were included in this portion of the study. The groups were 5 μM cromakalim alone, 5 μM cromakalim + 1 μM HMR-1098, 5 μM cromakalim + 3 μM HMR-1098, and 5 μM cromakalim + 100 μM 5-hydroxydecanoate.

Drugs. Pinacidil (Sigma-Aldrich, St. Louis, MO) was dissolved in acidicified buffer. Cromakalim (Sigma-Aldrich) was first dissolved in acidicified buffer. Cromakalim (Sigma-Aldrich) was first dissolved in acidicified buffer. Cromakalim (Sigma-Aldrich) was first dissolved in acidicified buffer. Cromakalim (Sigma-Aldrich) was first dissolved in acidicified buffer.
ethanol to make a stock solution. 5-HD (Sigma-Aldrich) and HMR-1098 (Aventis Pharmaceuticals Inc., Bridgewater, NJ) were dissolved in buffer. BMS-191086 (Bristol-Myers Squibb Co., Princeton, NJ), a selective mitoK-ATP channel opener, was dissolved in 0.04% DMSO.

Statistics. Continuous data are expressed as the mean ± the standard error of the mean. Statistical significance was tested using analysis of variance followed by a Tukey’s test for differences. The occurrence of ventricular fibrillation in each group was analyzed using Fisher’s exact test. All statistical tests were two-tailed and a p < 0.05 was considered statistically significant.

Results

Hemodynamic data are summarized in Table 1. Reversible third degree atrioventricular block developed in each heart during the period of hypoxia. Normal atrioventricular conduction returned within 5 min after commencing normoxic perfusion. None of the control or pinacidil-treated hearts developed VF during hypoxic perfusion or before the return of normal AV conduction. Of the five hearts treated with cromakalim, three developed VF during hypoxia and the remaining two shortly after beginning reoxygenation. Of the hearts treated with 5-HD and cromakalim, two of five developed VF during hypoxia as did three of three treated with 1 μM HMR-1098 and cromakalim.

In the absence of a pharmacological intervention, ventricular fibrillation was not observed in the hearts (n = 5) exposed to 12 min of hypoxic perfusion followed by reoxygenation (Fig. 2). In contrast, 12 of 14 (86%) hearts pretreated with pinacidil (1.25 μM) developed ventricular fibrillation within an average time of 19.5 min after the reintroduction of normoxic perfusion (p = 0.004 versus control hearts). Hearts pretreated with 5-HD (100 μM) developed VF in one of eight trials (N.S. versus control hearts). In the group of hearts perfused with 5-HD (100 μM) followed by exposure to pinacidil (1.25 μM), six of eight hearts developed VF (p < 0.05 versus control; N.S. versus pinacidil-treated hearts). The results indicate that inhibition of the mitoK-ATP channel does not result in a proarrhythmic effect. In addition, it is noted that 5-HD, a selective inhibitor of the mitoK-ATP channel, did not prevent the proarrhythmic action of pinacidil in hearts subjected to hypoxia and reoxygenation.

Ventricular fibrillation did not occur in any of the hearts subjected to hypoxic perfusion and reoxygenation in the presence of 6 μM BMS-191095 (n = 5) or when perfused in the presence of 1 μM HMR-1098 (n = 5). However, HMR-1098 (1 μM), a selective inhibitor of the sarcK-ATP channel, prevented the proarrhythmic action of pinacidil as demonstrated by only one of seven hearts developing VF when exposed to a combination of HMR-1098 and pinacidil during hypoxia and reoxygenation (p = 0.007 versus pinacidil-treated hearts; N.S. versus control hearts).

In the second series of isolated heart experiments designed to ensure that the proarrhythmic effects were due to the opening of the K-ATP channel and not due to a different effect of pinacidil, VF developed in five of five hearts treated with cromakalim alone and exposed to hypoxia-reoxygenation (p = 0.004 versus control hearts; N.S. versus pinacidil-treated hearts), all during hypoxia or immediately upon reoxygenation. Hearts pretreated with 5-HD (100 μM) were not protected from cromakalim’s proarrhythmic effects, and all (five of five) developed VF (p = 0.004 versus control hearts). In contrast, 12 of 14 (86%) hearts pretreated with 5-HD (100 μM) followed by exposure to pinacidil developed VF during hypoxia or immediately upon reoxygenation (Fig. 2). In contrast, 12 of 14 (86%) hearts pretreated with 5-HD (100 μM) followed by exposure to pinacidil developed VF during hypoxia or immediately upon reoxygenation (Fig. 2).

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hearts; N.S. versus pinacidil-treated hearts). Pretreatment with 1 μM HMR-1098 did not prevent VF (3 of 3); however, increasing the dose to 3 μM eliminated VF (0 of 3) (p < 0.01 versus pinacidil-treated hearts; N.S. versus control hearts).

Discussion

The nonselective K-ATP channel opener pinacidil exhibits proarrhythmic actions when the rabbit isolated heart is subjected to a brief period of hypoxic perfusion followed by reoxygenation (Chi et al., 1990, 1993; Fischbach et al., 2003). The results of the present study demonstrate that the increased propensity to develop VF is prevented by pretreatment with the specific sarcK-ATP channel blocker HMR-1098. Additional studies were conducted using the selective mitoK-ATP blocker 5-HD in combination with pinacidil, or the selective mitoK-ATP channel opener BMS-191095. The results demonstrate that the mitoK-ATP channel does not participate in the induction of proarrhythmic activity in hearts subjected to hypoxia-reoxygenation in the presence of pinacidil. An additional series of experiments were performed using cromakalim, which like pinacidil, is a nonselective opener of the myocardial K-ATP channel. The results of these studies also demonstrated that VF was prevented by selectively inhibiting the sarcK-ATP channel, demonstrating that this was not an effect unique to pinacidil. The results of this study provide compelling evidence to implicate the sarcK-ATP channel as being responsible for the induction of VF in rabbit isolated hearts treated with pinacidil and subjected to hypoxia and reoxygenation.

The induction of an ischemic or hypoxic insult results in the opening of the myocardial K-ATP channel (Noma, 1983), which is accompanied by a shortening of the membrane action potential and the myocardial refractory period. Whereas these effects may contribute to a cardioprotective effect by decreasing the metabolic demands on the heart and decreasing the intracellular calcium accumulation, they also establish an environment leading to a dispersion of refractoriness and altered conduction velocity, both of which favor the genesis of reentrant arrhythmias. It would stand to reason therefore, that blockade of the K-ATP channel should be antiarrhythmic during ischemia-reperfusion and/or hypoxia-reoxygenation. This has been demonstrated in several different animal models (Wolleben et al., 1989; Kantor et al., 1990; Smallwood et al., 1990; Gwilt et al., 1992) in which glibenclamide, a nonselective K-ATP channel blocker, prevented the electrophysiological and arrhythmogenic consequences of myocardial ischemia. However, glibenclamide is many times more specific for the pancreatic K-ATP channel than it is for the myocardial K-ATP channel, resulting in release of insulin. Due to the disproportionate effect on the pancreatic K-ATP channel, when used clinically, gliben-
clamide's hypoglycemic effects outweigh its potential beneficial effects as an antiarrhythmic agent.

Mammalian cells have two discrete types of K-ATP channels: those associated with the sarcolemmal membrane (sarK-ATP) and others in the mitochondrial inner membrane (mitoK-ATP). Cardiac mitoK-ATP channels are purported to be instrumental in mediating ischemic preconditioning and are viewed as potential drug targets (Oldenburg et al., 2002). The sarK-ATP channels are composed of a pore-forming, inwardly rectifying potassium channel subunit (Kir6.1 or Kir6.2) and a sulfonylurea receptor (SUR1, SUR2A, or SUR2B). The Kir and SUR subunits coassemble with a 4:4 stoichiometry, creating a hetero-octameric K-ATP channel (Inagaki et al., 1995, 1996). On the other hand, the molecular structure of the mitoK-ATP channel remains unresolved. Investigations into the structure and function of K-ATP channels indicate that the different subpopulations (mitochondrial, sarcolemmal, vascular, and pancreatic) are molecularly distinct.

K-ATP channel activators have been developed for a number of therapeutic indications that include, coronary vasodilators as potential antianginal agents, antispasmodics for urinary incontinence, bronchodilators for bronchial asthma, and vasodilators for the control of hypertension. To date, such agents have not achieved clinical acceptance, in part, due to a lack of specificity. Additional interest exists for developing a therapeutic agent to be used for myocardial preservation during cardiac bypass surgery or for use during organ preservation before transplantation. There are few published reports examining the proarrhythmic potential related to pharmacologically opening the sarK-ATP and/or mitoK-ATP channel under conditions of myocardial hypoxia or ischemic stress, which would render the channels more susceptible to the action of agonists (Wolleben et al., 1989; Chi et al., 1990; Billman et al., 1993; Chi et al., 1993).

Hypoxic perfusion of the isolated heart leads to a decrease in cellular ATP content and reduced cardiac function, while coronary flow remains unaltered. Under conditions in which coronary flow is maintained constant, it is unlikely that accumulation of K⁺ would occur in the extracellular space. Under normoxic conditions, the ATP-dependent K⁺ channel is blocked by the high intracellular ATP concentration. Hypoxia-induced depletion of cellular ATP releases the blockade of the channel and allows for K⁺ efflux to occur (Conrad et al., 1983; Chi et al., 1993). In contrast to other K-ATP channel subtypes, the cardiac sarK-ATP channel exhibits high sensitivity to potassium channel openers (Gribble et al., 2000), an effect that is further enhanced by a decrease in tissue ATP content.

Studies in large animal models of myocardial ischemia provide evidence that the opening of K-ATP channels is associated with the development of ventricular fibrillation (Chi et al., 1990; Billman, 1994), which can be prevented by interventions known to inhibit activation of the K⁺ channel (Friedrichs et al., 1998a; Billman et al., 1998; Friedrichs et al., 1998). There is the potential to develop K-ATP channel antagonists to prevent ischemia-induced reductions in refractory period and ventricular fibrillation. Therefore, the cited literature provides evidence to suggest that the activation of sarK-ATP may play an important role in both the reductions in refractory period and initiation of lethal arrhythmia formation associated with myocardial ischemia. The results of this study support this hypothesis. Previous data also indicate that inhibition of the mitoK-ATP channel does not provide protection from ischemia-induced ventricular fibrillation in the postinfarcted conscious canine (Friedrichs et al., 1996a).

Pinacidil has been demonstrated to nonselectively open K-ATP channels. Interestingly, pinacidil's action upon the atrium and ventricle differs. Pinacidil effectively opens K-ATP channels in the atrium in the basal state as demonstrated by a shortening of the atrial action potential; however, in the ventricle pinacidil requires a coincident metabolic stress to open the K-ATP channel. Our laboratory and others previously demonstrated that isolated rabbit hearts exposed to pinacidil and subjected to hypoxia-reoxygenation reliably develop ventricular fibrillation (Chi et al., 1993; Inagaki et al., 1996; Fischbach et al., 2003). In the series of experiments reported in this article, we have demonstrated that the opening of the sarK-ATP channel is responsible for the proarrrhythmic effect.

There are several limitations to this study. One concern is that the animal model is the rabbit isolated heart. The applicability of arrhythmia models in small mammals to humans should be viewed with caution. Additionally, the metabolic stress imposed on the hearts to induce ventricular fibrillation was global hypoxia. Although this successfully generated metabolic stress that is thought to open the K-ATP channels, it is an unusual clinical condition. The hearts exposed to pinacidil also did not fibrillate until well into reoxygenation. This has been a phenomenon that we have observed consistently. It is likely that this is a result of a heterogenous recovery time of the myocardium with some tissue becoming reoxygenated at different rates. This would therefore establish myocardium with heterogenous electrical properties thereby producing a proarrrhythmic substrate. Finally, we were unable to acquire any specific agonist for the sarK-ATP channel P-1075. Although this shortfall limits the study, the combination of pinacidil with 5-HD should approximate the same stimulus as would be obtained with a selective agonist of the sarK-ATP channel.

In summary, our data suggest that nonselective opening of the myocardial K-ATP channel is potentially arrhythmogenic. In particular, opening of the sarK-ATP channel in the face of hypoxia-reoxygenation consistently resulted in the induction of VF. The therapeutic implications are that caution needs to be exercised when developing pharmacological agents for preconditioning the myocardium. Agents should be designed that are selective agonists for the mitoK-ATP channel.

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