Role of K⁺ Channel Activators in Cardiac Electrophysiology and Arrhythmias

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The search for new antiarrhythmic agents has long centered around drugs capable of inhibiting one or more of the ionic currents responsible for transmembrane activity in cardiac tissues and drugs capable of interfering with the influence of the autonomic nervous system on the heart. As a consequence, we are today equipped with an armamentarium of sodium, calcium, and potassium channel blockers as well as a variety of adrenergic receptor blockers. Most have proved to be disappointments in preventing arrhythmic death. Recent studies have suggested a novel approach with the use of agents that activate or augment rather than inhibit ionic currents in the heart. A new class of agents that activate ATP-regulated K⁺ (KATP) channels in smooth and cardiac muscle have been the subject of recent experimental and clinical studies. These potassium channel activators or openers, initially evaluated for their antihypertensive properties, have in more recent studies been considered for their potential use as antiarrhythmic agents.

KATP channels are potassium channels in which activity is normally inhibited by physiological levels of intracellular ATP. They were first identified in cardiac muscle and subsequently in pancreatic β-cells, skeletal and smooth muscle, and neurons. Although extensively studied, their physiological role remains poorly understood.

Potassium channel activators were first introduced as a new class of antihypertensive agents that act by increasing membrane conductance to potassium, principally through augmentation of the ATP-regulated K⁺ channel current (I_KATP). The resulting hyperpolarization of the arterial smooth muscle cell membrane prevents the opening of voltage-dependent Ca²⁺ channels which, in turn, leads to vascular relaxation. In clinical trials to test their efficacy as antihypertensives, K⁺ channel activators were observed to produce electrocardiographic T wave changes (flat, inverted, or biphasic) in some patients, suggesting significant changes in repolarization of ventricular tissues. These findings coupled with those of other studies demonstrating direct effects of the K⁺ channel activators to facilitate repolarization of the cardiac action potential in vitro prompted a series of investigations into the potential antiarrhythmic as well as arrhythmogenic actions of these drugs.

The article by Carlsson et al in this issue of Circulation reports the results of an interesting study in which the effects of the potassium channel activator pinacidil and two of its pyridyloxyguanidine analogues (P1075 and P1188) are evaluated with respect to their effectiveness in suppressing arrhythmias caused by repolarization abnormalities in a rabbit model of the long QT syndrome in vivo and in rabbit ventricular tissues in vitro. All three potassium channel activators were shown to be highly effective in suppressing clofilium-induced polymorphous ventricular tachyarrhythmias in vivo and clofilium-induced early afterdepolarizations (EAD) and triggered activity in vitro. The study provides further evidence in support of the hypothesis that marked action potential prolongation and EAD-induced triggered activity are important factors contributing to the manifestation of polymorphous ventricular tachyarrhythmias such as torsade de pointes and suggests that activation of ATP-regulated (glibenclamide-sensitive) K⁺ channels may provide a novel therapeutic approach in the treatment of this type of arrhythmia often seen in patients with the acquired long QT syndrome and occasionally in patients receiving antiarrhythmic drugs possessing class III actions.

The antiarrhythmic potential of potassium channel activators such as pinacidil, cromakalim (BRL 34915), and nicorandil has been explored in a number of recent studies. In isolated canine ventricular myocytes, pinacidil has been shown to suppress or diminish EADs induced by Bay K 8644, ketanserin, or applied current, as well as delayed afterdepolarizations (DADs) induced by ouabain and abnormal automaticity induced by barium. Similarly, pinacidil and cromakalim have been shown to abolish EADs and triggered activity in canine Purkinje fibers exposed to quinidine, cesium, or sematilide. In canine Purkinje fibers surviving infarction or exposed to barium, cromakalim has been shown to decrease automaticity; in like manner, nicorandil was shown to exert antiarrhythmic effects by decreasing the pacemaker activity of canine Purkinje fibers bathed in Tyrode's solutions containing normal (2.7 mmol/l) and low (1.35 mmol/l) [K⁺]. In vivo data are more limited; in addition to the study by Carlsson and coworkers is a study by Fish and coworkers demonstrating an effect of pinacidil to blunt arrhythmias induced by cesium in a rabbit model and a study by Kerr et al demonstrating an antiarrhythmic effect of pinacidil in the subacute phase of myocardial infarction in a canine model.

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Contrasting results are provided in other studies. Despite its effects to diminish digitalis-induced DADs in isolated ventricular myocytes, pinacidil was shown to be ineffective in suppressing ouabain-induced arrhythmias in a canine model. Pinacidil was also without effect in altering the responsiveness of postischemized canine hearts with respect to electrical induction of tachyarrhythmias.

Like most drugs exhibiting antiarrhythmic activity, potassium channel activators have also been found to produce proarrhythmic or arrhythmogenic effects under some conditions. High concentrations of pinacidil were found to accelerate automaticity and induce spontaneous action potentials in barium-treated Purkinje fibers. More physiologically significant are the results of Chi and coworkers showing a proarrhythmic effect of pinacidil in the conscious dog exposed to acute ischemia superimposed on a previous infarction. This study suggested that pinacidil may promote reentrant activity by contributing to the development of a dispersion of refractoriness in the ventricle. Recent studies from our laboratory provide support for this hypothesis.

Pinacidil at low concentrations (1–5 μmol/l) was found to produce a slight abbreviation of the action potential in canine ventricular endocardium but either a marked abbreviation or a slight prolongation in epicardium. The data suggested that activation of ATP-regulated K+ current could account for the effects of pinacidil in both tissue types and that the presence of a prominent transient outward current (I_o) mediated spike and dome morphology of the action potential in epicardium but not endocardium was largely responsible for the differential responsiveness of the two tissue types to pinacidil. Thus, pinacidil was found to produce marked differences in repolarization times and refractoriness between epicardium and endocardium as well as between adjacent epicardial sites. This heterogeneity greatly facilitates the manifestation of reentrant arrhythmias in isolated sheets of epicardium. The mechanism responsible for reentrant activity under these conditions has been termed “phase 2 reentry” and is similar to that referred to by Brugada and Wells as “prolonged repolarization-dependent reexcitation.”

The results of these studies suggested that a relatively small increase in the intensity of the ATP-regulated K+ current, as may occur during ischemia or following exposure to low concentrations of potassium channel activators, can contribute importantly to the development of electrical inhomogeneity in the ventricles and thus to the genesis of cardiac arrhythmias.

It is noteworthy that the addition of either I_o blockers such as 4-aminopyridine or I_A TP blockers such as glibenclamide promptly restore electrical homogeneity and completely abolish pinacidil-induced reentrant activity in isolated canine ventricular epicardium. These findings suggest that selective blockade of the transient outward current (I_o) and/or the ATP-regulated K+ current (I_A TP) may be useful antiarrhythmic interventions under ischemic or ATP-depleted conditions or in the treatment of arrhythmias induced by potassium channel activators.

These observations serve to highlight the fact that different arrhythmogenic mechanisms may respond differently to various antiarrhythmic interventions. Despite recent advances, pharmacological control of cardiac arrhythmias in general remains an experiment conducted on a patient-by-patient basis, using a trial-and-error approach tempered by good clinical judgment. Treatment, especially of life-threatening ventricular arrhythmias, is often largely empiric because of our lack of understanding of the mechanisms responsible for cardiac rhythm disturbances as well as our incomplete understanding of the specific mechanisms by which antiarrhythmic agents act. Also confounding is the lack of criteria that can be applied to the differential diagnosis of particular arrhythmia mechanisms in the clinic.

Arrhythmias induced by repolarization abnormalities are therefore more easily identified because of their bradycardia dependence, unique electrocardiographic manifestations (long QTU intervals, prominent U waves, torsade de pointes), and their frequent association with hypokalemia and agents known to exert class III actions. The report by Carlsson and coworkers, taken together with the results of other recent studies, clearly suggests that potassium channel activators can exert important therapeutic effects in combating arrhythmias caused by repolarization abnormalities, that they may be without effect or indeed may be proarrhythmic when other pathophysiological substrates contribute to the underlying rhythm disturbance. As discussed by Carlsson and coworkers, the precise anatomic site at which the potassium channel activators exert their antiarrhythmic effect is not known. Indeed, in their study, as in several others, there is a discrepancy between observations made in vivo and those made in vitro. Deflections in the repolarization phase, consistent with early afterdepolarizations, were observed with monophasic action potential (MAP) recordings from the left ventricle of the clofilium-treated rabbit hearts but not in isolated ventricular tissues exposed to clofilium in a tissue bath. Moreover, the ventricular muscle (endocardium) studied in vitro showed little if any action potential prolongation after clofilium, whereas the MAP duration and QTU intervals measured in vivo prolonged dramatically in response to clofilium. Although Purkinje fibers from the same hearts showed a prolongation of the action potential as well as early afterdepolarization and triggered activity, it appears to be clear that these clofilium-induced changes in the Purkinje system cannot explain the electrocardiographic and MAP manifestations. It therefore seems unlikely that the action of potassium channel activators to suppress drug-induced early afterdepolarizations and triggered activity in the Purkinje system is the sole basis for their antiarrhythmic efficacy in models of the long QT syndrome.

Recent data from our laboratory may shed some light on this problem. We recently described the existence of a unique subpopulation of cells in the deep subepicardium of the canine ventricle. These cells, termed M cells, exhibit electrophysiological characteristics intermediate between those of muscle and conducting (Purkinje) tissues. M cells display a “spike and dome” morphology typical of epicardium but a maximal rate of rise of the action potential upstroke (Vmax) considerably greater than that of either endocardium or epicardium. Moreover, the rate dependence of action potential duration of cells in the M region is much more accentuated than that of epicardium or endocardium but...
more akin to that of Purkinje fibers. Phase 4 depolarization, however, is never observed in M cells, not even in the presence of catecholamines and low [K']o. In addition to these electrophysiological distinctions, M cells display pharmacological distinctions. Prominent among these is the ability of M cells to show marked action potential duration prolongation and to develop early afterdepolarizations and triggered activity in response to clofilium, cesium, quinidine, 4-aminopyridine, and a variety of other agents. The induction of prominent afterdepolarizations and triggered activity was limited to cells in the M region (deep subepicardium to midmyocardium) and never observed in adjacent epicardial or endocardial tissues excised from the free wall of the same ventricles. These data suggest that the development of marked action potential duration prolongation and/or EADs in M cells in response to agents like clofilium and quinidine may account for the manifestation of long QT intervals and/or U waves in the ECG. The capability of these deep subepicardial cells to generate triggered activity suggests that they may be the source of premature ventricular beats that trigger torsade de pointes in the long QT syndrome and thus may be another important site, if not the principal site, at which the potassium channel activators exert their antiarrhythmic effects. In support of the latter hypothesis, in preliminary experiments, we have been able to readily suppress clofilium-induced triggered activity in M cells with low concentrations of pinacidil (2–5 μmol/l).

Conclusions

The available data suggest that potassium channel activators may be valuable in combating arrhythmias caused by repolarization abnormalities but may be proarrhythmic in the face of other arrhythmias. Thus, cardioselective K+ channel activators, when available, are likely to play a significant although limited role in the pharmacological approach to therapy of cardiac arrhythmias in future years.

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References


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