Cardiovascular controversies

Blockers of ATP sensitive potassium current are of potential benefit in ischaemic heart disease

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Ischaemic heart disease is the consequence of an imbalance between cardiac oxygen supply and demand. Ideally, therapy will restore this mismatch in order to minimise loss of functional myocardium and reduce the risk of lethal ventricular arrhythmias. To have a positive influence on morbidity and mortality of this disease, myocardial protection and antiarrhythmic efficacy must both be goals of a therapeutic intervention.

The ATP sensitive potassium current (I_{KATP}) participates in the response of the myocardium to hypoxia. At the cellular level, this current is activated when ATP concentrations fall. A small increase in open probability of I_{KATP} results in a strong, outward movement of potassium ions (K+) and, as a result, cardiac action potential duration (APD) is shortened. Contractility is reduced when I_{KATP} is activated in myocytes because calcium ion influx via L_{C} is limited by the abbreviated APD. A reduction in mechanical function in ischaemic cells helps to protect myocytes since it reduces myocardial oxygen demand. Unfortunately, these same changes which protect against myocardial damage increase the risk of arrhythmic events. Shortened APD combined with a delay in electrical uncoupling and an increased dispersion of refractoriness between ischaemic and normal cells could predispose the heart to re-entrant arrhythmias. Secondly, the combined cellular potassium loss and extracellular potassium accumulation which occurs with I_{KATP} activation exacerbates the electrophysiological changes that underlie the early malignant phase of ventricular tachycardia following myocardial ischaemia. For the treatment of ischaemic heart disease via pharmacological modulation of I_{KATP}, the effects on both mechanical function and arrhythmogenic status need to be considered.

Potent, selective I_{KATP} activators (for example, cromakalim, pinacidil) and blockers (glibenclamide) have been used to explore the consequences of modulating this current in myocellular ischaemia and hypoxia. The majority of studies indicate that I_{KATP} activators are cardioprotective and proarrhythmic. Conversely, I_{KATP} blockers exacerbate mechanical recovery following ischaemia and are antiarrhythmic. This represents a dilemma for the treatment of ischaemic heart disease. For example, protection of mechanical function with an I_{KATP} activator could be at the expense of an increased risk of malignant ventricular arrhythmias and antiarrhythmic efficacy of an I_{KATP} blocker could be associated with a greater loss of mechanical function. Also, since I_{KATP} is already activated in ischaemia, the following should be considered: if the physiological level of I_{KATP} activation is beneficial, does further pharmacological activation provide additional benefit without additional risk? And, in severe ischaemia, can the risk (arrhythmia) to benefit (myocardial protection) ratio be improved by inhibiting I_{KATP}? These questions are difficult to address in small preclinical or clinical studies and will probably require large clinical trials to provide conclusions appropriate for clinical practice.

The effects of I_{KATP} modulators on cardiac arrhythmias are well documented. The antiarrhythmic activity of I_{KATP} blockers in settings of ischaemia or hypoxia have been consistently demonstrated in animal models and while the clinical use of currently available antiarrhythmic drugs has not been very successful. The use of selective I_{KATP} blockers to prevent arrhythmias in ischaemia has the advantage of targeting therapy at the mechanistic cause of arrhythmia rather than non-specific depression of conduction and/or excitability (eg. class I antiarrhythmic agents). Results from a clinical trial with diabetic patients found that glibenclamide significantly reduced the frequency of ventricular premature complexes and episodes of non-sustained ventricular tachycardia during transient myocardial ischaemia. Consistent with the selectivity of glibenclamide for I_{KATP} and activation of I_{KATP} during ischaemia, therapy with this agent did not reduce spontaneous ventricular arrhythmias in these patients.

Proarrhythmic activity of I_{KATP} activators is observed in many but not all studies. This is further complicated by the fact the I_{KATP} activators are antiarrhythmic in some non-ischaemia models (eg. repolarisation abnormalities). Therefore it may be difficult to predict the proarrhythmic risk of these agents in patients. There are parallels with the preclinical/clinical development of inotropic agents. Proarrhythmic events were observed in some but not all animal models. When two of these compounds (milrinone and xamoterol) were studied in large patient populations, mortality was significantly increased. The benefit of inotropic agents on haemodynamic and physical capacity of patients is impressive; however, the detrimental effect on mortality has stilled their development. Like inotropic agents, the proarrhythmic risk of I_{KATP} activators could be a major issue for their clinical development. This is highlighted by the findings in a canine model of sudden cardiac death where both an inotropic agent (milrinone) and an I_{KATP} activator (pinacidil) are profibrillatory. Although I_{KATP} activators have been studied extensively in hypertensive patients, there are no mortality studies reported and the dose requirement for cardioprotection will probably be larger than for hypertension.

For I_{KATP} modulators, an ideal therapy would combine the antiarrhythmic activity of I_{KATP} blockers with the cardio-protective efficacy of I_{KATP} activators. Since it is not possible to activate and antagonise I_{KATP} simultaneously, alternatives must be considered. Angiotensin converting enzyme inhibitors and β adrenergic blockers have a beneficial effect on mortality in post-myocardial infarction patients. The exact mechanism for the cardioprotection of these agents is unknown but is probably similar to I_{KATP} activators, ie, reduction in I_{C}, and myocardial oxygen demand. A combination of an I_{KATP} blocker with one of these agents could be cardioprotective with a significantly improved safety profile compared to an I_{KATP} activator alone. Since I_{KATP} blockers are very specific for hypoxia/ischaemia induced arrhythmias, this combination would be more practical than attempting to counteract the proarrhythmic activity of an I_{KATP} activator with traditional antiarrhythmic agents. Significant preclinical and clinical work will be required to define whether these combinations are, indeed, rational approaches for ischaemic heart disease.

In summary, the physiology and pharmacology of I_{KATP} is a very exciting area of research and the clinical development and
application of I_{\text{KATP}}, modulators for the treatment of ischaemic heart disease will be challenging.

**References:**
10. Cole WC, McPherson CD, Sontag D. ATP-dependent potassium channel openers accelerate the shortening of action potentials produced by ischaemia5 and thus reduce Ca" cycling during electrical systole. They can also speed up the loss of contractility of the cardiac myocyte throughout ischaemic episodes. Furthermore, in the cardiac myocyte exposed to K' channel openers (eg, aprikalim), ATP sensitive K' channels become activated at higher ATP levels than they characteristic of stunned but viable myocardium. In models of irreversible myocardial injury caused by prolonged ischaemia/reperfusion, the necrotic region that develops is 30-50% smaller in animals treated with K' channel openers. Aprikalim (RP 52891) can produce this effect without altering general or coronary haemodynamic indices before or during ischaemia. Contrast, glybenclamide, a sulphonylurea, blocks ATP-sensitive K' channels and increases ischaemic myocardial tissue damage; it also abolishes the beneficial effects of K' channel modulators under both in vitro and in vivo conditions.

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**ATP sensitive potassium channel openers are of potential benefit in ischaemic heart disease**

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**Cardiac ATP sensitive K' channels apparently do not operate under normal metabolic conditions; rather, they are activated when the oxygen supply and, consequently, intracellular high energy phosphates fall below critical levels.** Thus the opening of ATP sensitive K' channels may be seen as an "emergency system response to prevent energy failure" and is an aspect of the effort to preserve the biological integrity and viability of the cardiac myocyte throughout ischaemic episodes.

K' channel openers (aprikalim, binakalim, leveromakalim, nicorandil, and pinacidil) constitute a novel class of drugs, acting upon the heart and blood vessels to open ATP gated K' channels. What appears to be original about these compounds is their ability on the one hand to attenuate those aspects of experimental ischaemia that are intrinsically harmful for the heart, and on the other hand to accelerate or intensify those responses that benefit the heart suffering oxygen deprivation.

In isolated heart preparations, K' channel openers not only postpone the onset of contracture and attenuate the decline in ATP during no flow ischaemia, but also enhance the recovery of myocardial function and reduce the loss of intracellular enzymes during the period of reflow. In intact animals subjected to a brief period of coronary artery occlusion, pretreatment with several K' channel openers has been shown to accelerate the recuperation of contractile function and improve the biochemical status of the ischaemic region. Thus these agents can correct the flow-function mismatch characteristic of stunned but viable myocardium. In models of irreversible myocardial injury caused by prolonged ischaemia/reperfusion, the necrotic region that develops is 30-50% smaller in animals treated with K' channel openers. Aprikalim (RP 52891) can produce this effect without altering general or coronary haemodynamic indices before or during ischaemia. Contrast, glybenclamide, a sulphonylurea, blocks ATP-sensitive K' channels and increases ischaemic myocardial tissue damage; it also abolishes the beneficial effects of K' channel modulators under both in vitro and in vivo conditions. Thus opening ATP sensitive K' channels affords protection to the ischaemic heart whereas blocking them can be harmful.

K' channel openers appear to facilitate the opening of ATP sensitive K' channels or hasten their recruitment once it has been initiated by endogenous processes. Hence K' channel openers accelerate the shortening of action potentials produced by ischaemia and thus reduce Ca" cycling during electrical systole. They can also speed up the loss of contractility of the ischaemic region and therefore drive the myocardial cell faster into a resting state. Furthermore, in the cardiac myocyte exposed to K' channel openers (eg, aprikalim), ATP sensitive K' channels become activated at higher ATP levels than they would under control conditions. Nonetheless, whether these observed functional and biochemical effects actually constitute the fundamental mechanisms by which this class of agents confers cytoprotection, or are merely epiphenomena occurring.