

REVIEW

K⁺ channel opening: a new drug principle in cardiovascular medicine

Jens Erik Nielsen-Kudsk, Søren Boesgaard, Jan Aldershvile

Many drugs used in cardiology act by changing the gating properties of ion channels. This is true for Ca²⁺ antagonists which are blockers of voltage-operated L-type Ca²⁺ channels and for most antiarrhythmics. Class I agents are blockers of Na⁺ channels whereas class III antiarrhythmics prolong the cardiac action potential by blockade of K⁺ channels.¹ In the past decade much has been learnt about the physiology and pharmacology of ion channels. Pharmacological agents that selectively open K⁺ channels have been developed and this novel group of drugs is rapidly expanding.^{2,3} K⁺ channel openers are peripheral and coronary vasodilators^{4,5} but they additionally act on the myocardium and seem to protect it from damage during ischaemia and reperfusion.^{6,7}

The purpose of this paper is to review some of the pharmacology of cardiovascular K⁺ channels and to elucidate the potential clinical value of K⁺ channel opening as a new concept in cardiovascular medicine.

Basic aspects of K⁺ channels

K⁺ CHANNELS AND MEMBRANE POTENTIAL

K⁺ channels play a key role in the regulation of membrane potential and cell excitability and the function of these channels contributes to the electrical and mechanical properties of the heart and vasculature. The concentration of K⁺ inside cells (150 mM) is much higher than outside (3–5 mM) due to the action of the Na⁺/K⁺ pump. Opening of K⁺ channels makes K⁺ ions flow out of the cell along the outward directed electrochemical gradient for K⁺. This changes the membrane potential in a hyperpolarising direction. It becomes more negative and is moved towards the K⁺ equilibrium potential. In contrast, blockade of K⁺ channels shifts the membrane potential in a depolarising direction. In the heart, repolarisation of the cardiac action potential is largely caused by opening of K⁺ channels.¹ Membrane depolarisation and hyperpolarisation through blockade and opening of K⁺ channels are also important mechanisms regulating vascular smooth muscle contraction and relaxation.⁸

DIVERSITY OF K⁺ CHANNELS

K⁺ channels are the most heterogeneous of all ion channels. So far at least 16 major types of K⁺ channels have been characterised and sev-

eral subtypes exist within each major type of K⁺ channel. Each type of K⁺ channel serves a distinct function and the expression of K⁺ channels differs among tissues and organs. This high degree of diversity opens the fascinating possibility that pharmacologically selective openers or blockers of a specific K⁺ channel subtype may be developed to modulate specialised tissue functions. Identification of the different types of K⁺ channels have been made possible largely because of the development of the electrophysiological patch-clamp method which allows ion channels to be investigated at a single channel level. By this method it is possible to determine factors which open and close a channel (the gating properties) as well as the single channel conductance which is a measure of how easily ions flow through a channel (measured in pico Siemens). These variables are used to characterise and classify specific types of K⁺ channels. K⁺ channels can be divided into three major classes on basis of their gating properties: those that are gated by ligands such as ATP, Ca²⁺, neurotransmitters or G-proteins (*ligand gated*), those gated by changes in membrane potential (*voltage gated*) and those gated both by ligands and voltage. The voltage-gated K⁺ channels can be subdivided into *outward* or *delayed rectifiers* which are activated by cell membrane depolarisation and *inward rectifiers* which are closed by depolarisation.

Several K⁺ channels have now been cloned thus allowing the molecular and structural basis of the diversity of K⁺ channels to be determined.⁹ On the basis of molecular structure two major super-families of K⁺ channels can be discriminated. The S4 superfamily (fig 1), to which voltage-gated delayed rectifier K⁺ channels belong, is built up of large protein subunits of six membrane-spanning α -helical segments (S1–S6) and a seventh hairpin-shaped segment interposed between S5 and S6. The seventh segment forms a major part of the K⁺ channel pore itself (P-region) while S4 is believed to be the voltage sensor. K⁺ channels are tetramers formed by four subunits. Several different genes code for different K⁺ channel subunits and these assemble as heteromultimers, resulting in an enormous diversity. The inward rectifier K⁺ channel superfamily (fig 1) is characterised by subunits composed of only two membrane spanning segments (M1 and

Division of Cardiology,
Medical Department
B, Rigshospitalet,
University of
Copenhagen, Denmark
J E Nielsen-Kudsk
S Boesgaard
J Aldershvile

Correspondence to:
Dr J E Nielsen-Kudsk,
Department of Medicine
B2142, Rigshospitalet,
University of Copenhagen,
Blegdamsvej 9, DK-2100
Copenhagen, Denmark.

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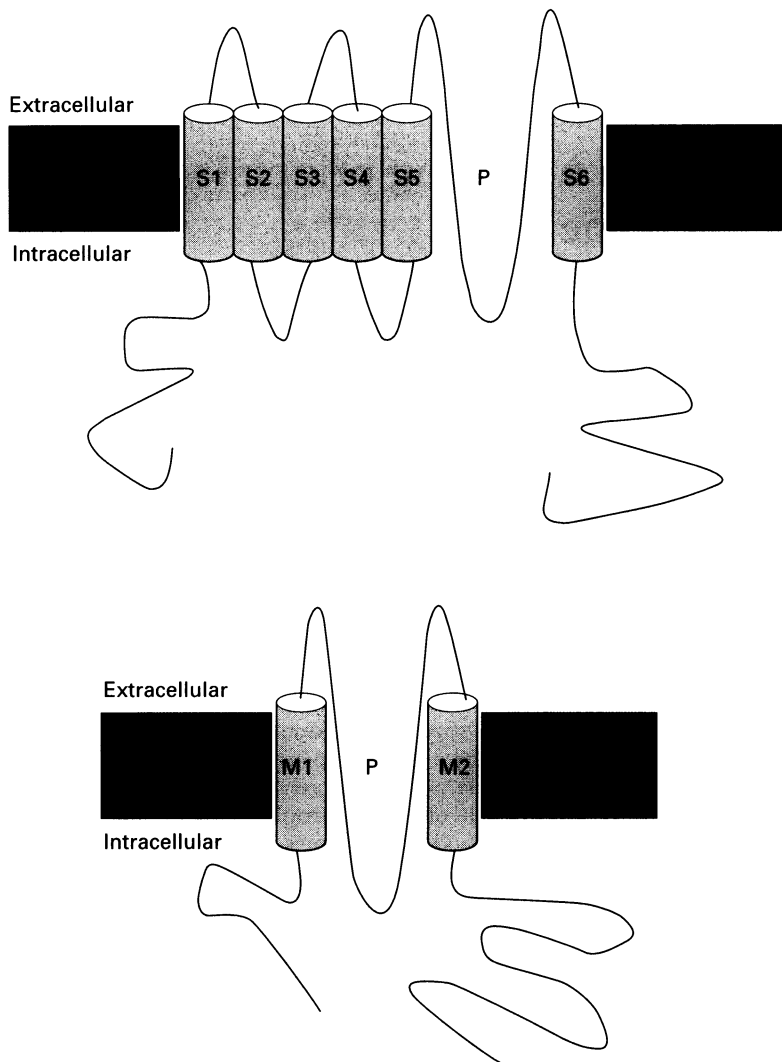


Figure 1 The presumed structure of K⁺ channel subunits belonging to the S4 superfamily (upper) and the inward rectifier superfamily (lower) of K⁺ channels.

M2). The pore region is shaped like a hairpin and is almost identical to that of the S4 superfamily.

CARDIOVASCULAR K⁺ CHANNELS

The most important cardiovascular K⁺ channels are listed in table 1. The outward rectifier or delayed rectifier (K_v) channel is activated by membrane depolarisation and gives rise to an outward directed K⁺ current which is responsible for repolarisation of the cardiac action potential. It can be blocked by class III antiarrhythmic agents. The inward rectifier

(K_{ir}) keeps the resting membrane potential stable during cardiac diastole. It is open at the resting membrane potential but closes during depolarisation. This type of channel is sparse in conduction tissue that undergoes spontaneous depolarisation in diastole. The acetylcholine activated K⁺ channel (K_{ACh}) is activated by the binding of acetylcholine released from vagal nerve endings to muscarinic receptors in atrial and atrioventricular (AV) nodal tissue. This channel mediates bradycardia and the decrease in AV-nodal conduction produced by vagal stimulation. The large conductance Ca²⁺-activated K⁺ channel (BK_{Ca}) acts as a negative feedback mechanism in vascular smooth muscle. It is activated when intracellular Ca²⁺ is increased by the action of vasoconstrictors and it limits depolarisation and excessive Ca²⁺ stimulation. The ATP-sensitive K⁺ channel (K_{ATP}) is inhibited by high intracellular ATP concentrations. It is the target K⁺ channel subtype for synthetic K⁺ channel openers and is considered below.

The ATP-sensitive K⁺ channel

The K_{ATP} channel was first identified in cardiac myocytes.¹⁰ It is believed to have a structure similar to the inward rectifying superfamily of K⁺ channels. This type of channel is inhibited by a high intracellular concentration of ATP and is closed under conditions of normal myocardial metabolism. The channel opens under conditions of myocardial ischaemia. Channel opening is stimulated by a fall in ATP concentration and by acidosis, lactate, adenosine, and nucleotide diphosphates such as ADP and GDP. These factors may act in concert to activate the channel during myocardial ischaemia.¹¹ The consequence of K_{ATP} opening is increased K⁺ efflux, accelerated repolarisation, and thereby a shortening of the cardiac action potential. Shortening of the plateau phase reduces the time available for Ca²⁺ influx which causes a decline in contractile function in the ischaemic zone. These effects reduce the energy consumption, spare high energy phosphates, and limit Ca²⁺ overload and hence tend to prolong survival of the ischaemic tissue. In this way K_{ATP} seems to represent an endogenous protective mechanism against myocardial metabolic stress.^{10 12}

K_{ATP} channels have also been identified in

Table 1 Major types of cardiovascular K⁺ channels

Type	Class	Conductance (pS)	Factors which induce opening	Blockers	Structure	Function
K _{ATP} (ATP sensitive)	Ligand gated	10–30	Decreased [ATP] _i , increased [NDP] _i , K ⁺ channel openers—eg cromakalim, pinacidil, nicorandil, minoxidil sulphate	High [ATP] _i , glibenclamide, 5-hydroxydecanoate	IR	Hyperpolarisation during metabolic stress and hypoxia/ischaemia
K _{ACh} (ACh activated)	Ligand gated	10–25	G-proteins through muscarinic receptor stimulation		IR	Bradycardia by vagus stimulation
K _v (delayed rectifier)	Voltage gated	5–15	Depolarisation, specific openers not yet available	4-Aminopyridine	S4	Repolarisation of cardiac action potential
K _{ir} (inward rectifier)	Voltage gated	10–15	Hyperpolarisation	Depolarisation	IR	Maintenance of resting potential
BK _{Ca} (Ca ²⁺ activated)	Ligand and voltage gated	100–150	Increased [Ca ²⁺] _i , depolarisation, specific openers not yet available	Charybotoxin, iberotoxin, TEA (1 mM)	S4	Reduction of excitability when [Ca ²⁺] _i rises

NDP, nucleotide diphosphates such as adenosine diphosphate (ADP), guanidine diphosphate (GDP), and uridine diphosphate (UDP); ACh, acetylcholine; IR and S4, inward rectifier and S4 superfamilies of K⁺ channels.

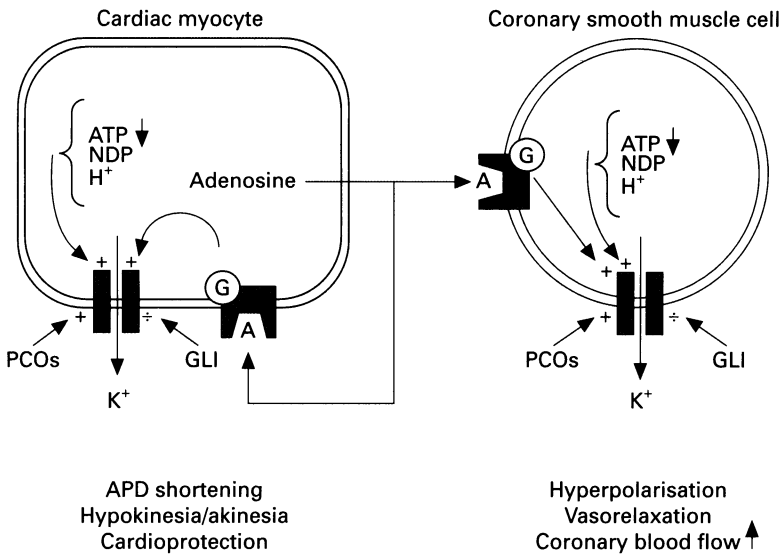


Figure 2 *K_{ATP} channels open during ischaemia. They are stimulated by acidosis, a fall in intracellular ATP, a rise in nucleotide diphosphates (NDP) such as ADP and GDP, and by accumulation of extracellular adenosine. Adenosine activates K_{ATP} by a G-protein dependent mechanism after stimulation of adenosine receptors (A) on the cell surface. Potassium channel openers (PCOs) are pharmacological activators of K_{ATP} whereas the antidiabetic sulfonylurea glibenclamide (GLI) is a specific blocker. Some of the consequences of K_{ATP} activation in the ischaemic myocardium and coronary vasculature are listed. APD, action potential duration. (Adapted with permission from Escande D, Caverio I. Potassium channel openers in the heart. In: Escande D, Standen N, eds. *K⁺ Channels in cardiovascular medicine*. Paris: Springer-Verlag, 1993;225–44°.)*

vascular smooth muscle.¹³ Like the cardiac K_{ATP} this channel is inhibited by ATP and stimulated by nucleotide diphosphates. It opens under conditions of hypoxia and K_{ATP} opening may be one of the principal mechanisms which underlie hypoxic coronary vasodilation.¹⁴ Figure 2 shows some of the important factors which gate the K_{ATP} in myocardial and coronary vascular smooth muscle cells.⁶

ENDOGENOUS MODULATION OF K_{ATP}
Adenosine opens K_{ATP} both in cardiomyocytes¹⁵ and coronary vascular smooth muscle cells¹⁶ probably through a G-protein dependent mechanism triggered by adenosine receptor stimulation. Other endogenous vasodilators such as calcitonin gene regulated peptide (CGRP), vasoactive intestinal peptide (VIP), endothelium derived hyperpolarising factor (EDHF), and prostacyclin act in part through K_{ATP} opening.¹³ Most recently it has been reported that nitric oxide (endothelium derived relaxing factor, EDRF) apart from its stimulating effect on guanylate cyclase directly activates K^+ channels of the BK_{Ca} type.¹⁷ In cultured coronary artery smooth muscle cells the vasoconstrictors angiotensin II and endothelin inhibit K_{ATP} ,¹³ but the functional significance of these findings is not yet clear.

PHARMACOLOGICAL MODULATION OF K_{ATP}
The best known of the new K_{ATP} channel opening drugs are cromakalim, levromakalim (the active enantiomer of cromakalim), pinacidil, nicorandil, and aprikalim. The chemical structures of these compounds are quite different and they have been subdivided into different groups (table 2). The first agent recognised as a K^+ channel opener was nico-

randil,¹⁸ which is now in clinical use as an antianginal drug. However, this drug also contains a nitrate moiety and has a nitrovasodilator action in addition to its ability to open K^+ channels. Cromakalim, which was developed as an arterial vasodilator, was the first specific synthetic K^+ channel opener.^{2,4} The mechanism of action of this drug was reported in 1986. Later, some of the classic vasodilator drugs such as minoxidil sulphate (the active metabolite of minoxidil) and diazoxide were found to act by K^+ channel opening.^{2,4} At present, all available synthetic K^+ channel openers seem to be openers of K_{ATP} . There have been attempts to develop openers of the BK_{Ca} channel (SCA40 and NS1619) but these agents are not selective. However, it is likely that selective pharmacological modulators for specific K^+ channel subtypes will be developed in the future.

The oral antidiabetic sulfonylurea drugs are selective blockers of K_{ATP} ,^{2,4} and glibenclamide is now used as an important pharmacological tool to detect actions produced by drugs or endogenous substances which involve K_{ATP} opening. K_{ATP} channels are also present in pancreatic islets where they are essential to the physiological regulation of insulin secretion.¹⁹ In this tissue the K_{ATP} channels are open under conditions of normal blood glucose but close when the intracellular concentration of ATP is raised by increased concentrations of glucose. Closure of K_{ATP} leads to islet cell depolarisation and insulin secretion. Glibenclamide and other sulfonylureas specifically block K_{ATP} and in this way promote insulin secretion. Concentrations of glibenclamide in the nM range are sufficient to block pancreatic K_{ATP} channels whereas μ M concentrations are required to block cardiovascular K_{ATP} channels. With the exception of diazoxide, very high concentrations of the K^+ channel openers are required to open pancreatic K_{ATP} and inhibit insulin secretion. Diazoxide does not discriminate between cardiovascular and pancreatic K_{ATP} channels and because of its hyperglycaemic action it is no longer in clinical use. Minoxidil sulphate which is another opener of cardiovascular K_{ATP} channels, actually blocks pancreatic K_{ATP} . Thus K_{ATP} is not a single distinct type of channel but rather a family of several K_{ATP} subtypes with important tissue-dependent differences in sensitivity to pharmacological modulators.

Effects of K^+ channel openers on the circulation

SYSTEMIC CIRCULATION
 K^+ channel openers have been shown to relax isolated systemic arteries contracted by a wide range of vasoconstrictors.⁵ These drugs are 10–100 times more potent on vascular smooth muscle than on the non-ischaemic myocardium.⁶ A unique characteristic of these drugs is their ability to relax contractions induced by moderately raised extracellular K^+ concentrations (20–30 mM) but not those induced by high concentrations of K^+ in the 40–120 mM range.^{4,5} As the extracellular K^+ concentration is raised the electrochemical

Table 2 Selected K_{ATP} openers

Benzopyrans:	
Cromakalim	
Levcromakalim (active enantiomer of cromakalim)	
Bimakalim	
HOE234	
Cyanoguanidines:	
Pinacidil	
P1705	
BMS-180448	
Thiiformamides:	
Aprikalim	
RP49356 (active enantiomer of aprikalim)	
Pyrimidines:	
Minoxidil sulphate	
Benzothiadiazines:	
Diazoxide	
Nitrate containing:	
Nicorandil	
KRN2391	

gradient for K^+ is reduced and as a consequence the K^+ efflux produced by K^+ channel opening becomes gradually diminished. The cellular events²⁰ which lead to vasorelaxation are shown in fig 3. The vasodilatation produced both in vitro and in vivo by these drugs can be blocked by glibenclamide.^{4,5}

The haemodynamic profile of K^+ channel openers in various animal species and man is characteristic of potent arterial vasodilators.⁵ They cause reflex stimulation of the sympathetic nervous system and of the renin-angiotensin system. Even at doses which greatly reduce blood pressure these drugs do not have a significant cardiodepressant action.

PULMONARY CIRCULATION

Vasoconstriction in response to hypoxia is a unique property of pulmonary arteries. It contrasts the hypoxic vasodilatation seen in coronary and systemic arteries. Pulmonary arteries depolarise during hypoxia and may even discharge action potentials.²¹ Evidence is accumulating that K^+ channel blockade is a key event which links hypoxia to pulmonary vasoconstriction.^{22,23} Exactly which type of K^+ channel is involved is not clear. K^+ channel openers relax isolated pulmonary arteries and some of these drugs have more potent relaxant effects in pulmonary arteries than in systemic arteries.²⁴ In addition they inhibit hypoxic pulmonary vasoconstriction in animals.²³ In a study of acute haemodynamics in patients with angina pectoris, cromakalim reduced pulmonary vascular resistance to the same extent as systemic vascular resistance.²⁵ Thus K^+

channel openers have a direct pulmonary vasodilator action in addition to their effect on the systemic circulation.

Effects of K^+ channel openers on the heart CORONARY CIRCULATION

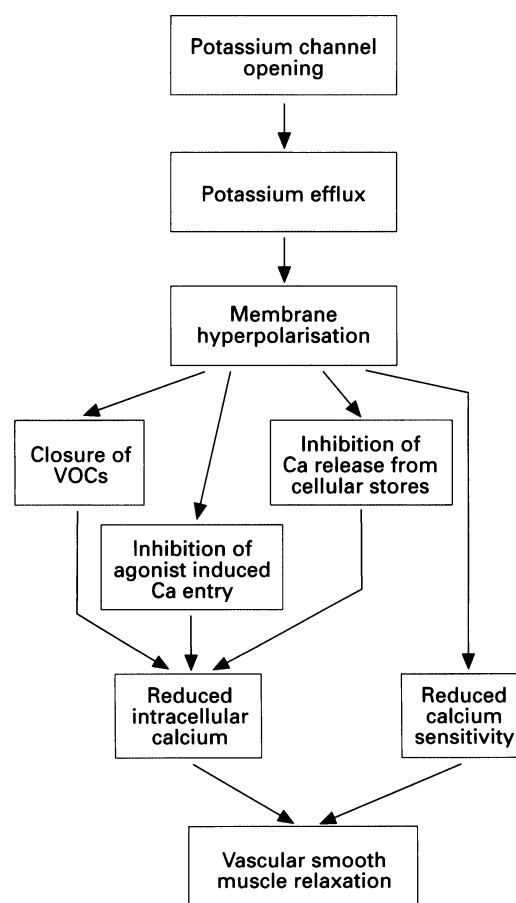
K_{ATP} channels seem to be important in regulating the coronary circulation. In isolated perfused guinea pig hearts the coronary vasodilatation induced by hypoxia and ischaemia was prevented by glibenclamide and mimicked by cromakalim, indicating that opening of K_{ATP} may be important in hypoxic and ischaemic coronary vasodilatation.¹⁴ The activation of K_{ATP} may result from a direct effect of hypoxia or ischaemia on coronary vascular smooth muscle cells,²⁶ but also from adenosine released from the surrounding myocardium. In the dog coronary circulation glibenclamide reduced both the reactive hyperaemic response after a brief coronary occlusion²⁷ and the autoregulatory vasodilatation in response to low perfusion pressure.²⁸ In addition glibenclamide causes vasoconstriction during basal coronary flow²⁹ suggesting that K_{ATP} may have several important regulatory actions in the coronary circulation.

Pharmacological openers of K_{ATP} are potent coronary vasodilators in vitro and in vivo. Regional haemodynamic studies have shown that these drugs preferentially produce coronary vasodilatation.⁵ The K^+ channel opener aprikalim even produces coronary vasodilatation in doses that have no effect on blood pressure.⁵ In vitro these drugs produce coronary vasorelaxation when the endothelium is present or when it is removed. Cromakalim, pinacidil, and nicorandil dilate large epicardial coronary arteries as well as small coronary resistance arteries in vivo. However, damage of the endothelium by balloon angioplasty in dogs greatly reduced the dilatation of large coronary arteries by cromakalim and pinacidil whereas that produced by nicorandil was unaffected.³⁰ Cromakalim and pinacidil therefore seem to dilate large coronary arteries in vivo partly by an endothelium-dependent mechanism possibly induced by an increase in proximal flow caused by dilatation of the small coronary resistance vessels. The endothelium-independent coronary vasodilatation of large coronary arteries produced by nicorandil is probably mediated by the additional nitrate action of the drug.

MYOCARDIUM

K^+ channel openers only influence the function of the non-ischaemic myocardium at concentrations that are much higher than those required for vascular smooth muscle relaxation. At such high concentrations these drugs shorten cardiac action potential duration and depress cardiac contractility.⁶ However, at much lower concentrations these drugs exert cardioprotective actions, with some K_{ATP} openers acting at concentrations which produce only minimal haemodynamic effects.³¹ In globally ischaemic rat hearts, cromakalim and pinacidil improved the post-ischaemic recovery of contractile function and cro-

Figure 3 Cellular mechanisms involved in vascular smooth muscle relaxation induced by potassium channel opening. VOC, voltage-operated Ca^{2+} channel.



makalim additionally reduced lactate dehydrogenase release.³² At cardioprotective concentrations, the K⁺ channel openers did not influence the contractile function of non-ischaemic hearts. Several other K_{ATP} openers have proved cardioprotective in isolated heart models. In animal models of myocardial stunning, K⁺ channel openers markedly improved the recovery of myocardial function after ischaemia.³³ In general these drugs are only cardioprotective when administered before reperfusion; they are ineffective if dosing is delayed and initiated during reperfusion.³³ Also in animal models of myocardial infarction K_{ATP} openers seem to be effective in reducing myocardial infarct size.³²

The precise mechanism underlying the cardioprotective effects of K⁺ channel openers is not yet clarified. Several studies have demonstrated that glibenclamide blocks the anti-ischaemic effects which therefore seem to be mediated by opening of K_{ATP}.³² Another consequent finding is that cardioprotection can be achieved without coronary vasodilatation or dilatation of coronary collaterals, indicating that the effect is not dependent upon coronary vascular smooth muscle relaxation but involves a direct myocardial effect.³² This is further supported by the development of K_{ATP} openers such as BMS-180448 that are selective for the ischaemic myocardium with a higher cardioprotective than vasorelaxant potency.³⁴ The fact that these drugs have to be administered before reperfusion to be effective, indicates that they do not inhibit reperfusion injury directly but rather are protective during ischaemia itself. A mechanism that may account for the cardioprotective effect of K_{ATP} openers is the accelerated shortening of cardiac action potential duration in early ischaemia caused by an enhanced K⁺ outward current. This would limit Ca²⁺ influx, counteract intracellular Ca²⁺ overload, enhance the decline of contractile function, and shorten the time to arrest of mechanical activity in the ischaemic zone of the myocardium.^{10 12 35} Such a cardioplegic mechanism would save energy and tend to prolong survival of the cardiomyocytes. Experiments have shown that cardioprotection by K_{ATP} openers is associated with preservation of myocardial ATP.³² However, in recent studies in dogs with bimakalim and cromakalim there seemed to be some dissociation between action potential shortening and cardioprotection, indicating that additional mechanisms may be involved.^{36 37} During reperfusion after global ischaemia in rat hearts, cromakalim improved oxygen efficiency; this suggests a direct effect on cardiac metabolism, possibly at the level of the mitochondria.³²

Ischaemic preconditioning is a fascinating endogenous cardioprotective mechanism of the heart. In this phenomenon one or more brief periods of coronary occlusion markedly reduce the size of the myocardial infarction that follows a subsequent prolonged coronary artery occlusion. There is now substantial experimental evidence suggesting that ischaemic preconditioning is mediated partly

or in whole by opening of K_{ATP}.³⁸ Gross and Auchampach³⁹ first showed that glibenclamide abolished the cardioprotective effect of preconditioning in dogs and that a K_{ATP} opener aprikalim mimicked the effect of preconditioning without producing any systemic haemodynamic effects. Later studies in dogs and pigs supported an essential role for K_{ATP} in preconditioning, whereas results of studies in rabbits and rats were somewhat conflicting.³⁸ In a recent study by Yao and Gross,⁴⁰ transient occlusion of the left anterior descending coronary artery (LAD) for only 3 min had no preconditioning effect. However, when bimakalim was given during the LAD occlusion period a significant preconditioning effect was seen. Bimakalim infusion alone did not influence infarct size, thus suggesting that pharmacological activation of K_{ATP} can sensitise the myocardium to preconditioning. Glibenclamide also blocks preconditioning in man.⁴¹ In patients with angina pectoris, coronary angioplasty with two subsequent balloon inflations resulted in markedly reduced ST segment changes and pain during the second balloon inflation. The beneficial preconditioning effect of the first inflation was completely abolished by glibenclamide given in an oral dose used in antidiabetic treatment.

Previous studies have also suggested a role for adenosine in mediating ischaemic preconditioning. Adenosine acts through adenosine receptor stimulation in the myocardium and activates K_{ATP} by a G-protein regulated mechanism.¹⁵ Thus it seems likely that K_{ATP} opening is the mechanism whereby adenosine produces its protective effect. This is supported by the observation that glibenclamide in dogs completely blocked the ability of exogenously administered adenosine to mimic preconditioning.⁴²

ELECTROPHYSIOLOGICAL ASPECTS

Concern has been raised that K⁺ channel openers may possibly be proarrhythmic because of their ability to shorten cardiac action potential duration (APD), an effect that is expected to reduce cardiac refractoriness. However, shortening of cardiac APD may be both proarrhythmic and antiarrhythmic depending on the type of arrhythmia in question and the state of the myocardium. As a consequence there are experimental studies reporting proarrhythmic, not proarrhythmic, and antiarrhythmic effects with these drugs.⁴³⁻⁴⁵ In the non-ischaemic myocardium, only very high and clinically irrelevant concentrations produce shortening of APD and a tendency to arrhythmias. In contrast, clinically relevant concentrations inhibit arrhythmias induced by triggered activity (early and late afterdepolarisations) which are of relevance in the long QT syndrome and torsades de pointes ventricular tachycardia. In the ischaemic myocardium, which favours reentry arrhythmias, these drugs shorten cardiac APD at clinically relevant concentrations and may facilitate arrhythmias. Whereas several studies have shown no proarrhythmia or even antiar-

rhythmic activity of K^+ channel openers in animal models of ischaemia-induced arrhythmias others have shown that proarrhythmias may be a risk particularly at the high concentrations that produce profound hypotension. In this context, K^+ channel openers by their cardioprotective action may produce indirect antiarrhythmic effects in myocardial ischaemia. To date, pinacidil and nicorandil have been given to thousands of patients without reports of adverse arrhythmias. If the cardioprotective effect can be separated from the ability of these drugs to shorten cardiac APD, and some observations have suggested that they can,³⁷ it should be possible to develop cardioprotective K_{ATP} openers without or with only a minimal proarrhythmic potential.

The ST segment and T wave changes in the electrocardiogram during myocardial ischaemia are believed to result from enhanced outwardly directed K^+ currents. K^+ channel openers may therefore mimic such changes even in the absence of myocardial ischaemia. Changes consisting of inversion or flattening of the T wave have been reported in 30% of patients treated with pinacidil.⁴⁶ Even though such changes are benign, they may give rise to difficulties in the interpretation of the electrocardiogram, particularly in patients with ischaemic heart disease.

Therapeutic potential of K^+ channel openers

ANGINA PECTORIS

Coronary vasodilatation induced by hypoxia/ischaemia is an endogenous beneficial mechanism which operates to improve perfusion of the ischaemic myocardium. The role of K_{ATP} in mediating metabolic coronary vasodilatation makes K_{ATP} openers of potential interest in the treatment of angina pectoris. In addition, these vasorelaxant drugs preferentially produce coronary vasodilatation, some of them even without systemic haemodynamic changes. Their ability to inhibit myocardial stunning, limit myocardial infarct size, and mimic ischaemic preconditioning may further stimulate the interest in these drugs in coronary artery disease. However, although clinical trials have been initiated, there are currently no clinical data on pure K^+ channel openers in patients with ischaemic heart disease.

Clinical data are available for nicorandil^{47, 48} which is now in clinical use as an antianginal agent. Although it is classified as a K^+ channel opener it is not a pure one, but a hybrid between a nitrate and a K_{ATP} opener. Nicorandil has proved effective for the treatment of stable angina pectoris in placebo controlled clinical trials, and in comparative studies it shows the same degree of antianginal efficacy as nitrates, Ca^{2+} antagonists, and β adrenoceptor blockers. In addition, clinical data indicate that it might be useful in the treatment of unstable angina and variant angina.

Nicorandil dilates large coronary arteries and has balanced preload and afterload reducing effects because of its nitrate and K_{ATP}

opener components, respectively. It increases cardiac output by haemodynamic changes and may be used in patients with poor left ventricular function. Interestingly nicorandil, unlike the nitrates, does not seem to induce the development of tolerance.

CARDIOPROTECTION

The cardioprotective effect of K_{ATP} openers is a most fascinating aspect of these new drugs. It implies that they may be able not only to prevent and relieve the symptoms of myocardial ischaemia but also to reduce some of the important consequences of myocardial ischaemia such as myocardial stunning and infarction. If this holds true in clinical practice, it is likely that these drugs will be of long-term benefit and reduce mortality in patients with ischaemic heart disease. These drugs may also have a therapeutic potential as adjuvant treatment in coronary angioplasty and coronary bypass surgery to protect the myocardium from ischaemic injury and to inhibit postoperative myocardial stunning.

HEART FAILURE

Hybrid drugs between nitrates and K_{ATP} openers such as nicorandil have a balanced haemodynamic profile of preload and afterload reduction.⁴⁸ This effect profile resembles that produced by the combined treatment of isosorbide dinitrate and hydralazine which was used in the V-HeFT studies. In the V-HeFT II study the ACE inhibitor enalapril was superior to isosorbide dinitrate and hydralazine in terms of mortality, whereas the latter combination was superior to enalapril in improving left ventricular function and exercise capacity of the patients. Nicorandil has so far shown favourable haemodynamic actions in heart failure in small short-term clinical studies.⁴⁸

HYPERTENSION

K^+ channel openers were originally developed as antihypertensive vasodilators. The best studied drug is pinacidil,⁴⁶ which is in clinical use for the treatment of hypertension. This drug is clearly effective in controlling hypertension, but as with other directly acting peripheral vasodilators it causes reflex tachycardia and fluid retention and is not suited to monotherapy. It can be used in combination with β adrenoceptor blockers, diuretics, or ACE inhibitors. It has no adverse effect on blood lipids, glucose tolerance, or insulin secretion. Other K^+ channel openers such as levromakalim have been selected for development as antihypertensive agents.

PULMONARY HYPERTENSION

A clinically useful vasodilator for the treatment of pulmonary hypertension should be selective for the pulmonary circulation and produce pulmonary vasodilatation without significant systemic hypotension and cardiodepression. Hypoxic vasoconstriction is a unique feature and probably the most powerful control mechanism of vascular tone in the pulmonary circulation.²¹ The essential role of inhibition of K^+ channels in this regulatory mechanism raises

the possibility that pharmacological openers of the K⁺ channel involved might be selective pulmonary vasodilators. Although the K⁺ channel subtype involved appears to be different from K_{ATP}, openers of this channel produce pulmonary vasodilatation in vitro and in vivo and inhibit hypoxic pulmonary vasoconstriction in animals.²³ Pinacidil and related cyanoguanidine derivatives were more potent relaxants of pulmonary than systemic arteries from the guinea pig.²⁴ So far there are no clinical data available on the effect of K⁺ channel openers in patients with pulmonary hypertension.

PERIPHERAL VASCULAR DISEASE

Vasodilators have been unsuccessful in the treatment of intermittent claudication probably because they dilate vessels supplying normally perfused skeletal muscle and thereby divert blood flow away from the ischaemic tissue. In contrast to other vasodilators K⁺ channel openers seem to enhance blood flow to ischaemic skeletal muscle and improve recovery of muscle energy stores in animal models of chronic occlusive arterial disease.⁴⁹ These beneficial effects were manifest at doses below those affecting systemic blood pressure and may reflect redistribution of blood flow to ischaemic muscle due to selective dilatation of collateral vessels. Hypersensitivity of such vessels to K⁺ channel openers might arise because ischaemic conditions would favour opening of K_{ATP}. Another possible explanation could be differences in nerve supply and populations of K⁺ channels between collaterals and other vessels. Clinical studies on the effect of K⁺ channel openers in patients with peripheral vascular disease have started.

IMPLICATIONS FOR DIABETIC PATIENTS TREATED WITH SULPHONYLUREA K_{ATP} BLOCKERS

Diabetes mellitus is an adverse risk factor in acute myocardial infarction. These patients have a poor prognosis after infarction with a three to four fold higher mortality risk than non-diabetics. The reason why diabetic patients do so badly is unclear. Non-insulin-dependent diabetes mellitus (NIDDM) accounts for 85% of all cases of diabetes and most of these patients are treated with oral antidiabetic sulfonylureas which can block not only pancreatic K_{ATP} channels but also cardiovascular K_{ATP} channels. The question arises whether treatment with antidiabetic sulfonylureas is hazardous from a cardiovascular point of view. In a large multicentre trial with an eight year observation period a twofold increase in cardiovascular mortality was observed among patients treated with tolbutamide when compared with placebo or insulin treated patients,⁵⁰ but the validity of this conclusion has been questioned and is the subject of much debate.⁵¹ If the knowledge derived from basic science of the interaction between antidiabetic sulfonylureas and cardiovascular K_{ATP} channels is clinically relevant the use of sulfonylureas in patients with diabetes should be considered carefully.

Conclusion

K⁺ channel openers are a group of novel drugs that target K_{ATP} channels in the cardiovascular system. This type of K⁺ channel opens during myocardial ischaemia and plays a part in important endogenous protective mechanisms such as hypoxic/ischaemic coronary vasodilatation and ischaemic preconditioning. By exploiting these natural protective mechanisms of the heart these drugs inhibit myocardial stunning, limit myocardial infarct size, and sensitise the myocardium to ischaemic preconditioning in animal experiments. The cardioprotective effects of the drugs are produced at low concentrations which have no effects in the non-ischaemic myocardium. Most of the drugs are also peripheral vasodilators and some of the first drugs developed are in clinical use as antihypertensive agents. K_{ATP} openers which are selective for the ischaemic myocardium have been synthesised and seem to have an interesting therapeutic potential in ischaemic heart disease. Clinical trials have started, but so far there is no clinical experience with pure K_{ATP} openers in ischaemic heart disease. Nicorandil, which is a hybrid between a nitrate and a K_{ATP} opener, is in clinical use as an effective agent for the treatment of angina pectoris. Pulmonary hypertension and peripheral vascular disease are other potential clinical applications for this novel pharmacological concept of opening cardiovascular K⁺ channels.

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