Is there a therapeutic future for ‘potassium channel openers’?

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1. Potassium channels, which control cell electrical activity, are among the most regulated of all ion channels in biology. Promotion of activity in K+ channels by a wide range of physiological factors tends to stabilize cell function.

2. The discovery of synthetic molecules (e.g. cromakalim) that ‘directly’ open ATP-sensitive K+ channels has led to a new direction in pharmacology. ATP-sensitive K+ channel-opening properties have subsequently been demonstrated in a diverse range of chemical structures (synthetic and endogenous).

3. The existence of so many different subtypes of K+ channels has been an impetus in the search of new potassium channel openers with different channel selectivities and thus biological profiles.

4. The decrease in cell excitability following K+ channel opening implies a broad clinical potential in a number of pathological conditions for K+ channel openers. Preclinical and clinical evidence supports therapeutic roles of K+ channel openers in disorders of a wide range of biological cells.

5. Although lack of selectivity of current compounds remains a major hurdle, advances in K+ channel openers and K+ channel pharmacology are encouraging. Differences already observed in the pharmacology of K+ channel openers are important factors for the development of second-generation compounds, when tissue selectivity is sought.

6. The availability of subtype-selective K+ channel openers will facilitate detailed study, through a combined effort of electrophysiology, functional pharmacology and molecular biology, leading to focused therapeutic approaches for defined pathological conditions.

INTRODUCTION

Proteins that permit movement of ions across the outer membranes of cells, i.e. ion channels, play a fundamental role in the regulation of cell function in all living tissues. Potassium (K+) channels in particular, a diverse and ubiquitous group, control cell electrical activity and excitability [1, 2]. In the resting state, the concentration of K+ outside the cell membrane (3–5 mmol/l) is at least 25-fold lower than that in the intracellular fluid (130–160 mmol/l). Consequently, an outward current of positively charged ions is generated by the opening of K+ channels. Efflux of K+ is a mechanism for recovering (repolarization), maintaining (clamping) and/or enhancing (hyperpolarization) the resting potential of the cell membrane. Thus, opening of K+ channels is a physiological process to counteract or restrict depolarization due to entry of Ca2+ and/or Na+ into and/or the efflux of Cl− from the cell. The functions of K+ channels, which subserve physiological responses, depend on the specific manner in which a particular K+ channel opens and closes, and its selective permeation by K+ ions. K+ channel classifications, generally according to the primary regulatory or gating mechanism [1], and their pharmacological properties have been extensively reviewed [2–9].

The physiological role of K+ channel opening by endogenous substances (neurotransmitters and hormones) is a recognized inhibitory mechanism [1, 2, 5]. Thus, the identification of a synthetic molecule, cromakalim, that evoked smooth muscle relaxation by the opening of K+ channels in cell membranes [3, 10] led to a new direction in the pharmacology of these ion channels. This finding has initiated major research efforts in the search for other molecules demonstrating this property and in the determination of the specific channel(s) involved. K+ channel-opening properties have subsequently been demonstrated in a diverse range of synthetic chemical structures and endogenous substances [8, 9, 11, 12]; hence, the term ‘potassium channel openers’ (KCOs) was introduced. KCOs evoke biological effects via a selective increase in

Key words: ATP-sensitive K channels, cromakalim, potassium channel openers, therapeutic targets.

Abbreviations: APD, action potential duration; CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; EDRF, endothelium-derived relaxing factor; GABA, gamma-aminobutyric acid; GPT, guinea pig isolated trachealis muscle; IOP, intraocular pressure; IP3, 1,4,5-inositol trisphosphate; KCO, K+ channel opener; NANC, non-adrenergic, non-cholinergic; PAOD, peripheral arterial occlusive disease; PI, phosphatidylinositol; PVD, peripheral vascular disease; SR, sarcoplasmic reticulum; VOC, voltage-operated calcium channel.

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membrane permeability to K\(^+\), leading to hyperpolarization such that the membrane potential difference approaches the K\(^+\) equilibrium potential (\(E_K\)). In this hyperpolarized state, excitable cells are less susceptible to chemical and electrical stimulation than under normal conditions.

The objective of this article is to present an overview of the potential clinical targets and associated pharmacology implicated in the biological effects of 'potassium channel openers'. For the purpose of this review these agents will be referred to as K\(_{\text{ATP}}\)COS, i.e. K\(^+\) channel openers postulated to act at ATP-sensitive K channels (see below). Advances made in this area of research have brought into question the use of the broad term 'potassium channel openers' for reference to a limited group of molecules (i.e. those typified by cromakalim, K\(_{\text{ATP}}\) openers). The existence of so many different subtypes of K\(^+\) channel has been an impetus in the search for new compounds with channel selectivities and biological profiles different from those exhibited by K\(_{\text{ATP}}\) openers. Recent progress has been reported in the search for agents that 'selectively' open calcium-activated K\(^+\) channels [13, 14].

**ATP-SENSITIVE K\(^+\) CHANNEL OPENERS**

The effects of K\(_{\text{ATP}}\)COS in preclinical studies [3, 8, 9, 12, 15–17] suggest a number of therapeutic targets for this group of compounds, such as hypertension, angina pectoris, coronary heart disease, asthma, urinary incontinence, epilepsy and glaucoma. ATP-sensitive K\(^+\) channels (K\(_{\text{ATP}}\)), initially identified in cardiac cells and pancreatic \(\beta\)-cells [9, 18], exist in virtually all tissues, including skeletal muscle, smooth muscle and neuronal cells [18]. The intracellular concentration of ATP determines the state (i.e. open, closed) of the K\(_{\text{ATP}}\) channel, such that raised intracellular ATP levels close the channel. Exogenous compounds, in particular the sulphonylureas (e.g. glibenclamide), can induce the release of insulin from pancreatic \(\beta\)-cells closing K\(_{\text{ATP}}\) channels. The success of the sulphonylureas in the management of non-insulin-dependent diabetes is an exceptional example of the usefulness of K\(^+\) channel pharmacology in the clinic.

Five different subtypes of K\(_{\text{ATP}}\) channels have been proposed as a consequence of selectivity to K\(^+\) and sensitivity to calcium, intracellular ATP concentration and pharmacological modulation. Pharmacological characterization of the putative subtypes of K\(_{\text{ATP}}\) channels is presently limited [8, 18]. Type 1 channels are blocked by micromolar concentrations of intracellular ATP and demonstrate sensitivity to sulphonylureas; however, the concentrations of these compounds required to block the K\(_{\text{ATP}}\) channels are tissue dependent [8, 9]. Modulation of pancreatic \(\beta\)-cell K\(_{\text{ATP}}\) channels resulting in insulin release occurs at nanomolar concentrations of glibenclamide, whereas micromolar concentrations are required in smooth muscle and cardiac muscle cells, suggesting at least two concentration ranges of activity. The rank order of potency of K\(_{\text{ATP}}\)COS on type 1 K\(_{\text{ATP}}\) channels is also dependent on the cell type [8, 9, 11], thus inviting further differentiation on the basis of pharmacological profile. The current subtyping does not take into account recent studies (albeit limited) using cloned K\(_{\text{ATP}}\) channels (ROMK1, ROMK2, ROMK3 [19]).

K\(^+\) channel-opening properties sensitive to sulphonylureas, identified in electrophysiological, ion efflux and functional pharmacological studies, have been demonstrated in a diverse range of synthetic chemical structures: benzothiadiazines (e.g. diazoxide), pyrimidines (e.g. minoxidil), pyridylcyanoguanidines (e.g. pinacidil), nicotinamides (e.g. nicorandil), benzopyrans (e.g. cromakalim) and carbothiamides (e.g. aprikalim) [8, 11, 15–17]. Certain common chemical structural features between benzopyrans, pyridylcyanoguanidines and carbothiamides have been described [15]. Although a primary common feature responsible for the grouping of these compounds has been the susceptibility of the biological effects to sulphonylureas, anomalies have been identified in the pharmacology of the different chemical families [17].

Radioligand binding assays have identified specific binding sites for \([\text{H}]\)P1075 (pinacidil analogue) and \([\text{H}]\)cromakalim in smooth muscle preparations [20, 21]. \([\text{H}]\)P1075 binding in rat aorta was inhibited by representatives from all chemical families of K\(_{\text{ATP}}\)COS with potencies that correlated with those obtained in \(86\text{Rb}^+\) efflux and vasorelaxation studies [20]. Of the various inhibitors of K\(^+\) channels tested, only the sulphonylureas inhibited \([\text{H}]\)P1075 binding with the rank order of potency similar to that for inhibition of P1075-induced \(86\text{Rb}^+\) efflux. Interestingly, differences between \([\text{H}]\)cromakalim and \([\text{H}]\)P1075 binding sites in smooth muscle preparations [20, 21] were evident. Glibenclamide inhibited the specific binding of \([\text{H}]\)P1075 with a pKi value of 6.4, but failed (up to 10 \(\mu\)mol/l) to modify that of \([\text{H}]\)cromakalim. Although levrocromakalim (BRL 38227) was significantly more potent (17 times) than SDZ PCO 400 (IC\(_{50}\) 11.5 \(\mu\)mol/l and 190 \(\mu\)mol/l respectively) in displacing \([\text{H}]\)cromakalim in vascular smooth muscle [21], the pKi values of levrocromakalim (7.33) and SDZ PCO 400 (7.21) were not different against \([\text{H}]\)P1075 binding [20]. These data would support the existence of two different binding sites, with benzopyran K\(_{\text{ATP}}\)COS having affinity for both sites, but different rank order of affinity. Ligand-binding studies on expressed cloned K\(^+\) channels (i.e. ROMK1, ROMK2, ROMK3 [19]), which will provide major advances in our understanding of how K\(_{\text{ATP}}\)COS interact with the channel, are awaited.

In functional pharmacological studies in vitro, the antagonism by glibenclamide of the effects of K\(_{\text{ATP}}\)COS on vascular and certain non-vascular
smooth muscle preparations has been described as competitive in nature [3, 11, 12]. The failure of glibenclamide (up to 10 μmol/l) to displace [3H]cromakalim from its binding site in rat aorta [21] does not support a competitive interaction between these two compounds at a single site. Glibenclamide evoked a concentration dependent increase in the dissociation rate of the [3H]P1075 binding complex on rat aorta [20], suggesting that the glibenclamide site is distinct from, but allosterically coupled to, the binding site for KATPCOs.

In vascular smooth muscle preparations, glibenclamide antagonized the effects of cromakalim competitively, whereas the effects of minoxidil sulphate were antagonized in a non-competitive manner [22]. These findings led to the suggestion of the existence of different subtypes of K+ channel sensitive to KATPCOs in, at least, vascular smooth muscle. In addition, minoxidil sulphate, in contrast to cromakalim and diazoxide, had no effect on 86Rb+ efflux in rat aorta but did increase 42K+ efflux [22]. Thus, in rat aorta, minoxidil sulphate may open a K+ channel impermeable to 86Rb+ and not recognized by other KATPCOs. Differences in the pharmacology of benzopyran and non-benzo-pyrans KATPCOs in vascular smooth muscle have also been identified [23, 24], with all compounds exhibiting definable KCO profiles. Such findings support the concept that there are differences in the way in which these agents act on KATP channels (whichever subtype it may be).

The attenuation by glibenclamide of the smooth muscle relaxant responses to KATPCOs in guinea pig trachea is not consistent with competitive antagonism (i.e. the maximum effect of the KATPCO is reduced in the presence of the antagonist [25, 26]). Thus, glibenclamide appears to interact differently with the KATPCO-sensitive K+ channel in guinea pig respiratory smooth muscle and vascular smooth muscle.

Thus, the nature of antagonism by sulphonylureas is dependent on the cell type and KATPCO being studied [8, 9, 11, 17]. Further, the pharmacological profile of (some) KATPCOs on the KATP channel also appears to be dependent upon cell type (e.g. diazoxide is an 'activator' in pancreatic cells, inactive in skeletal muscle cells and an 'antagonist' in cardiac cells [17]). A number of KATPCOs (e.g. pinacidil and nicorandil) possess additional properties (e.g. adenylyl cyclase or guanylate cyclase stimulation) to that of K+ channel opening that could account, in part, for pharmacological profiles differing from those of the benzopyrans (e.g. cromakalim) and carbothiamides (e.g. aprikalim) [3, 11]. The situation is further complicated by the fact that KATPCOs evoke effects on K+ channels other than KATP channels, Ca2+ channels and Cl− currents [11, 12, 27].

Heterogeneity in the pharmacology of the KATPCOs that can be identified could suggest heterogeneity of the sites of action and/or K+ channels. Interpretation is further complicated by a potential heterogeneity of sulphonylurea-sensitive sites of deactivation, independent of the KATP site(s) of action. A combined effort of electrophysiology, functional pharmacology and molecular biology with subsequent study of the expressed clone(s) will be required to address the real question of KATP subclassification and channel selectivity. The differences already observed in the pharmacology of KATPCOs are important factors to consider in the search and development of second-generation compounds, when tissue/organ selectivity is sought. Although the ability of glibenclamide to antagonize the actions of this group of compounds led to the suggestion of KATP channels being the site of action, this is still an active area of research [12, 28]. Such findings, however, highlight the complexity of biological systems and the need to investigate fully the specificity of channel–ligand interactions, to clearly define the site(s) of action of KATPCOs.

**MECHANISM(S) OF ACTION**

Although some of the mechanism(s) described are universal in excitatory and non-excitable cells, not all processes will be applicable to all tissue types. The majority of data presented have been obtained from smooth muscle cells and require confirmation in other cell types.

One of the standard criteria that initially identified a compound as a KATPCO is the ability to relax an *in vitro* smooth muscle preparation contracted by exposure to low, but not high (>30 mmol/l), concentrations of extracellular K+ [10, 11]. The opening of K+ channels by KATPCOs and subsequent efflux of K+ from the cytosol leads to an increase in negativity of the membrane potential (hyperpolarization) towards the calculated K+ equilibrium potential (EK) [3, 11]. This change in membrane potential is followed by a reduction in cytosolic free Ca2+ and/or an inhibition of mechanisms producing increases in cytosolic free Ca2+. The outcome is a reduction in membrane and cell excitability, resulting in a greater cellular resistance to activation by excitatory stimuli (Fig. 1). An excellent correlation exists between the potencies of KATPCOs for stimulation of 86Rb+ efflux and vasorelaxation in rat aorta and portal vein preparations *in vivo* [16], supporting the hypothesis that these functional responses are associated with the opening of K+ channels.

Although the hyperpolarization caused by K+ efflux was assumed to close voltage-operated Ca2+ channels (VOCs), preventing depolarization-induced Ca2+ entry into the cell, other mechanisms may also contribute to the effects produced by KATPCOs. Cromakalim-evoked increases in 86Rb+ efflux or hyperpolarization of vascular smooth muscle tissue are not influenced by lanthanum or the Ca2+ antagonist nifedipine, indicating that the action of
the K<sub>ATP</sub>COs is not dependent upon modifying the influx of external Ca<sup>2+</sup> through VOCs [11]. In rabbit cultured tracheal smooth muscle cells, cromakalim inhibits the release of 45Ca<sup>2+</sup> from the sarcoplasmic reticulum [29]. These findings support those obtained in vascular smooth muscle, in which contractile responses to noradrenaline, dependent on intracellular calcium stores, are attenuated by cromakalim [12]. Further, levocromakalim inhibits Ca<sup>2+</sup> release from intracellular stores of rabbit isolated mesenteric artery due to an action on the noradrenaline-stimulated 1,4,5-inositol trisphosphate (IP<sub>3</sub>) production [30]. Hyperpolarization of the cell membrane of canine coronary artery by K<sub>ATP</sub>COs has been associated with an inhibition of the production of IP<sub>3</sub> and, hence, Ca<sup>2+</sup> release from intracellular stores [31]. In contrast, K<sub>ATP</sub>COs have no effect upon phosphatidylinositol (PI) turnover in brain tissue [32]. The hyperpolarization induced by K<sub>ATP</sub>COs (e.g. levocromakalim) may also be linked with a reduction in the sensitivity of the contractile elements of vascular smooth muscle to Ca<sup>2+</sup> [33]. Further studies are required to determine whether these are properties unique to cromakalim (or benzopyran K<sub>ATP</sub>COs).

Vasorelaxant effects of K<sub>ATP</sub>COs that are independent of membrane hyperpolarization or ion efflux have also been reported [34]. Such findings suggest that these drugs can exert a response through mechanisms other than the opening of K<sup>+ </sup>channels. The possibility that K<sub>ATP</sub>COs interact not directly with an ion channel but, for example, with an enzyme system involved in intracellular phosphorylation provides a novel explanation for some of the apparently anomalous effects of these agents [28].

Thus, the mode(s) of action of K<sup>+ </sup>channel openers may not be as simple as first thought, and more research effort is required in this area. The mechanism of action involved in a given response may depend not only on the subtype of K<sup>+</sup> channel, but also on how the K<sub>ATP</sub>CO interacts with the channel to evoke an effect.

**POTENTIAL THERAPEUTIC TARGETS**

Theoretically, the general decrease in cell excitability after K<sup>+</sup> channel opening implies a broad therapeutic potential in a number of pathological conditions for drugs demonstrating this property (Table 1).

**Cardiovascular system**

The preclinical profile of K<sub>ATP</sub>COs clearly supports a therapeutic potential for use in cardiovascular pathologies that require a decrease in peripheral vascular resistance, an inhibition of excessive vasoconstriction and/or a prolongation of
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myocardial tissue viability during transient oxygen deficiency. The pharmacology of K_ATP COs in in vitro vascular smooth muscle tissues and in vivo models of vascular disorders (e.g. hypertension, peripheral vascular disease, angina) have been extensively reviewed [11, 12]. In arterial and venous tissues from a range of species, K_ATP COs relax smooth muscle by inhibiting spontaneous tone and preventing or reversing contraction to spasmsogens. Arterial smooth muscle tone, of which K⁺ channels are important regulators, is the main determinant of peripheral vascular resistance and blood pressure. Defects in K⁺ channels may lead to vasoconstriction or compromise the ability of an artery to dilate in pathological conditions, such as vasospasm, hypertension, ischaemia and diabetes. In contrast, activation of K_ATP channels in response to the metabolic state of the cell may be involved in arterial dilatation associated with reactive hyperaemia, septic shock, ischaemia and hypoxia. Although the involvement of K_ATP channels in these clinical conditions is not exclusive, the absence of selective agents of other K⁺ channels presently limits characterization of their role in the aetiology of such diseases.

K_ATP COs can lower both normal and experimentally elevated blood pressure in animal models by actively decreasing total peripheral vascular resistance [11, 12]. Further, pinacidil, diazoxide and minoxidil sulphate reduce elevated blood pressure in hypertensive patients [27]. The clinical use of these drugs has been restricted by unwanted effects: pinacidil evokes a reflex tachycardia and, in approximately 30% of patients, weight gain; diazoxide increases blood glucose levels (restricting its use to hypertensive emergencies); and relatively high incidence of fluid retention is observed with minoxidil sulphate. Clinical experience with cromakalim on blood pressure control is less extensive than for the above agents, and there are very few published reports of clinical trials with other K_ATP COs. In mild to moderate hypertensive patients, cromakalim (0.5–1.5 mg) was found to lower systolic and diastolic blood pressure after a single oral dose or chronic once-daily administration, with no such effects observed when placebo was administered or in parallel normotensive groups [11, 27]. Bimakalim (single oral dose of 0.25, 0.5 or 1.0 mg at weekly intervals) has been found to reduce total peripheral resistance and increase left ventricular ejection fraction, stroke volume and heart rate, but does not affect systolic and diastolic blood pressure, in normal subjects [35], thus demonstrating a potent vasodilating effect that may have a role in the management of patients with compromised left ventricular function. As direct vasodilators, the use of K_ATP COs to reduce blood pressure can produce a series of undesirable effects (e.g. tachycardia, headache, flushing, increase in renin, aldosterone and catecholamine secretion and sodium and water retention) that are not acceptable in clinical practice. Current K_ATP COs could only become useful antihypertensive therapy if appropriately formulated or co-prescribed with selected agents to reduce or prevent these undesirable events. Because of apparent cardioprotective properties (see below), low doses of K_ATP COs could provide myocardial protection to hypertensive patients, an area where current drugs do not substantially reduce mortality and morbidity [36, 37].

One therapeutic approach to congestive heart failure (CHF), although of a symptomatic nature, is to reduce peripheral vascular resistance, a property demonstrated by K_ATP COs [8]. Down-regulation of ventricular K_ATP channel, 1,4-dihydropyridine-sensitive Ca²⁺ channel and β-adrenoceptor densities have been observed in an in vivo rat cardiac failure model [8]. Nicorandil remains haemodynamically effective during a 24-h period of infusion to patients with CHF [38]. In contrast, CHF patients develop haemodynamic tolerance to nitroglycerin (current available therapy) with 12 h of continuous infusion. The beneficial effects of nicorandil in CHF are probably due to K_ATP CO actions, not nitrate activity. K_ATP COs, in preclinical studies, relaxed coronary conductance arteries and selectively increased coronary blood flow [11]. Thus, these agents demonstrate properties desirable to improve oxygen delivery, as well as reduce oxygen consumption, within ischaemic regions of patients with transient and chronic heart disease (e.g. angina pectoris). Reports on the effects of K_ATP COs in angina pectoris, however, are primarily restricted to nicor-

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<th>Tissue/organ</th>
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<td>Eye</td>
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Table 1. Potential therapeutic targets of K_ATP COs

- Hypertension
- Angina
- Congestive heart disease
- Cardioplegia
- Arrhythmias
- PAOD
- COPD
- Asthma
- Premature labour
- Dysmenorrhoea
- Impotence
- Incontinence
- Hyperactive bladder
- Irritable bowel syndrome
- Neurodegeneration
- Epilepsy
- Parkinson's disease
- Analgesia
- Depression (?)
- Myotonic dystrophy
- Fatigue/paralysis
- Alopecia
- Glaucoma
andil or cromakalim (one trial). Nicorandil is a balanced arterial and venodilator with a haemodynamic profile that should make it effective in the treatment of angina, including the unstable and variant forms [39]. The clinical benefits of nicorandil probably result from both K⁺ channel-opening properties and direct stimulation of smooth muscle guanylate cyclase. Cromakalim (15 mg/kg intravenously over 10 min) demonstrates arteriolar vasodilator properties (decreased systolic arterial pressure, systemic and pulmonary vascular resistance) in patients with stable angina pectoris, producing an improvement in cardiac performance (up to a 30% increase in cardiac output) [40].

Interestingly, pinacidil- and nicorandil-induced dilatation of canine large coronary arteries in vivo, an indirect flow-mediated effect, is entirely dependent on the endothelium [41]. Pinacidil also opens K<sub>ATP</sub> channels in both rat aorta and brain microvascular endothelial cells [42]. In addition, levrocromakalim is a more potent vasorelaxant in rat aortic ring preparations with endothelium than in denuded tissues, an effect that involves nitric oxide [43]. These functional findings are supported by the observation that pinacidil and cromakalim increase intracellular Ca<sup>2+</sup> concentration in porcine aortic endothelial cells by inducing membrane hyperpolarization after K⁺ channel activation [44], an effect that can promote Ca<sup>2+</sup>-dependent formation of endothelium-derived relaxant factor (EDRF). K<sub>ATP</sub> channels may play a role in regulation of endothelial cell resting membrane potential and therefore modulate the release of endothelium-derived vasoactive factors.

K<sub>ATP</sub>COs demonstrate cardioprotective effects in animal studies as a consequence of improving oxygen delivery and reducing oxygen consumption within ischaemic regions [36, 45, 46]. Depletion of ATP in the myocardium and subsequent opening of cardiac K<sub>ATP</sub> channels in response to ischaemia may lead to a rapid reduction in tissue contractility to protect against further ischaemic injury. In support of this hypothesis, cromakalim, aprikalim and pinacidil, in animal models, cause a glibenclamide-sensitive reduction in the severity of ischaemia–reperfusion injury of the myocardium. Thus, K<sub>ATP</sub>COs play a cardioprotective role, whereas K<sub>ATP</sub> channel blockade by glibenclamide worsens myocardial stunning [36, 47]. Analogies have been observed between the cardioprotection conferred by K<sub>ATP</sub>COs and ischaemic preconditioning (i.e. increased tolerance of cardiac myocytes to an ordinarily lethal ischaemic insult, achieved by an initial brief exposure to ischaemia), for example both are sensitive to glibenclamide blockade [48]. Thus, therapy with K<sub>ATP</sub>COs may offer a ‘chemical preconditioning’ that confers on the heart improved ability to withstand transient oxygen deprivation and consequently to suffer less tissue damage during acute myocardial infarction. Although K<sub>ATP</sub>COs (e.g. SR 44866) activate ATP-sensitive K⁺ channels present in the atria and ventricles of the human heart [49], clinical evidence of the benefits of K<sub>ATP</sub>COs in patients with heart disease is awaited.

Whether K<sub>ATP</sub>COs exert beneficial effects on the ischaemic heart by a direct (myocardial) or indirect (vascular) action remains to be determined. U-89,232 (cromakalim analogue [50]) and BMS 180448 (pinacidil analogue [46]), both devoid of vascular effects, demonstrate cardioprotection against ischaemia in rat and rabbit models, suggesting a direct myocardial action. These second-generation K<sub>ATP</sub>COs provide an opportunity to explore cardioprotection without possible vascular complications (e.g. hypotension, coronary steal). The mechanism(s) of observed tissue selectivity is not clear, but it may be related to the existence of K<sub>ATP</sub>CO ‘receptor’ subtypes in different tissues [51].

While K<sub>ATP</sub> channel opening in response to ischaemia may offer a cardioprotective mechanism, there are other physiological consequences. An increase in K⁺ efflux (accelerated repolarization) shortens the cardiac action potential duration (APD) and contributes to the extracellular K⁺ accumulation observed during an ischaemic episode in cardiac tissue [37]. These changes have been proposed to be responsible for ischaemia-induced arrhythmias. Although K<sub>ATP</sub>COs demonstrated arrhythmogenic properties in some animal studies [52, 53], the concentrations that affect the APD of myocardial cells, and thus accelerate automaticity and promote re-entrant activity, are considerably higher (10- to 100-fold) [54] than those needed for effects on vascular smooth muscle cells or to afford cardioprotection. While K<sub>ATP</sub>COs may be contraindicated in some types of arrhythmia, they may be of use in the treatment of certain other types of arrhythmia resulting from a repolarization defect [55]. K<sub>ATP</sub>COs suppress rhythm abnormalities (e.g. polymorphic ventricular tachyarrhythmias) related to delayed repolarization and early after-depolarizations in anaesthetized rabbits and may provide a novel intervention in the clinical occurrence of acquired long QT syndrome [56]. The relevance of such experimental studies to the clinical situation is still unclear. Although there appear to be good theoretical arguments why K<sub>ATP</sub>COs would be of use in the treatment of some arrhythmias and in ischaemic heart disease, there are major hurdles to overcome.

Activation of K⁺ channels can improve the energy metabolism and the mechanical performance of skeletal muscles suffering oxygen deficiency [57]. This is achieved partly by a selective dilatation of collateral vessels supplying the ischaemic skeletal muscle and partly by a better utilization of high-energy phosphates. In a rat skeletal muscle model of peripheral vascular disease (PVD), K<sub>ATP</sub>COs, but not Ca<sup>2+</sup> antagonists or hydralazine, selectively increased blood flow to collateral vessels in a previously ischaemic limb, with little or no effect on blood supply to normally perfused skeletal muscle
Further, cromakalim and SDZ PCO 400 (benzopyran) have been shown to improve recovery of muscle energy stores from ischaemia or to preserve performance under conditions of ischaemic contraction [57]. These beneficial effects in rat PVD models were reported at doses of KATPCOs below those affecting systemic blood pressure, demonstrating therapeutic potential for treating patients with peripheral vascular disease, a disabling disorder characterized by poor blood supply to the limbs due mostly to atherosclerosis. The stable analogue of prostacyclin, iloprost, which demonstrates beneficial effects in peripheral arterial occlusive disease (PAOD), hyperpolarizes smooth muscle cells through the activation of glibenclamide-sensitive K+ channels [59]. The role of K+ channel activation by iloprost in the treatment of PAOD remains to be determined. Cromakalim (10 μmol/l) increased 86Rb+ efflux in control cultured arterial smooth muscle cells, but was without effect in cholesterol-enriched cells [60]; thus, the benefit of KATPCOs in certain clinical conditions associated with excess may be questionable.

Finally, cromakalim, celikalim and pinacidil inhibited white thrombus formation in a rabbit arteriovenous shunt model, although they had no effect on human platelet aggregation [61]. The antithrombotic activity of KATPCOs in vivo may be related to effects on blood rheology and reduction of red blood cell deformability.

Respiratory system

Administration (oral, inhalation or intravenous) of cromakalim and other KATPCOs to conscious or anesthetized guinea pigs protects against 5-hydroxytryptamine, histamine or (in sensitized animals) ovalbumin-induced bronchoconstriction [11]. In anesthetized animals, in which protective cardiovascular reflexes are inhibited, a reduction in diastolic blood pressure was observed after oral or intravenous administration of KATPCOs. Nevertheless, inhalation of levromakalim evoked bronchodilatation at doses that failed to reduce arterial blood pressure, thus demonstrating a level of ‘selectivity’ [62]. Respiratory dynamics measurements in anesthetized guinea pigs revealed that cromakalim and BRL 55834 (benzopyran) resembled theophylline by eliciting similar inhibition of histamine-induced increase in airways resistance and decrease in lung compliance, while salbutamol, a β-agonist, was more effective against resistance than compliance. Thus, KATPCOs, compared with β-agonists, are more effective dilators of small airways (in which constriction decreases compliance) for identical large airways effects (which constriction increases resistance). Activation of high-conductance calcium-activated K+ channels (BKca) has been implicated in the relaxant responses of respiratory smooth muscle to β-agonists [11]. Thus, these findings may be suggestive of the distribution of KATP and KCa channels within the respiratory system.

The direct relaxant properties of KATPCOs have been assessed predominantly in guinea pig isolated trachealis muscle (GPT) [11]. This tissue has also been used for ion flux studies and intracellular recording of change in membrane potential. KATPCOs prevent or reverse contractions to a variety of spasmogens in respiratory smooth muscle. Blockade with glibenclamide of relaxant responses to KATPCOs in the GPT is not consistent with competitive antagonism [25, 26], but is consistent with a lack of spare ‘receptors/channels’. Thus, the pharmacological profile of glibenclamide in functional in vitro studies in GPT contrasts with that observed in vascular and some non-vascular (e.g. vas deferens) smooth muscle preparations in which competitive antagonism has been described. The lack of competitive antagonism by glibenclamide in GPT suggests the involvement of more than one mechanism in the relaxant effect(s) of KATPCOs. Interestingly, relaxations of bovine (and guinea pig) tracheal smooth muscle to BRL 55834 are mediated by, at least, a glibenclamide-sensitive K+ channel and a glibenclamide-resistant K+ channel [63]. The physiological consequences of the latter are, as yet, unknown. Cromakalim, levromakalim, pinacidil, HOE 234, SR 47063, SDZ PCO 400 and KC 399 demonstrate relaxant effects in human bronchiol smooth muscle [64–67], in which differences (primarily in potency) from the findings in guinea pig preparations suggest that the latter are not good predictors of the inhibitory responses of KATPCOs in human tissue.

The apparent efficacy of KATPCOs as anti-asthmatic drugs seems not to be attributable solely to their bronchodilator activity. These agents can reduce obstruction to airflow by suppressing antigen- or immune complex-induced hyperreactivity of intact airways in animals, at doses that are too low to relax airway smooth muscle in normal animals [67, 68]. An almost universal characteristic of asthmatic subjects is airways hyper-responsiveness to a wide range of stimuli [69]. Although several animal models have been developed to emulate this response, the causes in man are not well defined. In general, however, the degree of hyper-responsiveness achieved in animals is less than that in man. Compounds that open K+ channels and impair airway hyper-reactivity in the absence of direct smooth muscle spasmylosis will provide a novel approach to symptomatic therapy in asthma [68]. KATPCOs show no efficacy on allergen-induced leucocyte accumulation in bronchial alveolar lavage [57], a property that would need to be addressed in second-generation compounds.

In addition to smooth muscle relaxant properties, KATPCOs also inhibit neurotransmitter release from cholinergic neurons and non-adrenergic, non-cholinergic (NANC) excitatory neurons in guinea pig lung in vitro and in vivo [11]. A more effective
inhibition by K<sub>ATP</sub>COS was observed against responses to neurally derived than exogenously administered peptidergic excitatory neurotransmitter(s), leading to the proposal of a prejunctional site of action. The K<sub>ATP</sub>COS do not interfere with NANC inhibitory neuroeffector transmission in GPT [70]. The inhibition of [3H]acetylcholine release by cromakalim in rat isolated trachea was only observed in tube preparations, in which the mucosal/submucosal environment would be better preserved, suggesting an epithelium-dependent mechanism [71]. Levocromakalim and YM-934 inhibit plasma leakage in the trachea, main bronchi and central and peripheral intrapulmonary airways of the guinea pig evoked by stimulation of vagal nerves, but not that evoked by exogenously administered substance P [72, 73]. Thus, K<sub>ATP</sub>COS can inhibit airway neurogenic inflammation by modulating the release of neuropeptides from the sensory nerve endings. These neural effects of K<sub>ATP</sub>COS will be very relevant to the potential treatment of airways disease, because not only does bronchoconstriction frequently have a significant parasympathetic component, but neurogenic inflammation of the lung may also contribute to the pathology of asthma and chronic obstructive pulmonary disease (COPD).

Single (0.5 mg) or repeat (0.25, 0.5 mg) oral doses of cromakalim attenuate the morning dip in lung function of patients with nocturnal asthma [74]. The predicted peak plasma concentration in these studies was about fivefold less than the threshold concentration of cromakalim for relaxation of tone in human bronchi [64]. Studies in animal models suggest that the positive results of K<sub>ATP</sub>COS in the clinic will be due to actions other than just bronchial smooth muscle relaxation [11, 68], and may influence mechanisms underlying airways hyper-responsiveness. Interestingly, passive sensitization (incubation in serum from atopic asthmatic patients) of human isolated bronchial rings reduces the relaxant responses to levocromakalim and the calcium antagonist verapamil, but not those to modulators of the β-adrenoceptor signal transduction pathway (isoprenaline, forskolin and dibutyryl cAMP) [75]. The failure of a higher dose of cromakalim (1.5 mg, single oral dose) to improve lung function in patients with nocturnal asthma and of levocromakalim to improve lung function in histamine- or methacholine-challenged asthmatic subjects was as a consequence of headache, probably resulting from cerebral vasodilatation [74, 76]. Bimakalim lacks bronchodilatory effects after inhaled administration to adult patients with mild to moderate bronchial asthma [77]. Whether this is a true lack of bronchial efficacy or whether the dose of drug selected, to avoid other effects (no headaches or cardiovascular effects reported), was too low requires further investigation.

Thus, to be useful just as oral bronchodilators, K<sub>ATP</sub>COS must demonstrate selectivity for airways relative to vascular smooth muscle. The concept of antihyper-reactivity as a treatment in asthma and COPD, however, is independent of airways smooth muscle function. Thus, the use of K<sub>ATP</sub>COSs in control of mucus secretion and bronchial hyper-reactivity, especially as an inhaled therapy, can be envisaged, giving important clinical benefit.

Reproductive system

By virtue of their smooth muscle-relaxing effects, K<sub>ATP</sub>COS may be useful in the treatment of premature labour and dysmenorrhea [78, 79]. Cromakalim and RP 49356 cause glibenclamide-sensitive relaxation of rat uterine smooth muscle both in vitro and in vivo [80]. Cromakalim also inhibits spontaneous phasic activity and spasmogen-induced contractions of isolated uterus from term pregnant rats. Further, levocromakalim and pinacidil exhibit glibenclamide-sensitive inhibition of spontaneous and oxytocin-induced contractions in pregnant human isolated myometrium obtained before and after the onset of labour [78, 81]. Thus, K<sub>ATP</sub>COS may have potential as a new generation of tocolytic agents. Interestingly, K<sub>ATP</sub>COSs are more potent as tocolytic agents in non-pregnant than pregnant human myometrium suggesting that K<sub>ATP</sub>COSs demonstrate greater therapeutic potential for dysmenorrhea. In addition, not all women with preterm uterine contraction are candidates for tocolysis [79].

Although channels permeable to K<sup>+</sup> and Rb<sup>+</sup> exist in human isolated myometrium, Rb<sup>+</sup> differentiates the effects of levocromakalim and P1060 (a pinacidil analogue) on spontaneous contraction [82]. Although K<sub>ATP</sub>COSs may demonstrate therapeutic benefit in uterine associated disorders via a glibenclamide-sensitive mechanism, the profile of the K<sup>+</sup> channel(s) requires confirmation. Indeed, more work is needed to increase our understanding of K<sup>+</sup> channels in the myometrium.

Locally administered vasodilators are commonly used in the treatment of impotence, thus K<sub>ATP</sub>COSs, owing to their vascular smooth muscle relaxant properties, may offer an alternative approach. Pinacidil increases <sup>86</sup>Rb<sup>+</sup> efflux and inhibits spontaneous contractile activity as well as electrically induced and noradrenaline-induced contractions in human isolated cavernosum [83]. Recently, cromakalim was reported to increase intracavernous pressure in a simian monkey model, resulting in an erectile response of the penis [84]. Although topically applied minoxidil has been reported to be effective in facilitating erection when used to treat organic impotence in man, this finding is not supported [85, 86].

Urinary bladder

Bladder hyperactivity secondary to hypertrophy or partial outflow obstruction resulting in urinary
incontinence is common, and existing therapeutic approaches are often ineffective or poorly tolerated. In animal and human urinary bladder preparations, KATP COS inhibit myogenic activity and contractions to a variety of spasmogens, indicating potential in the treatment of urinary incontinence [11]. In isolated detrusor muscle preparations from human unstable bladder (due to urinary outflow obstruction), cromakalim and pinacidil inhibit elevated basal tone and spontaneous contractile activity. In addition, levrocromakalim, pinacidil and RP 49356 increase $^{42}$K$^+$ efflux in bladder tissues from a variety of species; however, as found in other smooth muscle systems, the concentrations of drug required are higher than those inhibiting myogenic activity [11]. Nevertheless, both the relaxant activity and enhancement of $^{42}$K$^+$ efflux due to KATP COS are sensitive to glibenclamide. The ability of KATP COS to inhibit electrically induced contractions of urinary bladder tissues is variable and may be related to the degree of depolarization produced by neuronal stimulation in these models.

Evaluation of KATP COS in in vivo urinary bladder models have been limited because of vascular effects. Comparison of the effects of levrocromakalim, pinacidil, Ro 31-6930, RP 49356 and S 0121 did not reveal selectivity for the rat isolated detrusor muscle over isolated portal vein [87]. A series of novel KATP COS (anilide tertiary carbinols, e.g. ZD 6169) have been reported to act selectively on urinary bladder smooth muscle, without producing significant cardiovascular effects, after oral administration to rats [88]; these agents may have potential for treating patients with urge incontinence. Observations in animal models with KATP COS have yet to be supported by clinical trials, as initial studies in humans were disappointing. In patients with urinary bladder hyperactivity and outflow obstruction (secondary to prostatic hyperplasia), pinacidil failed to demonstrate improvement in bladder function [89]. Levrocromakalim increased the duration of bladder contraction, but was without effect on other urodynamic parameters in patients with high spinal cord lesions [90]. Hypotensive responses led the authors to suggest that higher doses of levrocromakalim could only be evaluated if administered intravesically.

Gastrointestinal tract

KATP COS inhibit spontaneous slow-wave contractile activity and/or contractile responses to spasmogens in a variety of gastrointestinal tissues (e.g. taenia caeci, ileum, colon, muscle myenteric plexus, oesophagus, stomach) [11]. These effects are associated with glibenclamide-sensitive K$^+$ efflux and hyperpolarization. Pinacidil (1–10 mg/kg per os) and cromakalim (0.5–10 mg/kg per os) dose-dependently delay the intestinal transit and protected against castor oil-induced diarrhoea in mice [91]. Thus, data from animal studies suggest that KATP COS may have utility in conditions associated with disturbances in gastrointestinal motility, such as irritable bowel syndrome. Interestingly, the evaluation of such drugs for other clinical conditions has not revealed an incidence of adverse effects on the gastrointestinal tract, such as constipation; however, this would be influenced by the pharmacokinetics and site of absorption of these agents. To gain a full appreciation of the potential therapeutic benefit of KATP COS, compounds that will not be removed from the gastrointestinal tract may be required.

Central nervous system

K$^+$ channels play a pivotal role in the control of neuronal excitability, action potentials and neurotransmitter release within the central nervous system (CNS) [1, 3, 7]. Activation of a variety of receptors (e.g. opioid, 5-hydroxytryptamine, somatostatin, $a_2$-adrenoceptors) by the appropriate neurotransmitters alters K$^+$ ion efflux from neurons. Because of this fundamental role in normal physiology, defects in the function of K$^+$ channels may underlie several CNS diseases. The distributions of binding sites in the rat brain for the three ligands [125]iodoglyburide, [125]apamin and [125]charybdotoxin, as markers for KATP, SKc, (low-conductance calcium-activated K$^+$ channels) and BKc (or voltage-gated K$^+$) channels respectively, are dramatically different [92]. These data indicate that pharmacological modulation by agents specific for each K$^+$ channel subtype should result in distinct, but different, effects on brain function. [125]Iodoglyburide binding exhibits a very broad distribution in the brain, being found in the majority of brain regions; the globus pallidus and the zona reticulata of the substantia nigra (involved in movement co-ordination) contain the highest density of these binding sites. Sulphonylurea-binding studies, however, can provide only indirect evidence of KATP channels. Although the KATP CO ligands [3H]P1075 and [3H]cromakalim [20, 21] exist, the distribution of their binding site(s) within the CNS is not yet available.

Anoxia-induced neuronal depolarization is due, at least in part, to the release of large concentrations of excitatory amino acids (e.g. glutamate), which may be involved in long-term ischaemia-induced brain damage [93]. Dizoxide prevents anoxia-induced depolarization of rat CA3 hippocampal neurons in vitro after the opening of K$^+$ channels; these effects are inhibited by glibenclamide. In addition, levrocromakalim and aprikalim block ischaemia-induced glutamate release in rat hippocampal slices [93]. Thus, KATP COS may prevent anoxia-induced damage to hippocampal neurons by inhibiting the release of excitatory amino acids. Levrocromakalim, nicorandil and pinacidil also block ischaemia-induced expression of the genes c-fos and c-jun and the mRNAs for 70-kDa heat-
shock protein and a form of the amyloid β-protein precursor in rat hippocampus [94]; these effects are abolished by glipizide. In addition to totally blocking the ischaemia-induced expression of the different genes, the KATPCOs protect the neuronal cells against degeneration. Levocromakalim, diazoxide and pinacidil protect rat cultured hippocampal neurons against oxidative injury induced by exposure to ferrous sulphate and amyloid β-peptide [95]. Thus, KATPCOs are neuroprotectant drugs and, because of the broad distribution of KATP channels, most neuronal populations in the CNS would benefit.

Movement disorders associated with Parkinson’s disease are due to a selective loss of dopaminergic neurons in the substantia nigra, where the highest density of [125I]iodothyrybude binding in the rat brain is found [92]. Sulphonylureas and increased extracellular glucose concentration augment the release of [3H]gamma-aminobutyric acid (GABA) from the substantia nigra, effects that are inhibited by KATPCOs [96]. The order of potency of the KATPCOs in this study (levrocromakalim > nicorandil > cromakalim > diazoxide > pinacidil) was found to be different from that to evoke responses in either pancreatic β-cells or smooth muscle cells, suggesting differences between the target K+ channel in CNS and those in peripheral tissues. The KATP channel in neuronal tissue is not the type 1 channel as found in pancreatic β-cells or muscle cells, but a large-conductance non-rectifying subtype (type 2 KATP channel [18]).

The genesis and propagation of non-physiological electrical impulses are the hallmark of epilepsy; thus, hyperpolarization (and restraining) of excitatory cells through the opening of K+ channels could be of therapeutic benefit in this setting. Cromakalim and aprikalim reduced seizures in genetically epileptic rats [97]. In a diltiazem-induced model of tonic–clonic seizures in rat, cromakalim completely inhibited both EEG and behavioural seizures, whereas pentobarbitone prevented only behavioural activity [98]. Interestingly, the antiepileptic drugs carbamazepine and oxcarbazepine increase potassium currents in neuronal tissue [99]; whether this property of the drug is linked to the pharmacological actions and of clinical importance is not known.

Opioids exert analgesic effects by the stimulation of opiate receptors, leading to the opening of K+ channels and neuronal hyperpolarization. Morphine-induced antinociception in the mouse tail-flick test is mediated by the opening of KATP channels [100], suggesting a role for KATPCOs as analgesics. This proposal is supported by the finding that intrathecal administration of BRL-38227 (levocromakalim), minoxidil or diazoxide produces antinociception in the mouse tail-flick test [101]. Cross-tolerance to the effects of morphine was not exhibited in this model, suggesting that the KATPCOs and opioids probably do not act on a common site, but do have a common second messenger. In addition, intracerebroventricular administration of pinacidil evokes a dose-dependent increase in the effects of morphine in rats during the hot-plate and tail-flick tests [102]. Interestingly, tachykinins (particularly substance P) are important mediators in the nociceptive pathways [103], and their release from nerve endings in the respiratory system can be modified by KATPCOs [11, 72]; data on the effects of KATPCOs on neurotransmission in the nociceptive pathways are awaited. Benzopyran derivatives of cromakalim (e.g. SR 46142A) exert antidepressant activity shown as improvement of swimming performance in mice, in the absence of a cardiovascular effect [104]. These findings suggest that modifications of the benzopyran nucleus would allow tissue selectivity (i.e. CNS over vascular smooth muscle) to be achieved. Whether the antidepressant effects of SR 46142A (and related compounds [105]) are mediated by modulation of K+ channels remains to be confirmed.

Data from the above in vitro and in vivo studies support KATPCOs as a therapeutic approach for CNS disorders. Although these studies are encouraging, neuron-selective agents that cross the blood–brain barrier are needed to realize the true potential clinical applications of KATPCOs in the CNS. The promiscuity of KATPCOs does not invoke adverse CNS effects, for example cromakalim, like d-amphetamine, enhances spontaneous locomotor activity in the rat through a glibenclamide-sensitive mechanism [106].

**Skeletal muscle**

In skeletal muscle, KATP channel activity has been shown to increase upon intracellular acidification owing to a reduction in the inhibitory effects of ATP [3, 8, 9]. This suggests that, during increased muscle exercise and consequent lowering of pH, KATP channel-induced hyperpolarization will prevent spontaneous contractions from occurring.

Cromakalim, pinacidil and RP 49356 increase the opening time of a glibenclamide-sensitive K+ channel in mouse skeletal muscle [11]. Although diazoxide activates KATP channels in smooth muscle and pancreatic β-cells, this KATPCO had very little effect in skeletal muscle even at very high concentrations. Interestingly, this sulphonamide (diazoxide is structurally related to the sulphonylureas) inhibits ATP-sensitive channels in ventricular cardiac muscle cells [17]. These differing effects of diazoxide suggest that the KATP channels in mouse skeletal muscle are more like those in cardiac cells than those in smooth muscle and pancreatic β-cells. Cromakalim also enhances K+ efflux in human skeletal fibres, an effect blocked by tolbutamide. Cromakalim, pinacidil and RP 49356 evoke larger hyperpolarizations in skeletal muscle fibres from patients with myotonic dystrophy or hypokalaemic
periodic paralysis than in those from normal subjects [11, 27]. Thus, KATP COs could have a role in the treatment of pathological muscle fatigue or paralysis resulting from excessive membrane depolarization.

Hair growth

The occurrence of hypertrichosis during anti-hypertensive treatment with minoxidil led to subsequent evaluation of the drug (applied topically) to enhance hair regrowth in certain forms of male baldness [107]. Although this effect has been suggested to involve K+ channels, hypertrichosis occurs in 80-100% of minoxidil-treated patients but in only 2-13% of pinacidil-treated patients. In cultured whisker follicles, minoxidil, but not the pinacidil analogue P1075, preserves the root sheath; however, both drugs stimulate cysteine incorporation [108]. Minoxidil has also been shown to stimulate DNA synthesis in mouse epidermal keratinocytes and whole hair follicle cultures [109]. The root sheath may be the target for minoxidil, thus stimulating hair growth through a direct effect on the hair follicle. The role, if any, of KATP channels in hair growth requires confirmation.

Intraocular pressure

Repeated topical applications of pinacidil, cromakalim or nicorandil lower the intraocular pressure (IOP) of rabbits, suggesting potential benefit of KATP COs in eye disorders such as glaucoma [110]. In an isolated arterially perfused bovine eye preparation, pinacidil caused a sustained decrease in IOP with no effect on arterial perfusion pressure [111]. Thus relaxation of resistance vessels is not responsible for the KATPCO-induced fall in IOP. Whether these effects in the eye may be attributed to enhanced K+ ion movement and consequent effects on smooth muscle or epithelial cells requires further investigation.

CONCLUSION

K+ channels control cell electrical activity, and their opening and closure are influenced by a wide range of physiological factors; thus, they are among the most regulated of all ion channels in biology. Promotion of activity in K+ channels tends to stabilize cell function, and the discovery of synthetic molecules that 'directly' open K+ channels has led to a new direction in the pharmacology of ion channels. The identification of the KATP channel-opening property of cromakalim initiated major research efforts in the search for other such agents and in the determination of the specific channel(s) involved. KATP channel-opening properties have subsequently been demonstrated in a diverse range of chemical structures (synthetic and endogenous). Although the ability of glibenclamide to antagonize the actions of this group of compounds led to the suggestion of KATP channels being the site of action, this is still an active area of research.

The decrease in the excitability of cells that follows K+ channel opening implies a broad clinical potential in a range of pathological conditions for drugs demonstrating this property. Consequently, therapeutic roles for KATP COs can be envisaged in disorders of a wide range of cells (e.g. vascular and non-vascular smooth muscle, cardiac muscle, neuronal and skeletal muscle cells). Although lack of selectivity of current compounds remains a major hurdle in this area, advances in prototype KATP COs and our knowledge of KATP channel pharmacology are encouraging. A combined effort of electrophysiology, functional pharmacology and molecular biology with subsequent studies of the expressed clone(s) will be required to address the real question of channel selectivity and potential KATP CO sub-classification. The differences already observed in the pharmacology of KATP COs, therefore, will be important factors to consider in the development of second-generation compounds, when tissue/organ selectivity is sought. The development of KATP COs providing positive results in extensive clinical trials to give an appreciation of the full therapeutic potential are eagerly awaited.

Finally, the existence of so many different subtypes of K+ channels has been an impetus in the search for new molecules that would have different biological profiles and channel selectivities (e.g. KATP, BKCa). Availability of KCOs acting selectively on K+ channel subtypes should facilitate more detailed study under normal and pathophysiological conditions, leading to focused therapeutic approaches for defined pathological conditions.

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