

Focused issue on  $K_{ATP}$  channels

## $K_{ATP}$ channel therapeutics at the bedside

A. Jahangir \*, Andre Terzic

*Division of Cardiovascular Diseases, Departments of Medicine, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic College of Medicine, Guggenheim 7, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*

Received 2 February 2005; received in revised form 17 March 2005; accepted 26 April 2005

### Abstract

The family of potassium channel openers regroups drugs that share the property of activating adenosine triphosphate-sensitive potassium ( $K_{ATP}$ ) channels, metabolic sensors responsible for adjusting membrane potential-dependent functions to match cellular energetic demands.  $K_{ATP}$  channels, widely represented in metabolically-active tissue, are heteromultimers composed of an inwardly rectifying potassium channel pore and a regulatory sulfonylurea receptor subunit, the site of action of potassium channel opening drugs that promote channel activity by antagonizing ATP-induced pore inhibition. The activity of  $K_{ATP}$  channels is critical in the cardiovascular adaptive response to stress, maintenance of neuronal electrical stability, and hormonal homeostasis. Thereby,  $K_{ATP}$  channel openers have a unique therapeutic spectrum, ranging from applications in myopreservation and vasodilatation in patients with heart or vascular disease to potential clinical use as bronchodilators, bladder relaxants, islet cell protector, antiepileptics and promoters of hair growth. While the current experience in practice with potassium channel openers remains limited, multitude of ongoing investigations aims at defining the benefit of this emerging family of therapeutics in diverse disease conditions associated with metabolic distress.

© 2005 Elsevier Ltd. All rights reserved.

**Keywords:** ATP-sensitive  $K^+$  channels; Kir6.2; Kir6.1; SUR1; SUR2; Angina pectoris; Hypertension; Ischemic heart disease; Peripheral vascular disease; Asthma; Alopecia; Impotence; Neuroprotection

### 1. Introduction

Therapeutic agents, collectively termed potassium channel opening drugs, have been developed to target adenosine triphosphate-sensitive potassium ( $K_{ATP}$ ) channels with the recognition that these metabolism-sensing channels play a vital role in matching membrane electrical excitability with changes in energetic state. In this way,  $K_{ATP}$  channels serve as endogenous homeostatic transducers balancing cellular resources in response to altered demand [1–13]. Indeed, in the heart,  $K_{ATP}$  channels protect against the metabolic insult of ischemia, and contribute as molecular mediators in the adaptive response to distress. Moreover,  $K_{ATP}$  channels regulate vascular tone, and thereby the delivery of metabolic resources to match demand [4–6,11]. Furthermore, these channels are central in setting blood glucose levels by regulating insulin secretion in pancreatic  $\beta$ -cells and insulin-dependent glucose uptake in skeletal muscle [5,6]. In the brain,

$K_{ATP}$  channel activation also serves a protective role against metabolic challenge [9]. Thus,  $K_{ATP}$  channels, integrated with cellular and systemic metabolism, act at various levels to ensure metabolic well being under the challenge of stress [13]. By promoting  $K_{ATP}$  channel activity, potassium channel openers stabilize membrane excitability and preserve metabolic expenditure [9,13] making this class of therapeutics highly desirable as cytoprotective agents under diverse conditions of excessive demand [1–6,14]. In particular, potassium channel openers have shown promise in myocardial protection, as antihypertensive vasodilators, bronchodilators, bladder relaxants, islet cell protectors, antiepileptics, and promoters of hair growth (Fig. 1).

Potassium channel openers are chemically diverse [1,2], and belong to a number of structural classes (Fig. 2). These include benzopyrans (levromakalim, bimakalim), benzothiadiazines (diazoxide), cyanoguanidines (pinacidil), cyclobutenediones (WAY-151616), nicotinamides (nicorandil), pyrimidines (minoxidil), tertiary carbonoles (ZD-6169), thioformamides (aprikalim), and dihydropyridine-like structures (ZM-244085) [1–4].

\* Corresponding author. Tel.: +1 507 284 6753; fax: +1 507 284 9111.  
E-mail address: [jahangir.arshad@mayo.edu](mailto:jahangir.arshad@mayo.edu) (A. Jahangir).

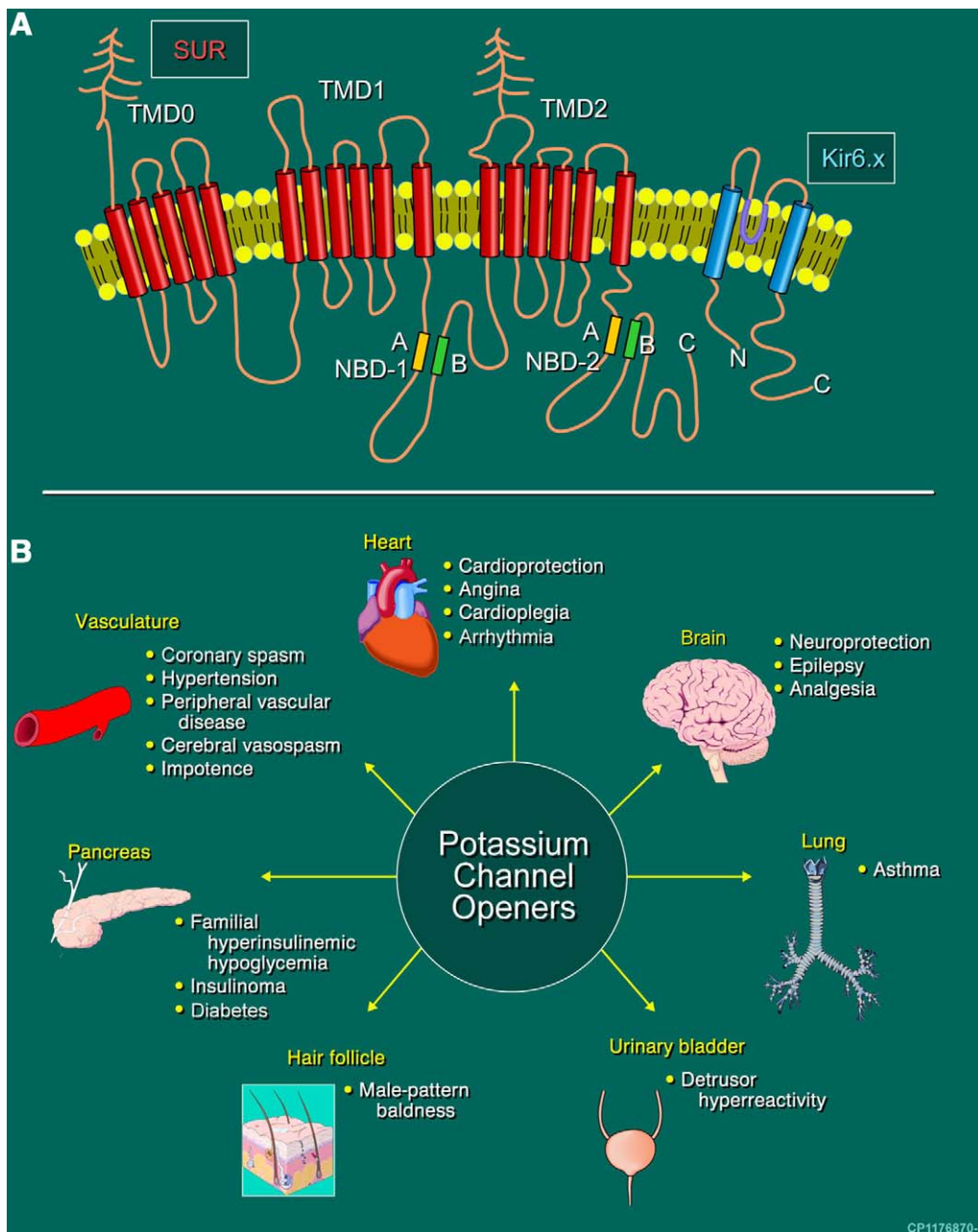


Fig. 1. ATP-sensitive potassium channel subunits (A) and potential clinical use of potassium channel openers. The  $K_{ATP}$  channel complex consists of the pore-forming Kir6.x (Kir6.2 or Kir6.1) subunit and the regulatory sulfonylurea receptor (SUR1, SUR2A or SUR2B) subunit, which serves as a metabolic sensor and target of drug action. The SUR subunit has 17 transmembrane segments (TMs) arranged in three domains, TMD0 (5 TMs), TMD1 (6 TMs) and TMD2 (6 TMs). Two critical sites for KCO binding exist in TMD2 at position Tyr1059 to Leu1087 (KCO I) and Arg1218 to Asn1320 (KCO II). Nucleotide binding folds (NBD-1 and NBD-2) with Walker A and B consensus motifs are present on two large intracellular loops and are implicated in channel regulation by ATP and MgADP. N and C represent respective amino and carboxy termini of constitutive channel subunits and are intracellularly located. **B**). Clinical conditions in which potassium channel openers have therapeutic promise.

The primary target for potassium channel opener action is through the regulatory subunit of the  $K_{ATP}$  channel, known as the sulfonylurea receptor or SUR, an ATP-binding cassette protein [5,6,15–17]. This subunit contains nucleotide binding domains, implicated in decoding and processing of metabolic signals. Through physical association with the pore-forming Kir6.x inwardly rectifying potassium channel, the SUR subunit forms a heteromultimeric  $K_{ATP}$  channel complex (Fig. 1A [5,6,15]). While the precise molecular mecha-

nism of action remains only partially understood, activation of  $K_{ATP}$  channels has been ascribed to the ability of potassium channel openers to reduce the ATP-induced pore inhibition [8]. This can be achieved by promoting stabilization of the MgADP-bound state at the nucleotide binding domain 2 of the SUR subunit associated with positive channel gating and pore opening [8]. Progress has been made in identifying the residues, which determine potassium channel opener action [18–24]. These include amino acids located within

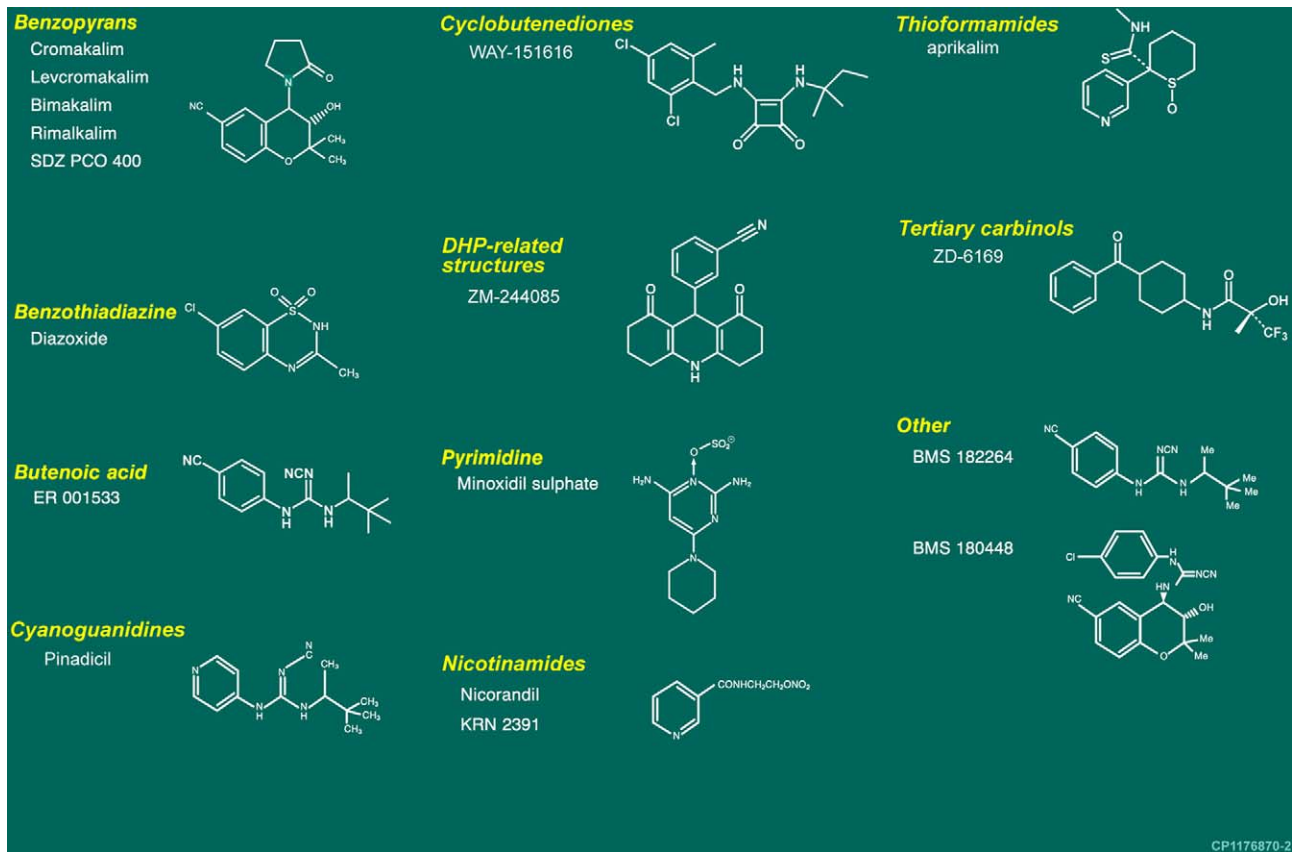


Fig. 2. Classification of potassium channel openers based on chemical structure.

the last transmembrane domain TMD2 of SUR (Fig. 1A [18]), the cytoplasmic loop connecting TM helices 13 and 14, a region encompassing TM helices 16 and 17 and a short segment of the nucleotide binding domain NBD2, [23] along with two residues within TM helix 17 (L1249 and T1253 in the SUR2A, T1286 and M1290 in the SUR1 isoform) [18]. These recent findings have provided information on the tissue-specificity and selectivity of the pharmacological response to potassium channel openers [18–25]. Indeed, the SUR2A isoform, predominantly expressed in cardiac and skeletal muscles and its splice variant SUR2B in smooth muscle, are activated by a broad range of potassium channel openers [16,17,23–27], whereas the isoform SUR1, expressed in neuronal and pancreatic  $\beta$ -cells, is activated by a limited number of openers [5,6,26]. The distribution of SUR isoforms with differential responsiveness to potassium channel openers thus provides unique targets for the development of tissue-specific therapeutics.

## 2. Potassium channel openers in ischemic heart disease

Potassium channel openers have proven useful in limiting myocardial dysfunction under conditions of ischemia–reperfusion and heart failure through direct actions on the myocardium [27–32]. This protective action exploits the essential role of  $K_{ATP}$  channels in cardiac stress adaptation, ranging from preservation of contractile performance under

imposed load to myocardial salvage following ischemic challenge [13]. Overexpression of  $K_{ATP}$  channel genes enhances cytoprotection, while knockout of channel subunits has been associated with predisposition to myocardial damage and survival disadvantage under stress [13,31], along with loss of the cardioprotective response to ischemic preconditioning [10,27–33]. Disease-induced  $K_{ATP}$  channel dysregulation compromises cardiac stress adaptation [30], and mutations in the regulatory SUR subunit increases susceptibility for inherited cardiomyopathy [34]. The benefit of potassium channel openers apparently stems from prevention of intracellular  $Ca^{2+}$  overload, as opening of plasma membrane  $K_{ATP}$  channels shortens the action potential duration (APD) limiting cellular injury by preserving cellular energetics and ultimately cell survival (Fig. 3 upper panel) [27–31]. Additional, subcellular sites of potassium channel opener action have been identified, including the inner membrane of the mitochondria where a protective outcome has been linked to prevention of mitochondrial  $Ca^{2+}$  overload [27,35–38], modulation of reactive oxygen species generation [35,39], and preservation of energetics and nucleotide pools [35–45].

In addition to direct effects on heart muscle per se, potassium channel openers through regulation of vascular smooth muscle (Fig. 3 lower panel) are also potent vasodilators [11]. This is due to  $K_{ATP}$  channel-dependent membrane hyperpolarization, reduction in  $Ca^{2+}$  influx through the voltage-gated  $Ca^{2+}$  channels and regulation of intracellular  $Ca^{2+}$  mobilization in smooth muscle cells [46,47]. Knockout of  $K_{ATP}$  chan-

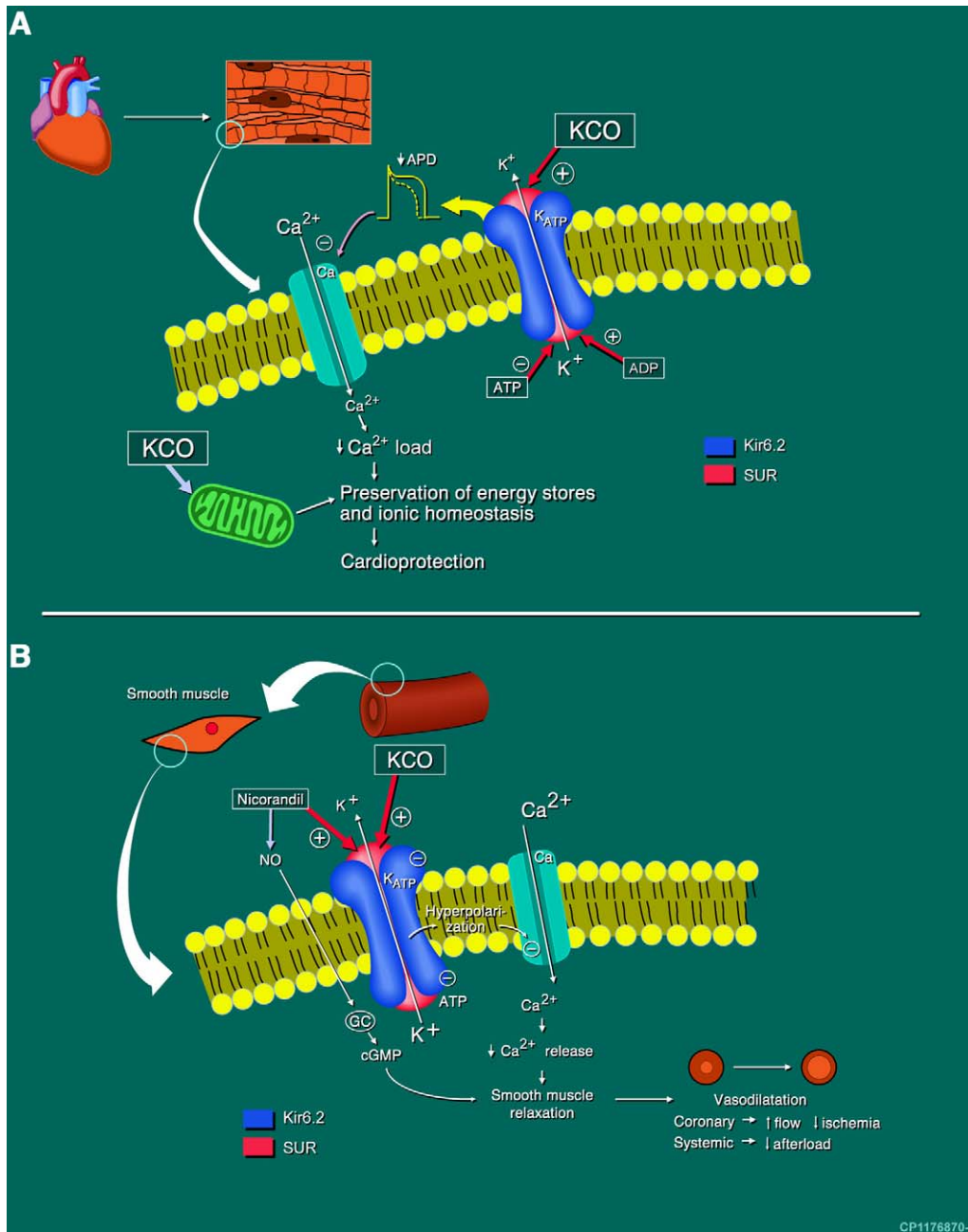


Fig. 3. Potassium channel openers (KCO) effect on (A) cardiac and (B) vascular smooth muscle. **A**). KCO decreases intracellular  $\text{Ca}^{2+}$  influx through the voltage-gated  $\text{Ca}^{2+}$  channels by activating cardiac sarcolemmal  $\text{K}_{\text{ATP}}$  channel and shortening of APD. Opening of  $\text{K}_{\text{ATP}}$  channels is promoted in ischemia and hypoxia through adenine nucleotide-dependent channel gating, increase in intracellular protons ( $\text{H}^+$ ) or lactate, and release of adenosine (Ado). KCO also modulate mitochondrial membrane potential, prevent mitochondrial  $\text{Ca}^{2+}$  overload and free radical production. ATP, adenosine triphosphate, ADP, adenosine diphosphate. **B**). KCO promote vascular smooth muscle relaxation and vasodilatation by membrane hyperpolarization and decrease in intracellular  $\text{Ca}^{2+}$ . Nicorandil may also vasodilate through a nitric oxide (NO)-dependent activation of guanylate cyclase (GC) and cyclic guanosine monophosphate (cGMP).

nel subunits promotes vasospasm [12], and hypertension. Potassium channel openers primarily vasodilate arterioles and arteries [46–48]. Venodilation does not occur with most potassium channel openers, although nicorandil and KRN by means of a nitrate moiety also dilate venous capacitance vessels and thereby reduce cardiac preload [49].

Due to combined cardioprotective and vasodilatory properties, potassium channel openers are considered for therapy in a number of cardiac conditions. These include protecting the myocardium under cardiopulmonary bypass [45,50], pre-

serving donor transplant heart [51,52], treating ischemic heart disease [49,53], hypertension [48], peripheral vascular disease [54], and arrhythmia related to abnormal repolarization [55–60].

In cardiac surgery, openers of  $\text{K}_{\text{ATP}}$  channels may serve as adjuncts or main components in cardioplegic solutions. In several experimental models of surgical ischemia and cardiopulmonary bypass, potassium channel openers, including nicorandil, aprikalim and pinacidil, provide greater cardioprotection than conventional cardioplegia [50–52]. In patients

undergoing coronary artery graft surgery, the time required to achieve cardiac arrest, ST-segment changes on the electrocardiogram after aortic unclamping, plasma levels of peak creatine kinase-MB, malondialdehyde and human-heart fatty acid-binding protein and dosage of inotropic agents required were all lower in the group treated with nicorandil compared to controls on conventional therapy [61]. Potassium channel openers are also considered for preservation of donor heart for transplantation, and when used before storage provides superior preservation of cardiac function following prolonged hypothermic storage [51].

In ischemic heart disease, the value of potassium channel openers in protecting the myocardium is clinically best documented with nicorandil [49]. In patients, nicorandil has been shown to be useful in the management of both stable and unstable angina with minimum adverse effects [49]. In placebo-controlled, single- and double-blind studies of patients with stable angina pectoris, nicorandil attenuated rest and effort angina, prolonged the duration of exercise and the time to onset of angina or ischemic ST-T changes [62]. In a multicenter trial enrolling more than 5000 subjects with stable angina pectoris, long-term use of nicorandil was associated with reduction in cardiovascular events and the combined endpoints of death, myocardial infarction and hospitalization due to chest pain [63].

In patients with unstable angina, nicorandil, when added to aggressive anti-anginal treatment, reduces transient myocardial ischemia, and arrhythmias when compared to placebo [64]. Nicorandil improves ischemia-induced regional wall motion abnormalities, and perfusion in infarct-related areas [65–67]. In patients undergoing angioplasty, nicorandil preconditions the heart, improves coronary hemodynamics, dilates stenotic and non-stenotic segments, and ameliorates the “no-reflow” phenomenon [44,51,53,65–68]. Intravenous nicorandil, in conjunction with coronary angioplasty, preserves microvascular integrity and myocardial viability in patients with acute myocardial infarction [49,63,65]. Nicorandil also reduces preload and afterload, enhances cardiac endothelial nitric oxide synthase expression and has antiplatelet, fibrinolytic and antioxidant properties [49,69]. Unlike nitroglycerin, no development of tolerance to the anti-anginal effect of nicorandil has been reported [49]. Nicorandil is an effective anti-anginal agent at a dose of 10 to 40 mg twice a day, controlling stable chronic angina in 70 to 80 percent of patients [49]. The response to nicorandil is maintained for 12 h, with an efficacy that compares favorably with that of nitrates [70],  $\beta$ -adrenoceptor [71] and  $\text{Ca}^{2+}$ -channel blockers [72]. Main side-effects include headache, gastrointestinal disturbances and dizziness [3,49]. Recently, nicorandil use has been associated with mucosal ulceration, including stomatitis and mouth and anal ulcerations [49]. No evidence of proarrhythmia, conduction disturbance, exacerbation of myocardial ischemia, infarction, abrupt withdrawal syndrome, symptomatic decrease in blood pressure or change in heart rate has been observed [49,63]. Also, no adverse interaction has been reported in patients on oral anticoagulants or

hypoglycemic agents. The pharmacokinetics of nicorandil is unaltered in the elderly or patients with renal or hepatic insufficiency [49].

In vasospastic angina, nicorandil, with potent vasospasmolytic activity, relieves both ergonovine-evoked and spontaneous coronary spasm, attenuates episodes of variant angina, suppresses ST-segment changes and improves perfusion defects [73,74]. Levromakalim, aprikalim and KRN4884 relax conduit arteries (internal mammary and gastroepiploic arteries) used as coronary artery bypass grafts and could be useful in preventing spasm of bypass grafts in patients undergoing surgery for atherosclerotic heart disease [75,76].

### 3. Potassium channel openers in rhythm disturbances

Potassium channel openers by shortening the cardiac action potential may prevent arrhythmias related to triggered activity resulting from abnormal repolarization and early or delayed after depolarization [58,77–82]. In models of prolonged QT syndrome and drug-induced ventricular arrhythmias, pinacidil and nicorandil are effective in suppressing abnormal automaticity, triggered activity and Torsade de pointe [81]. In fact, genetic deletion of the  $\text{K}_{\text{ATP}}$  channel predisposes to catecholamine-induced ventricular dysrhythmia [82]. In patients with congenital long QT syndrome and history of syncope, nicorandil improved repolarization abnormalities, abolishes early after depolarization and prevents recurrence of syncope [59,83]. Potassium channel openers are therefore an attractive therapeutic consideration in conditions with congenital or acquired prolongation of repolarization. Because of their heterogeneous effect on shortening of refractoriness in the epicardium versus endocardium and ischemic versus non-ischemic areas, concerns have been raised that potassium channel openers may further increase dispersion of refractoriness and therefore facilitate reentrant arrhythmias by increasing electrical inhomogeneity [84,85]. However, in clinical trials aggravation of arrhythmia or induction of life-threatening arrhythmias has not been documented for any of the potassium channel openers tested [49,63,86]. In fact, a recent study in patients with acute myocardial infarction treated with intravenous nicorandil at the time of coronary angioplasty showed a reduction in both dispersion of repolarization and incidence of malignant ventricular arrhythmias [79].

### 4. Potassium channel openers in peripheral vascular disease

Potassium channel openers may be advantageous for symptomatic control of peripheral ischemia. Drugs such as calcium channel blockers or direct vasodilators are typically not beneficial in peripheral vascular disease, and could worsen ischemia due to reduction in perfusion pressure in the affected

area with diversion of blood to vasodilated non-ischemic regions [54]. Potassium channel openers do not promote such “steal phenomenon”. Accordingly, potassium channel openers improve blood flow and oxygen availability to the chronically ischemic muscle. This restores the high-energy phosphate content and improves muscle performance during acute ischemia in models of occlusive arterial disease [54,87].

### 5. Potassium channel openers in systemic and pulmonary hypertension

Potassium channel openers control blood pressure in 70–85% of patients with systemic hypertension [88]. Their efficacy in reducing high blood pressure is similar to other conventional antihypertensive medications in most individuals [88] but in those with resistant hypertension where therapy has failed with multi-drug regimens they are especially effective [88,89]. Diazoxide and minoxidil are currently recommended for the management of hypertensive emergencies and severe resistant hypertension, especially in patients with advanced renal disease [89] (Table 1). Tachyphylaxis to the

antihypertensive effect of potassium channel openers and rebound hypertension on abrupt withdrawal has not been reported. Their routine use as antihypertensive agents is limited because of a reflex increase in heart rate due to the stimulation of the sympathetic nervous system in response to arterial vasodilatation causing flushing, headache and/or sodium and water retention [88]. Therefore, potassium channel openers should be administered in conjunction with a diuretic and  $\beta$ -adrenergic blocker to control reflex increase in heart rate [89]. An increase in plasma renin activity (largely due to activation of the sympathetic nervous system) and aldosterone level may also occur. Hyperglycemic effects of diazoxide and possible hypertrichosis with minoxidil also limit their long-term use, particularly in women [89]. Although potassium channel openers are effective in reducing blood pressure, the accompanying neurohumoral and hemodynamic changes may partially attenuate or offset the antihypertensive effect and preclude their routine use, especially when other antihypertensive with lesser side-effects are available. However, cardioprotective and antiischemic properties of potassium channel openers, beneficial effects on glycation and plasma lipids or bronchial smooth muscle relaxation still makes potassium

Table 1  
Potassium channel openers in clinical use

|   | Therapeutic uses  | Dosage   | FDA labeled uses   | Contraindications and precautions   | Adverse effects   |
|---|---|--|--|---|---|
| Diazoxide <sup>a,b</sup><br>(Hyperstat®<br>Proglycem®)                | HTN (malignant, pregnancy)<br>Pulmonary hypertension<br>Hypoglycemia<br>Uterine hyperactivity                             | HTN (13 mg/kg IV bolus Q<br>5–15 min)<br>Hypoglycemia (3–8 mg/kg PO QD in Q8–12 h)<br>Hypoglycemia infants (8–15 mg/kg PO QD in Q8–12 h) | Hypertension<br>Hypoglycemia                                       | Hypersensitivity to diazoxide<br>Functional hypoglycemia<br>Recent myocardial infarction                  | Hypotension<br>Reflex tachycardia<br>Aggravation of angina<br>Gastric disturbances<br>Hyperglycemia               |
| Minoxidil <sup>a,b</sup><br>(Loniten®, Rogaine®)                      | Alopecia (drug induced)<br><i>Alopecia androgenica</i><br><i>Alopecia areata</i><br>Malignant/refractory HTN<br>Impotence | Hypertension 2.5–80 mg PO (QD–BID (with $\beta$ -blocker &/or diuretic)<br>Alopecia: topically 2% (1 ml BID)                             | <i>Alopecia androgenica</i><br>Hypertension (refractory/resistant) | Hypersensitivity to minoxidil   | Hypertrichosis<br>Pleural/pericardial effusion<br>Reflex tachycardia<br>Fluid retention                           |
| Nicorandil <sup>b</sup> (SG-75® Adancor®, Dancor®, Ikorel®, Sigmart®) | <i>Angina pectoris</i><br>Arrhythmia<br>CHF<br>Hypertension   | Angina 10–40 mg PO BID<br>Angina, CHF 2–6 mg/h IV  | N/A  | Hypersensitivity<br>Symptomatic hypotension<br>Cardiac conduction defects<br>Recent myocardial infarction | Headache<br>Postural hypotension<br>Gastric disturbances<br>Flushing<br>Rash<br>Mouth ulceration                  |
| Pinacidil <sup>b</sup><br>(Pindac®)                                   | Hypertension  | <i>Hypertension</i> 12.5 mg BID (in combination with diuretic)   | N/A  | Hypersensitivity<br>Acutely after myocardial infarction or cerebral vascular accidents                    | Headache, Fluid retention<br>Dizziness, Flushing<br>Postural hypotension<br>Reflex tachycardia<br>Hypertrichosis, |

PO = by mouth; IV = intravenous; HTN = hypertension; BID = twice daily; QD = once daily; QID = four times daily.

<sup>a</sup> Approved in USA.

<sup>b</sup> Approved outside USA.

channel openers an attractive antihypertensive class in patients with ischemic heart disease, diabetes mellitus and bronchospastic disease [90].

In pulmonary hypertension, potassium channel openers have been useful by inhibiting hypoxic pulmonary vasoconstriction [91,92]. Potassium channel openers also decrease mean pulmonary artery pressure and pulmonary resistance in models of pulmonary hypertension, which are otherwise resistant to conventional pharmacotherapy [93,94]. Also, a beneficial effect on decreasing pulmonary vascular resistance and limitation of reperfusion injury after lung allotransplantation has been reported [95].

## 6. Potassium channel openers and pulmonary disease

Bronchial hyperreactivity, the hallmark of asthma, occurs due to an increased excitability of the bronchial smooth muscle, airway microvascular leakage or increased mucus secretion in response to allergens and irritants. Currently available therapies for bronchial asthma provide symptomatic relief but are unable to normalize the exaggerated airways response to bronchospasmogens [96,97] raising the need for novel therapies to reverse or prevent airway hyperreactivity [97,98]. Potassium channel openers with their capacity to induce hyperpolarization of smooth muscle, neurons and secretory cells can reduce bronchial hyperresponsiveness both by a direct effect on smooth muscle relaxation and through an indirect inhibition of excitatory cholinergic and non-adrenergic/non-cholinergic neurotransmission (Fig. 4A [97–102]). Both experimental and clinical studies with potassium channel openers demonstrate bronchorelaxation, prevention of bronchoconstriction, reduction in microvascular leakage and goblet cell secretion, thereby provide the foundation for the therapeutic use of these agents in bronchial asthma and chronic obstructive pulmonary disease (Fig. 4A). Dyspnea, evoked by inflammatory mediators and airway hyperresponsiveness induced by a variety of stimuli, is suppressed by potassium channel openers through smooth muscle and neuroinhibitory effects [96–99]. In contrast to the conventional therapy with beta-adrenoceptor agonists [96], potassium channel openers do not cause hyperreactivity or development of tolerance to the smooth muscle relaxation with long-term use [101]. It has been suggested that the use of potassium channel openers may decrease the requirement for higher doses of glucocorticosteroids, thereby limiting their potential side effects. Several clinical trials have demonstrated the potential therapeutic efficacy of potassium channel openers for bronchospastic disease [99,102,103]. Moreover, certain but not all potassium channel openers have been shown to protect against histamine-induced bronchoconstriction [98] and controlled bronchospasm in patients with nocturnal asthma, by prevention of the early morning fall in forced expiratory volume [103,104].

Despite the potent effect of potassium channel openers on airway hyperreactivity, the clinical potential of such com-

pounds has been compromised mainly by the lack of selectivity for bronchial smooth muscle, and cardiovascular and cerebrovascular side-effects causing hypotension and headaches [98,99]. Development of bronchoselective potassium channel openers with greater efficacy and inhaled drug preparations with advantageous pharmacokinetics (poor absorption from airways and rapid systemic clearance) to limit adverse effects may be necessary before these drugs can be considered for clinical use [105].

## 7. Potassium channel openers use in urology

Urinary incontinence caused by detrusor muscle hyperactivity and involuntary contraction of the bladder is common particularly in the elderly impacting quality of life. No effective or well-tolerated therapeutic regimen is available [106]. Detrusor muscle hyperactivity is mainly due to supersensitivity to neurogenic and/or myogenic stimuli causing depolarization and increased membrane excitability [106]. Hyperpolarization of the membrane through opening of  $K^+$  channels provides an approach to suppress bladder hyperactivity [100,107]. This has been shown to be the case in normal and hypertrophic bladder including models of bladder outflow obstruction [106–109], where potassium channel openers inhibit abnormal spontaneous increase in detrusor pressure without impairing the ability to respond to intrinsic nerve stimulation and to void urine [110,106]. Potassium channel openers are of interest to eliminate unwanted bladder contractions during the filling phase without affecting normal micturition [106]. In clinical pilot studies in patients with detrusor muscle overactivity, cromakalim improved symptoms of urinary frequency and increased the mean voided volume but the benefit was limited by cardiovascular side-effects with hypotension and tachycardia [108]. Uroselective potassium channel openers, which can target urinary bladder smooth muscle without adverse cardiovascular effects are currently being developed [111].

In patients with erectile dysfunction, vasorelaxants are injected intracorporeally to achieve penile erection, but such treatment produces priapism, local fibrosis and pain [112]. By activating  $K_{ATP}$  channels [113], potassium channel openers hyperpolarize and relax corpus cavernosum smooth muscle tone to produce penile tumescence and erection, which could be of therapeutic benefit in patients with impotence [114,115]. In a prospective, double-blind trial in patients with neurogenic impotence, minoxidil applied as a lubricating gel on the glans penis was more effective than placebo or nitroglycerin in facilitating erection with fewer side-effects [116]. In a placebo-controlled clinical trial involving men with erectile dysfunction of vascular etiology encouraging results with a potassium channel opener with no cardiovascular side-effects or penile pain were reported [112]. Nicorandil-like compounds, with potassium channel opening properties and additional vasodilatory effect due to nitric oxide release and guanylate cyclase stimulation, seem particularly attractive in



[118]. In muscle biopsies from patients with hypokalemic periodic paralysis due to mutation of dihydropyridine receptor, abnormal  $K_{ATP}$  channel with subconductance states was demonstrated with lack of sensitivity to ADP and insulin stimulation, suggesting a possible role of  $K_{ATP}$  channel in determining the phenotype of hypokalemic periodic paralysis [119]. A reduction in overall sarcolemma  $K_{ATP}$  current was present, which was partially restored by cromakalim [119]. In skeletal muscle from other patients with hypokalemic periodic paralysis, cromakalim and pinacidil, decreased the membrane potential and increased the force of muscle contraction [120]. Similarly, in skeletal muscle bundles from patients with hyperkalemic paralysis [121], cromakalim restored the membrane potential of depolarized fibers and in patients with myotonia congenita and myotonic dystrophy, cromakalim and bimakalim suppress myotonic activity, after-contractions and spontaneous twitches [122]. Potassium channel openers, thus by restoration of the membrane potential of abnormally depolarized myopathic fibers could be of therapeutic use in muscular diseases related to abnormal membrane depolarization [121,123]. In addition, potassium channel openers by promoting pharmacological preconditioning could also be of therapeutic benefit in protecting skeletal muscle against ischemia–reperfusion injury in patients with vascular disease with peripheral ischemia [124,125].

### 9. Potassium channel openers use in neurological disorders

In cerebral vasospasm, several potassium channel openers, including nicorandil, cromakalim and aprikalim have been shown to relax basilar artery preventing and reversing the vasospasm after subarachnoid hemorrhage, without adversely affecting systemic hemodynamics [126–128]. Potassium channel openers have also been shown to exert strong neuroprotective effects when injected prior to severe ischemic or epileptic insult [129–131]. Activation of potassium channels and associated hyperpolarization inhibit release of excitatory amino acids, glutamate and aspartate, which are released during hypoxia with neuronal depolarization [129–131]. Thus, the neurotransmitter-induced postsynaptic depolarization and  $Ca^{2+}$  loading is inhibited by potassium channel openers, decreasing excitability and preventing neuronal injury (Fig. 4B). Moreover, potassium channel openers have been shown to inhibit apoptosis induced by oxidative stress in cerebellar granule neurons [132] and to protect neuronal and vascular endothelial cells from beta-amyloid toxicity, which contributes to cerebrovascular amyloidosis, a major neuropathological feature of Alzheimer's disease and senescence [133,134]. Although, these promising observations indicate a role for potassium channel openers in neuroprotection [135], selective openers which can readily cross the blood–brain barrier while avoiding effects on peripheral hemodynamics needs to be developed.

Impaired repolarization contributes to generation of convulsion and movement disorders [136]. Potassium channel

openers by hyperpolarizing the membrane decrease neuronal excitability and epileptiform discharges [137] preventing seizures [131,138]. Potassium channel openers also have an antinociceptive effect [139,140], mediated through the release of endorphins and enkephalins and activation of opioid receptors [139]. Pinacidil and cromakalim both have been shown to augment the analgesic effect of opioids [140,141] and cromakalim and diazoxide prevent signs of morphine withdrawal precipitated by naloxone [142]. These studies suggest a role for potassium channel openers as analgesics in the treatment of chronic pain syndromes and in the management of narcotic withdrawal in addicted patients. Indeed, potassium channel openers may serve as a substitute for morphine by attenuating the withdrawal syndrome in morphine-dependent patients, and may be useful in the management of chronic pain by augmenting the analgesic effects of, or substituting for, narcotics [139–142]. Potassium channel openers are therefore potential drug candidates for the treatment of diseases related to neuronal hyperexcitability such as epilepsy, neuropathic pain, and neurodegeneration.

### 10. Potassium channel openers use in endocrinology

$K_{ATP}$  channels are essential in regulating insulin secretion in pancreatic  $\beta$ -cells (Fig. 4C) [5,6]. While sulfonylureas, which block pancreatic  $K_{ATP}$  channels, have been widely used as oral hypoglycemics in diabetic patients, potassium channel openers, in particular diazoxide, have been used in the management of hypoglycemia due to hyperinsulinism, associated with several conditions, such as inoperable islet cell adenoma/carcinoma, extra-pancreatic malignancy, leucine sensitivity, islet cell hyperplasia, and nesidioblastosis [143]. This includes familial persistent hyperinsulinemic hypoglycemia of infancy, in which impaired regulation of insulin secretion has been linked to mutations in  $K_{ATP}$  channel subunits [143–146].

Potassium channel openers, through pancreatic  $\beta$ -cell hyperpolarization, can also improve the insulin release pattern in type-2 diabetes [147], which is characterized by fasting hyperinsulinemia, insulin resistance and impaired insulin release. It is therefore proposed that in prediabetic conditions, characterized by impaired glucose tolerance and peripheral insulin resistance, potassium channel openers by inhibiting insulin release can reduce  $\beta$ -cell workload and long-term exhaustion preventing functional deterioration and failure, thus delaying onset of diabetes [148]. Chronic treatment with diazoxide [147] or NN414, a SUR1/Kir6.2-selective compound, has demonstrated an antidiabetic effect with improvement in first-phase insulin release and glucose tolerance [149]. Potassium channel openers reduced basal hyperglycemia, improved glucose tolerance, and reduced hyperinsulinemia during oral glucose tolerance test and improved insulin secretory responsiveness in a model of type-2 diabetes [149].

## 11. Potassium channel openers use in dermatology

Potassium channel openers promote hair growth by a direct effect on hair follicles, and by improving blood supply to follicles [150,151]. In particular minoxidil stimulates DNA synthesis in epidermal keratinocytes and whole-hair follicles enhancing proliferation and differentiation of the epithelial hair shaft and increase hair density by induction of anagen or an increase in anagen duration. [150,151]. Topical minoxidil maintain and stimulate new hair growth and helps stop the loss of hair in men with androgenic alopecia and women with female pattern hair loss [150–153]. The increase in hair growth, measured by hair counts or hair weight is evident within 6–8 weeks of starting treatment and generally peaks by 12–16 weeks [153]. Although no beneficial effect in the prevention of chemotherapy-induced alopecia in women has been demonstrated [154], minoxidil decreased the period of baldness from maximal hair loss to first regrowth after chemotherapy [155]. The role of these agents in promoting hair growth and stabilizing hair loss, especially in male-pattern baldness, is thus highly promising.

## 12. Conclusion

The clinical experience with potassium channel openers is summarized in Table 1. Modulation of  $K_{ATP}$  channels, a critical homeostatic metabolic sensor, is a novel pharmacological principle with significant clinical potential under conditions of metabolic challenge. Extensive experimental studies have identified a variety of potential indications, with limited clinical experience pointing toward the safety and efficacy of potassium channel openers in human use. This is illustrated in the recently completed IONA trial, a multicenter study enrolling more than 5000 subjects with stable angina pectoris treated with the prototypic nicorandil, that has further highlighted the promise of long-term use of potassium channel openers in clinical medicine [63]. With advances in our understanding of the molecular structure, organ-specific and integrative function, tissue-selective distribution and regulation of  $K_{ATP}$  channel subunit isoforms [16–26,156,157], a framework to develop new generations of potassium channel opening drugs with enhanced specificity is envisioned [2,25,26]. Moreover, with the further understanding of the pathogenesis of disease conditions associated with an alteration in expression or regulation of potassium channel-based channelopathies [4,158,159], a rational design of potassium channel openers may provide a unique opportunity to correct disease-associated deficiency.

## Acknowledgments

A.J. is supported by grants from the National Institute on Aging (RO1 AG21201), American Heart Association (0230133N) the Mayo Clinic College of Medicine (CR75

award). A.T. is an Established Investigator of the American Heart Association and is supported by the National Institutes of Health, Miami Heart Research Institute and the Marriott Foundation.

## References

- [1] Coghlan MJ, Carroll WA, Gopalakrishnan M. Recent developments in the biology and medicinal chemistry of potassium channel modulators: update from a decade of progress. *J Med Chem* 2001;44:1627–53.
- [2] Mannhold R.  $K_{ATP}$  channel openers: structure–activity relationships and therapeutic potential. *Med Res Rev* 2004;24:213–66.
- [3] Jahangir A, Shen WK, Terzic A. Potassium channel openers: therapeutic potential in cardiology and medicine. *Expert Opin Pharmacother* 2001;2:1995–2010.
- [4] Lawson K, Dunne MJ. Peripheral channelopathies as targets for potassium channel openers. *Expert Opin Invest Drugs* 2001;10:1345–59.
- [5] Aguilar-Bryan L, Bryan J, Nakazaki M. Of mice and men:  $K(ATP)$  channels and insulin secretion. *Recent Prog Horm Res* 2001;56:47–68.
- [6] Minami K, Miki T, Kadowaki T, Seino S. Roles of ATP-sensitive  $K^+$  channels as metabolic sensors: studies of Kir6.x null mice. *Diabetes* 2004;53:S176–80.
- [7] Carrasco AJ, Dzeja PP, Alekseev AE, Pucar D, Zingman LV, et al. Adenylate kinase phosphotransfer communicates cellular energetic signals to ATP-sensitive potassium channels. *Proc Natl Acad Sci USA* 2001;98:7623–8.
- [8] Zingman LV, Alekseev AE, Bienengraeber M, Hodgson D, Karger AB, Dzeja PP, et al. Signaling in channel/enzyme multimers. ATPase transitions in SUR module gate ATP-sensitive  $K^+$  conductance. *Neuron* 2001;31:233–45.
- [9] Yamada K, Ji JJ, Yuan HJ, Miki T, Sato S, Horimoto N, et al. Protective role of ATP-sensitive potassium channels in hypoxia-induced generalized seizure. *Science* 2001;292:1543–6.
- [10] Gumina RJ, Pucar D, Bast P, Hodgson DM, Kurtz CE, Dzeja PP, et al. Knockout of Kir6.2 negates ischemic preconditioning-induced protection of myocardial energetics. *Am J Physiol* 2003;284:H2106–H2113.
- [11] Cole WC, Clement-Chomienne O. ATP-sensitive  $K^+$  channels of vascular smooth muscle cells. *J Cardiovasc Electrophysiol* 2003;14:94–103.
- [12] Miki T, Suzuki M, Shibasaki T, Uemura H, Sato T, Yamaguchi K, et al. Mouse model of Prinzmetal angina by disruption of the inward rectifier Kir6.1. *Nat Med* 2002;8:466–72.
- [13] Zingman LV, Hodgson DM, Bast PH, Kane GC, Perez-Terzic C, Gumina RJ, et al. Kir6.2 is required for adaptation to stress. *Proc Natl Acad Sci USA* 2002;99:13278–83.
- [14] Campbell JD, Sansom MS, Ashcroft FM. Potassium channel regulation. *EMBO J* 2003;4:1038–42.
- [15] Fujita A, Kurachi Y. Molecular aspects of ATP-sensitive  $K^+$  channels in the cardiovascular system and  $K^+$  channel openers. *Pharmacol Ther* 2000;85:39–53.
- [16] Bryan J, Vila-Carriles WH, Zhao G, Babenko AP, Aguilar-Bryan L. Toward linking structure with function in ATP-sensitive  $K^+$  channels. *Diabetes* 2004;53:S104–12.
- [17] Yamada M, Kurachi Y. The nucleotide-binding domains of sulfonylurea receptor 2A and 2B play different functional roles in nicorandil-induced activation of ATP-sensitive  $K^+$  channels. *Mol Pharmacol* 2004;65:1198–207.
- [18] Moreau C, Jacquet H, Prost AL, D’hahan N, Vivaudou M. The molecular basis of the specificity of action of  $K(ATP)$  channel openers. *EMBO J* 2000;19:6644–51.

- [19] Shyng S, Ferrigni T, Nichols CG. Regulation of  $K_{ATP}$  channel activity by diazoxide and MgADP. Distinct functions of the two nucleotide binding folds of the sulfonylurea receptor. *J Gen Physiol* 1997;110:643–54.
- [20] Terzic A, Vivaudou M. Molecular pharmacology of ATP-sensitive  $K^+$  channels: how and why? Potassium channels in cardiovascular biology. In: Archer SL, Rusch NJ, editors. San Diego: Academic Press; 2001. p. 257–77.
- [21] Schwanstecher M, Sieverding C, Dorschner H, Gross I, Aguilar-Bryan L, et al. Potassium channel openers require ATP to bind to and act through sulfonylurea receptors. *EMBO J* 1998;17:5529–35.
- [22] Uhde I, Toman A, Gross I, Schwanstecher C, Schwanstecher M. Identification of the potassium channel opener site on sulfonylurea receptors. *J Biol Chem* 1999;274:28079–82.
- [23] Cartier A, Shen S, Shyng SL. Modulation of the trafficking efficiency and functional properties of ATP-sensitive potassium channels through a single amino acid in the sulfonylurea receptor. *J Biol Chem* 2003;278:7081–90.
- [24] D'hahan N, Moreau C, Prost AL, Jacquet H, Alekseev AE, Terzic A, et al. Pharmacological plasticity of cardiac ATP-sensitive  $K^+$  channels toward diazoxide revealed by ADP. *Proc Natl Acad Sci* 1999;96:12162–7.
- [25] Moreau C, Gally F, Jacquet-Bouix H, Vivaudou M. The size of a single residue of the sulfonylurea receptor dictates the effectiveness of  $K_{ATP}$  channel openers. *Mol Pharmacol* 2005;67:1026–33.
- [26] Dabrowski M, Ashcroft FM, Ashfield R, Lebrun P, Pirotte B, et al. The novel diazoxide analog 3-Isopropylamino-7-Methoxy-4H-1,2,4-benzothiadiazine 1,1-dioxide is a selective  $K_{IR6.2/SUR1}$  channel opener. *Diabetes* 2002;51:1896–906.
- [27] Gross GJ, Peart JN.  $K_{ATP}$  channels and myocardial preconditioning: an update. *Am J Physiol* 2003;285:H921–H930.
- [28] Grover GJ, Garlid KD. ATP-sensitive potassium channels: a review of their cardioprotective pharmacology. *J Mol Cell Cardiol* 2000;32:677–95.
- [29] Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev* 2003;83:1113–51.
- [30] Hodgson DM, Zingman LV, Kane GC, Perez-Terzic C, Bienengraeber M, et al. Cellular remodeling in heart failure disrupts  $K_{ATP}$  channel-dependent stress tolerance. *EMBO J* 2003;22:1732–42.
- [31] Kane GC, Behfar A, Yamada S, Perez-Terzic C, O'Coilain F, et al. ATP-sensitive  $K^+$  channel knockout compromises the metabolic benefit of exercise training, resulting in cardiac deficits. *Diabetes* 2004;53:S169–75.
- [32] Tomai F, Crea F, Gaspardone A, Versaci F, De Paulis R, et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive  $K^+$  channel blocker. *Circ* 1994;90:700–5.
- [33] Suzuki M, Sasaki N, Miki T, Sakamoto N, Ohmoto-Sekine Y, et al. Role of sarcolemmal  $K_{ATP}$  channels in cardioprotection against ischemia/reperfusion injury in mice. *J Clin Invest* 2002;109:509–16.
- [34] Bienengraeber M, Olson TM, Selivanov VA, Kathmann EC, O'Coilain F, et al. ABCC9 mutations identified in human dilated cardiomyopathy disrupt catalytic  $K_{ATP}$  channel gating. *Nat Genet* 2004;36:382–7.
- [35] Ozcan C, Holmuhamedov EL, Jahangir A, Terzic A. Diazoxide protects mitochondria from anoxic injury: implications for myopreservation. *J Thorac Cardiovasc Surg* 2001;121:298–306.
- [36] Holmuhamedov EL, Jovanovic S, Dzeja PP, Jovanovic A, Terzic A. Mitochondrial ATP-sensitive  $K^+$  channels modulate cardiac mitochondrial function. *Am J Physiol* 1998;44:H1567–H1576.
- [37] Liu Y, Sato T, O'rourke B, Marban E. Mitochondrial ATP-dependent potassium channels: novel effectors of cardioprotection? *Circulation* 1998;97:2463–9.
- [38] Jahangir A, Ozcan C, Holmuhamedov EL, Terzic A. Increased  $Ca^{2+}$  vulnerability of senescent cardiac mitochondria: protective role for a mitochondrial  $K^+$  channel opener. *Mech Ageing Dev* 2001;122:1073–86.
- [39] Dzeja PP, Bast P, Ozcan C, Valverde A, Holmuhamedov EL, Van Wylen DG, et al. Targeting nucleotide-requiring enzymes: implications for diazoxide-induced cardioprotection. *Am J Physiol* 2003;284:H1048–H1056.
- [40] Holmuhamedov EL, Ozcan C, Jahangir A, Terzic A. Restoration of  $Ca^{2+}$ -inhibited oxidative phosphorylation in cardiac mitochondria by mitochondrial  $Ca^{2+}$  unloading. *Mol Cell Biochem* 2001;220:135–40.
- [41] Akao M, Teshima Y, Marbán E. Antiapoptotic effect of nicorandil mediated by mitochondrial ATP-sensitive potassium channels in cultured cardiac myocytes. *J Am Coll Cardiol* 2002;40:803–10.
- [42] Holmuhamedov EL, Jahangir A, Oberlin A, Komarov A, Colombini M, Terzic A. Potassium channel openers are uncoupling protonophores: implication in cardioprotection. *FEBS Lett* 2004;568:167–70.
- [43] Holmuhamedov EL, Wang L, Terzic A. ATP-sensitive  $K^+$  channel openers prevent  $Ca^{2+}$  overload in rat cardiac mitochondria. *J Physiol* 1999;519:347–60.
- [44] Saito S, Mizumura T, Takayama T, Honye J, Fukui T, Kamata T, et al. Antiischemic effects of nicorandil during coronary angioplasty in humans. *Cardiovasc Drugs Ther* 1995;9:257–63.
- [45] Hoenicke EM, Sun XW, Strange RG, Damiano RJ. Donor heart preservation with a novel hyperpolarizing solution: superior protection compared with University of Wisconsin solution. *J Thorac Cardiovasc Surg* 2000;120:746–54.
- [46] Quast U, Guillon JM, Cavero I. Cellular pharmacology of potassium channel openers in vascular smooth muscle. *Cardiovasc Res* 1994;28:805–10.
- [47] Okada Y, Yanagisawa T, Taira N. BRL 38227 (levcromakalim)-induced hyperpolarization reduces the sensitivity to  $Ca^{2+}$  of contractile elements in canine coronary artery. *Naunyn Schmiedebergs Arch Pharmacol* 1993;347:438–44.
- [48] Donnelly R, Elliott HL, Meredith PA, Reid JL. Clinical studies with the potassium channel activator cromakalim in normotensive and hypertensive subjects. *J Cardiovasc Pharmacol* 1990;16:790–5.
- [49] Simpson D, Wellington K. Nicorandil: a review of its use in the management of stable angina pectoris, including high-risk patients. *Drugs* 2004;64:1941–55.
- [50] McCully JD, Levitsky S. Mitochondrial ATP-sensitive potassium channels in surgical cardioprotection. *Arch Biochem Biophys* 2003;420:237–45.
- [51] Kevelaitis E, Oubenaissa A, Peynet J, Mouas C, Menasche P. Preconditioning by mitochondrial ATP-sensitive potassium channel openers - An effective approach for improving the preservation of heart transplants. *Circulation* 1999;100:345–50.
- [52] Steensrud T, Nordhaug D, Husnes KV, Aghajani E, Sorlie DG. Replacing potassium with nicorandil in cold St. Thomas' Hospital cardioplegia improves preservation of energetics and function in pig hearts. *Ann Thorac Surg* 2004;77:1391–7.
- [53] Suryapranata H. Coronary haemodynamics and vasodilatory profile of a potassium channel opener in patients with coronary artery disease. *Eur Heart J* 1993;14:16–21.
- [54] Angerbach D, Nicholson CD. Enhancement of muscle blood cell flux and  $pO_2$  by cromakalim (BRL 34915) and other compounds enhancing membrane  $K^+$  conductance, but not by  $Ca^{2+}$  antagonists or hydralazine, in an animal model of occlusive arterial disease. *Naunyn Schmiedebergs Arch Pharmacol* 1988;337:341–6.
- [55] Jahangir A, Terzic A, Kurachi Y. Intracellular acidification and ADP enhance nicorandil induction of ATP sensitive potassium channel current in cardiomyocytes. *Cardiovasc Res* 1994;28:831–5.
- [56] Terzic A, Jahangir A, Kurachi Y. HOE-234, a second generation  $K^+$  channel opener, antagonizes the ATP-dependent gating of cardiac ATP-sensitive  $K^+$  channels. *J Pharmacol Exp Ther* 1994;268:818–25.
- [57] Saito T, Sato T, Miki T, Seino S, Nakaya H. Role of ATP-sensitive  $K^+$  channels in electrophysiological alterations during myocardial ischemia: a study using  $K_{IR6.2}$ -null mice. *Am J Physiol* 2005;288:H352–H357.

- [58] Haverkamp W, Borggreffe M, Breithardt G. Electrophysiologic effects of potassium channel openers. *Cardiovasc Drugs Ther* 1995;9:195–202.
- [59] Shimizu W, Kurita T, Matsuo K, Suyama K, Aihara N, et al. Improvement of repolarization abnormalities by a K<sup>+</sup> channel opener in the LQT1 form of congenital long-QT syndrome. *Circulation* 1998;97:1581–8.
- [60] Shimizu W, Antzelevitch C. Effects of a K(+) channel opener to reduce transmural dispersion of repolarization and prevent torsade de pointes in LQT1, LQT2, and LQT3 models of the long-QT syndrome. *Circulation* 2000;102:706–12.
- [61] Hayashi Y, Sawa Y, Ohtake S, Nishimura M, Ichikawa H, Matsuda H. Controlled nicorandil administration for myocardial protection during coronary artery bypass grafting under cardiopulmonary bypass. *J Cardiovasc Pharmacol* 2001;38:21–8.
- [62] Markham A, Plosker GL, Goa KL. Nicorandil—an updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs* 2000;60:955–74.
- [63] The Iona Study Group. Trial to show the impact of nicorandil in angina (IONA): design, methodology, and management. *Heart* 2001;85:e9.
- [64] Patel DJ, Purcell HJ, Fox KM. Cardioprotection by opening of the KATP channel in unstable angina: Is this a clinical manifestation of myocardial preconditioning? Results of a randomized study with nicorandil. *Eur Heart J* 1999;20:51–7.
- [65] Ito H, Taniyama Y, Iwakura K, Nishikawa N, Masuyama T, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol* 1999;33:654–60.
- [66] Schlepper M, Thormann J, Berwing K, Strasser R, Mitrovic V. Effects of nicorandil on regional perfusion and left ventricular function. *Cardiovasc Drugs Ther* 1995;9:203–11.
- [67] Sakata Y, Kodama K, Komamura K, Lim YJ, Ishikura F, et al. Salutary effect of adjunctive intracoronary nicorandil administration on restoration of myocardial blood flow and functional improvement in patients with acute myocardial infarction. *Am Heart J* 1997;133:616–21.
- [68] Yasuda T, Hashimura K, Matsu-ura Y, Kato Y, et al. Nicorandil, a hybrid between nitrate and ATP-sensitive potassium channel opener, preconditions human heart to ischemia during percutaneous transluminal coronary angioplasty. *Jpn Circ J* 2001;65:526–30.
- [69] Jaraki O, Strauss WE, Francis S, Loscalzo J, Stamler JS. Antiplatelet effects of a novel antianginal agent, nicorandil. *J Cardiovasc Pharmacol* 1994;23:24–30.
- [70] Doring G. Antianginal and anti-ischemic efficacy of nicorandil in comparison with isosorbide-5-mononitrate and isosorbide dinitrate: Results from two multicenter, double-blind, randomized studies with stable coronary heart disease patients. *J Cardiovasc Pharmacol* 1992;20:S74–81.
- [71] Di Somma S, Liguori V, Petitto M, Carotenuto A, Bokor D, et al. A double-blind comparison of nicorandil and metoprolol in stable effort angina pectoris. *Cardiovasc Drugs Ther* 1993;7:119–23.
- [72] Ulvenstam G, Diderholm E, Frithz G, Gudbrandsson T, Hedback B, et al. Antianginal and anti-ischemic efficacy of nicorandil compared with nifedipine in patients with angina pectoris and coronary heart disease: a double-blind, randomized, multicenter study. *J Cardiovasc Pharmacol* 1992;20:S67–73.
- [73] Kaski JC. Management of vasospastic angina—role of nicorandil. *Cardiovasc Drugs Ther* 1995;9:221–7.
- [74] Chen JW, Lee WL, Hsu NW, Lin SJ, Ting CT, Wang SP, et al. Effects of short-term treatment of nicorandil on exercise-induced myocardial ischemia and abnormal cardiac autonomic activity in microvascular angina. *Am J Cardiol* 1997;80:32–8.
- [75] Akar F, Uydes-Dogan BS, Tufan H, Aslamaci S, Koksoy C, Kanzik I. The comparison of the responsiveness of human isolated internal mammary and gastroepiploic arteries to levcromakalim: an alternative approach to the management of graft spasm. *Br J Clin Pharmacol* 1997;44:49–56.
- [76] He GW, Yang CQ. Inhibition of vasoconstriction by potassium channel opener aprikalim in human conduit arteries used as bypass grafts. *Br J Clin Pharmacol* 1997;44:353–9.
- [77] Antzelevitch C, Di Diego JM. Role of K<sup>+</sup> channel activators in cardiac electrophysiology and arrhythmias. *Circ* 1992;85:1627–9.
- [78] Kondo M, Tsutsumi T, Mashima S. Potassium channel openers antagonize the effects of class III antiarrhythmic agents in canine Purkinje fiber action potentials—implications for prevention of proarrhythmia induced by class III agents. *Jpn Heart J* 1999;40:609–19.
- [79] Ueda H, Nakayama Y, Tsumura K, Yoshimaru K, Hayashi T, Yoshikawa J. Intravenous nicorandil can reduce the occurrence of ventricular fibrillation and QT dispersion in patients with successful coronary angioplasty in acute myocardial infarction. *Can J Cardiol* 2004;20:625–9.
- [80] Horinaka S, Kobayashi N, Yabe A, Asakawa H, Yagi H, Mori Y, et al. Nicorandil protects against lethal ischemic ventricular arrhythmias and up-regulates endothelial nitric oxide synthase expression and sulfonylurea receptor 2 mRNA in conscious rats with acute myocardial infarction. *Cardiovasc Drugs Ther* 2004;18:13–22.
- [81] Yang Z, Shi G, Li C, Wang H, Liu K, Liu Y. Electrophysiologic effects of nicorandil on the guinea pig long QT1 syndrome model. *J Cardiovasc Electrophysiol* 2004;15:815–20.
- [82] Liu XK, Yamada S, Kane GC, Alekseev AE, Hodgson DM, et al. Genetic disruption of Kir6.2, the pore-forming subunit of ATP-sensitive K<sup>+</sup> channel, predisposes to catecholamine-induced ventricular dysrhythmia. *Diabetes* 2004;53:S165–8.
- [83] Sato T, Hata Y, Yamamoto M, Morita H, Mizuo K, Yamanari H, et al. Early afterdepolarization abolished by potassium channel opener in a patient with idiopathic long QT syndrome. *J Cardiovasc Electrophysiol* 1995;6:279–82.
- [84] Robert E, Aya AGM, De La Coussaye JE, Peray P, Juan JM, Brugada J, et al. Dispersion-based reentry: mechanism of initiation of ventricular tachycardia in isolated rabbit hearts. *Am J Physiol* 1999;45:H413–H423.
- [85] Wilde AA, Janse MJ. Electrophysiological effects of ATP sensitive potassium channel modulation: implications for arrhythmogenesis. *Cardiovasc Res* 1994;28:16–24.
- [86] Miyazaki T, Moritani K, Miyoshi S, Asanagi M, Zhoo LS, Mitamura H, et al. Nicorandil augments regional ischemia-induced monophasic action potential shortening and potassium accumulation without serious proarrhythmia. *J Cardiovasc Pharmacol* 1995;26:949–56.
- [87] Das B, Sarkar C. Mitochondrial K ATP channel activation is important in the antiarrhythmic and cardioprotective effects of non-hypotensive doses of nicorandil and cromakalim during ischemia/reperfusion: a study in an intact anesthetized rabbit model. *Pharmacol Res* 2003;47:447–61.
- [88] Friedel HA, Brogden RN. Pinacidil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of hypertension. *Drugs* 1990;39:929–67.
- [89] Sica DA. Minoxidil: an underused vasodilator for resistant or severe hypertension. *J Clin Hypertens* 2004;6:283–7.
- [90] Yamauchi T, Matzno S, Imada T, Eda M, Inoue Y, Nakamura N. AL0671, a new potassium channel opener, inhibits nonenzymatic glycation of protein and LDL oxidation. *Gen Pharmacol* 1996;27:257–62.
- [91] Dumas JP, Bardou M, Goirand F, Dumas M. Hypoxic pulmonary vasoconstriction. *Gen Pharmacol* 1999;33:289–97.
- [92] Clapp LH, Gurney AM. ATP-sensitive K<sup>+</sup> channels regulate resting potential of pulmonary arterial smooth muscle cells. *Am J Physiol* 1992;262:H916–H920.
- [93] Oka M, Morris KG, Mcmurtry IF. NIP-121 is more effective than nifedipine in acutely reversing chronic pulmonary hypertension. *J Appl Physiol* 1993;75:1075–80.
- [94] Xie W, Wang H, Wang H, Hu G. Effects of iptakalim hydrochloride, a novel K<sub>ATP</sub> channel opener, on pulmonary vascular remodeling in hypoxic rats. *Life Sci* 2004;75:2065–76.

- [95] Yamashita M, Schmid RA, Fujino S, Cooper JD, Patterson GA. Nicorandil, a potent adenosine triphosphate-sensitive potassium-channel opener, ameliorates lung allograft reperfusion injury. *J Thorac Cardiovasc Surg* 1996;112:1307–14.
- [96] Pauwels R. Bronchial hyperresponsiveness. In: Kay AB, editor. *Allergy and allergic diseases*. London: Blackwell Science; 1997. p. 682–91.
- [97] El-Hashim AZ, Buchheit KH, Fozard J, Page C. Effect of the K<sup>+</sup>(ATP) channel opener, KCO912, on baseline and allergen induced airway hyperresponsiveness in allergic rabbits. *Eur J Pharmacol* 2004; 484:351–6.
- [98] Pelaia G, Gallelli L, Vatrella A, Grembiale RD, Maselli R, De Sarro GB. Potential role of potassium channel openers in the treatment of asthma and chronic obstructive pulmonary disease. *Life Sci* 2002;70:977–90.
- [99] Fozard JR, Manley PW. Potassium channel openers: agents for the treatment of airways hyperreactivity. In: Hansel TT, Barnes PJ, editors. *New drugs for asthma, allergy and COPD*. *Prog. Respir. Res.*; 2001. p. 77–80 (31).
- [100] Ramnarine SI, Liu YC, Rogers DF. Neuroregulation of mucus secretion by opioid receptors and K(ATP) and BK(Ca) channels in ferret trachea in vitro. *Br J Pharmacol* 1998;123:1631–8.
- [101] Buchheit KH, Manley PW, Quast U, Russ U, Mazzoni L, Fozard JR. KCO912: a potent and selective opener of ATP-dependent potassium K(ATP) channels which suppresses airways hyperreactivity at doses devoid of cardiovascular effects. *Naunyn Schmiedebergs Arch Pharmacol* 2002;365:220–30.
- [102] Wajima Z, Yoshikawa T, Ogura A, Imanaga K, Shiga T, Inoue T, et al. Intravenous nicorandil prevents thiamylal-fentanyl-induced bronchoconstriction in humans. *Crit Care Med* 2003;31:485–90.
- [103] Williams AJ, Lee TH, Cochrane GM, Hopkirk A, Vyse T, Chiew F, et al. Attenuation of nocturnal asthma by cromakalim. *Lancet* 1990; 336:334–6.
- [104] Kidney JC, Fuller RW, Wordsell YM, Lavender EA, Chung KF, Barnes PJ. Effect of oral potassium channel activator, BRL 38227, on airway function and responsiveness in asthmatic patients: comparison with oral salbutamol. *Thorax* 1993;48:130–3.
- [105] Ando T, Kume H, Urata Y, Takagi K. Effects of JTV-506, a new K<sup>+</sup> channel activator, on airway smooth muscle contraction and systemic blood pressure. *Clin Exp Allergy* 1997;27:705–13.
- [106] Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev* 2004;84:935–86.
- [107] Fey TA, Gopalakrishnan M, Strake JG, King LL, Brioni JD, Sullivan JP, et al. Effects of ATP-sensitive K<sup>+</sup> channel openers and tolterodine on involuntary bladder contractions in a pig model of partial bladder outlet obstruction. *NeuroUrol Urodyn* 2003;22:147–55.
- [108] Nurse D, Restorick JM, Mundy AR. The effect of cromakalim on the normal and hyper-reflexic human detrusor muscle. *Br J Urol* 1991;68: 27–31.
- [109] Wojdan A, Freedman C, Woods M, Oshiro G, Spinelli W, Colatsky TJ, et al. Comparison of the potassium channel openers, WAY-133537, ZD6169, and celikalim on isolated bladder tissue and in vivo bladder instability in rat. *J Pharmacol Exp Ther* 1999;289:1410–8.
- [110] Sudoh K, Masuda N, Uchida W. Different effect of anticholinergic agents and K<sup>+</sup> channel openers on urinary bladder response to pelvic nerve stimulation in anaesthetized dogs. *J Auton Pharmacol* 1997;17: 91–6.
- [111] Gopalakrishnan M, Shieh CC. Potassium channel subtypes as molecular targets for overactive bladder and other urological disorders. *Exp Opin Ther Targets* 2004;8:437–58.
- [112] Bella AJ, Brock GB. Intracavernous pharmacotherapy for erectile dysfunction. *Endocrine* 2004;23:149–55.
- [113] Venkateswarlu K, Giraldi A, Zhao W, Wang HZ, Melman A, Spektor M, et al. Potassium channels and human corporeal smooth muscle cell tone: diabetes and relaxation of human corpus cavernosum smooth muscle by adenosine triphosphate sensitive potassium channel openers. *J Urol* 2002;168:355–61.
- [114] Hedlund P, Holmquist F, Hedlund H, Andersson KE. Effects of nicorandil on human isolated corpus cavernosum and cavernous artery. *J Urol* 1994;151:1107–13.
- [115] Trigo-Rocha F, Donatucci CF, Hsu GL, Nunes L, Lue TF, Tanagho EA. The effect of intracavernous injection of potassium channel openers in monkeys and dogs. *Int J Impot Res* 1995;7:41–8.
- [116] Cavallini G. Minoxidil versus nitroglycerin: a prospective double-blind controlled trial in transcutaneous erection facilitation for organic impotence. *J Urol* 1991;146:50–3.
- [117] Gong B, Legault D, Miki T, Seino S, Renaud JM. KATP channels depress force by reducing action potential amplitude in mouse EDL and soleus muscle. *Am J Physiol Cell Physiol* 2003;285:C1464–C1474.
- [118] Tricarico D, Pierno S, Mallamaci R, Brigiani GS, Capriulo R, Santoro G, et al. The biophysical and pharmacological characteristics of skeletal muscle ATP-sensitive K<sup>+</sup> channels are modified in K<sup>+</sup>-depleted rat, an animal model of hypokalemic periodic paralysis. *Mol Pharmacol* 1998;54:197–206.
- [119] Tricarico D, Servidei S, Tonali P, Jurkat RK, Camerino DC. Impairment of skeletal muscle ATP-sensitive K<sup>+</sup> channels in patients with hypokalemic periodic paralysis. *J Clin Invest* 1999;103:675–82.
- [120] Grafe P, Quasthoff S, Strupp M, Lehmann-Horn F. Enhancement of K<sup>+</sup> conductance improves in vitro the contraction force of skeletal muscle in hypokalemic periodic paralysis. *Muscle Nerve* 1990;13: 451–7.
- [121] Spuler A, Lehmann-Horn F, Grafe P. Cromakalim (BRL 34915) restores in vitro the membrane potential of depolarized human skeletal muscle fibers. *Naunyn Schmiedebergs Arch Pharmacol* 1989;339: 327–31.
- [122] Quasthoff S, Spuler A, Spittelmeister W, Lehmann-Horn F, Grafe P. K<sup>+</sup> channel openers suppress myotonic activity of human skeletal muscle in vitro. *Eur J Pharmacol* 1990;186:125–8.
- [123] Hong SJ, Chang CC. Trauma-induced changes of skeletal muscle membrane: decreased K<sup>+</sup> and increased Na<sup>+</sup> permeability. *J Appl Physiol* 1997;83:1096–103.
- [124] Pang CY, Neligan P, Xu H, He W, Zhong A, Hopper R, et al. Role of ATP-sensitive K<sup>+</sup> channels in ischemic preconditioning of skeletal muscle against infarction. *Am J Physiol* 1997;273:H44–H51.
- [125] Grover GJ, Burkett DE, Parham CS, Scalsese RJ, Sadanaga KK. Protective effect of mitochondrial KATP activation in an isolated gracilis model of ischemia and reperfusion in dogs. *J Cardiovasc Pharmacol* 2003;42:790–2.
- [126] Harder DR, Dernbach P, Waters A. Possible cellular mechanism for cerebral vasospasm after experimental subarachnoid hemorrhage in the dog. *J Clin Invest* 1987;80:875–80.
- [127] Rosenblum WI. ATP-sensitive potassium channels in the cerebral circulation. *Stroke* 2003;34:1547–52.
- [128] Veltkamp R, Domoki F, Bari F, Busija DW. Potassium channel activators protect the N-methyl-D-aspartate-induced cerebral vascular dilatation after combined hypoxia and ischemia in piglets. *Stroke* 1998; 29:837–42.
- [129] Kis B, Nagy K, Snipes JA, Rajapakse NC, Horiguchi T, Grover GJ, et al. The mitochondrial K(ATP) channel opener BMS-191095 induces neuronal preconditioning. *Neuroreport* 2004;15:345–9.
- [130] Blondeau N, Plamondon H, Richelme C, Heurteaux C, Lazdunski M. K-ATP channel openers, adenosine agonists and epileptic preconditioning are stress signals inducing hippocampal neuroprotection. *Neurosci* 2000;100:465–74.
- [131] Wickenden AD. Potassium channels as anti-epileptic drug targets. *Neuropharmacology* 2002;43:1055–60.
- [132] Teshima Y, Akao M, Li RA, Chong TH, Baumgartner WA, Johnston MV, et al. Mitochondrial ATP-sensitive potassium channel activation protects cerebellar granule neurons from apoptosis induced by oxidative stress. *Stroke* 2003;34:1796–802.
- [133] Chi X, Sutton ET, Hellermann G, Price JM. Potassium channel openers prevent beta-amyloid toxicity in bovine vascular endothelial cells. *Neurosci Lett* 2000;290:9–12.

- [134] Heurteaux C, Bertaina V, Widmann C, Lazdunski M. K<sup>+</sup> channel openers prevent global ischemia-induced expression of c-fos, c-jun, heat shock protein, and amyloid (protein precursor genes and neuronal death in rat hippocampus. *Proc Natl Acad Sci USA* 1993;90:9431–95.
- [135] Ballanyi K. Protective role of neuronal K<sub>ATP</sub> channels in brain hypoxia. *J Exp Biol* 2004;207:3201–12.
- [136] Biervert C, Schroeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ, et al. A potassium channel mutation in neonatal human epilepsy. *Science* 1998;279:403–6.
- [137] Alzheimer C, Ten Bruggencate G. Actions of BRL 34915 (Cromakalim) upon convulsive discharges in guinea pig hippocampal slices. *Naunyn Schmiedebergs Arch Pharmacol* 1988;337:429–34.
- [138] Gandolfo G, Romettino S, Gottesmann C, Van Luijckelaar G, Coenen A, Bidard JN, et al. K<sup>+</sup> channel openers decrease seizures in genetically epileptic rats. *Eur J Pharmacol* 1989;167:181–3.
- [139] Campbell VC, Welch SP. The role of minoxidil on endogenous opioid peptides in the spinal cord: a putative co-agonist relationship between K-ATP openers and opioids. *Eur J Pharmacol* 2001;417:91–8.
- [140] Picolo G, Cassola AC, Cury Y. Activation of peripheral ATP-sensitive K<sup>+</sup> channels mediates the antinociceptive effect of *Crotalus durissus terrificus* snake venom. *Eur J Pharmacol* 2003;469:57–64.
- [141] Kang Y, Zhang Z, Yang S, Qiao J, Dafny N. ATP-sensitive K<sup>+</sup> channels are involved in the mediation of intrathecal norepinephrine- or morphine-induced antinociception at the spinal level: a study using EMG planimetry of flexor reflex in rats. *Brain Res Bull* 1998;45:269–73.
- [142] Robles LI, Barrios M, Baeyens JM. ATP-sensitive K<sup>+</sup> channel openers inhibit morphine withdrawal. *Eur J Pharmacol* 1994;251:113–5.
- [143] Dunne MJ, Kane C, Shepherd RM, Sanchez JA, James RF, Johnson PR, et al. Familial persistent hyperinsulinemic hypoglycemia of infancy and mutations in the sulfonylurea receptor. *N Engl J Med* 1997;336:703–6.
- [144] Abraham MR, Jahangir A, Alekseev AE, Terzic A. Inwardly-rectifying K<sup>+</sup> channels and associated diseases. *FASEB J* 1999;13:1901–10.
- [145] Tornovsky S, Crane A, Cosgrove KE, Hussain K, Lavie J, Heyman M, et al. Hyperinsulinism of infancy: novel ABCC8 and KCNJ11 mutations and evidence for additional locus heterogeneity. *J Clin Endocrinol Metab* 2004;89:6224–34.
- [146] Bryan J, Vila-Carriles WH, Zhao G, Babenko AP, Aguilar-Bryan L. Toward linking structure with function in ATP-sensitive K<sup>+</sup> channels. *Diabetes* 2004;53:S104–12.
- [147] Guldstrand M, Grill V, Bjorklund A, Lins PE, Adamson U. Improved beta cell function after short-term treatment with diazoxide in obese subjects with type 2 diabetes. *Diabetes Metab* 2002;28:448–56.
- [148] Skak K, Gottfredsen CF, Lundsgaard D, Hansen JB, Sturis J, Markholst H. Improved beta-cell survival and reduced insulinitis in a type 1 diabetic rat model after treatment with a beta-cell-selective K(ATP) channel opener. *Diabetes* 2004;53:1089–95.
- [149] Carr RD, Brand CL, Bodvarsdottir TB, Hansen JB, Sturis J. NN414, a SUR1/Kir6.2-selective potassium channel opener, reduces blood glucose and improves glucose tolerance in the VDF Zucker rat. *Diabetes* 2003;52:2513–8.
- [150] Buhl AE, Conrad SJ, Waldon DJ, Brunden MN. Potassium channel conductance as a control mechanism in hair follicles. *J Invest Dermatol* 1993;101:148S–152S.
- [151] Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol* 2004;150:186–94.
- [152] Lucky AW, Piacquadro DJ, Ditre CM, Dunlap F, Kantor I, Pandya AG, et al. A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol* 2004;50:541–53.
- [153] Olsen EA, Dunlap FE, Funicella T, Koperski JA, Swinehart JM, Tschen EH, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol* 2002;47:377–85.
- [154] Granai CO, Frederickson H, Gajewski W, Goodman A, Goldstein A, Baden H. The use of minoxidil to attempt to prevent alopecia during chemotherapy for gynecologic malignancies. *Eur J Gynaecol Oncol* 1991;12:129–32.
- [155] Duvic M, Lemak NA, Valero V, Hymes SR, Farmer KL, Hortobagyi GN, et al. A randomized trial of minoxidil in chemotherapy-induced alopecia. *J Am Acad Dermatol* 1996;35:74–8.
- [156] Gumina RJ, Jahangir A, Gross GJ, Terzic A. Cardioprotection: emerging pharmacotherapy. *Exp Opin Pharmacother* 2001;2:739–52.
- [157] Enkvetchakul D, Nichols CG. Gating mechanism of KATP channels: function fits form. *J Gen Physiol* 2003;122:471–80.
- [158] Saito T, Sato T, Miki T, Seino S, Nakaya H. Role of ATP-sensitive K<sup>+</sup> channels in electrophysiological alterations during myocardial ischemia: a study using Kir6.2-null mice. *Am J Physiol* 2005;288:H352–H357.
- [159] Atwal KS, Grover GJ, Lodge NJ, Normandin DE, Traeger SC, Sleph PG, et al. Binding of ATP-sensitive potassium channel K<sub>ATP</sub> openers to cardiac membranes: correlation of binding affinities with cardioprotective and smooth muscle relaxing potencies. *J Med Chem* 1998;41:271–5.