
Potassium Channel Openers

Agents for the Treatment of Airway Hyperreactivity

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Summary

ATP-sensitive potassium (K_{ATP}) channels link the metabolic status of the cell to the plasma membrane potential and thus play a key role in regulating cellular excitability. K_{ATP} channel openers (KCOs) may impact positively on respiratory disease by suppressing bronchoconstriction, mucus hypersecretion, cough and airway hyperreactivity (AHR). A major recent development is the emergence of KCOs which can obviate experimental AHR at doses which are devoid of cardiovascular effects. This new generation of compounds with selectivity for the airways may constitute a new class of drugs for the treatment of asthma.

ATP-sensitive potassium (K_{ATP}) channels are found in a wide variety of tissues, including skeletal and smooth muscle cells, secretory cells (such as insulin-secreting pancreatic β -cells), cardiac myocytes and neurons [1–3]. Conceptually, the presence of K_{ATP} channels in bronchiolar smooth muscle [2] and airway sensory and autonomic neurons [4] raises the possibility of their involvement in the pathophysiology of respiratory disease through the modulation of direct and reflex-induced bronchoconstriction [5], mucus secretion [6] and cough [7]. In practice, it is the phenomenon of airway hyperreactivity (AHR), whose underlying mechanisms remain ill-defined [8, 9], which is emerging as the key target with clinical relevance to respiratory disease [10]. For this reason, the emphasis in this review will be placed on the role and therapeutic significance of K_{ATP} channels in the phenomenon of AHR.

Mechanism of Action

Potassium channel openers (KCOs) act by stimulating ion flux through a distinct class of potassium channels which are inhibited by intracellular ATP and activated by intracellular nucleoside diphosphates. Such K_{ATP} chan-

nels link the metabolic status of the cells to the plasma membrane potential and in this way play a key role in regulating cellular activity [1–3]. In most excitatory cells, K_{ATP} channels are closed under normal physiological conditions and open when the tissue is metabolically compromised (e.g. when the [ATP]:[ADP] ratio falls). This promotes K^+ efflux and the cell hyperpolarizes, thereby preventing voltage-operated Ca^{2+} channels (VOCs) from opening (fig. 1). K_{ATP} channels are composed of a pore-forming tetrameric complex of inward rectifying K^+ channel (K_{ir}) subunits (either $K_{ir}6.1$ or $K_{ir}6.2$), with each subunit being associated with a regulating protein of the sulphonylurea receptor type (SUR1, SUR2A or SUR2B) [11, 12] (table 1). SUR proteins are members of the ATP-binding-cassette transporter family and their nucleotide-binding domains are believed to render the K_{ATP} channels sensitive to [ATP]/[ADP]. SURs are also the target proteins for KCOs [14]. It is likely that the various combinations of SUR and $K_{ir}6$ subunits account for the clear differences between K_{ATP} channels in various tissues, with respect to their channel properties and sensitivity to ligands which both activate and inhibit their opening (table 1).

Range of Therapies

K_{ATP} channels are activated by a diverse group of compounds which include the anti-hypertensive agents, minoxidil sulphate, diazoxide and pinacidil, as well as a variety of benzopyran derivatives such as levcromakalim (or its racemate, cromakalim), SDZ PCO 400, bimakalim, JTV 506, YM 934, KC-399, BRL 55834, rilmakalim and SDZ 217-744 (fig. 2). Only the benzopyran derivatives have been profiled as therapies for asthma [15]. K_{ATP} channels are inhibited by sulphonylurea derivatives, such as glibenclamide and tolbutamide, and the high affinity of these agents for K_{ATP} channels in pancreatic β -cells is the

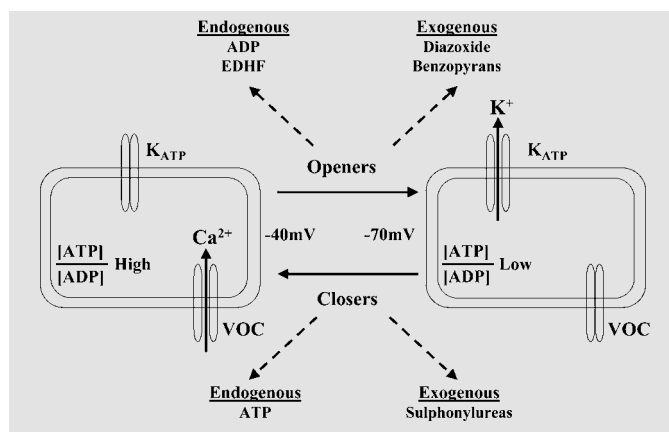


Fig. 1. Diagrammatic representation of the role of K_{ATP} channels in cell excitability. For further details see text.

Table 1. Composition and pharmacological properties of K_{ATP} channels in different tissues

Tissue	Channel composition	Inhibition by glibenclamide IC_{50} , μM	Activation by	
			diazoxide EC_{50} , μM	levcromakalim EC_{50} , μM
Pancreatic β -cell	(SUR1/ $K_{ir}6.2$) ₄	0.005–0.030	20–100	>100
Cardiac myocyte	(SUR2A/ $K_{ir}6.2$) ₄	0.003–0.005	>500	300
Vascular myocyte	(SUR2B/ $K_{ir}6.1$) ₄	0.025	200	0.5
Skeletal muscle	(SUR2B/ $K_{ir}6.2$) ₄	0.01–0.2	>500	>100
Neurons	(SUR1/ $K_{ir}6.2$) ₄ ¹	2.1 ²	<200	not available

From Quast [1], Quayle et al. [2], Fujita and Kurachi [3], Babenko et al. [11] and Sakura et al. [13].

¹ A novel SUR variant, SUR1B [13].

² Figure refers to inhibition by the sulphonylurea, tolbutamide.

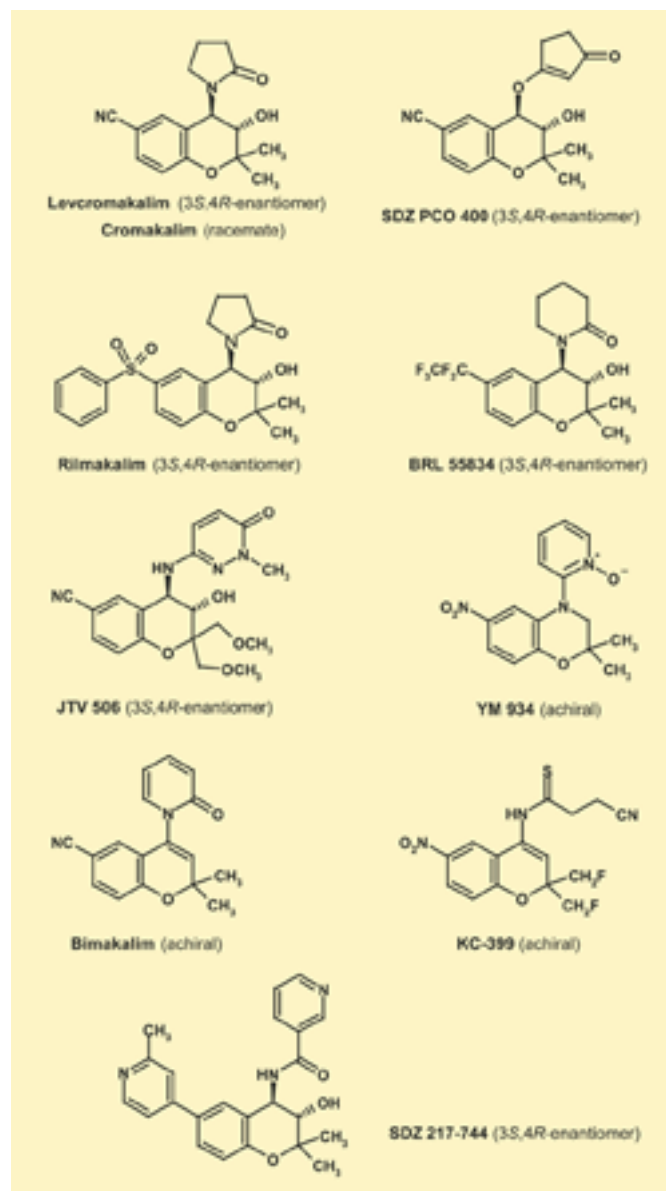


Fig. 2. KCOs profiled for asthma.

basis for their efficacy in stimulating insulin release and use in diabetes [1, 16].

Rationale for the Utility of Potassium Channel Openers in Airway Hyperreactivity

The heightened sensitivity of the airways of asthmatics to a range of bronchoconstrictor stimuli which do not usually affect normal subjects is a defining feature of asthma [17]. The phenomenon, termed bronchial (or airway) hyperreactivity (AHR), results in facilitation of broncho-

spasm and contributes to the airway obstruction characteristic of asthma [8, 9, 18–20]. The principal clinical symptoms of asthma, wheezing and breathlessness are a direct consequence of airway obstruction. Although the underlying mechanisms of AHR in asthma are unknown, both preclinical and clinical evidence points to an increased excitability of smooth muscle cells and/or the nervous elements of the airways as important contributory factors [18, 19]. By increasing the efflux of potassium from these cells, KCOs would induce hyperpolarization and a decrease in responsiveness to excitatory stimuli.

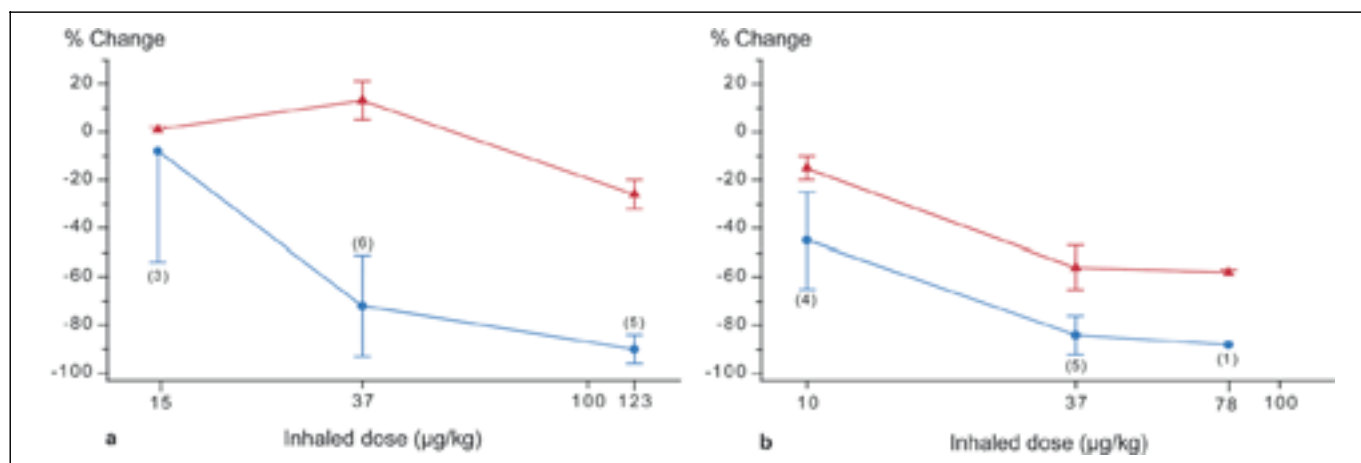


Fig. 3. Dose-response curves for the effects of SDZ 217-744 (a) and bimakalim (b) given by aerosol inhalation on the bronchoconstrictor response to inhaled methacholine (●) and diastolic blood pressure (▲) in the anaesthetized rhesus monkey. Effects were measured 5 min after the end of drug administration and are the maxima observed at each dose level. Mean values (\pm SEM) of the number of individual experiments shown in parentheses are presented. For further details see text.

Effects of Potassium Channel Openers in Animal Models of Airway Hyperreactivity

AHR can be induced in guinea pigs by intravenous administration of immune complexes [21, 22] or exposure to ozone [23]. Representative KCOs reverse AHR when administered locally to the airways although there are significant differences between these agents in their potencies in the two models (table 2). KCOs are significantly more potent in reversing AHR than in inducing bronchodilation in animals with normoreactive airways [20, 22]. The effects of bimakalim to suppress AHR can be blocked by pretreatment of the animals with glibenclamide, which is consistent with the involvement of K_{ATP} channels in the response [24]. The first generation KCOs, levromakalim, bimakalim and YM 934, markedly reduce blood pressure at the doses required to inhibit AHR. In contrast, BRL 55834, JTV 506 and particularly SDZ 217-744, showed a clear separation between the two activities (table 2). Unlike salbutamol, SDZ 217-744 does not cause AHR on prolonged administration to guinea pigs; indeed, concomitant administration of SDZ 217-744 inhibits AHR induced in the same model by chronic administration of salbutamol [25]. Confirmation of the difference between first- and second-generation KCOs with respect to their therapeutic ratios for inhibiting AHR and inducing cardiovascular effects has come from experiments in rhesus monkeys (fig. 3). Thus, in animals displaying spontaneous AHR, bimakalim and SDZ 217-744 were found to be potent inhibitors of methacholine-induced bronchoconstriction.

Table 2. Comparison of potencies of benzopyran-type KCOs for their inhibition of AHR in guinea pigs induced by either immune complex (IC-AHR) or ozone (O_3 -AHR) compared with their potencies in reducing mean arterial blood pressure (Δ BP)

Compound	IC-AHR ED ₅₀ , µg/kg	O_3 -AHR ED ₅₀ , µg/kg	Δ BP ED ₂₀ , µg/kg
Levcromakalim	22	n.d.	10
Bimakalim	0.5	0.3	2
Rilmakalim	0.2	n.d.	10
JTV 506	0.5	n.d.	19
SDZ PCO 400	3.2	n.d.	30
YM 934	2.1	>100	3.4
BRL 55834	0.1	>100	10
SDZ 217-744	0.08	3	>100

From Buchheit and Hofmann [22], Yeadon et al. [23] and Buchheit [unpubl. obs.].

However, whereas bimakalim induced hypotension at similar doses, SDZ 217-744 was devoid of cardiovascular effects at doses which markedly suppressed bronchoconstriction (fig. 3). Thus, a new generation of KCOs, exemplified by SDZ 217-744, is emerging with a wide therapeutic window following local administration.

Clinical Studies with Potassium Channel Openers

There have been just four clinical studies with KCOs published and all concern first generation compounds. In a study in normal volunteers, oral administration of cromakalim inhibited bronchoconstrictor responses to hista-

mine [26]. However, in a second study with levromakalim, the active enantiomer of cromakalim, the finding could not be confirmed and headache was reported by 19 out of the 25 patients who received the drug [27]. Nevertheless, in a study in nocturnal asthma, orally administered cromakalim attenuated the fall in the early morning FEV₁; again, though, headache was a significant side effect [28]. In a further study, bimakalim showed neither bronchodilation nor cardiovascular side effects when given by inhalation to asthma patients at cumulative doses up to 175 µg [29].

Conclusions

Major recent developments in our understanding of the structural basis of the heterogeneity of K_{ATP} channels

promise to reveal opportunities for novel therapies for a variety of diseases. Nowhere is this more evident than in the area of respiratory disease where a unique approach to the treatment of AHR, one of the defining characteristics of asthma, is emerging [10] supported by a wealth of pre-clinical evidence. The key development has been the demonstration that certain KCOs of the benzopyran class can obviate experimentally induced AHR at doses substantially below those which produce cardiovascular side effects. Since the clinical potential of earlier, first-generation KCOs was compromised by cardiovascular side effects, the new generation of compounds with selectivity for the airways may constitute a new class of drugs for the treatment of asthma.

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