Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2003; 6 (1-4), 7-14

KATP Channels in Vascular Smooth Muscle: Structure, Regulation and Functional Roles

Standen NB

Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

K_{ATP} Channels in Vascular Smooth Muscle: Structure, Regulation and Functional Roles

N. B. Standen

K_{ATP} channels link membrane K^+ permeability to metabolism. In vascular smooth muscle, the molecular composition of the channel isoforms expressed has not been determined definitively, though there is good evidence that a channel comprising the pore-forming subunit Kir6.1 and the sulphonylurea receptor SUR2B plays important roles. It is also likely that there is molecular diversity among K_{ATP} channels of smooth muscle, with the possible involvement of heterotetramers of pore-forming subunits. In addition to metabolic regulation, vascular K_{ATP} channels are regulated by endogenous vasoactive agents by way of cellular signalling pathways. Protein kinase A has been shown both to cause tonic channel activation, and to be important in activation by several vasodilators. These actions require PKA localization by an A-kinase anchoring protein (AKAP). Vasoconstrictors cause channel inhibition by way of protein kinase C, and vascular K_{ATP} channels have also been shown to be inhibited by intracellular calcium, an effect mediated by protein phosphatase 2B. Physiologically, K_{ATP} channels appear to be involved in the maintenance of resting blood flow in a number of vascular beds, notably the coronary circulation, as well as in vasodilation in response to metabolic demand. There is also increasing evidence for a pathophysiological role in the catastrophic vasodilation and vascular hyporeactivity of circulatory shock. Clinically, the K_{ATP} opener nicorandil is increasingly used in angina, where it may show maximum potency in ischaemic tissue, while increased understanding of these channels may offer future therapeutic opportunities. *J Clin Basic Cardiol 2003; 6: 7–14.*

Key words: K_{ATP} channel, smooth muscle, coronary blood flow, blood flow, shock, exercise, AKAP, vasodilation, vasoconstriction

It is rather over a decade since vascular ATP-sensitive potassium (K_{ATP}) channels were first identified. Since then these channels have been the subject of extensive research, and much of this work has been reviewed quite recently [1–3]. K_{ATP} channels link membrane K^+ permeability to cellular metabolism. They are inhibited by intracellular ATP, and activated by ADP and other nucleoside diphosphates. They also form targets for therapeutic drugs that act either as channel openers or blockers. In vascular smooth muscle, opening K_{ATP} channels causes membrane hyperpolarization, decreased intracellular calcium concentration, and vasorelaxation. In addition to metabolic sensitivity, the channels are opened by vasodilators, while many vasoconstrictors close them, and such modulation represents a major component of their physiological regulation. Functional work has shown that K_{ATP} channels in arterial smooth muscle cells provide a background potassium conductance important in the regulation of membrane potential and so arterial tone and blood flow in a number of vascular beds. K_{ATP} activation can contribute both to basal blood flow, and to changes in flow in response to metabolic changes, as in exercise. Under pathological conditions, excessive K_{ATP} channel activation may play a role in the catastrophic vasodilation and vascular hyporeactivity associated with shock. This review concentrates on some recent developments in understanding the molecular structure, regulation, and some of the functional significance of vascular K_{ATP} channels.

Molecular Structure

K_{ATP} channels are heteromultimers of potassium channel subunits of the Kir6 family and sulphonylurea receptors (SUR). The pore of the channel is formed by a tetramer of Kir6 subunits, which appear to associate with SURs with 1:1 stoichiometry so that the complete channel forms as an octamer [4]. The Kir6 subunit confers sensitivity to inhibition by ATP, conductance and rectification properties. SUR modulates the sensitivity to ATP inhibition, and is also responsible for the activating effects of nucleoside diphosphates (NDPs). As their name suggests, sulphonylurea drugs inhibit K_{ATP} channels by interacting with SUR, and drugs that open K_{ATP} channels also act through this subunit [5]. Two Kir6 genes have been found: Kir6.1 and Kir6.2, while two SUR genes are also known, SUR1 and SUR2. SUR2 has two main splice variants, encoding the receptors SUR2A and SUR2B, and certain other minor variants have been identified at the RNA level [4]. Interaction of the two types of subunit is required for trafficking of correctly assembled channels to the cell membrane [6]. Consistent with this, a C-terminal truncated version of Kir6.2 that lacks the endoplasmic reticulum retention sequence can form functional channels in the absence of SUR [7]. K_{ATP} channels of different molecular composition are expressed in different tissues, and their varied properties are significant both for their physiological functions and for selective pharmacology. Correlation of the properties, regulation and pharmacology of K_{ATP} channels with their molecular structure is currently the subject of intensive research.

There is good evidence that the K_{ATP} channel of the pancreatic β-cell comprises Kir6.2/SUR1, while that of the sarcolemma of cardiac muscle is Kir6.2/SUR2A [4, 5]. Thus coexpression of the cloned subunits in *Xenopus* oocytes or mammalian cell lines reproduces the major properties of the channel in native tissue, while knockout studies have also shown the predicted abolition of channel activity [8, 9]. However, the molecular nature of the K_{ATP} channel, or channels, of vascular smooth muscle has not yet been definitively determined, and is complicated by diversity in vascular K_{ATP} channels [1, 2].

K_{ATP} channels of vascular smooth muscle show a different pharmacology with respect to K_{ATP} opening drugs from that of pancreatic or cardiac channels, being activated by pinacidil, levcromakalim, and diazoxide [3]. This pattern of sensitivity to KCOs is conferred on recombinant channels by the

From the Department of Cell Physiology and Pharmacology, University of Leicester, United Kingdom.
Correspondence to: N. B. Standen, Department of Cell Physiology and Pharmacology, University of Leicester, PO Box 138, Leicester LE1 9HN, United Kingdom; e-mail: NBS@le.ac.uk

SUR2B subunit, suggesting that this subunit might form a common component of K_{ATP} channels in VSM. In non-vascular smooth muscle cells of colon, bladder, and urethra it has been suggested on the basis of reverse transcription polymerase chain reaction (RTPCR) and mRNA measurements that K_{ATP} channels comprise Kir6.2/SUR2B [10–12]. Currently, the best evidence for the molecular composition of a particular vascular smooth muscle K_{ATP} channel is that for the nucleoside diphosphate (NDP)-activated channel, sometimes called K_{NDP} [13, 14]. K_{NDP} is activated by ATP at low concentrations, but inhibited above about 1 mmol/l, is sensitive to activation by NDPs in the presence of the K_{ATP} channel opener pinacidil, and has a relatively small unitary conductance of 30–35 pS in symmetrical high $[K^+]$ [13–15]. Both Kir6.1 and SUR2B show widespread expression [16, 17]. When co-expressed in heterologous systems they form a channel with ATP and NDP sensitivity and single channel conductance comparable to that of native K_{NDP}. Thus it seems likely that K_{NDP} is formed by the combination of Kir6.1 and SUR2B [18]. Recent evidence suggests that this subunit combination may also underlie K_{ATP} channels of pulmonary arterial smooth muscle. Cultured human pulmonary arterial smooth muscle cells expressed a channel with a conductance in the appropriate range (28–29 pS), and RTPCR revealed transcripts for Kir6.1 and SUR2B, but not Kir6.2, SUR2A or SUR1 [19].

There is considerable evidence that K_{ATP} channels of vascular smooth muscle can differ in terms of their single channel conductance and sensitivity to regulation by ATP and other nucleotides (reviewed in [1, 2]). Recent work on cloned K_{ATP} channels has raised the possibility that some of this diversity might arise from the co-assembly of the pore-forming subunits Kir6.1 and Kir6.2 to form heterotetramers [20, 21]. Channels formed by cloned Kir6.1 or Kir6.2 alone show conductances of 30–35 pS and 70–80 pS respectively, while Kir6.1–Kir6.2 dimers form channels with an intermediate conductance [16, 22, 23]. Co-expression of Kir6.1 and Kir6.2 together with SUR2B in HEK293 cells leads to channels with a range of conductances consistent with the formation of tetramers with 1, 2, 3, or 4 of either channel subunit [20]. Further evidence for Kir6.1–Kir6.2 co-assembly in heterologous expression systems has been provided by the use of dominant negative subunits in which the conserved GFG sequence is mutated so that the subunit cannot form a functional pore; such subunits can prevent pore formation by wild-type subunits in a tetramer. In HEK293 cells, dominant negative Kir6.1 subunits can suppress currents through channels formed by wild-type Kir6.2 (or Kir6.1) subunits expressed with either SUR2B or SUR2A, and dominant negative Kir6.2 has similar effects [20, 21]. In addition, coimmunoprecipitation studies have provided evidence that Kir6.1 and Kir6.2 interact at a biochemical level in HEK293 cells [20, 21]. Co-assembly of Kir6.1 and Kir6.2 may not be possible in all systems, since Seharaseyon et al. found no evidence for co-assembly in either A549 cells or cardiac ventricular myocytes [24]. With respect to vascular smooth muscle, however, it is of interest that dominant negative Kir6.2 suppressed K_{ATP} currents in the aortic-derived cell line A10 [25], where the reported properties of the K_{ATP} channel expressed are suggestive of Kir6.1 [26], consistent with co-assembly being possible in these cells. Finally, studies in Kir6.2 knockout mice show that both pinacidil-induced K_{ATP} currents of aortic smooth muscle cells and pinacidil relaxations of aortic rings were unaffected in the absence of Kir6.2, suggesting that Kir6.1 alone forms the K_{ATP} channel pore in this tissue [9]. Further investigations of the molecular basis for K_{ATP} channel diversity in smooth muscle will form an important area of future research, and it may be that such diversity may also offer potential for future selective pharmacology.

Regulation by Cellular Signalling Pathways

Arterial K_{ATP} channels are regulated by multiple mechanisms. In general, regulation is consistent with their metabolic sensitivity and a role in adjusting blood vessel diameter and so blood flow to tissue metabolic demand. Like K_{ATP} channels of other tissues, they can be inhibited by intracellular ATP, though their reported sensitivity varies in different smooth muscle preparations. The reported effects of ATP may be complicated by the role of MgATP in maintaining channel function, and by the effects of ATP levels on tonic channel activation by protein kinase A, discussed below. Since intracellular ATP levels usually change little except in relatively severe metabolic compromise, it is more likely that inhibition by ATP provides a background level of activity against which other regulatory mechanisms operate. Among these, activation by nucleoside diphosphates seems important for many smooth muscle K_{ATP} channels [14, 15], and may account for some of the metabolic sensitivity of such channels. The role of nucleotides in K_{ATP} channel regulation has been reviewed recently [1]. K_{ATP} channels of vascular smooth muscle are also regulated by a wide range of vasodilators and vasoconstrictors. It is likely that such regulation forms an important part of their control under physiological conditions, and such regulation is discussed below, with an emphasis on experiments where currents through K_{ATP} channels have been measured directly from vascular smooth muscle cells using the patch clamp technique.

Activation by Vasodilators

Several vasodilators have been shown to activate vascular K_{ATP} channels, including calcitonin gene-related peptide, adenosine, and b-adrenoceptor agonists [27–30]. There is good evidence that activation by these vasodilators can occur through the classical adenylyl cyclase-protein kinase A pathway [30–32] (see [1] for review). In addition, intracellular application of either cyclic AMP or the catalytic subunit of protein kinase A (PKA) has been shown to activate K_{ATP} channels [30–32]. Recent work, discussed below, suggests that in addition to activation in response to binding of vasodilators to their receptors, PKA exerts a tonic drive on K_{ATP} channel activity in the absence of receptor activation. The molecular mechanism by which PKA activates vascular K_{ATP} channels remains to be determined. The simplest hypothesis is that the channel is phosphorylated directly, and both Kir and SUR subunits have consensus sites for phosphorylation by PKA [4]. In Kir6.2, PKA phosphorylates T224 to cause channel activation [33]. Little is known of Kir6.1 or SUR2B in this respect, though the consensus PKA site is conserved in Kir6.1 at T234.

Tonic Channel Activation by PKA

Most experimental work using patch clamp to study vascular K_{ATP} channels has used a low intracellular ATP concentration (usually 0.1 mmol/l) to reduce channel inhibition by ATP and so increase K_{ATP} current. It has been shown recently, however, that low intracellular ATP obscures a tonic activation of the channels by PKA, which is revealed by increasing ATP towards physiological levels. Thus K_{ATP} current is reduced by block of PKA when intracellular ATP is 1 mmol/l, but not when it is 0.1 mmol/l [34]. Such tonic activation by PKA does not require the presence of receptor agonists. Further, block of phosphatases with calyculin A leads to small but significant increases in K_{ATP} current. Such tonic channel acti-

vation by PKA may be important for the tonic contribution of the channels to resting blood flow discussed below, and inhibition of tonic PKA activation may also provide a new pathway for vasoconstrictor inhibition of the channels.

K_{ATP} Channel Inhibition by Vasoconstrictors

Vasoconstrictors cause an increase in the intracellular Ca^{2+} concentration of vascular smooth muscle and so in contractile force, by increasing influx of extracellular Ca^{2+} and by releasing Ca^{2+} from intracellular stores [35–37]. Closure of K^+ channels will contribute to membrane depolarization, and therefore to increased Ca^{2+} entry through voltage-dependent Ca^{2+} channels [36]. Many studies have shown that vasoconstrictors can inhibit a variety of potassium channels [38], and a number of vasoconstrictors have been shown to inhibit K_{ATP} channels of vascular smooth muscle. These include angiotensin II, endothelin, vasopressin, serotonin, phenylephrine, neuropeptide Y and histamine [39–42], (see [1] for review). Several of these vasoconstrictors have been shown to inhibit K_{ATP} channels through protein kinase C (PKC) [41, 42], and in mesenteric artery such inhibition is entirely prevented by the peptide translocation inhibitor of PKC epsilon, suggesting that this is the isoform involved [34]. Constitutively active PKC has also been shown to inhibit nucleotide diphosphate-sensitive K_{ATP} channels when applied to inside-out membrane patches excised from rabbit or rat pulmonary vein [43]. As for PKA, the means by which PKC affects channel activity at the molecular level remains to be determined. As for PKA, one possibility is through phosphorylation of Kir6.1 itself. PKC has been shown to modulate the activity of cardiac K_{ATP} channels by phosphorylation of threonine 180 on Kir6.2 [44], and this consensus site is conserved at T190 in Kir6.1.

Initial studies that implicated PKC in the actions of vasoconstrictors showed that block of PKC abolished K_{ATP} channel inhibition by vasoconstrictors, suggesting that this was the sole pathway for their action [41, 42]. Recent work, however, has provided intriguing new possibilities for the mechanisms by which vasoconstrictors may inhibit K_{ATP} channels. The tonic K_{ATP} activation by PKA described above raises the possibility that vasoconstrictors might inhibit such activation. The earlier studies that showed entire dependence on PKC were done under conditions of low intracellular ATP, where tonic activation would have been absent, and so would not have revealed such a pathway. When intracellular ATP is higher, however, about half the K_{ATP} channel inhibition by angiotensin II can be attributed to reduction in tonic activation by PKA [34]. Whether this effect involves inhibition of adenylyl cyclase or occurs elsewhere in the pathway is currently unknown. It will also be of great interest to determine whether inhibition of tonic PKA drive forms a widespread pathway for the action of vasoconstrictors.

Recent work in aortic smooth muscle cells has provided evidence that K_{ATP} channel activity can also be regulated by the intracellular Ca^{2+} concentration by way of the calcium-sensitive protein phosphatase 2B (calcineurin) [45]. K_{ATP} currents were maximally activated when $[Ca^{2+}]_i$ was 10 nM, but were strongly inhibited at 300 nM. Inhibition of calcineurin (with cyclosporin A, FK-506, or calcineurin autoinhibitory peptide) increased K_{ATP} currents, even when Ca^{2+} was high. It is presently unclear how calcineurin exerts its action on the channel, but it is likely to regulate the degree of phosphorylation of a site that causes channel activation, either on the channel itself or on an accessory regulatory protein [45]. One possible such target is the site at which PKA activates the channel. These findings suggest another pathway that might contribute to vasoconstrictor inhibition of K_{ATP} channels: vasoconstrictor-induced increases in $[Ca^{2+}]_i$ may increase the activity of calcineurin to reduce channel activity.

Anchoring proteins and signalling complexes

The work discussed above has provided evidence that vascular K_{ATP} channels are influenced by multiple regulators, including protein kinases A and C and protein phosphatase 2B. The tonic activation of K_{ATP} channels by protein kinase A suggests an intimate spatial relationship between kinase and channel. In recent years subcellular targeting of PKA through association with A-kinase anchoring proteins, or AKAPs, has been shown to account for the specificity of PKA phosphorylation in a number of cellular pathways [46–48]. AKAPs have a conserved helical region that binds the regulatory (RII) subunits of the PKA holoenzyme, and an anchoring domain that tethers the PKA-AKAP complex close to its site of action. Membrane targeting of PKA by AKAPs has been shown to be involved in the regulation of several types of ion channel (eg [49–51]). We have recently shown that an AKAP is involved in PKA regulation of arterial K_{ATP} channels [52]. Ht31 peptide binds to the RII subunit of PKA with nanomolar affinity, thus competing for PKA with native AKAPs, and so disrupting PKA anchoring within cells [53]. Intracellular application of Ht31 peptide blocked K_{ATP} current activation either by CGRP, which activates adenylyl cyclase, or by cAMP itself [52]. In addition, it prevented tonic K_{ATP} channel activation by PKA. However, intracellularly applied PKA catalytic subunit, which should act independently of native PKA localisation, was still able to activate K_{ATP} channels. These findings provide strong evidence for a key role of an AKAP in PKA-K_{ATP} channel signalling.

AKAPS do not only bind PKA. The prototypic AKAP, AKAP79, can bind both PKC and PP2B in addition to PKA [54]. Thus AKAPs can assemble multi-enzyme complexes that act in concert to regulate the phosphorylation state of cellular substrates. Such AKAP complexes may themselves be part of large signalling complexes that may involve both upstream activators and downstream targets [55]. Since PKA, PKC and PP2B are all involved in K_{ATP} regulation, it is an attractive idea that all of these enzymes might be localised by

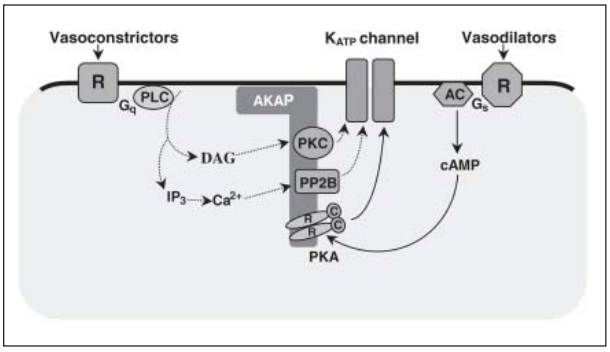

Figure 1. Schematic diagram of factors that regulate vascular K_{ATP} channels. Activation pathways are shown with solid arrows and inhibitory pathways with dotted arrows. The A-kinase anchoring protein (AKAP) may be important in localising key regulatory enzymes close to the channel to form a regulatory complex. Many vasodilators act through adenylyl cyclase (AC) and PKA to cause channel activation, while PKA also provides tonic channel activation. Vasoconstrictors acting through phospholipase C (PLC) inhibit the channel through PKC and might also do so by activation of PP2B or inhibition of AC. Whether these kinases and phosphatases act directly on the channel proteins as indicated remains to be determined, as do the detailed interactions between the regulatory pathways and other structural elements that may link receptors, AKAP and channel into a signalling complex.

the same AKAP, and that their functions in regulating the K_{ATP} channel might be integrated by anchoring into a signalling complex. Figure 1 shows a hypothetical scheme for such a complex. The identity of the AKAP involved remains to be determined, as do possible scaffolding links between receptors for vasoactive agonists, AKAP, and K_{ATP} channel.

Physiological and Pathophysiological Roles

Opening arterial K_{ATP} channels causes membrane hyperpolarization, decreased intracellular [Ca^{2+}], and vasorelaxation, and the mechanisms involved have been reviewed previously [1, 36]. The following sections consider functional roles played by K_{ATP} channels in circulatory responses under physiological and pathophysiological conditions.

Resting Arterial Tone and Blood Flow

The initial evidence that vascular K_{ATP} channels have the potential to contribute to vasodilation came from studies that preceded the identification of the channels. A series of pharmacological agents including nicorandil, cromakalim, and pinacidil proved to be effective vasorelaxants of systemic and coronary blood vessels [56–62]. These drugs caused membrane hyperpolarization of smooth muscle, increased ^{86}Rb or ^{42}K efflux, and were ineffective at relaxing vessels constricted with high extracellular [K^+], consistent with their acting by opening K^+ channels. They are now generally named K^+ channel openers. Following the demonstration that K_{ATP} channels occurred in smooth muscle, it became clear that these openers exert their hyperpolarizing and vasorelaxant effects by activating these K_{ATP} channels (see [1] for review). More recently, pharmacological K_{ATP} channel openers have been shown to increase blood flow or decrease vascular tone in the systemic [63, 64], coronary [63, 65, 66], and pulmonary [64, 67, 68] circulations. These studies with K_{ATP} openers demonstrate the potential of K_{ATP} channel activation to contribute to vasodilation under physiological conditions.

Over the past ten years substantial evidence has accumulated that K_{ATP} channels contribute a tonic vasodilator component in the coronary and systemic circulations, so contributing to blood flow at rest. Much of this evidence has come from studies of the effects of K_{ATP} channel inhibition with the sulphonylurea blocker glibenclamide on tone, vascular resistance or blood flow. Thus glibenclamide has been shown to increase vascular resistance in mesenteric and renal vascular beds [69–71]. K_{ATP} channels have also been reported to influence resting vascular tone in the skeletal muscle bed in some preparations [70, 72–74], but not in others [64, 75–77]. In the pulmonary circulation, evidence for functional K_{ATP} channels comes from vasodilator responses to K_{ATP} channel agonists in a number of species [64, 67, 68, 78, 79], and glibenclamide has been reported to decrease pulmonary vascular conductance in newborn piglets [68]. However, K_{ATP} channel blockade did not affect pulmonary vascular conductance in rats, cats, dogs or adult pigs, suggesting that these channels make little contribution to the regulation of basal pulmonary vascular tone [67, 76, 79].

Much experimental work has concentrated on the contribution of K_{ATP} channels to basal coronary blood flow, and here there is good evidence that a substantial component of resting flow depends on K_{ATP} channel activity. In anaesthetised dogs, glibenclamide can increase coronary resistance by up to 67 % [80–83], while equivalent responses have been reported in the coronary circulation of isolated hearts from rabbits, rats and mice [84–86]. Experiments on chronically implanted awake dogs and pigs at rest are consistent with these findings: here glibenclamide also increased coronary vascular resistance [66, 79]. Together, this work suggests that K_{ATP} channels in the coronary vasculature are tonically active under basal conditions, and contribute a degree of vasodilation that is important for resting blood flow.

Studies on Genetically Altered Mice

Two recent studies on mice in which genes encoding K_{ATP} channel subunits were disrupted have given important insights into both the role and composition of arterial K_{ATP} channels. Disruption of the gene encoding Kir6.1 abolished pinacidil-activated currents in aortic smooth muscle cells and also abolished vasodilator responses to pinacidil, suggesting that this subunit is an essential component of arterial K_{ATP} channels [87]. Kir6.1-null mice had a high rate of sudden cardiac death associated with spontaneous elevation of the ST segment in the electrocardiogram followed by atrioventricular node block, indicative of periods of cardiac ischaemia resulting from coronary arterial vasospasm. The vasoconstrictor ergometrine induced ST elevation followed by cardiac death in Kir6.1 mice, but not in wild-type animals [87]. Thus the Kir6.1-null animals have hypercontractile coronary arteries, consistent with a critical role for the K_{ATP} channel in regulating vascular tone and in protecting against vasospasm. Very similar effects are seen in mice with disruption of the gene encoding SUR2 [88]. SUR2-null mice also lack vascular K_{ATP} channels and show ST segment elevation, coronary vasospasm and sudden cardiac death. Focal narrowing of coronary arteries was also observed in these animals. In addition, SUR2-null mice have significantly elevated resting blood pressure [88]. Together, these genetic studies confirm the results of pharmacological studies in intact animals in indicating the importance of K_{ATP} channels for regulating vascular tone and so blood pressure and blood flow.

Vasodilator Responses to Metabolic Demand and Exercise

In many vascular beds, blood flow is closely correlated to metabolic demand. Thus local vasodilator signals released by metabolically active tissue lead to adjustments of blood vessel diameter to provide appropriate blood flow. These signals may include falls in oxygen tension, falls in pH and release of local regulators such as adenosine and prostacyclins. K_{ATP} channel activation appears important in hypoxic vasodilation in the coronary circulation and several other vascular beds. Recent studies of reactive hyperaemia in both the guinea-pig heart and human forearm suggest that K_{ATP} channels play an important role in post-ischaemic vasodilation [89, 90]. The role of K_{ATP} channels in the cerebral circulation has been reviewed recently by Faraci and Heistad [91]. Here, though K_{ATP} channels are clearly present and functional in many vessels, a number of studies have provided little evidence for a role of K_{ATP} channels in resting tone. However, several endogenous substances, including EDHF, CGRP, prostacyclin, opioids, and adenosine, that hyperpolarize and relax cerebral vascular smooth muscle, appear to do so via activation of K_{ATP} channels. Similarly, several studies have suggested that K_{ATP} channels may contribute to cerebral vasodilation in response to hypoxia [92–97] and K_{ATP} channels may also contribute to cerebral vascular autoregulation [98].

The roles of K_{ATP} channels in metabolic vasodilation suggests that they might be involved in circulatory responses to the increased metabolic demands induced by exercise. There have been relatively few studies in this area, but work on exercising dogs has provided interesting results. K_{ATP} channel blockade with glibenclamide reduced resting coronary blood flow and the reactive increase in blood flow in response to ischaemia, but did not prevent exercise-induced vasodilation [66]. However, when adenosine receptors were inhibited,

blockade of K_{ATP} channels blunted exercise-induced coronary vasodilation [99], an effect that became very severe when nitric oxide (NO) synthase was inhibited as well [100]. Neither adenosine nor nitric oxide-dependent mechanisms appear obligatory for maintaining either resting coronary flow or the increase in coronary flow on exercise, since these parameters were unaffected by blockade of both pathways [100]. The findings suggest that K_{ATP} channels are important for maintaining coronary vasodilation during exercise under normal conditions, but that adenosine and NO can act to increase coronary blood flow in exercise when K_{ATP} channels are blocked [100]. Interestingly, hypertrophied hearts seem to have an increased dependence on K_{ATP} channel opening to increase coronary blood flow in exercise, since here glibenclamide alone blunted the exercise-induced increase in flow [101]. A recent study has extended these investigations to the systemic and pulmonary circulations in exercising pigs. This work showed that K_{ATP} channel activation contributed to vasodilation both at rest and during exercise in the systemic as well as coronary circulations, but was not essential for exercise-induced vasodilation. In contrast, pulmonary vascular conductance was unaffected by glibenclamide, either at rest or in exercise [79].

Shock

Circulatory shock is characterized by hypotension, low systemic resistance and inadequate tissue perfusion, and vascular hyporesponsiveness to vasoconstrictors. Activation of potassium channels in the peripheral circulation seems important in the refractory vasodilation of shock, since K^+ channel blockers have been shown to reduce such vasodilation [2, 102]. In particular, there is considerable evidence that increased activity of K_{ATP} channels occurs in both endotoxic and haemorrhagic shock.

In 1992 Landry and Oliver provided the first evidence for a role of K_{ATP} channels in the vasodilation induced by shock, showing that glibenclamide caused vasoconstriction and restored blood pressure in dogs with endotoxic hypotension [103]. Since then studies in rat and pig models in which shock is induced with bacterial endotoxins (lipopolysaccharides) have also shown at least partial restoration of arterial pressure by glibenclamide [104–108]. In the conscious rat, the major effect of glibenclamide on haemodynamics appears to be in the hindquarters vascular bed, where vascular resistance is increased and flow reduced [107]. Glibenclamide also abolished endotoxin-induced hyporesponsiveness to phenylephrine in rats [108]. Additional evidence for involvement of K_{ATP} channels comes from experiments showing that vasorelaxations to the K_{ATP} channel openers cromakalim and pinacidil were enhanced in endotoxic shock, consistent with an increase in K_{ATP} channel activity under such conditions [108]. Aortic smooth muscle from endotoxaemic rats has recently been shown to have a hyperpolarized membrane potential compared to control animals, and this hyperpolarization was partially reversed by blockers of either K_{ATP} or large-conductance Ca^{2+}-activated K^+ channels [109].

Blockade of K_{ATP} channels has also been reported to be beneficial in haemmorhagic shock. In anaesthetized rats subjected to severe haemorrhagic shock, glibenclamide increased arterial pressure [110, 111] and also improved survival rate [110]. In similar experiments using pigs, glibenclamide caused a sustained recovery of blood pressure, improved a number of haemodynamic variables, and restored tissue perfusion and metabolism to pre-shock levels [112]. In rats, glibenclamide has also been reported to reverse shock-induced arteriolar smooth muscle hyperpolarization and to improve intracellular Ca^{2+} responses and vascular hyporesponsiveness to noradrenaline [113], but not to affect hyporesponsiveness to angiotensin II [111].

Together, these findings provide good evidence that the activity of K_{ATP} channels is increased in circulatory shock, but the mechanism by which this occurs is still unclear. There is substantial evidence that increased synthesis of NO contributes to the vascular hypotension and hyporeactivity of shock [102, 114]. One possibility is that this leads to K_{ATP} channel activation via nitric oxide (NO) and cGMP. NO has been shown to cause glibenclamide-sensitive membrane potential hyperpolarization in rat and rabbit mesenteric arteries [115, 116], and may also play a role in hypoxic dilation of pial arteries [97, 117]. NO has also been reported to activate K_{ATP} channels in cultured smooth muscle cells [118]. However, studies in freshly isolated cells from rabbit mesenteric or pig coronary arteries failed to find K_{ATP} channel activation by NO or NO donors [30, 31]. In addition, glibenclamide did not inhibit NO donor-induced vasodilation in normal animals [103, 119]. A common theme in these studies has been the use of glibenclamide to define the involvement of K_{ATP} channels. Two recent brief reports suggest that K_{ATP} channels may have an altered pharmacology in endotoxaemia. Thus the compound PNU-37883A, which blocks K_{ATP} channels by interaction with the pore-forming subunit rather than the sulphonylurea receptor, inhibited both hyporeactivity to phenylephrine and relaxations to L-arginine in lipopolysaccharide-pretreated rat mesenteric artery or aortic rings under conditions where glibenclamide was ineffective [120, 121]. The suggestion that endotoxaemia can reduce K_{ATP} channel sensitivity to glibenclamide, maybe through an action of NO, indicates that the possibility of K_{ATP} channel activation by NO requires further experimental study using pore-blocking agents.

CGRP levels are also increased in shock, and can contribute to shock-induced hypotension [122–124]. Since CGRP is a potent activator of K_{ATP} channels, it may also contribute to their activation in shock. A further possibility is that tissue metabolic changes might contribute to K_{ATP} channel activation, since lactic acidosis-induced hypotension in dogs could also be reversed by glibenclamide [103]. Finally, in addition to acute activation of K_{ATP} channels by one or all of these mechanisms, it is also possible that they affect gene regulation to upregulate K_{ATP} channel expression in shock.

Clinical Pharmacology

Both K_{ATP} channel opening and blocking drugs are used clinically, though vascular K_{ATP} channels are not always their intended target. Openers include the antihypertensives diazoxide and minoxidil sulphate, and the anti-anginal drug nicorandil which is currently in increasing use in Europe. In theory, at least, K_{ATP} channel openers might be expected to have advantageous properties in the treatment of ischaemic conditions like angina. The intrinsic metabolic sensitivity of vascular K_{ATP} channels should increase channel open probability in ischaemic tissue. If the action of K_{ATP} channel openers is synergistic with such intrinsic activation, such openers should have a self-targetting property, being more effective as vasodilators in ischaemic tissue. Studies on isolated coronary arteries suggest that this is the case for nicorandil [125]. Nicorandil also combines a nitrovasodilator action with its K_{ATP} channel opening properties, and this may contribute to a combination of rapid onset of action with lack of the development of the tolerance seen with classical nitrovasodilators [126]. Further interest in the drug has come from recent evidence that it is able to confer cardioprotection similar to that induced by ischaemic preconditioning [126], an effect that appears to be mediated by cardiac rather than vascular K_{ATP} channels.

K_{ATP} channels of pancreatic beta cells form the therapeutic target for a widely-used family of drugs, the antidiabetic sulphonylureas. While such drugs show selectivity for the beta-cell form of the channel, they can block cardiac and vascular K_{ATP} channels at higher concentrations, and there has been a long-standing controversy as to whether this may contribute to possible adverse cardiovascular effects associated with sulphonylurea therapy for type 2 diabetes [127, 128].

Conclusions and Future Perspectives

We have accumulated a large amount of information about vascular K_{ATP} channels since they were discovered. However, important questions remain to be answered. Definitive information on molecular structure and the relationship between structure and the variations in K_{ATP} channel properties in smooth muscle will be an important goal. Achieving a full understanding of K_{ATP} channel regulation by cellular signalling pathways will be a major task, given the complexity that is already becoming apparent. It is likely that such an understanding will require information about the structural as well as functional relationships between the components of the signalling complexes involved. Functional studies in intact tissues and whole animals will also continue to be important in further defining the functional roles of vascular K_{ATP} channels. These should benefit from developing understanding of the channels and their regulation at a molecular and cellular level. Recent evidence suggests that the use of pore blocking drugs as well as K_{ATP} channel inhibitors will be important to help define these functions. As information about channel regulation becomes more precise, it is very likely that transgenic animals developed in the light of such knowledge will also play an important apart in elucidating channel function. Increased understanding of the regulation and functions of these channels should also have the potential to improve clinical practice in situations where they are involved, either to positive effect as in angina, or negatively as in shock. In the longer term, it is possible that new drugs designed to target aspects of K_{ATP} channel regulation may prove to be valuable therapeutic agents.

Acknowlegements

This work was supported by the Wellcome Trust, British Heart Foundation and Medical Research Council.

References

1. Quayle JM, Nelson MT, Standen NB. ATP-sensitive and inwardly rectifying potassium channels in smooth muscle. Physiol Rev 1997; 77: 1165–232.
2. Clapp LH, Tinker A. Potassium channels in the vasculature. Curr Opin Nephrol Hypertens 1998; 7: 91–8.
3. Yokoshiki H, Sunagawa M, Seki T, Sperelakis N. ATP-sensitive K^+ channels in pancreatic, cardiac, and vascular smooth muscle cells. Am J Physiol 1998; 274: C25–C37.
4. Aguilar-Bryan L, Clement JP, Gonzalez G, Kunjilwar K, Babenko A, Bryan J. Toward understanding the assembly and structure of K_{ATP} channels. Physiol Rev 1998; 78: 227–45.
5. Ashcroft FM, Gribble FM. Correlating structure and function in ATP-sensitive K^+ channels. Trends Neurosci 1998; 217: 288–94.
6. Zerangue N, Schwappach B, Jan YN, Jan LY. A new ER trafficking signal regulates the subunit stoichiometry of plasma membrane K_{ATP} channels. Neuron 1999; 22: 537–48.
7. Tucker SJ, Gribble FM, Zhao C, Trapp S, Ashcroft FM. Truncation of Kir6.2 produces ATP-sensitive K^+ channels in the absence of the sulphonylurea receptor. Nature 1997; 387: 179–83.
8. Seino S, Iwanaga T, Nagashima K, Miki T. Diverse roles of K_{ATP} channels learned from Kir6.2 genetically engineered mice. Diabetes 2000; 493: 311–8.
9. Suzuki M, Li RA, Miki T, Uemura H, Sakamoto N, Ohmoto-Sekine Y, Tamagawa M, Ogura T, Seino S, Marban E, Nakaya H. Functional roles of cardiac and vascular ATP-sensitive potassium channels clarified by Kir6.2-knockout mice. Circ Res 2001; 88: 570–7.
10. Koh SD, Bradley KK, Rae MG, Keef KD, Horowitz B, Sanders KM. Basal activation of ATP-sensitive potassium channels in murine colonic smooth muscle cell. Biophys J 1998; 75: 1793–800.
11. Gopalakrishnan M, Whiteaker KL, Molinari EJ, Davis-Taber R, Scott VE, Shieh CC, Buckner SA, Milicic I, Cain JC, Postl S, Sullivan JP, Brioni JD. Characterization of the ATP-sensitive potassium channels (K_{ATP}) expressed in guinea pig bladder smooth muscle cells. J Pharmacol Exp Ther 1999; 289: 551–8.
12. Teramoto N, Yunoki T, Tanaka K, Takano M, Masaki I, Yonemitsu Y, Sueishi K, Ito Y. The effects of caffeine on ATP-sensitive K^+ channels in smooth muscle cells from pig urethra. Br J Pharmacol 2000; 131: 505–13.
13. Beech DJ, Zhang H, Nakao K, Bolton TB. Single channel and whole-cell K-currents evoked by levcromakalim in smooth muscle cells from the rabbit portal vein. Br J Pharmacol 1993; 110: 583–90.
14. Beech DJ, Zhang H, Nakao K, Bolton TB. K channel activation by nucleotide diphosphates and its inhibition by glibenclamide in vascular smooth muscle cells. Br J Pharmacol 1993; 110: 573–82.
15. Zhang H, Bolton TB. Activation by intracellular GDP, metabolic inhibition and pinacidil of a glibenclamide-sensitive K-channel in smooth muscle cells of rat mesenteric artery. Br J Pharmacol 1995; 114: 662–72.
16. Inagaki N, Tsuura Y, Namba N, Masuda K, Gonoi T, Horie M, Seino Y, Mizuta M, Seino S. Cloning and functional characterization of a novel ATP-sensitive potassium channel ubiquitously expressed in rat tissues, including pancreatic islets, pituitary, skeletal muscle, and heart. J Biol Chem 1995; 270: 5691–4.
17. Isomoto S, Kondo C, Yamada M, Matsumoto S, Higashiguchi O, Horio Y, Matsuzawa Y, Kurachi Y. A novel sulfonylurea receptor forms with BIR (Kir6.2) a smooth muscle type ATP-sensitive K^+ channel. J Biol Chem 1996; 271: 24321–4.
18. Yamada M, Isomoto S, Matsumoto S, Kondo C, Shindo T, Horio Y, Kurachi Y. Sulphonylurea receptor 2B and Kir6.1 form a sulphonylurea-sensitive but ATP-insensitive K^+ channel. J Physiol 1997; 499: 715–20.
19. Cui Y, Tran S, Tinker A, Clapp LH. The molecular composition of K_{ATP} channels in human pulmonary artery smooth muscle cells and their modulation by growth. Am J Respir Cell Mol Biol 2002; 26: 135–43.
20. Cui Y, Giblin JP, Clapp LH, Tinker A. A mechanism for ATP-sensitive potassium channel diversity: Functional coassembly of two pore-forming subunits. Proc Natl Acad Sci U S A 2001; 98: 729–34.
21. Pountney DJ, Sun Z-Q, Porter LM, Nitabach MN, Nakamura TY, Holmes D, Rosner E, Kaneko M, Manaris T, Holmes TC, Coetzee WA. Is the molecular composition of K_{ATP} channels more complex than originally thought? J Mol Cell Cardiol 2001; 33: 1541–6.
22. Kondo C, Repunte VP, Satoh E, Yamada M, Horio Y, Matsuzawa Y, Pott L, Kurachi Y. Chimeras of Kir6.1 and Kir6.2 reveal structural elements involved in spontaneous opening and unitary conductance of the ATP-sensitive K^+ channels. Receptors Channels 1998; 6: 129–40.
23. Repunte VP, Nakamura H, Fujita A, Horio Y, Findlay I, Pott L, Kurachi Y. Extracellular links in Kir subunits control the unitary conductance of SUR/Kir6.0 ion channels. EMBO J 1999; 18: 3317–24.
24. Seharaseyon J, Sasaki N, Ohler A, Sato T, Fraser H, Johns DC, O'Rourke B, Marban E. Evidence against functional heteromultimerization of the K_{ATP} channel subunits Kir6.1 and Kir6.2. J Biol Chem 2000; 275: 17561–5.
25. Lalli MJ, Johns DC, Janecki M, Liu Y, O'Rourke B, Marban E. Suppression of K_{ATP} currents by gene transfer of a dominant negative Kir6.2 construct. Pflugers Arch 1998; 436: 957–61.
26. Russ U, Metzger F, Kickenweiz E, Hambrock A, Krippeit-Drews P, Quast U. Binding and effects of K_{ATP} channel openers in the vascular smooth muscle cell line, A10. Br J Pharmacol 1997; 122: 1119–26.
27. Nelson MT, Huang Y, Brayden JE, Hescheler J, Standen NB. Arterial dilations in response to calcitonin gene-related peptide involve activation of K^+ channels. Nature 1990; 344: 770–3.
28. Dart C, Standen NB. Adenosine-activated potassium current in smooth muscle cells isolated from the pig coronary artery. J Physiol 1993; 471: 767–86.
29. Miyoshi H, Nakaya Y. Activation of ATP-sensitive K^+ channels by cyclic AMP-dependent protein kinase in cultured smooth muscle cells of porcine coronary artery. Biochem Biophys Res Commun 1993; 193: 240–7.
30. Wellman GC, Quayle JM, Standen NB. ATP-sensitive K^+ channel activation by calcitonin gene-related peptide and protein kinase A in pig coronary arterial smooth muscle. J Physiol 1998; 507: 117–29.
31. Quayle JM, Bonev AD, Brayden JE, Nelson MT. Calcitonin gene-related peptide activated ATP-sensitive K^+ currents in rabbit arterial smooth muscle via protein kinase A. J Physiol 1994; 475: 9–13.
32. Kleppisch T, Nelson MT. Adenosine activates ATP-sensitive potassium channels in arterial myocytes via A2 receptors and cAMP-dependent protein kinase. Proc Natl Acad Sci U S A 1995; 92: 12441–5.
33. Lin YF, Jan YN, Jan LY. Regulation of ATP-sensitive potassium channel function by protein kinase A-mediated phosphorylation in transfected HEK293 cells. EMBO J 2000; 19: 942–55.
34. Hayabuchi Y, Davies NW, Standen NB. Angiotensin II inhibits rat arterial K_{ATP} channels by inhibiting steady-state protein kinase A activity and activating protein kinase Ce. J Physiol 2001; 530: 193–205.
35 Somlyo AP. Excitation-contraction coupling and the ultrastructure of smooth muscle. Circ Res 1985; 57: 497–507.
36. Nelson MT, Patlak JB, Worley JF, Standen NB. Calcium channels, potassium channels, and voltage dependence of arterial smooth muscle tone. Am J Physiol 1990; 259: C3–C18.
37. Sanders KM. Invited review: mechanisms of calcium handling in smooth muscles. J Appl Physiol 2001; 91: 1438–49.
38. Beech DJ. Actions of neurotransmitters and other messengers on Ca^{2+} channels and K^+ channels in smooth muscle cells. Pharmacol Ther 1997; 73: 91–119.
39. Miyoshi Y, Nakaya Y, Wakatsuki T, Nakaya S, Fujino K, Saito K, Inoue I. Endothelin blocks ATP-sensitive K^+ channels and depolarizes smooth muscle cells of porcine coronary artery. Circ Res 1992; 70: 612–6.

40. Wakatsuki T, Nakaya Y, Inoue I. Vasopressin modulates K^+-channel activities of cultured smooth muscle cells from porcine coronary artery. Am J Physiol 1992; 263: H491–H496.
41. Bonev AD, Nelson MT. Vasoconstrictors inhibit ATP-sensitive K^+ channels in arterial smooth muscle through protein kinase C. J Gen Physiol 1996; 108: 315–23.
42. Kubo M, Quayle JM, Standen NB. Angiotensin II inhibition of ATP-sensitive K^+ currents in rat arterial smooth muscle cells through protein kinase C. J Physiol 1997; 503: 489–96.
43. Cole WC, Malcolm T, Walsh MP, Light PE. Inhibition by protein kinase C of the K_{NDP} subtype of vascular smooth muscle ATP-sensitive potassium channel. Circ Res 2000; 87: 112–7.
44. Light PE, Bladen C, Winkfein RJ, Walsh MP, French RJ. Molecular basis of protein kinase C-induced activation of ATP-sensitive potassium channels. Proc Natl Acad Sci U S A 2000; 97: 9058–63.
45. Wilson AJ, Jabr RI, Clapp LH. Calcium modulation of vascular smooth muscle ATP-sensitive K^+ channels: role of protein phosphatase-2B. Circ Res 2000; 87: 1019–25.
46. Rubin CS. A kinase anchor proteins and the intracellular targeting of signals carried by cyclic AMP. Biochim Biophys Acta 1994; 1224: 467–79.
47. Pawson T, Scott JD. Signaling through scaffold, anchoring, and adaptor proteins. Science 1997; 278: 2075–80.
48. Colledge M, Scott JD. AKAPs: from structure to function. Trends Cell Biol 1999; 9: 216–21.
49. Rosenmund C, Carr DW, Bergeson SE, Nilaver G, Scott JD, Westbrook GL. Anchoring of protein kinase A is required for modulation of AMPA/kainate receptors on hippocampal neurons. Nature 1994; 368: 853–6.
50. Zhong J, Hume JR, Keef KD. Anchoring protein is required for cAMP-dependent stimulation of L-type Ca^{2+} channels in rabbit portal vein. Am J Physiol 1999; 277: C840–C844.
51. Dart C, Leyland ML. Targeting of an A Kinase-anchoring Protein, AKAP79, to an inwardly rectifying potassium channel, Kir2.1. J Biol Chem 2001; 276: 20499–505.
52. Hayabuchi Y, Dart C, Standen NB. Evidence for involvement of A-kinase anchoring protein in activation of rat arterial K_{ATP} channels by protein kinase A. J Physiol 2001; 536: 421–7.
53. Carr DW, Stofko-Hahn RE, Fraser ID, Bishop SM, Acott TS, Brennan RG, Scott JD. Interaction of the regulatory subunit (RII) of cAMP-dependent protein kinase with RII-anchoring proteins occurs through an amphipathic helix binding motif. J Biol Chem 1991; 266: 14188–92.
54. Klauck TM, Faux MC, Labudda K, Langeberg LK, Jaken S, Scott JD. Coordination of three signaling enzymes by AKAP79, a mammalian scaffold protein. Science 1996; 271: 1589–92.
55. Dodge K, Scott JD. AKAP79 and the evolution of the AKAP model. FEBS Lett 2000; 476: 58–61.
56. Itoh T, Furukawa K, Kajiwara M, Kitamura K, Suzuki H, Ito Y, Kuriyama H. Effects of 2-nicotinamidoethyl nitrate on smooth muscle cells and on adrenergic transmission in the guinea-pig and porcine mesenteric arteries. J Pharmacol Exp Ther 1981; 218: 260–70.
57. Furukawa K, Itoh T, Kajiwara M, Kitamura K, Suzuki H, Ito Y, Kuriyama H. Vasodilating actions of 2-nicotinamidoethyl nitrate on porcine and guinea-pig coronary arteries. J Pharmacol Exp Ther 1981; 218: 248–59.
58. Hamilton TC, Weir SW, Weston AH. Comparison of the effects of BRL 34915 and verapamil on electrical and mechanical activity in rat portal vein. Br J Pharmacol 1986; 88: 103–11.
59. Weir SW, Weston AH. The effects of BRL 34915 and nicorandil on electrical and mechanical activity and on 86Rb efflux in rat blood vessels. Br J Pharmacol 1986; 88: 121–8.
60. Bray KM, Newgreen DT, Small RC, Southerton JS, Taylor SG, Weir SW, Weston AH. Evidence that the mechanism of the inhibitory action of pinacidil in rat and guinea-pig smooth muscle differs from that of glyceryl trinitrate. Br J Pharmacol 1987; 91: 421–9.
61. Cook NS, Quast U, Hof RP, Baumlin Y, Pally C. Similarities in the mechanism of action of two new vasodilator drugs: pinacidil and BRL 34915. J Cardiovasc Pharmacol 1988; 11: 90–9.
62. Videbaek LM, Aalkjaer C, Mulvany MJ. Pinacidil opens K^+-selective channels causing hyperpolarization and relaxation of noradrenaline contractions in rat mesenteric resistance vessels. Br J Pharmacol 1988; 95: 103–8.
63. Sassen LM, Duncker DJ, Gho BC, Diekmann HW, Verdouw PD. Haemodynamic profile of the potassium channel activator EMD 52692 in anaesthetized pigs. Br J Pharmacol 1990; 101: 605–14.
64. Minkes RK, Kvamme P, Higuera TR, Nossaman BD, Kadowitz PJ. Analysis of pulmonary and systemic vascular responses to cromakalim, an activator of K^+_{ATP} channels. Am J Physiol 1991; 260: H957–H966.
65. Sato K, Kanatsuka H, Sekiguchi N, Akai K, Wang Y, Sugimura A, Kumagai T, Komaru T, Shirato K. Effect of an ATP sensitive potassium channel opener, levcromakalim, on coronary arterial microvessels in the beating canine heart. Cardiovasc Res 1994; 28: 1780–6.
66. Duncker DJ, Van Zon NS, Altman JD, Pavek TJ, Bache RJ. Role of K^+_{ATP} channels in coronary vasodilation during exercise. Circulation 1993; 88: 1245–53.
67. Hasunuma K, Rodman DM, McMurtry IF. Effects of K^+ channel blockers on vascular tone in the perfused rat lung. Am Rev Respir Dis 1991; 144: 884–7.
68. Pinheiro JM, Malik AB. K^+_{ATP}-channel activation causes marked vasodilation in the hypertensive neonatal pig lung. Am J Physiol 1992; 263: H1532–H1536.
69. Moreau R, Komeichi H, Kirstetter P, Yang S, Aupetit-Faisant B, Cailmail S, Lebrec D. Effects of glibenclamide on systemic and splanchnic haemodynamics in conscious rats. Br J Pharmacol 1994; 112: 649–53.
70. Gardiner SM, Kemp PA, March JE, Fallgren B, Bennett T. Effects of glibenclamide on the regional haemodynamic actions of alpha- trinositol and its influence on responses to vasodilators in conscious rats. Br J Pharmacol 1996; 117: 507–15.
71. Parekh N, Zou AP. Role of prostaglandins in renal medullary circulation: response to different vasoconstrictors. Am J Physiol 1996; 271: F653–F658.
72. Jackson WF. Arteriolar tone is determined by activity of ATP-sensitive potassium channels. Am J Physiol 1993; 265: H1797–H1803.
73 Vanelli G, Chang HY, Gatensby AG, Hussain SN. Contribution of potassium channels to active hyperemia of the canine diaphragm. J Appl Physiol 1994; 76: 1098–105.
74. Comtois A, Sinderby C, Comtois N, Grassino A, Renaud JM. An ATP-sensitive potassium channel blocker decreases diaphragmatic circulation in anesthetized dogs. J Appl Physiol 1994; 77: 127–34.
75. Lippton H, Choe E, Franklin E, Grivas T, Flint L, Hyman A, Ferrara J. Femoral vasodilation to cromakalim is blocked by U37883A, a non- sulphonylurea that selectively inhibits K_{ATP} channels. J Pharm Pharmacol 1995; 47: 243–5.
76. DeWitt BJ, Cheng DY, McMahon TJ, Marrone JR, Champion HC, Kandowitz PJ. Effects of U-37883A, a vascular selective K^+_{ATP} channel antagonist, in the pulmonary and hindlimb circulation. Am J Physiol 1996; 271: L924–L931.
77. Thomas GD, Hansen J, Victor RG. ATP-sensitive potassium channels mediate contraction-induced attenuation of sympathetic vasoconstriction in rat skeletal muscle. J Clin Invest 1997; 99: 2602–9.
78. Seki S, Sato K, Nakayama M, Murray PA. Halothane and enflurane attenuate pulmonary vasodilation mediated by adenosine triphosphate-sensitive potassium channels compared to the conscious state. Anesthesiology 1997; 86: 923–35.
79. Duncker DJ, Oei HH, Hu F, Stubenitsky R, Verdouw PD. Role of K^+_{ATP} channels in regulation of systemic, pulmonary, and coronary vasomotor tone in exercising swine. Am J Physiol Heart Circ Physiol 2001; 280: H22–H33.
80. Imamura Y, Tomoike H, Narishige T, Takahashi T, Kasuya H, Takeshita A. Glibenclamide decreases basal coronary blood flow in anesthetized dogs. Am J Physiol 1992; 263: H399–H404.
81. Samaha FF, Heineman FW, Ince C, Fleming J, Balaban RS. ATP-sensitive potassium channel is essential to maintain basal coronary vascular tone in vivo. Am J Physiol 1992; 262: C1220–C1227.
82. Mori H, Chujo M, Tanaka E, Yamakawa A, Shinozaki Y, Mohamed MU, Nakazawa H. Modulation of adrenergic coronary vasoconstriction via ATP-sensitive potassium channel. Am J Physiol 1995; 268: H1077–H1085.
83. Narishige T, Egashira K, Akatsuka Y, Imamura Y, Takahashi T, Kasuya H, Takeshita A. Glibenclamide prevents coronary vasodilation induced by beta 1-adrenoceptor stimulation in dogs. Am J Physiol 1994; 266: H84–H92.
84. Jackson WF, Konig A, Dambacher T, Busse R. Prostacyclin-induced vasodilation in rabbit heart is mediated by ATP-sensitive potassium channels. Am J Physiol 1993; 264: H238–H243.
85. Nakhostine N, Lamontagne D. Adenosine contributes to hypoxia-induced vasodilation through ATP-sensitive K^+ channel activation. Am J Physiol 1993; 265: H1289–H1293.
86. Randall MD. The involvement of ATP-sensitive potassium channels and adenosine in the regulation of coronary flow in the isolated perfused rat heart. Br J Pharmacol 1995; 116: 3068–74.
87. Miki T, Suzuki M, Shibasaki T, Uemura H, Sato T, Yamaguchi K, Koseki H, Iwanaga T, Nakaya H, Seino S. Mouse model of Prinzmetal angina by disruption of inward rectifier Kir6.1. Nature Medicine 2002; 8: 466–72.
88. Chutkow WA, Pu J, Wheeler MT, Wada T, Makielski JC, Burant CF, McNally EM. Episodic coronary artery vasospasm and hypertension develop in the absence of Sur2 K_{ATP} channels. J Clin Invest 2002; 110: 203–8.
89. Kingsbury MP, Robinson H, Flores NA, Sheridan DJ. Investigation of mechanisms that mediate reactive hyperaemia in guinea- pig hearts: role of K_{ATP} channels, adenosine, nitric oxide and prostaglandins. Br J Pharmacol 2001; 132: 1209–16.
90. Bank AJ, Sih R, Mullen K, Osayamwen M, Lee PC. Vascular ATP-dependent potassium channels, nitric oxide, and human forearm reactive hyperemia. Cardiovasc Drugs Ther 2000; 14: 23–9.
91. Faraci FM, Heistad DD. Regulation of the cerebral circulation: role of endothelium and potassium channels. Physiol Rev 1998; 78: 53–97.
92. Reid JM, Paterson DJ, Ashcroft FM, Bergel DH. The effect of tolbutamide on cerebral blood flow during hypoxia and hypercapnia in the anaesthetized rat. Pflugers Arch 1993; 425: 362–4.
93. Fredricks KT, Liu Y, Rusch NJ, Lombard JH. Role of endothelium and arterial K^+ channels in mediating hypoxic dilation of middle cerebral arteries. Am J Physiol 1994; 267: H580–H586.
94. Taguchi H, Heistad DD, Kitazono T, Faraci FM. ATP-sensitive K^+ channels mediate dilatation of cerebral arterioles during hypoxia. Circ Res 1994; 74: 1005–8.
95. Reid JM, Davies AG, Ashcroft FM, Paterson DJ. Effect of L-NMMA, cromakalim, and glibenclamide on cerebral blood flow in hypercapnia and hypoxia. Am J Physiol 1995; 269: H916–H922.
96. Shankar V, Armstead WM. Opioids contribute to hypoxia-induced pial artery dilation through activation of ATP-sensitive K^+ channels. Am J Physiol 1995; 269: H997–1002.
97. Armstead WM. Relationship among NO, the KATP channel, and opioids in hypoxic pial artery dilation. Am J Physiol 1998; 275: H988–H994.
98. Lee WS, Kwon YJ, Yu SS, Rhim BY, Hong KW. Disturbances in autoregulatory responses of rat pial arteries by sulfonylureas. Life Sci 1993; 52: 1527–34.
99. Duncker DJ, Van Zon NS, Pavek TJ, Herrlinger SK, Bache RJ. Endogenous adenosine mediates coronary vasodilation during exercise after K^+_{ATP} channel blockade. J Clin Invest 1995; 95: 285–95.

100. Ishibashi Y, Duncker DJ, Zhang J, Bache RJ. ATP-sensitive K^+ channels, adenosine, and nitric oxide-mediated mechanisms account for coronary vasodilation during exercise. Circ Res 1998; 82: 346–59.
101. Melchert PJ, Duncker DJ, Traverse JH, Bache RJ. Role of K^+_{ATP} channels and adenosine in regulation of coronary blood flow in the hypertrophied left ventricle. Am J Physiol 1999; 277: H617–H625.
102. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001; 345: 588–95.
103. Landry DW, Oliver JA. The ATP-sensitive K^+ channel mediates hypotension in endotoxemia and hypoxic lactic acidosis in dog. J Clin Invest 1992; 89: 2071–4.
104. Wu CC, Thiemermann C, Vane JR. Glibenclamide-induced inhibition of the expression of inducible nitric oxide synthase in cultured macrophages and in the anaesthetized rat. Br J Pharmacol 1995; 114: 1273–81.
105. Vanelli G, Hussain SN, Aguggini G. Glibenclamide, a blocker of ATP-sensitive potassium channels, reverses endotoxin-induced hypotension in pig. Exp Physiol 1995; 80: 167–70.
106. Vanelli G, Hussain SN, Dimori M, Aguggini G. Cardiovascular responses to glibenclamide during endotoxaemia in the pig. Vet Res Commun 1997; 21: 187–200.
107. Gardiner SM, Kemp PA, March JE, Bennett T. Regional haemodynamic responses to infusion of lipopolysaccharide in conscious rats: effects of pre- or post-treatment with glibenclamide. Br J Pharmacol 1999; 128:1772–8.
108. Sorrentino R, d'Emmanuele d, V, Lippolis L, Sorrentino L, Autore G, Pinto A. Involvement of ATP-sensitive potassium channels in a model of a delayed vascular hyporeactivity induced by lipopolysaccharide in rats. Br J Pharmacol 1999; 127: 1447–53.
109. Chen SJ, Wu CC, Yang SN, Lin CI, Yen MH. Abnormal activation of K^+ channels in aortic smooth muscle of rats with endotoxic shock: electrophysiological and functional evidence. Br J Pharmacol 2000; 131: 213–22.
110. Szabo C, Salzman AL. Inhibition of ATP-activated potassium channels exerts pressor effects and improves survival in a rat model of severe hemorrhagic shock. Shock 1996; 5: 391–4.
111. Pieber D, Horina G, Sandner-Kiesling A, Pieber TR, Heinemann A. Pressor and mesenteric arterial hyporesponsiveness to angiotensin II is an early event in haemorrhagic hypotension in anaesthetised rats. Cardiovasc Res 1999; 44: 166–75.
112. Salzman AL, Vromen A, Denenberg A, Szabo C. K_{ATP}-channel inhibition improves hemodynamics and cellular energetics in hemorrhagic shock. Am J Physiol 1997; 272: H688–H694.
113. Zhao K, Liu J, Jin C. The role of membrane potential and calcium kinetic changes in the pathogenesis of vascular hyporeactivity during severe shock. Chin Med J (Engl) 2000; 113: 59–64.
114. Thiemermann C. The role of the L-arginine: nitric oxide pathway in circulatory shock. Adv Pharmacol 1994; 28: 45–79.
115. Garland CJ, McPherson GA. Evidence that nitric oxide does not mediate the hyperpolarization and relaxation to acetylcholine in the rat small mesenteric artery. Br J Pharmacol 1992; 105: 429–35.
116. Murphy ME, Brayden JE. Nitric oxide hyperpolarizes rabbit mesenteric arteries via ATP-sensitive potassium channels. J Physiol 1995; 486: 47–58.
117. Armstead WM. Role of ATP-sensitive K^+ channels in cGMP-mediated pial artery vasodilation. Am J Physiol 1996; 270: H423–H426.
118. Miyoshi H, Nakaya Y, Moritoki H. Nonendothelial-derived nitric oxide activates the ATP-sensitive K^+ channel of vascular smooth muscle cells. FEBS Lett 1994; 345: 47–9.
119. Kontos HA, Wei EP. Arginine analogues inhibit responses mediated by ATP-sensitive K^+ channels. Am J Physiol 1996; 271: H1498–H1506.
120. O'Brien AJ, Thakur G, Cui Y, Singer M, Clapp LH. Inhibition of the pore-blocking subunit of the K_{ATP} channel partially reverses endotoxin-induced vascular hyporeactivity in rat superior mesenteric artery. Br J Pharmacol 2002; 135: 116P.
121. Wilson AJ, Clapp LH. Structurally dissimilar ATP-sensitive K^+ channel inhibitors have variable effects on relaxation to L-arginine in LPS-treated rat aortic rings. Br J Pharmacol 2002; 135: 117P.
122. Griffin EC, Aiyar N, Slivjak MJ, Smith EF, III. Effect of endotoxicosis on plasma and tissue levels of calcitonin gene-related peptide. Circ Shock 1992; 38: 50–4.
123. Huttemeier PC, Ritter EF, Benveniste H. Calcitonin gene-related peptide mediates hypotension and tachycardia in endotoxic rats. Am J Physiol 1993; 265: H767–H769.
124. Arden WA, Fiscus RR, Wang X, Yang L, Maley R, Nielsen M, Lanzo S, Gross DR. Elevations in circulating calcitonin gene-related peptide correlate with hemodynamic deterioration during endotoxic shock in pigs. Circ Shock 1994; 42: 147–53.
125. Davie CS, Standen NB. Enhancement of the vasorelaxant potency of nicorandil by metabolic inhibition and adenosine in the pig coronary artery. Cardiovasc Res 1998; 37: 791–8.
126. Gomma AH, Purcell HJ, Fox KM. Potassium channel openers in myocardial ischaemia: therapeutic potential of nicorandil. Drugs 2001; 61:1705–10.
127. Brady PA, Terzic A. The sulfonylurea controversy: more questions from the heart. J Am Coll Cardiol 1998; 31: 950–6.
128. Klamann A, Sarfert P, Launhardt V, Schulte G, Schmiegel WH, Nauck MA. Myocardial infarction in diabetic vs non-diabetic subjects. Survival and infarct size following therapy with sulfonylureas (glibenclamide). Eur Heart J 2000; 21: 220–9.

Mitteilungen aus der Redaktion

Besuchen Sie unsere

zeitschriftenübergreifende Datenbank

☑ **Bilddatenbank** ☑ **Artikeldatenbank** ☑ **Fallberichte**

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☑ **Bestellung e-Journal-Abo**