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REVIEW

Two-pore potassium channels in the cardiovascular system

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Abstract Two-pore domain (K_{2P}) channels emerged about a decade ago and since then have been an expanding area of interest. This is because their biophysical and pharmacological properties make them good candidates to support background potassium currents and membrane potential in many cell types. There is clear evidence for TREK-1 and TASK-1 in the heart and these channels are likely to regulate cardiac action potential duration through their regulation by stretch, polyunsaturated fatty acids, pH, and neurotransmitters. TREK-1 may also have a critical role in mediating the vasodilator response of resistance arteries to polyunsaturated fatty acids, thus contributing to their protective effect on the cardiovascular system. TASK-1, on the other hand, is a strong candidate for a role in hypoxic vasoconstriction of pulmonary arteries. Many other members of the K_{2P} channel family have been identified in the cardiovascular system, although their functional roles are still to be demonstrated. This review provides an up to date summary of what is known about the involvement of members of the K_{2P} channel family in cells of the heart and arterial circulation. Our knowledge of their roles will improve with the rapidly increasing interest in them and as new selective pharmacological tools emerge. As their physiological roles emerge, the K_{2P} family of potassium channels may offer promising therapeutic solutions to target cardiovascular diseases.

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Abbreviations

AA	Arachidonic acid
ALA	α-Linolenic acid
EET	Epoxyeicosatrienoic
ETYA	5,8,11,14-Eicosatetraynoic acid
GPCR	G-protein coupled receptor
HPV	Hypoxic pulmonary vasconstriction
MAPK	Mitogen-activated protein kinase
L-NNA	N^G-nitro-L-arginine
PASMC	Pulmonary artery smooth muscle cell
PIP_2	Phosphatidylinositol 4,5 biphosphate
PKC	Protein kinase C
PUFA	Polyunsaturated fatty acid
TMD	Transmembrane domains
VGCC	Voltage-gated calcium channels

Introduction

The dynamic properties of the cardiovascular system rely on the ability of muscular tissues to contract or relax and to adapt their activity in response to changes in the homeostasis of the whole body. In the heart, cardiomyocytes contract in a rhythmic fashion according to spontaneous action potential generation and propagation through the tissue (Nerbonne and Kass 2005). Blood vessels are able to constrict or dilate, due to smooth muscle cell contraction or relaxation, and thus regulate the vascular resistance. The contractile activity of both tissues is under the control of nervous (e.g. sympathethic neurones) and humoral (e.g. circulating vasoconstrictor peptides, such as angiotensin II) signals, many of which produce their

effects by altering electrical activity (Liu et al. 2007; Zankov et al. 2006).

Contraction is stimulated by a rise in the Ca^{2+} concentration of the cytosol ($[Ca^{2+}]_i$) in the muscle cells. This $[Ca^{2+}]_i$ increase is the endpoint of many different pathways, which often depend on the electrical status of the cell. The membrane potential (E_m) is the potential difference across the plasma membrane and usually sits in resting (non-contracting) conditions at a negative value. The negative potential maintains voltage-gated calcium channels (VGCC) in the closed state, preventing Ca^{2+} influx. Depolarisation induces the activation of VGCC, leading to an influx of Ca^{2+} into the cytosol and contraction. Background K^+ conductances are crucial for stabilizing the E_m toward the potassium equilibrium potential, which is usually around −90 mV, and are counterbalanced by opposing cationic and/or chloride leakage conductances. The resting potential is determined by the balance of these different ionic conductances across the membrane. In cardiomyocytes, where resting potential is around −80 mV (Powell et al. 1980), the K^+ conductance predominates. Vascular smooth muscle cells have less negative resting potentials, between −40 and −60 mV, but they are very sensitive to changes in K^+ conductance (Casteels et al. 1977; Gurney et al. 2002; Nelson and Quayle 1995).

The K^+ conductances in heart and blood vessels have been extensively studied (for review see Carmeliet 1999; Cole et al. 2005; Gurney 2004; Gurney and Joshi 2006; Mandegar and Yuan 2002). Inward rectifier K^+ channels play a major role in determining the resting potential of cardiac myocytes (Noma et al. 1984) and smooth muscle cells in a range of small arteries and arterioles (Quayle et al. 1997; Zaritsky et al. 2000). They are not found in all arteries, however, and they cannot account for all of the properties of the background K^+ conductance in some vessels, for example, oxygen sensing in pulmonary artery (Gurney et al. 2002). Other categories of K^+ channel, such as voltage-gated channels supporting delayed rectifier currents, Ca^{2+}-activated K^+ channels and ATP-sensitive K^+ channels, have also been shown to regulate the membrane potential in vascular myocytes (Chen et al. 2006; Moudgil et al. 2006; Remillard et al. 2007; Zhang et al. 2006). Their properties (e.g voltage and/or Ca^{2+}-dependent gating) are not well matched, however, to the resting conditions in some vessels. They make poor candidates for the resting conductance in these tissues (Gurney et al. 2002; Prior et al. 1998). The recently discovered and fast growing family of two pore domain K^+ (K_{2P}) channels have properties well suited to a role in mediating background K^+ conductance (Goldstein et al. 2001, 2005; Lesage and Lazdunski 2000) and they are providing interesting insight for the understanding of background conductance and resting potential in the cardiovascular system.

In mammals, the K_{2P} proteins share common structural features, including four transmembrane domains (TMD) and two pore-forming P loops arranged in tandem, one between the first and second TMD and the other between the third and fourth TMD. The proteins mainly form functional homodimers, although heterodimers combining different K_{2P} subunits have been reported (Berg et al. 2004; Czirjak and Enyedi 2002; Lesage and Lazdunski 2000). The K^+ selectivity, voltage-independent gating and Goldman–Hodgkin–Katz rectification of K_{2P} currents are characteristics that make them strong candidates for mediating background K^+ currents. Importantly, the sensitivity of K_{2P} proteins to numerous chemical and physical physiological stimuli, such as pH, oxygen, phospholipids, neurotransmitters, G-protein coupled receptors (GPCRs), volatile anaesthetics and stretch (for review see Lesage and Lazdunski 2000; Mathie 2007) suits them well to a role in regulating the membrane potential and excitability in various cell types under a range of physiological and pathological situations. Members of the K_{2P} channel family are present in numerous tissues and have been extensively reported in the central nervous system (Lesage 2003; Medhurst et al. 2001; Talley et al. 2001) where they display specific patterns of expression. The sensitivity of K_{2P} channels to volatile anaesthetics are providing interesting insight into the mechanism of action of these important drugs and their effects on neuronal function (Linden et al. 2006; Westphalen et al. 2007). Important roles for K_{2P} channels in the kidney are also emerging (Davies et al. 2008; Lesage and Lazdunski 2000).

TWIK-related acid-sensitive K^+ channels (TASK) are a subfamily that share sensitivity to variations in extracellular pH over a narrow physiological range (Duprat et al. 1997), as well as inhibition by the endocannabinoid, anandamide (Maingret et al. 2001). TASK-1 (KCNK3) and TASK-3 (KCNK9) subunits are functional when associated as homodimers or heterodimers (Czirjak and Enyedi 2002). The TASK-5 (KCNK15) subunit is not functional (Lesage 2003), although its association with other subunits to form a functional channel has not been ruled out. TASK channels display strong basal currents with very fast activation and inactivation kinetics. Membrane currents with TASK-like properties have been extensively studied in cerebellar neurones, where TASK is a molecular substrate for the standing outward current IK_{SO} (Aller et al. 2005; Brickley et al. 2001, 2007 Millar et al. 2000), and in many other types of neuron TASK channels form leak conductances (for review see Lesage 2003; Mathie 2007). Heterodimerisation of TASK subunits to form functional channels may hamper the identification of molecular entities in functional studies, but intermediate pH sensitivity of heterodimers and the use of transgenic models is helpful in specifying the molecular correlates of native currents (Meuth et al. 2006). TASK-like currents were recently shown to be modulated by numerous

neurotransmitters known to stimulate Gq/11-coupled receptors, which affect neuronal excitability (for review see Lesage 2003; Mathie 2007). The sensitivity of TASK currents to pH and O_2 (Buckler et al. 2000; O'Kelly et al. 1999) suit them to a role as general chemical sensors. The TWIK-related alkali-activated K^+ (TALK) channel family, which includes TASK-2, are activated in alkaline conditions and have been described in the exocrine pancreas (Duprat et al. 2005).

TWIK-related K^+ (TREK) channels, which comprise TREK-1 (KCNK2), TREK-2 (KCNK10) and TRAAK (KCNK4), are another well-documented subfamily of K2P channels. They display low basal activity, but are stimulated by stretch of the cell membrane, lysophospholipids and arachidonic acid, and are inactivated by hypo-osmolarity and phosphorylation by protein kinases A and C (Lesage 2003). TREK channels may have an important role in modulating the excitability of neurones, as suggested by the facilitated neurotransmission observed in 5HT-neurones of TREK-1 knockout mice (Heurteaux et al. 2006). TREK-like currents are also regulated through G-protein coupled receptor pathways, being inhibited by $G\alpha_q$ and $G\alpha_s$ activation but activated by $G\alpha_i$ activation (Mathie 2007). Finally, like other K^+ channels, an increasing number of studies describe the regulation of K_{2P} channels by partner chaperone proteins (reviewed in Plant et al. 2005), as demonstrated for TASK-1 and TASK-3 with 14-3-3 (O'Kelly et al. 2002; Rajan et al. 2002). Post-translational regulation, like sumoylation of TWIK, can also be crucial for channel activity (Rajan et al. 2005).

Several members of the K_{2P} channel family have been shown to be expressed in the heart and the systemic or pulmonary circulations (Table 1) and some have been shown to contribute to background K^+ currents and the control of membrane potential in vascular smooth muscle cells as summarized in Fig. 1. The scope of this review is to provide an up to date summary of what is known about the involvement of members of the K_{2P} channel family in the background K^+ currents underlying the regulation of the resting membrane potential in cells of the heart and arterial circulation.

K_{2P} channels and heart function: contribution to cardiac electromechanical coupling

In working atrial and ventricular myocytes, background K^+ currents have a critical role, since they maintain the

Table 1 Expression of members of the K_{2P} channel family in the heart and vasculature

Channel	Heart	Pulmonary artery	Mesenteric artery	Cerebral arteries	Aorta	Other vessels
TASK-1	RNA[1–6] RNA+protein[7,8]	RNA+protein (rat, rabbit and human)[9–11]	RNA+protein[9]		RNA+protein[13]	Placental circulation: RNA+protein[14]
TASK-2	RNA[15]	RNA+protein[9]	RNA+protein[9]		RNA+protein[13]	Femoral artery: RNA+protein[16]
TASK-3	RNA[2,15]	No[9]	No[9]		RNA[13]	
TASK-4					RNA[13]	
TASK-5	No[2]				No[13]	
TREK-1	RNA[2,18,19] RNA+protein[20]	No[9]	RNA+protein[9]	RNA (middle cerebral artery)[21] RNA+protein (rat and mouse basilar artery)[12]		Femoral artery: RNA+protein[17] No[12] carotid artery (rat, mouse): No[12]
TREK-2	RNA[2,15]	RNA[9]	No[9]	RNA[21]		Femoral artery: RNA[17]
THIK-1	RNA[2]	RNA[9]	RNA[9]	RNA[21]		Femoral artery: RNA[17]
THIK-2	No[2]					
TRAAK	RNA[15] No[2]	No[9]	RNA[9]	RNA[21]		
TALK	No[2]					
TWIK-2	RNA[2,6,15]	RNA+protein[9]	RNA+protein[9]	RNA+protein[21]		Femoral artery: RNA+protein[17]
TWIK-1	RNA[2,6,15]	No[9]	RNA[9]			

Detection of mRNA was by RT-PCR or northern blot and protein by western blot or immuno-staining. Data is from rat unless another species is specified. No indicates the absence of expression. [1]Kim et al. 1998; [2]Putzke et al. 2007; [3]Duprat et al 1997; [4]Leonoudakis et al. 1998; [5]Kim et al. 1999; [6]Medhurst et al. 2001; [7]Lopes et al. 2000; [8]Jones et al. 2002; [9]Gardener et al. 2004; [10]Gurney et al. 2003; [11]Olschewski et al. 2006; [12]Blondeau et al. 2007; [13]Kiyoshi et al. 2006; [14]Wareing et al. 2006; [15]Liu and Saint 2004; [16]Goonettilleke et al. 2007; [17]Goonettilleke 2007; [18]Aimond et al. 2000; [19] Tan et al. 2004; [20]Terrenoire et al. 2001; [21]Bryan et al. 2006

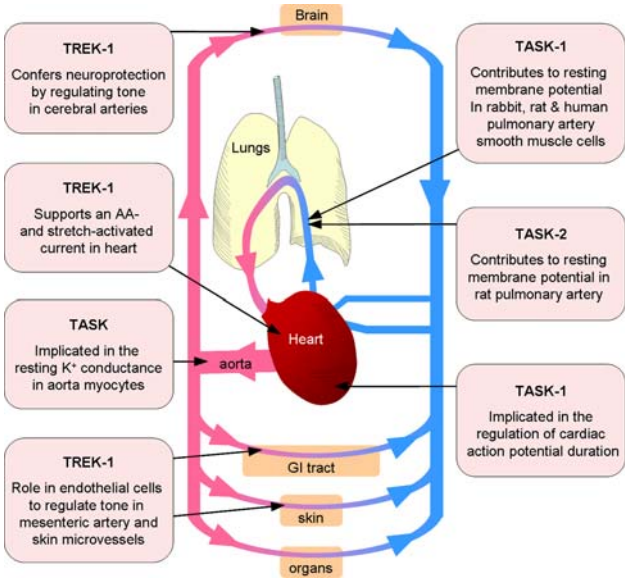

Fig. 1 The main proposed sites of expression and function of members of the K_{2P} channel family in the circulatory system. *PA*: pulmonary artery and *GI*: gastro-intestinal

membrane potential at a hyperpolarized value and regulate action potential duration in various physiological and pathological conditions. The background current is mainly carried by inward rectifier channels. Contributing currents include I_{K1}, I_{KAch} and I_{KATP}, the molecular correlates of which are Kir2.1, Kir3.1 and Kir6.2-SUR2A, respectively (Inagaki et al. 1996; Krapivinsky et al. 1995; Kubo et al. 1993; Seino 1999). Several K_{2P} channels in the heart were recently found to be expressed and proposed to contribute to the cardiac background current. Among them, TREK-1 and TASK-1 have been the most extensively studied.

A TREK-1 like current in the atria and ventricles

I_{KAA} is a stretch- and arachidonic acid- (AA) sensitive current that was first described over 10 years ago in neonatal and adult rat atrial and ventricular cells (Hu and Sachs 1997; Kim 1992; Kim and Clapham 1989; Kim and Duff 1990). In 2000 and 2001, two groups provided strong evidence that I_{KAA} has close functional similarities to the TREK-1 channel current. TREK-1 is activated by changes in membrane tension (stretch), by arachidonic acid and other polyunsaturated fatty acids (PUFA), by intracellular acidification and by some volatile anesthetics (Chemin et al. 2005; Fink et al. 1998; Maingret et al. 1999; Patel et al. 1999). Aimond et al. recently showed that, consistent with the involvement of TREK-1, AA and intracellular acidosis activated a sustained K^+ current in rat ventricular myocytes, which could also be activated by purinergic receptor stimulation with ATP (Aimond et al. 2000). The current was only slightly inhibited by extracellular acidosis ($pH_0 = 6.8$), which ruled out the involvement of the TASK-1 channel (Duprat et al. 1997). Further characterization came from Terrenoire et al., who demonstrated that I_{KAA} in rat atrial myocytes had a number of properties similar to TREK-1 (Terrenoire et al. 2001). These included the single-channel conductance (41pS in physiological K^+ and 118pS in symmetrical 150 mM K^+), no voltage dependency, flickering openings that occurred in bursts as long as the stimulus was maintained, sensitivity to 10 μM lisophosphatidylcholine and no sensitivity to tetraethylammonium (TEA) ions, glibenclamide or Ca^{2+} (Terrenoire et al. 2001). The authors stressed that I_{KAA} and TREK-1 displayed a similar pattern of sensitivity to volatile anesthetics (activation by chloroform, isoflurane and halothane), which is not shared by any of the other K^+ channels described in heart. In addition, TREK is known to be inhibited by cAMP-dependent phosphorylation of Ser333 in the C-terminal domain (Patel et al. 1998) and consistent with this, I_{KAA} was shown to be inhibited by the membrane permeant analog of cAMP, CPT-cAMP, and by the β-adrenoceptor agonist, isoproterenol (Terrenoire et al. 2001). Those results were corroborated in cardiac ventricular cells by data from Tan et al. in 2002, who additionally showed that the TREK-like current was activated by intracellular ATP in the millimolar range (Tan et al. 2002). The kinetics of current activation were too fast to be due to ATP-dependent phosphorylation, ruling out the possible involvement of the muscarinic receptor in the response.

The expression of TREK-1 mRNA was identified in rat left and right ventricles, atria and septum, and in ventricular myocytes (Aimond et al. 2000; Tan et al. 2004; Terrenoire et al. 2001), while TREK-1 protein was identified in adult rat ventricular and atrial microsomes (Terrenoire et al. 2001). Surprisingly though, no TREK channel expression has so far been reported in human myocardium. Confocal imaging and immunostaining, using a well-characterized antibody, showed that TREK-1 channel proteins are arranged in longitudinal stripes at the surface of cardiomyocytes (Li et al. 2006) (see Fig. 2), a pattern that appears suitable for sensing longitudinal stretch of the cells. However, there was no obvious co-localization with membrane-associated cytoskeletal proteins, which are mostly arranged as ''costameres'' (Kostin et al. 1998).

An interesting heterogeneity was observed in the TREK-like currents recorded from rat cardiomyocytes (Li et al. 2006): single-channel, outside-out recordings presented two distinct types of current, one with a large conductance (132 pS at +60 mV) and one with a small conductance (41 pS at positive potentials). Furthermore, the authors detected two distinct splice variants of TREK-1 in the myocytes, TREK-1a and TREK-1b, of which TREK-1a was barely expressed. The two isoforms differ by 16 amino acids in exon 1, but could not be segregated according to

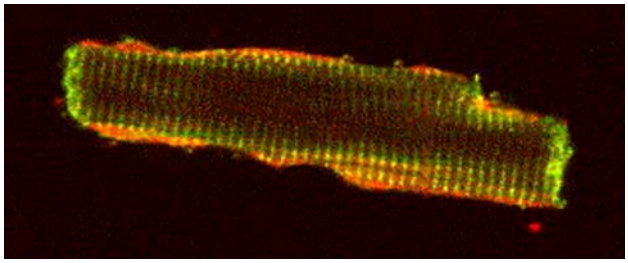

Fig. 2 Subcellular localization of TREK-1 and TASK-1 in a rat cardiomyocyte. Confocal image showing co-staining for TREK-1 (*red*) and TASK-1 (*green*). Adapted from (Li et al. 2006)

their biophysical properties in expression models, because both channels presented large and small conductance openings. This suggests that post-translational regulation of TREK-1 may affect the conductance of the channel.

It is proposed that, in the working heart, TREK-1, as an outwardly rectifying current, may participate in balancing the membrane potential and action potential duration (Terrenoire et al. 2001). Indeed, on a beat to beat basis, it could be involved in a negative feedback loop, hyperpolarizing the membrane potential in response to a stretch stimulus following the stretch activation of non-selective cation channels (Terrenoire et al. 2001; Li et al. 2006). The expression of TREK-1 appears to be non-uniform in the heart, with stronger TREK-1 mRNA expression and a larger chloroform-induced current found in endocardial cells compared with epicardial cells (Tan et al. 2004). It was suggested that this reflects different amounts of stretch experienced by muscle cells in different parts of the ventricle wall, leading to differential mechanoelectrical feedback, thereby reducing action potential repolarization in areas of the myocardium where conduction velocity is slower (Lab 1999; Ravens 2003). Mechanoelectric feedback following an increase in atrial volume may be arrythmogenic, changing the shape of the action potential (Nazir and Lab 1996). Such a role is difficult to investigate due to a lack of good quantitative models of mechanoelectric feedback (Tan et al. 2004). Physiological evidence of the direct involvement of TREK-1 current in mechanoelectric feedback in the heart has still to be provided. The only study to look at its involvement in cardiac function showed that in vivo deletion of the TREK-1 gene in mice does not alter the systolic blood pressure response to stress, brought about by tail pinching or angiotensin II injection (Garry et al. 2007). The authors did not mention if they investigated cardiac mechanoelectric feedback or membrane potential.

TREK-1 activity may have some importance in pathological conditions such as ischemia, when released purinergic agonists such as ADP and ATP lead to AA production. In rat ventricular myocytes, the activation of TREK-like current upon purinergic stimulation requires the involvement of the p38 mitogen activated protein kinase (MAPK) and p42/44 MAPK pathways (Aimond et al. 2000). The activation of these MAPK pathways may lead to activation of the mitogen- and stress-activated protein kinase (MSK-1), leading to cytosolic phospholipase A2 translocation and AA release (Aimond et al. 2000). Activation of TREK-1 by ATP during ischemia may contribute to electrophysiological disturbances in the ventricle wall. As a stretch activated K^+ channel in atrial cells, TREK-1 could additionally be involved in regulating the release of atrial natriuretic peptide, which is released by a stretch-induced increase in $[Ca^{2+}]_i$ (Ruskoaho 1992). Further work will be necessary to clarify the possible role of TREK or other stretch-dependent channels in the pathological heart. Mechanical rather than electrical changes were recently implicated in ventricular electrical remodeling in a canine model (Jeyaraj et al. 2007) and the effect of mechanical stress in the development of myocardial hypertrophy is widely acknowledged (Ruwhof and van der Laarse 2000).

Are TASK currents major contributors to the cardiac action potential?

The TASK channel has been implicated in the background conductances of neuronal cells, including the oxygen-sensitive background current in carotid body cells (Buckler et al. 2000) and the "standing" outward current, $I_{K_{SO}}$, in cerebellar granule neurones (Millar et al. 2000). A K_{2P} channel, denoted cTBAK-1, was cloned in 1998 from a mouse cardiac cDNA library by Kim et al. (1998) and was shown to be mainly expressed in heart. The cTBAK-1 is essentially identical to the TASK channel (Kim et al. 1999) cloned from a mouse brain cDNA library and described by Duprat et al. (1997). TASK channels are inhibited by acidosis and activated by alkaline pH (Duprat et al. 1997). TASK-1 has also been shown to be blocked by Zn^{2+} (Leonoudakis et al. 1998), the endocannabinoid, anandamide, and its stable analog methanandamide in the micromolar range of concentrations (Maingret et al. 2001). TASK-1 is potentiated by the local anaesthetic halothane (Patel et al. 1999). The pharmacology of these drugs, however, is far from specific (Van den Bossche and Vanheel 2000).

TASK-1 mRNA has been widely detected in the human, mouse and rat hearts, although its relative abundance in atria and ventricles has been controversial (Duprat et al. 1997; Jones et al. 2002; Kim et al. 1999; Leonoudakis et al. 1998; Liu and Saint 2004; Lopes et al. 2000; Medhurst et al. 2001; Putzke et al. 2007). Immunostaining of isolated rat ventricular myocytes, using a well-characterized antibody, has however provided convincing evidence of TASK-1 localization at the intercalated disks and the T tubule network, similar to TASK-1 staining in Fig. 2 (Jones et al. 2002). Atrial myocytes presented a more punctate

pattern and weaker staining, presumably due to the undeveloped T tubule network in those cells (Jones et al. 2002). Given those data, and the fact that TASK-1 expression in the heart is robust compared to other K_{2P} channels (Liu and Saint 2004; Putzke et al. 2007), it is perhaps surprising that a recording of TASK-like current in cardiomyocytes was not reported until recently.

TASK-1 has been considered as a candidate for the molecular correlate of the cardiac background current, I_{Kp}, in guinea pig ventricular myocytes, which has a role in determining action potential duration (Backx and Marban 1993; Jones et al. 2002). In 2002, Barbuti et al. described a current in mouse cardiomyocytes that was inhibited by the inflammatory phospholipid, carbamyl-platelet activating factor (c-PAF), a non-metabolized analog of platelet activating factor, and displayed the characteristics of a TASK-1 current (Barbuti et al. 2002). Anandamide and methanandamide, acidosis and Zn^{2+} all inhibited the c-PAF-sensitive current, and TASK-1 expressed in CHO cells was shown to be inhibited by c-PAF. This effect appeared to require PAF receptors and involved a protein kinase Cε (PKCε)-dependent mechanism. Thus, the authors proposed a role for TASK-1 in PAF-induced arrhythmias, which can be observed upon liberation of PAF by polymorphonuclear leucocytes following ischemia. Consistent with this hypothesis, a TASK-1-like current has been described in rat ventricular myocytes, which may contribute to the net outward current during the plateau phase of the cardiac action potential (Putzke et al. 2007). Consequently, a recently developed TASK-1 channel inhibitor, A293, was found to increase significantly the action potential duration (at 50 and 90% of total duration) (Putzke et al. 2007). Action potentials in that study were, however, recorded using a high, non-physiological stimulation rate (4 Hz), at room temperature, which by itself increases action potential duration. Further studies will be necessary to clarify the exact contribution of TASK-1 to repolarisation in more physiological conditions, and to consider possible differences between endocardial and epicardial myocytes, which display action potentials of different duration (Charpentier 2007).

The cardiac action potential duration is well known to be increased by stimulating α_{1A}-adrenergic receptors, which produces the effect by inhibiting a sustained outward current (Ravens et al. 1989). Interestingly, the outward current inhibited by stimulation with the α_1-agonist, phenylephrine, was shown in rat cardiomyocytes to be time independent and the effect of phenylephrine was prevented by extracellular acidosis (Choisy et al. 2004). Although acid sensitivity is suggestive of TASK channel involvement, the same study reported that acidosis had little effect on the current in the absence of phenylephrine and the α_1-adrenergic current was not effectively blocked by the TASK channel inhibitors anandamide, Zn^{2+} or ruthenium red (Choisy et al. 2004). Moreover, the single-channel conductance estimated by noise analysis of the phenylephrine-sensitive current was too large (at least 78 pS) to be carried by TASK-1, which has a much smaller conductance of 14 pS under similar conditions (Kim et al. 1999). In contrast to that study, which does not support a role for TASK channels in the α-adrenergic response, Putzke et al. recently proposed that TASK-1 could carry the current (Putzke et al. 2007). They found that the outward current inhibited by another selective α_1-adrenoceptor agonist, methoxamine, was almost abolished at pH 6, and inhibition of the effect of methoxamine by the α_{1A}-adrenergic receptor blocker, 5-methylurapidil, confirmed the involvement of α_1-adrenoceptors. Moreover, methoxamine inhibited TASK-1 heterologoulsy expressed in CHO cells, although it also inhibited TASK-3 and, in a less potent manner, TREK-1. As α_1-adrenergic receptors couple to Gq and mediate the activation of phospholipase C, with subsequent hydrolysis of phosphatidylinositol 4,5 biphosphate (PIP_2), this result is consistent with recent studies showing that PIP_2 is a regulator of TASK channels (Lopes et al. 2005). It can be hypothesised that the pathway is similar to that activated by all Gq-coupled receptors, including the angiotensin II receptor, which is involved in the development of arrhythmia in the context of ischemia-reperfusion (Charpentier 2007). Still, Putzke et al. (2007) did not report the effects of methanandamide or A293 on the methoxamine-sensitive current, which could have allowed a comparison of that study with the data from Choisy's group (Choisy et al. 2004). Further work seems necessary to clarify the nature of the channel responsible for the current sensitive to α_{1A}-adrenergic receptor stimulation in cardiomyocytes. Interestingly, the current inhibited by phenylephrine shares some properties of another type of voltage-gated K^+ channel, Slick, which was also shown to be expressed in heart (Bhattacharjee et al. 2003; Choisy et al. 2004). Additional K_{2P} channel transcripts have also been identified in different chambers of the heart and they are also candidates for background currents (Liu and Saint 2004). This latter study suggests that, according to the level of their expression, TASK-1, TREK-1 and TWIK-2 are the most likely to have a relevant functional role.

K_{2P} channels as chemosensors in blood vessels: a role in homeostasis

The K_{2P} channel mRNAs seems to be widely expressed in the systemic and pulmonary circulations (Table 1). The sensitivity of K_{2P} channels to a wide range of physiological signals (PUFA, pH, O_2) that are important in regulating blood flow makes them candidates for regulators of vascular

tone, especially in small resistance vessels of the systemic circulation, such as mesenteric and cerebral arteries (Blondeau et al. 2007; Garry et al. 2007), and the pulmonary circulation (Gardener et al. 2004; Gurney et al. 2003; Olschewski et al. 2006).

Arachidonic acid sensitive K_{2P} channels in the vasculature

Arachidonic acid dilates a number of different arteries (Campbell et al. 1996; Miura and Gutterman 1998; Rosolowsky and Campbell 1993). In some vessels its actions are mediated by metabolites of arachidonic acid formed in the endothelium, because they are inhibited by removing the endothelium and mimicked by epoxyeicosatrienoic acids (EETs), which are metabolites of endothelial cytochrome P450 epoxygenase (Campbell and Falck 2007). Nevertheless, in cerebral arteries, AA produced a vasodilation that was not prevented by classical inhibitors of AA metabolism via the lipoxygenase, epoxygenase or cyclooxygenase signaling pathways (Bryan et al. 2006). It was, moreover, reproduced by the stable AA analog 5,8,11,14-eicosatetraynoic acid (ETYA), suggesting that AA itself was responsible for the observed dilation. The vasodilator effects of AA and EETs in bovine- and human coronary and mammary arteries are thought to result from the activation of smooth muscle, large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels, and are blocked by inhibitors of these channels, as well as by high extracellular K^+ concentrations (Archer et al. 2003; Campbell et al. 1996; Miura and Gutterman 1998). In rat cerebral artery, the dilator effect of AA was also prevented by elevating the extracellular K^+ concentration, consistent with the involvement of a K^+ channel. The dilation was not, however, inhibited by blockers of large or small conductance K_{Ca} channels (charybdotoxin, apamin) or by classic inhibitors of K_v (4-aminopyridine), K_{ir} (Ba^{2+}) or K_{ATP} (glibenclamide) channels (Bryan et al. 2006). In isolated smooth muscle cells from cerebral artery, AA was able to hyperpolarize the membrane potential and activate an outwardly rectifying K^+ current in the presence of BK_{Ca} channel blockade by TEA ions (Bryan et al. 2006). Consistent with the effects of AA on vessel tone, the current was also unaffected by 4-aminopyridine (4-AP), glibenclamide and Ba^{2+}, implying that it was not mediated by K_v, K_{ATP} or K_{ir} channels. The molecular correlate of the AA-activated current is not yet certain, but the sensitivity of K_{2P} channels to AA makes them attractive candidates. The mRNAs for numerous AA-sensitive K_{2P} channels were found to be expressed in middle cerebral artery: TREK-1, TREK-2, TWIK-2, TRAAK and THIK-1 (Bryan et al. 2006). The wide variety of channels identified, combined with the absence of specific pharmacology, makes it difficult to conclude the exact nature of the channel giving rise to AA-induced hyperpolarisation and vasodilation. However, only TWIK-2 message and protein were detected in smooth muscle cells dispersed from the arteries (Bryan et al. 2006), suggesting that this channel may be responsible for the AA effects.

Expression of AA-sensitive K_{2P} channels has been detected in other arteries. Like the cerebral artery, rat mesenteric and femoral arteries express TREK-1, TREK-2 and THIK, although TRAAK was reported in mesenteric but not femoral artery (Gardener et al. 2004; Goonetilleke 2007). Carotid arteries lack TREK-1 (Blondeau et al. 2007) and although pulmonary arteries express TREK-2 and THIK-1, they also appear to lack TREK-1 and TRAAK (Gardener et al. 2004). This may reflect differential physiological regulation and function in the circulation of different tissues, although the functions of these channel subunits are not yet known. Recent studies on mice deficient in TREK-1 suggest that it has a role in endothelial cells to regulate vascular tone (Blondeau et al. 2007; Garry et al. 2007). In these TREK-$1^{-/-}$ mice, responses of mesenteric and cutaneous arteries to the endothelium-dependent vasodilators, actetylcholine and bradykinin, were attenuated compared to wild type littermates, while responses to the endothelium-independent dilator, sodium nitroprusside, were unchanged (Garry et al. 2007). In contrast, endothelium-dependent vasodilatation induced by the Ca^{2+} ionophore A23187 was retained in TREK-$1^{-/-}$ mice, implying that events upstream of Ca^{2+} influx into endothelial cells were altered. This contribution of TREK-1 to endothelial function was corroborated by immuno-localization of the channel in endothelial cells, in addition to myocytes (Blondeau et al. 2007; Garry et al. 2007).

Neuronal TREK-1 has been implicated in the neuroprotective effect of PUFAs following ischemia (Buckler and Honore 2005; Heurteaux et al. 2004). A recent study suggested that this contribution could be due to the activity of TREK-1 in cerebral arteries (Blondeau et al. 2007). The authors showed that the PUFA, α-linolenic acid (ALA), dilates the rat basilar artery and reduces cerebral blood flow in vivo, at doses potently activating TREK-1 (10 and 100 μM, but has no effect on carotid artery, which lacks TREK-1 expression. Dilation was also produced by another PUFA, docosahexanoic acid (DHA), but not by the saturated fatty acid, palmitic acid, consistent with the PUFA sensitivity of TREK-1 (Patel et al. 1998). The involvement of TREK-1 channels was strongly implicated by the loss of effect of PUFAs on basilar artery and cerebral blood flow in TREK-$1^{-/-}$ mice (Blondeau et al. 2007). The vasodilator effects of PUFAs in wild type mice were unaffected by treatment with the nitric oxide synthase inhibitor, N^G-nitro-L-arginine (L-NNA), and the cyclooxygenase inhibitor, indomethacin. PUFAs, therefore, seem to induce dilation of basilar arteries via a nitric oxide and prostacyclin independent mechanism. Although their effects could be

mediated by another endothelial component, such as endothelium-derived hyperpolarising factor (Busse et al. 2002), the results are consistent with an action of PUFAs on smooth muscle TREK-1 channels to cause hyperpolarisation, as described above for AA (Bryan et al. 2006, 2007). The authors did not investigate the effects of PUFA on endothelium-free vessels, which would have clarified the localization of PUFA action on TREK-1.

Taken together, these data emphasize the role of TREK-1 in the regulation of tone in systemic arteries by vasodilators. The mechanism of action of the neuroprotective effect of TREK-1 has still to be determined. Nevertheless, because of their vascular localization and sensitivity to PUFAs, which are of popular interest in preventive medication, TREK-1 channels are of considerable therapeutic interest for future treatment of cardiovascular disorders.

TASK channels support background current in pulmonary artery smooth muscle cells

The membrane potential of vascular smooth muscle cells is a key regulator of blood vessel tone, thus regulating flow and pressure in the circulation. Specific regional characteristics of tone allow blood flow and pressure to adapt according to the needs of the organs they perfuse. Under physiological conditions, the pulmonary circulation has the important property of constricting in response to hypoxia, thus directing blood to better oxygenated areas of the lung and ensuring optimum matching between blood perfusion and air ventilation. Since hypoxia depolarizes pulmonary artery smooth muscle cells (Post et al. 1992), it is thought that an oxygen-sensitive component of the resting membrane potential may contribute to this hypoxia-induced pulmonary vasoconstriction (HPV). The depolarisation reflects inhibition of a K^+ conductance by hypoxia and it evokes the opening of VGCC, raising $[Ca^{2+}]_i$ (Gurney 2004; Gurney and Joshi 2006; Gurney et al. 2002; Mauban et al. 2005; Moudgil et al. 2006). The nature of the specific K^+ conductance responsible for HPV has been debated for many years and remains to be convincingly demonstrated (Gurney 2004; Gurney and Joshi 2006; Gurney et al. 2002; Mauban et al. 2005; Moudgil et al. 2006). Delayed rectifier Kv channels, the strongest candidates of which are Kv1.5 and Kv 2.1, have been proposed to maintain the membrane potential in PASMC and mediate the response to hypoxia (Archer et al. 2001, 2004; Patel et al. 1997; Platoshyn et al. 2006; Pozeg et al. 2003; Remillard et al. 2007). Their role as principal regulators of the resting membrane potential is, however, controversial, largely because their open probability at the resting potential is small and the pharmacology of these Kv channels differs from the background conductance giving rise to the resting potential (Gurney and Joshi 2006; Gurney et al. 2002). This is an important point, because inhibition of a channel by hypoxia will depolarize the membrane only if the channel is open and contributing to K^+ permeability under resting conditions. Other classical K^+ channels present in PASMC, such as K_{Ca} and K_{ATP}, contribute little to the resting potential and are unlikely mediators of HPV (Gurney et al. 2002). K_{IR} channels, which contribute to resting potential in systemic resistance arteries, have been reported in cultured human pulmonary artery myocytes (Tennant et al. 2006), but they have not been found in other pulmonary artery smooth muscle cells. Moreover, the inability of millimolar Ba^{2+} to depolarize pulmonary artery smooth muscle cells (Osipenko et al. 1997) argues against K_{IR} involvement in the resting potential.

In 1996, rabbit pulmonary artery smooth muscle cells were shown to display a non-inactivating K^+ conductance, I_{KN}, which persisted in the presence of glibenclamide and TEA and after inactivation of delayed rectifier currents with prolonged depolarization (Evans et al. 1996). This current displayed properties appropriate for a background K^+ conductance and was shown to be an important regulator of the resting potential (Evans et al. 1996; Osipenko et al. 1997). I_{KN} was insensitive to classical inhibitors of Ca^{2+}-activated K^+ channels (TEA, charybdotoxin, iberiotoxin, apamin), K_{IR} channels ($BaCl_2$) and the Na^+/K^+ ATPase (ouabain, digitoxin), as well as non-specific K^+-channel inhibitors like quinine ($\leq$100 μM) and clofilium (1 mM; inhibits Kv1.5, TASK-2, KCNQ1). The current in rabbit cells was sensitive to 4-AP, with 50% inhibition at 1 mM, although the degree of inhibition was variable. Voltage ramp recordings in symmetrical K^+ conditions suggested that I_{KN} reflects the co-existence of separate voltage-dependent and voltage-independent components and 4-AP may block only one of them (Gurney and Joshi 2006). Similar studies in human pulmonary artery cells reported an I_{KN}-like current that was voltage independent and showed no inhibition by 3 mM 4-AP (Olschewski et al. 2006), suggesting that the 4-AP sensitive current in rabbit is mediated by a voltage-gated channel. Importantly, I_{KN} in both species was inhibited reversibly by acute hypoxia, which is compatible with it being responsible for the oxygen sensitivity of the membrane potential (Olschewski et al. 2006; Osipenko et al. 1997).

The molecular nature of the channels giving rise to I_{KN} remained unclear until 2003, when it was proposed that the K_{2P} channel, TASK-1, was responsible for this current (Gurney et al. 2003). Like TASK-1 expressed in heterologous expression systems (Duprat et al. 1997; Lesage and Lazdunski 2000; Maingret et al. 2001; Patel et al. 1999), I_{KN} in rabbit was demonstrated to be inhibited by acidosis and activated by alkalosis, with 50% activation at pH 7.3. Consistent with this, the resting potential of pulmonary artery smooth muscle cells was depolarized by 20 mV at pH 6.5 and hyperpolarized at pH 8.5. Further similarities to

TASK-1 pharmacology included facilitation by halothane and inhibition by Zn^{2+} and anandamide (Maingret et al. 2001). A more recent study suggests that the potency of Zn^{2+} at inhibiting I_{KN} may more closely resemble its effects on TASK-3 (Clarke et al. 2004). On the other hand, since TASK-3 does not appear to be expressed in pulmonary arteries (Gardener et al. 2004), it is unlikely to be involved. The involvement of TASK-1 in I_{KN} has been demonstrated in human pulmonary artery cells, where a small interfering RNA targeted against TASK-1 caused the loss of I_{KN} and depolarization of the membrane (Olschewski et al. 2006). There is, therefore, compelling evidence that TASK-1 is a major contributor to I_{KN} and that its inhibition by hypoxia underlies hypoxia-induced depolarisation. This is consistent with the role of TASK channels in the background conductances of other cell types, such as I_{KSO} in cerebellar granule neurones (Millar et al. 2000) and the oxygen-sensitive current in cells of the carotid body (Buckler et al. 2000).

The TASK-1 channels have been shown to be expressed at both the mRNA and protein level in pulmonary artery smooth muscle (Gardener et al. 2004; Gurney et al. 2003; Olschewski et al. 2006). It is unlikely, however, that TASK channels can account for all of I_{KN}, at least in rabbit pulmonary artery smooth muscle cells where it contains a voltage-dependent component. Involvement of additional channels is also suggested by the finding (Gurney et al. 2003) that halothane had a variable effect on I_{KN}, occasionally causing inhibition, and anandamide, at a concentration sufficient to inhibit more than 90% of TASK-1 current in heterologous systems (Maingret et al. 2001), reduced I_{KN} by only 25%. Another K_{2P} channel that could contribute is THIK-1, which is inhibited by halothane, acid pH and hypoxia and was reported to mediate oxygen sensitivity in glossopharyngeal neurones (Campanucci et al. 2003). Although its involvement has not been tested, THIK-1 expression has been detected in pulmonary arteries, in addition to several other K_{2P} channels: TASK-2, TREK-2 and TWIK-2 (Gardener et al. 2004). The finding that TREK-2 is expressed in pulmonary but not mesenteric artery, whereas TRAAK and TREK-1 are present in mesenteric but not pulmonary artery (Gardener et al. 2004), suggests different roles for these channels in vessel function, which may be relevant to the differential effect of hypoxia on pulmonary and systemic vessels.

While the above studies investigated TASK channels in isolated pulmonary artery smooth muscle cells, evidence for TASK channel involvement in hypoxic pulmonary vasoconstriction has also come from microelectrode studies on intact vessels from the rat (Gardener et al. 2004; Gonczi et al. 2006). Membrane potential in intact pulmonary arteries was modulated by pH and anandamide in the same way as isolated smooth muscle cells. Another, non-specific TASK channel inhibitor, bupivacaine, also caused depolarisation, although less potently than anandamide. Modulation by all of these agents was unaltered in the presence of a cocktail of inhibitors of classical K^+ channels and in endothelium-free vessels. Moreover, the effects of TASK channel modulators were less pronounced in mesenteric arteries, which do not constrict in response to hypoxia (Gardener et al. 2004). Although TASK-1 has been implicated as the main K_{2P} channel mediating responses to hypoxia in pulmonary artery, microelectrode studies on intact vessels also suggest a role for hypoxic inhibition of TASK-2 (Gonczi et al. 2006). Thus transfection with small interfering RNA targeted against TASK-2 resulted in a small depolarization and partially inhibited membrane potential responses to changes in pH. Together TASK-1 and TASK-2 could therefore each contribute several millivolts to the resting potential of pulmonary artery smooth muscle cells and the inhibition of both channels may be required for the full depolarising effect of acidosis.

Prostacyclin is a potent and important physiological and therapeutic dilator of pulmonary arteries (Humbert et al. 2004; Watkins et al. 1980). Recent evidence suggests that TASK-1 may be a target of the prostacyclin analog, treprostinil (Humbert et al. 2004), which is currently prescribed in the treatment of pulmonary hypertension. The drug was found to enhance I_{KN} in human pulmonary artery smooth muscle cells at clinically relevant concentrations ($IC_{50} = 1.2$ μM) via a mechanism involving cAMP-dependent phosphorylation (Olschewski et al. 2006). This effect was insensitive to iberiotoxin, ruling out BK_{Ca} channels, but was prevented by small interfering RNA directed against TASK-1. The beneficial action of prostanoids in the therapy of pulmonary arterial hypertension may therefore be explained, at least in part, by an action on TASK-1 channels, suggesting that they may be an important drug target.

Although TASK channels have clearly been shown to participate in membrane potential regulation, their real role in regulating the tone of pulmonary arteries has still to be clarified. Despite producing substantial depolarisation, anandamide and bupivicaine cause only a small increase in pulmonary artery tone (Gardener et al. 2004). Although this could be because TASK channel inhibition is insufficient to depolarise cells in the intact vessel to the activation threshold for VGCC, it could alternatively reflect the poor selectivity of TASK channel inhibitors. Bupivicaine inhibits a wide range of K^+ channels, while anandamide blocks $K_v1.2$ (Poling et al. 1996), which is widely expressed in pulmonary and systemic arteries (Cox and Rusch 2002; Wang et al. 1997). The IC_{50} for blocking Kv1.2 is 2.4 μM, only a little higher than the IC_{50} (0.7 μM) for anandamide or methanandamide interactions with TASK-1 (Maingret et al. 2001), and importantly, anandamide has been shown to block delayed rectifier current in rat aorta smooth muscle

cells (Van den Bossche and Vanheel 2000). Additionally, anandamide induces endothelium-independent relaxation of various arteries (Randall et al. 1996; White et al. 2001), which would counteract any constrictor effect of blocking TASK-1. Future studies will clarify the link between the effects of hypoxia on membrane potential and tone and elucidate the role of TASK channels in HPV and the pulmonary vasodilator effect of prostacyclin. This will require more selective tools, such as TASK-selective drugs and/or targeted gene knockdown.

TASK channels in the systemic vasculature

TASK channel expression has been detected in mesenteric and femoral arteries (Gardener et al. 2004; Goonetilleke et al. 2007), the placental circulation (Wareing et al. 2006) and aorta (Kiyoshi et al. 2006). Although modulators of TASK channels were found to alter membrane potential in mesenteric artery smooth muscle, their effects were blunted in comparison with the pulmonary circulation (Gardener et al. 2004), suggesting that they play a less prominent role in setting the background K^+ conductance and resting membrane potential in these vessels. The presence of TASK-1 in the placental circulation is of interest, because hypoxia causes fetoplacental vasoconstriction (Byrne et al. 1997). The K^+ conductance encoded by TASK-1 channels has not, however, been identified in mesenteric or placental vessels. Rat aortic smooth muscle cells displayed a K^+ conductance with pharmacological properties similar to TASK-1 and the current was smaller in cells from spontaneously hypertensive rats (Kiyoshi et al. 2006). The current was associated with a resting membrane potential that was significantly more depolarised in spontaneously hypertensive rats, implicating the loss of TASK channels in hypertension. The expression of TASK-1, TASK-2, TASK-3 and TASK-4 was reported, but TASK-1 was most abundant and only TASK-1 showed reduced expression in spontaneously hypertensive rats (mRNA by 50%, protein by ~30%). Thus, although contributions of other TASK channels to the background K^+ current and resting potential in aorta cannot be ruled out, TASK-1 seems to be of major importance and could provide a therapeutic target for antihypertensive drugs.

Conclusion

To summarize this review, important breakthroughs have emerged during the last decade about the role of the K_{2P} channel family in the cardiovascular system. There is clear evidence for TREK-1 and TASK-1 in the heart, and they are likely to contribute to cardiac function through their regulation by stretch, PUFAs, pH, and neurotransmitters. Furthermore, compelling evidence supports roles for TREK-1 and TASK-1 in regulating arterial tone. TREK-1 has neuroprotective properties, which may be related to its relaxing effects on cerebral arteries. TASK-1, on the other hand, is a strong candidate for contributing to hypoxic vasoconstriction of pulmonary arteries. Although numerous other members of the K_{2P} family have been shown to be expressed in various parts of the cardiovascular system, their physiological importance is still obscure, partly due to the lack of pharmacological tools that have selectivity for these channels. Genetic approaches using knockout animals and RNA interference technology have been providing helpful data, and will be invaluable in the future for unravelling the physiological functions of the many K_{2P} channels that appear to be expressed in muscle and endothelial cells of the cardiovascular system. Our understanding of K_{2P} channels in the cardiovascular system is still embryonic, but it is becoming clear that they are likely to be important in the normal physiological regulation of the heart and arteries and in pathological processes. Although the pharmacology of the K_{2P} channels is currently poor, as our understanding of the channels improves new drugs with greater selectivity are likely to emerge. The K_{2P} channels in the cardiovascular system therefore offer potential for the future development of therapeutic agents to use in cardiovascular diseases.

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