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COMMENTARY

Vascular KCNQ channels in humans: the sub-threshold brake that regulates vascular tone?

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Contraction of arterial smooth muscle cells results in vasoconstriction, which in turn reduces blood flow and increases blood pressure. There has been a great deal of interest in understanding the ionic mechanisms that regulate smooth muscle contraction, in part because ion channels represent potential pharmacological targets for therapies directed towards cardiovascular diseases and other conditions. Potassium channels have been recognized for their roles in maintaining or stabilizing negative membrane voltages. Activation of potassium channels opposes opening of voltage-sensitive calcium channels which conduct calcium ions into the smooth muscle cells to stimulate contraction. KCNQ potassium channels were recently discovered in arterial smooth muscle cells from rats and mice. These channels have distinctive pharmacological and biophysical characteristics that have led them to be implicated as important regulators of membrane voltage and as novel pharmacological targets for modulation of vascular contractility. In this issue of *British Journal of Pharmacology*, Ng *et al.*, extend the findings from rodent models to the human vasculature and establish that KCNQ channels also regulate constriction of human arteries. The findings have important implications for the use of pharmacological KCNQ channel modulators to treat human diseases.

LINKED ARTICLE

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Abbreviations

V_m, membrane voltage; VSCC, voltage-sensitive calcium channel

Blood pressure is determined to a large extent by constriction and dilation of the arteries through which the blood flows. Arterial constriction is a function of the contractile state of the smooth muscle cells within the artery wall, which is in turn governed by intricate actions of various ion channels in the smooth muscle cells. In particular, K^+ channel activity largely determines the resting membrane voltages (V_ms), and thereby controls the activity of voltage-sensitive Ca^{2+} channels (VSCCs), which conduct Ca^{2+} into the cells to activate the contractile apparatus. Despite their importance as determinants of arterial smooth muscle contractility, K^+ channels, which constitute the largest class of ion channels, have surprisingly not emerged as clinically favoured targets to modulate blood flow and blood pressure.

The KCNQ voltage-sensitive K^+ channels (K_v7 channel family; channel nomenclature follows Alexander *et al.*, 2009) are relatively newly found members of the K^+ channel class. The first member of this family – K_vLQT1 (later renamed KCNQ1) was discovered in the heart (Sanguinetti *et al.*, 1996), where four of these subunits combine to form channels that conduct the slowly activating delayed rectifier K^+ current (I_{Ks}). The interest in K_v7 channels then exploded with the identification of $K_v7.2/7.3$ heterotetrameric channels as molecular correlates of the 'M-currents' (Wang *et al.*, 1998), which were

recognized as regulators of membrane excitability in neurons. At present, five KCNQ genes, encoding $K_v7.1$–7.5 channel subunits, have been cloned and these subunits have been found to have important functions in various excitable tissues (Jentsch, 2000). A great deal of research focused on the role of K_v7 channels in membrane excitability of neurons and QT-interval regulation in cardiac myocytes. With increasing recognition that a number of human diseases involve alterations in K_v7 channel function, a variety of pharmacological modulators were developed to target K_v7 channels in the nervous system (Dalby-Brown *et al.*, 2006).

Only recently were K_v7 channels found to be expressed and functional in smooth muscle cells of various vascular beds in rodent models (Yeung *et al.*, 2007; Mackie *et al.*, 2008; Joshi *et al.*, 2009). In this issue of *British Journal of Pharmacology*, Iain Greenwood and colleagues (Ng *et al.*, 2010) provide the first evidence for the existence of the K_v7 K^+ channels in human vascular tissue. Ng *et al.* describe important new results demonstrating that K_v7 channels are expressed and functional in human arteries and that clinically used drugs that modulate K_v7 channel function have pronounced effects on human artery constriction or dilation. These findings address the relevance of a number of studies published over the past few years that have suggested an important role of K_v7 channels as modulators of vascular tone in rodent arteries (Yeung *et al.*, 2007; Mackie *et al.*, 2008; Joshi *et al.*, 2009) and that have implicated K_v7 channels as potential antihypertensive effectors that determine differential cardiovascular risk among human subjects taking selective cyclooxygenase-2 inhibitors (Brueggemann *et al.*, 2009).

Ng *et al.* (2010) found that the human proximal mesenteric artery and small resistance arteries from visceral adipose tissue, constrict in response to pharmacological blockade of K_v7 channels and dilate in response to pharmacological K_v7 channel activators. These findings implicate K_v7 channels as regulators of V_m of vascular myocytes in both conduit and resistance arteries. The responses observed here still need to be confirmed by *in vivo* studies to determine the effect of K_v7 channel modulators on various vascular beds and the consequent effects on blood pressure and heart rate. Although a previous study reported a reduction in blood pressure in patients following chronic use of the K_v7 channel activator flupirtine (Herrmann *et al.*, 1987), the effects of K_v7 channel modulators on cardiovascular parameters need to be more carefully scrutinized in clinical studies that take into account patient demographics and co-morbid conditions.

In vascular myocytes, K_v7 channels conduct outwardly rectifying currents with a threshold for voltage-dependent activation negative to –60 mV (Mackie *et al.*, 2008). Thus, K_v7 channels activate at resting V_ms, negative to the threshold for activation of the VSCCs (~–40 mV), providing a hyperpolarizing influence that will tend to prevent the activation of the Ca^{2+} channels. Hence, K_v7 channels act as a physiological 'sub-threshold brake' in regulating vascular contractility (Figure 1). Their very negative threshold for voltage-dependent activation distinguishes K_v7 channels from other voltage-sensitive K^+ channels previously proposed to regulate vascular tone in humans. Ca^{2+}-activated K^+ channels and 4-aminopyridine-sensitive K_v channels activate at much more positive V_ms (positive to –20 mV) under physiological conditions, enabling them to serve a distinct but important role in limiting the depolarization and influx of Ca^{2+}, following activation of VSCCs.

The distinctive biophysical characteristics of the K_v7 channels dispose these channels to be potential targets for various physiological regulators of vascular tone. In fact, suppression of K_v7 channel activity has been proposed as a mechanism by which the vasoconstrictor hormone vasopressin produces its physiological constrictor effects (Mackie *et al.*, 2008). The inhibitory effects of vasopressin are dependent on protein kinase C activation (Mackie *et al.*, 2008), a common signal transduction intermediate of $G_{q/11}$-coupled-receptor activation. Other effectors of K_v7 channel inhibition, including depletion of phosphatidylinositol-4,5-bisphosphate (PIP_2) and activation of Ca^{2+}-calmodulin (Delmas and Brown, 2005), are also common signalling events for $G_{q/11}$-coupled vasoconstrictor agonists, although their roles in regulating the function of vascular K_v7 channels need to be clarified. Activation of protein kinase A, which has been shown to enhance the activity of certain K_v7 channel subtypes (Chambard and Ashmore, 2005), may contribute to vasodilation, for example in response to activation of G_s-coupled β-adrenoceptors. K_v7 channels are therefore well placed to function as common signal transduction effectors to regulate vascular tone in response to vasoconstrictors or dilators. Elucidating vasoconstrictor and vasodilator signal transduction pathways is likely to reveal new mechanisms involved in modulation of K_v7 channels by endogenous vasoactive substances. Furthermore, the actions of pharmacological K_v7 channel activators like celecoxib (Brueggemann *et al.*, 2009) may also tie into these pathways, leading to the possibility of developing novel pharmacological modulators based on signal transduction mechanisms.

The findings of Ng *et al.* provide pharmacological evidence that of the four K_v7 subtypes they found to be expressed in human arteries, K^+ channels formed by $K_v7.3$, 7.4 and 7.5, but not $K_v7.1$ subunits are the important contributors for regulation of vascular reactivity in humans. The conclusions are based on the ability of retigabine and acrylamide S1 to dilate the pre-constricted human arteries and the inability of chromanol 293B to constrict human arteries (retigabine and acrylamide S1 activate all K_v7 subunits except $K_v7.1$, whereas chromanol 293B is a selective blocker of $K_v7.1$ channel subunits).

Based on their selective activation of channels comprised of $K_v7.2$–7.5 subunits, drugs such as retigabine may be attractive agents to treat clinical conditions associated with dysregulation of vascular tone, such as cerebral vasospasm, coronary vasospasm and resistant hypertension, without affecting the $K_v7.1$-mediated cardiac I_{Ks} and hence the QT interval of the electrocardiogram. As a corollary it should be noted that K_v7 channel activators already in clinical use, or new K_v7 channel modulators that are likely to become available to treat clinical conditions like epilepsy or neuropathic pain (Dalby-Brown *et al.*, 2006), may produce vascular side effects. Further studies are needed to elucidate the predominant K_v7 channel subunits (along with accessory subunits) that combine to form functional tetrameric channels in the human vascular smooth muscle cells. This will help direct the development of isoform-specific K_v7 channel activators that are 'vascular-selective' or even 'vascular bed-selective' to treat conditions with dysregulated vascular tone. Similarly,

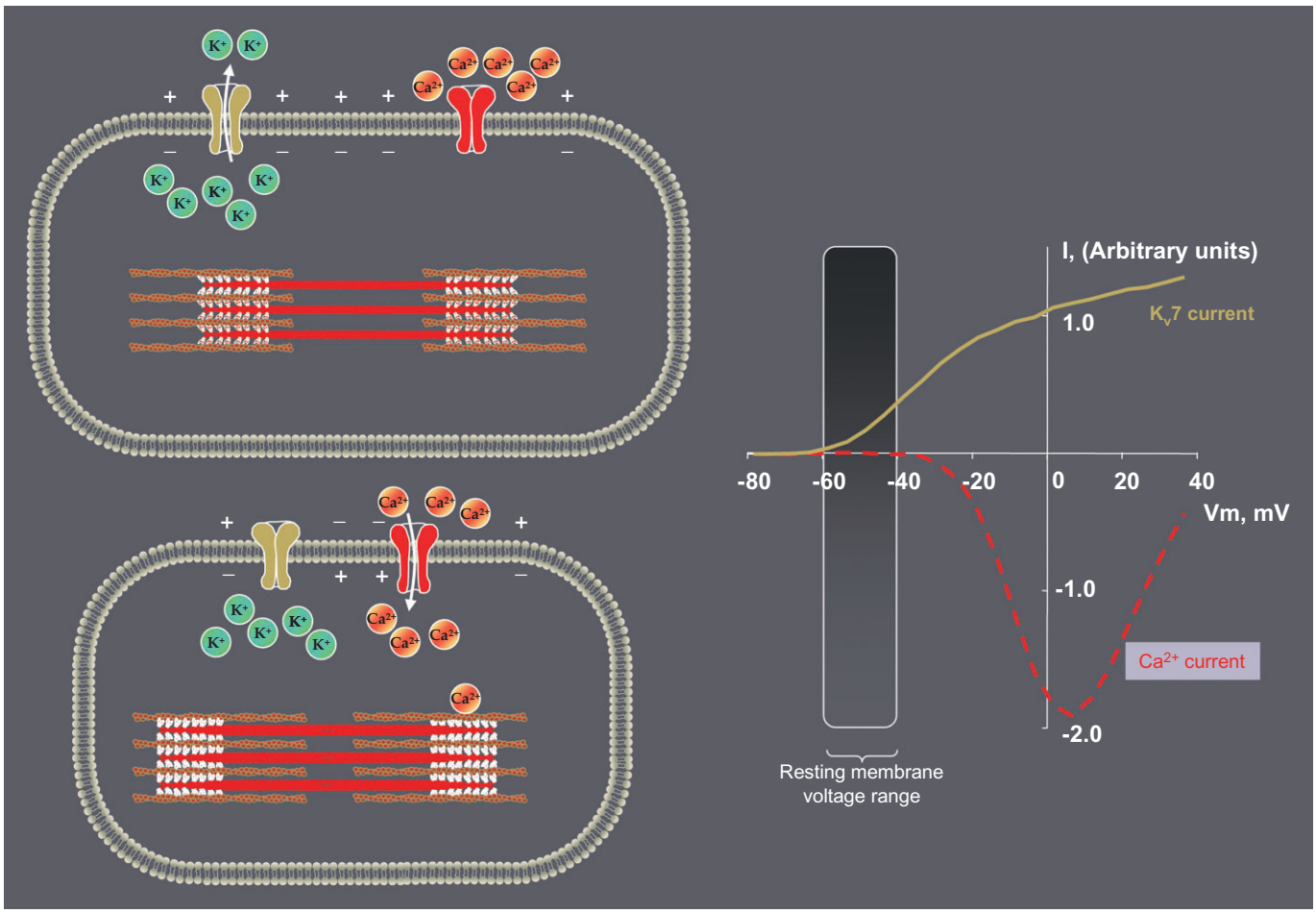

Figure 1

K_v7 channels act as a sub-threshold brake to prevent activation of voltage-sensitive Ca^{2+} channels (VSCCs). Outward K^+ conductance through K_v7 channels (yellow colour) maintains the membrane voltage (V_m) negative to the threshold for activation of VSCC (red colour) in vascular smooth muscle cells (top left). Current-voltage (I-V) relationship (right) shows the activation of K_v7 currents (yellow line) at voltages around the resting V_m (rectangular column) that maintains V_m negative to the threshold (~–40 mV) for activation of voltage-sensitive Ca^{2+} currents (broken red line). Inhibition of the K_v7 currents depolarizes the membrane to voltages more positive to –40 mV, activating the VSCC to allow Ca^{2+} influx and the ensuing contraction of vascular smooth muscle cells (bottom left).

neuronal K_v7 subtype-selective compounds may be identified for treatment of neuronal disorders while minimizing cardiovascular complications. Development of compounds that selectively bind to $K_v7.2$ channel subunits might be beneficial to target human neuronal K_v7 channels and avoid vascular channels because KCNQ2 expression was not detected in human vascular smooth muscle cells (Ng *et al.*, 2010).

Although the functional responses observed *ex vivo* in the Ng *et al.* study did not vary with patient demographics, large cohort studies need to be undertaken to study the expression and/or (de)regulation of this channel in cardiovascular pathological conditions including hypertension, septic shock and vasospasm. It is noteworthy that K_v7 channels are prone to mutations, with several of these reported to produce life-threatening neuronal and cardiac disorders (Brown, 2008). This makes a compelling case to study the possibility of K_v7 channel polymorphisms that may contribute to vascular disorders.

In summary, the findings of expression and function of K_v7 channels in human arteries by Ng *et al.* (2010) sets the pace for unravelling the mysteries of what promises to be the first K^+ channel family amenable to pharmacological intervention for the treatment of vascular disorders.

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