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INVITED EDITORIAL

Kv7.2 and Kv7.3 potassium channel subunits as new central regulators of blood pressure

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This editorial refers to 'Impaired Kv7 channel activity in the central amygdala contributes to elevated sympathetic outflow in hypertension' by Z.-F. Sheng *et al.*, pp. 613–624.

About 200 million hypertensive patients worldwide are resistant to standard pharmacological treatments, requiring at least three drugs to control blood pressure; 5–10 million people do not reach adequate blood pressure control even with five drugs.[1] Therefore, there is urgent need of innovative therapeutic strategies directed at novel targets for the treatment of hypertension. Emerging research has raised new interest in the role of sympathetic nervous system (SNS), based on evidence showing that overactivity of SNS occurs in many hypertensive patients (neurogenic hypertension), and that the renin–angiotensin system (RAS) is engaged in a bidirectional control of sympathetic nerve activity (SNA).[2] Consistent with these findings, surgical strategies to reduce SNA such as carotid baroreflex stimulation and renal denervation are effective in resistant hypertension.[3,4] In addition, sympathetic overdrive may induce damage of target organs such as heart, kidney, and arteries independently from blood pressure overload, being an independent adverse prognostic marker for cardiovascular morbidity and mortality. Drugs reducing SNA acting at either peripheral (i.e. ganglionic blockers, guanethidine) and/or central (adrenergic α_2 receptor agonists, reserpine) SNS sites have been known for decades[2]; however, antihypertensive therapy with these molecules is often limited by their adverse effects profile. In search for additional SNS components acting as new therapeutic targets, Sheng *et al.* identified for the first time Kv7 channels as critical regulators of the activity of central neurons controlling sympathetic outflow.[5] These novel results add a new layer of complexity to the multiple contributions of Kv7 channels in the modulation of cardiovascular function (*Figure 1*). The Kv7 family of voltage-gated potassium channels comprises five members (Kv7.1-5) that mediate repolarizing currents blunting cell excitability; in the nervous system, Kv7 channels mediate a potassium conductance termed 'M current' whose opening silences neuronal activity.[6] Using biochemical and functional techniques, the Authors identified Kv7.2 and Kv7.3 in the neurons projecting from the central nucleus of the amygdala (CeA) to the rostral ventrolateral medulla (RVLM), a brainstem region involved in the regulation of sympathetic outflow via projections to preganglionic neurons in the intermediolateral cell column of the spinal cord. Expression and function of these channels were down-regulated in the CeA from spontaneous hypertensive rats (SHR); such reduced Kv7.2/3 function increased the firing of CeA-RVLM neurons which, in turn, augmented SNA. Interestingly, a down-regulation of Kv7.2 and Kv7.3 channels was also found in the paraventricular nucleus of the hypothalamus, where sensory and emotional inputs from different areas of the Central Nervous System are integrated and 'translated' in autonomic responses via the RVLM. Moreover, the selective pharmacological blockade of Kv7 channels in the CeA of normotensive rats increased both renal SNA and blood pressure, further reinforcing the physiological relevance of these findings.

The contribution of Kv7 channels in SNS function has long been known, as the M current was first identified in peripheral sympathetic neurons[7]; subsequent studies have further shown that Kv7 channels play a relevant role in the baroreceptor reflex that reduces sympathetic activity in response to high blood pressure. Baroreceptors in the aortic arch send their signals through the sensory neurons of the nodose ganglia (NG) to the nucleus of the solitary tract (NTS), which is indirectly connected to the RVLM; the increased activity of baroreceptors reduces the firing of RVLM neurons, thus diminishing sympathetic outflow. Wladyka *et al.*[8] identified Kv7.2, Kv7.3, and Kv7.5 in NG neurons and their aortic baroreceptors terminals; opening of these channels increased the activation threshold of baroreceptors and reduced the firing rate of the visceral neurons projecting to the NTS, thus decreasing the 'efficacy' of the baroreflex. The M current regulates heart rate via the modulation of neurotransmitter release at vagal (i.e. parasympathetic) and sympathetic terminals,[9,10] and it has been suggested that the reduced vagal control of heart rate observed in SHR (the same animal model investigated by Sheng *et al.*) might be due to a reduced firing of pre-ganglionic parasympathetic fibres consequent to an increased function of Kv7.2/3 channels.[9] The work by Sheng *et al.* integrates the role of Kv7 channels in SNS peripheral neurons by showing their relevant contribution also in central neurons that regulate SNA. Moreover, these data expand our knowledge about the distribution and function of the Kv7 channel family in the brain, beyond the well-known role played by Kv7.2 and Kv7.3 in epilepsy as well as other neurological and psychiatric diseases.[6]

In addition to the modulation of cardiovascular function at neuronal sites, Kv7 channels play a crucial role in the regulation of blood pressure also at the vascular level. Indeed, Kv7.4 and Kv7.5 are expressed in

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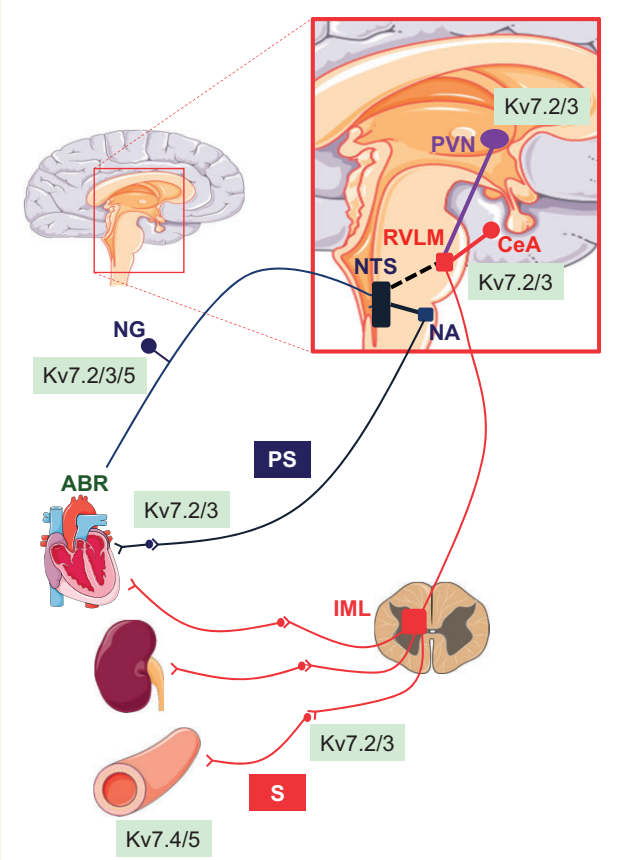

Figure 1 Distinct Kv7 channels are involved in blood pressure control at different anatomical sites. Brain areas that regulate cardiovascular function are shown in the inset; direct (solid lines) and indirect (dashed lines) connections between brain areas, and projections from central areas to peripheral ganglia and target organs (heart, kidney, and arteries) are also shown. Specific Kv7 members expressed in both central and peripheral neurons, as well as in ABR and arteries are indicated in the figure (see text for further details). Parasympathetic and sympathetic components are shown in blue and red, respectively. ABR, aortic baroreceptors; CeA, central nucleus of amygdala; IML, intermediolateral cell column; NA, nucleus ambiguus; NG, nodose ganglion; NTS, nucleus of the solitary tract; PS, parasympathetic neurons; PVN, paraventricular nucleus of hypothalamus; RVLM, rostral ventrolateral medulla; S, sympathetic neurons.

vascular smooth muscle cells from different arterial beds, where they regulate contractility and mediate responses to vasopressors. Interestingly, Kv7.4 channels are also expressed in the renal arteries where, by regulating arterial diameter, they might modulate RAS activation.[6] Moreover, reduced expression and function of Kv7.4 has been observed in murine models of hypertension,[11] possibly due to post-transcriptional mechanisms prompted by the hyperactivation of RAS.[12]

Overall, the results of the study by Sheng *et al.* highlight Kv7 channel members as possible new therapeutic targets for the treatment of resistant hypertension. However, the modulation of Kv7 channels in these central components might require therapeutic tools and strategies alternative to those currently available. In fact, most Kv7 modulators lack selectivity for 'neuronal' Kv7.2/3 versus 'vascular' Kv7.4/5 channels;[6] moreover, targeting distinct neurons without affecting others might require specific, yet unavailable formulation or delivery strategies. Nevertheless, the study by Sheng *et al.* identifies for the first time a role for Kv7 channels in central brain areas involved in the pathogenesis of hypertension, and contributes to elucidate the aberrant processes underlying the maladaptive responses occurring in cardiovascular diseases.

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