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Commentary: Ions from eons: A hidden therapeutic potential of the resting potential?

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Calcium-activated potassium channels, particularly, large conductance potassium channels (BK_{Ca}), have been identified in virtually every type of smooth muscle. In blood vessels, they are involved in vascular tone regulation. In the uterus, BK_{Ca} channels participate in the control of myometrial cell membrane potentials.¹ In the airway, BK_{Ca} channels regulate the tone and contractility of bronchioles.¹ In gastrointestinal tract, BK_{Ca} channels are involved in the regulation of colonic motility.¹

Potassium is one of the most common ions in living cells, and potassium channels are ubiquitous to all domains of life. The ion-channel superfamilies are thought to be as ancient as the last common ancestor of all organisms on earth.² Because of their wide distribution, potassium channels are thought to be one of the first ion

Regulation of vascular tone via calcium-activated potassium channels.

CENTRAL MESSAGE

Large calcium-activated potassium channels may play an important role in vasodilation of the internal thoracic artery.

channels to have evolved. The evolution of potassium channels has been traced back to the prokaryotic world.³ Furthermore, small potassium channels have been found in viruses, which are some of the simplest potassium channels, and this has been suggested to predate the more complex channels seen in early bacteria. There have been both major (gene fusion and gene duplications) and minor (single-base mutations and deletions) genetic events that have led to the fascinating diversity of potassium channels that we see today.³ Amazingly, the general molecular characteristics of the BK_{Ca} channels are evolutionarily conserved from worms to mammals.^{1,4} A single mammalian gene may generate many variants of BK_{Ca} channels that may explain the variation in calcium sensitivity in blood vessels.

BK_{Ca} channels appear to play a crucial role in arterial smooth muscle tone by providing a negative feedback loop to regulate the degree of depolarization and

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FIGURE 1. Regulation of vascular tone and restoration of cellular resting potential via calcium-activated potassium channels. A decrease in blood pressure causes the cell to depolarize. This opens calcium channels flow into the smooth muscle cell. The increase in intracellular calcium causes vasoconstriction and activates potassium channels, which opens and allows potassium to leave the smooth muscle cell. The potassium efflux has a negative effect on depolarization and restores the cell's resting potential. An increase in blood pressure causes the cell to hyperpolarize. This closes calcium channels and, thus, lowers intracellular calcium. A reduction in intracellular calcium causes vasodilation and closure of potassium channels. Keeping potassium inside the cell causes the hyperpolarized cell to return to it resting potential.

hyperpolarization.⁵ Small arteries exist in a partially contracted state from which they can either constrict further or dilate depending on the end-organ demand for blood.⁵ Although several pathways are responsible for the contraction or relaxation of vascular smooth muscle, increases in intracellular calcium that occur during cell depolarization increase vascular tone and open the BK_{Ca} channels to restore the cell's resting potential (Figure 1).⁵ Conversely, a reduction in intracellular calcium that occurs during cell hyperpolarization decreases vascular tone and closes BK_{Ca} channels to, again, restore the cell's resting potential.⁵

The study by Sun and colleagues⁶ in this issue of the *Journal* has demonstrated a remarkable difference in the BK_{Ca} subtypes within the internal thoracic artery and saphenous vein, pointing at a potential therapeutic target to treat internal thoracic artery spasm. They demonstrated a greater proportion of BK_{Ca} channels within the internal thoracic artery, which may explain the greater variability

in vasodilatory properties of the vessel.⁶ Although systemic therapy may wreak havoc on the whole body, given the widespread distribution of these channels, a targeted therapy at the time of surgery may prove to be potentially beneficial.

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