Before 1996, all known mammalian K+ channels were classified into only two different structural families according to the number of transmembrane (TM) spanning and pore-forming (P) domains in their α subunit. One family is characterized by K+ channels composed of two TM domains and one P domain, and includes the inwardly rectifying and ATP-sensitive K+ channels. The second family represents K+ channels characterized by six or seven TM domains and one P domain, and includes the voltage-gated and Ca2+-activated K+ channels. To form one functional channel for either of these families, four α subunits assemble to establish one K+ permeable pore.

In the mid 1990s, researchers took advantage of the fact that the P domain of each K+ channel’s pore-forming α subunit is highly conserved across species and represents a common structural motif.1 Genome searches for DNA sequences coding for the P domain revealed a unique K+ channel in yeast and Caenorhabditis elegans that contained two P domains within a single α subunit polypeptide having eight potential TM domains.2 The following year a human K+ channel was cloned that also showed the unique feature of two P domains, but displayed four TM domains in a single α subunit (Figure 1).3 The channel was given the name TWIK-1 (Tandem of P domains in a Weak Inward rectifying K+ channel). Since the cloning of TWIK-1, a total of fifteen genes coding for K+ channels having two P domains (K2P) and four TM domains have been identified and assigned to the KCNK gene family.4 KCNK can be subdivided into six classes of channels: 1) weak inward rectifiers (TWIK-1, TWIK-2, KCNK7); 2) mechanosensitive (TREK-1, TREK-2, TRAAK); 3) alkaline-activated (TALK-1, TALK-2, TASK-2), 4) acid-inhibited (TASK-1, TASK-3, TASK-5), 5) halothane-inhibited (THIK-1, THIK-2); and 6) calcium-activated (TRESK). All but KCNK7, KCNK15 (TASK-5), and KCNK12 (THIK-2) have been shown to encode for functional K+ channels in heterologous expression systems.

The Ksp channels are typically open at negative membrane potentials and, therefore, are often referred to as “leak”, “background”, or “baseline” K+ channels. They are ubiquitously expressed throughout the body with the brain being a particular rich source, and are postulated to importantly contribute to the resting membrane potential in neurons.4,5 Specific antagonists for the Ksp channels are not available, and these channels are typically resistant to conventional inhibitors of K+ channels including tetraethylammonium and 4-aminopyridine. Thus, defining the properties, regulation and function of Ksp channels in specific cell types often relies on using multiple approaches to detect the channel protein, identify K+ current of matching phenotype, and alter channel activity using recognized modulators. In this regard, different types of Ksp channels can be regulated by protein kinases, changes in internal or external pH, anesthetic agents, heat, stretch, and compounds that alter the curvature of the membrane.5

In this issue of Circulation Research, Blondeau et al6 report that polyunsaturated fatty acids (PUFA), and particularly α-linolenic acid, induce dilation of the basilar artery by activation of TREK-1 (TWIK RELated K) channels (Figure 2). They propose that this event contributes to the neuroprotective effect of PUFA that previously was attributed to the activation of neuronal TREK-1 channels, and subsequently, reduced neuronal excitability.7 Notably, vascular tissues express many Ksp channels including TREK-1, the second Ksp channel to be cloned.8–11 However, the vasodilator functions of K+ channels have been attributed almost exclusively to earlier classical K+ channels, and only recently has a dilator function of vascular Ksp channels been reported. For example, Gurney et al12 concluded that TASK-1 channels are major contributors to the resting membrane potential of the vascular smooth muscle cells (VSMCs) of rabbit pulmonary artery. Recently, Bryan et al13 reported that arachidonic acid activates K+ currents likely belonging to the Ksp family in VSMCs of rat middle cerebral arteries, which induces vasodilation of these vessels. The latter report supports the contention of Blondeau and colleagues6 that Ksp channels regulate cerebrovascular reactivity as targets of vasoactive lipids. Notably, lipids are known to activate or inhibit TREK-1 channels in nonvascular cells depending on whether they deform the membrane in an outward or inward direction, respectively.9 Lipids including arachidonic acid and other PUFAs that produce an outward curvature result in channel activation,12–14 whereas saturated fatty acids have no effect on TREK-1 activity.15 The regulation of TREK-1 channels by membrane stretch, pH, temperature, signaling molecules and
anesthetic agents, and by binding to A kinase anchoring protein, also has been documented.\textsuperscript{7,12–21}

The work of Blondeau et al\textsuperscript{6} gains additional impact by using multiple approaches to characterize the expression of TREK-1 channels in cerebral arteries, and implicating them in the dilator response of the cerebral circulation to PUFA. Initially, immunohistochemistry was used to detect TREK-1 protein in the medial and intimal layers of rat basilar arteries. Interestingly, it was not detected in rat carotid arteries, suggesting site-specific expression. Vascular reactivity assays demonstrated that dilator responses to PUFA also were limited to basilar and not carotid arteries, and several lines of evidence suggested that PUFA–induced dilations relied on K\textsuperscript{+} efflux. Subsequently, laser-Doppler measurements verified that PUFA increased cerebral blood in anesthetized rats. As a critical test of hypothesis, similar vascular reactivity and laser-Doppler studies were repeated in basilar arteries of TREK-1 mice. The findings showed that the dilator response to PUFA was abolished in isolated basilar arteries of TREK-1 mice, and the corresponding increase in blood flow in vivo also was abolished. Thus, the study by Blondeau et al\textsuperscript{6} provides compelling evidence that TREK-1 channels are important mediators of PUFA-induced dilation in the cerebral circulation. Perhaps the only missing piece of evidence is the direct demonstration using patch-clamp techniques of PUFA-induced K\textsuperscript{+} currents in rat or mouse cerebral endothelial cells or VSMCs. The authors do not establish whether the TREK-1 channels activated by PUFA in the basilar artery are of endothelial or VSMC origin. The TREK-1 channel displays outwardly rectifying currents because of a block of inward current by external Mg\textsuperscript{2+} and an intrinsic voltage-dependent mechanism.\textsuperscript{22,23} However, although it displays voltage-dependent gating, it is still considered a “leak” channel because TREK-1 channels are open over a wide voltage range.\textsuperscript{5}

Blondeau et al\textsuperscript{6} also demonstrated that endothelium-mediated dilations to acetylcholine in basilar arteries were completely abolished in TREK-1 mice. This finding complements a recent study by the same group in which endothelium-induced dilations were severely attenuated in the mesenteric arteries of TREK-1 mice.\textsuperscript{24} In the latter study, the deletion of the TREK-1 channel appeared to disrupt signaling between receptors and endothelial NO synthase. This mechanism of endothelial dysfunction appears distinct from the loss of PUFA-induced dilation in the cerebral circulation of TREK-1 mice, which did not rely on nitric oxide as a vasodilator. Regardless, the new findings of Blondeau et al\textsuperscript{6} contribute to the growing body of evidence that TREK-1 channels, as unique members of the K\textsubscript{2P} family, may mediate several important dilator responses that are critical for the regulation of arterial reactivity in different vascular beds.

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\textbf{Disclosures}

None.

\textbf{References}


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