Anestheticsensitive 2P Domain K⁺ Channels
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VO L A T I L E anesthetics induce neuron hyperpolarization and consequent depression of the central nervous system.1–10 In addition to the well-known potentiation of γ-aminobutyric acid type A and glycine chloride channels,2,5 evidence demonstrates that in both invertebrates and vertebrates, volatile anesthetics open background K⁺ channels and thus increase the resting membrane potential.8,9,11,12 For instance, in the mollusk Lymnaea, halothane opens a class of baseline K⁺ channels (IKa) that hyperpolarize and silence pacemaker neurons (figs. 1A and B).9,11,15 In Aplysia californica, halothane-medicated neuronal hyperpolarization is caused by the opening of the background S-type (serotonin-sensitive) K⁺ channel.12 Similarly, opening of baseline acid-sensitive K⁺ channels by volatile anesthetics produces rat hypoglossal and locus coeruleus neuron hyperpolarization.8,14

Recent reports demonstrate that the volatile anesthetic-sensitive background K⁺ channels belong to the family of mammalian K⁺ channel subunits with four transmembrane segments and two P regions (fig. 2 and table 1).8,15–17 Interestingly, the yeast 2P domain K⁺ channel, which is characterized by eight instead of four transmembrane segments, is also activated by volatile anesthetics, demonstrating the conservation of this pharmacology.18,19

The mammalian 2P domain K⁺ channel subunits are characterized by diverse patterns of expression and functional properties.8,15,20–24 Volatile anesthetics selectively open human TREK-1, TREK-2, TASK-1, TASK-2, TASK-3, and TALK-2 channels.15–17,25,26 On the contrary, local anesthetics reversibly inhibit the 2P domain K⁺ channels.20–29 In the current report, the expression and properties of these anesthetic-sensitive K⁺ channels are reviewed, and their possible functional role in the mechanisms of anesthesia and analgesia is discussed.

Mammalian 2P Domain K⁺ Channels

Mammalian K⁺ channels belong to three main structural classes made of two, four, or six transmembrane segments (TMSs).30,31 The common feature of all K⁺ channels is the presence of a conserved motif called the P domain (the K⁺ channel signature sequence or putative pore-forming region), which is part of the K⁺ conduction pathway.32 The two TMS and six TMS classes are characterized by the presence of a single P domain, whereas the most recently discovered class of four TMS subunits is characterized by the presence of a tandem of P domains (fig. 2A).30,31 Functional K⁺ channels are tetramers of pore-forming subunits for the two and six TMS classes and possibly dimers in the case of the four TMS class.33 The 2TMS–1P K⁺ channels encode the inward rectifiers. These K⁺ channels close with depolarization because of channel block by intracellular Mg²⁺ and polyamines (for review, see report by Ruppersberg54). The conductance increases on hyperpolarization, and, consequently, the inward K⁺ currents recorded at potentials below the equilibrium potential EK⁺ (approximately –90 mV in a physiological K⁺ gradient) are much larger than the outward K⁺ currents recorded at depolarized potentials. Although the amplitude of the outward currents flowing through the inward rectifiers is limited, they will have a major influence on the resting membrane potential.35 The voltage at which channel gating by intracellular Mg²⁺ and polyamines occurs will set the range in which the K⁺ channel will influence the cell membrane potential. Because they are blocked at depolarized potentials, these channels will have a small but limited role in the repolarization of the action potential.

By contrast, the outward rectifiers encoded by the 6TMS–1P subunits open on depolarization (Kv channels) and after intracellular Ca²⁺ increase (BK and SK channels). Depolarization is sensed by the positively charged fourth TMS of Kv channels, which is coupled to activation gates. Opening of the voltage-gated K⁺ channels is time-dependent (delayed rectifiers) and contributes to repolarize and terminate the action potential.35 Several voltage-gated K⁺ channels are also characterized by a fast (N-type) inactivation process. The inactivation gate is the positively charged amino terminus of these specific subunits (ball-and-chain mechanism).
TWIK-1, the first mammalian 2P domain \( \text{K}^+ \) channel to be identified, self-associates to form disulfide-bridged homodimers.\(^{35}\) The extracellular M1P1 interdomain, predicted to form an amphipathic helix, promotes self-dimerization. A cysteine located in this domain appears to be important for the dimerization of some, but not all 2P domain \( \text{K}^+ \) channels, for instance, TASK-1.\(^{35}\) A dimer contains 4P domains, which are essential in the formation of \( \text{K}^+ \)-selective pores. No evidence for heteromultimerization has yet been reported for the 2P domain \( \text{K}^+ \) channels.

Leak channels, which are opened pores in the membrane, have no voltage or time dependency by definition.\(^{35}\) Activation is instantaneous on depolarization as the channels are always opened at rest. Because of an asymmetrical physiological \( \text{K}^+ \) gradient (approximately 150 m\( \text{M} \) intracellular and \( \text{5 mM} \) extracellular), the current-to-voltage relation of a \( \text{K}^+ \) leak channel is predicted to be outwardly rectifying (Goldman, Hodgkin, and Katz constant-field theory, also called the open rectification) (fig. 2C).\(^{35}\) In a symmetrical \( \text{K}^+ \) gradient, the current-to-voltage relation of the leak channel is expected to be linear, as observed for TASK-1, TRAAK, and TALK-1 (fig. 2C). These \( \text{K}^+ \) channels thus behave as open rectifiers. Because of this leak characteristic, the background 4TMS–2P \( \text{K}^+ \) channels are expected to influence both the resting membrane potential (along with the inward rectifiers) and the repolarization phase of the action potential (along with the voltage-gated and \( \text{Ca}^{2+} \)-activated outward rectifiers). Several 4TMS–2P background \( \text{K}^+ \) channels are, however, more than a simple open rectifier leak channel (figs. 2D and E). For instance, TREK-1 is a \( \text{K}^+ \) channel that displays a strong outward rectification in a symmetrical \( \text{K}^+ \) gradient (fig. 2D).\(^{20,29}\)

This rectification is at least partly caused by a voltage-dependent gating.\(^{29}\) Similar outward rectification has also been observed for TALK-2, TASK-2, TREK-2, and TASK-3.\(^{17,25,28,46}\) Moreover, the activation of TASK-2 and TREK-2 is time-dependent.\(^{16,17,40}\) On the contrary, TWIK-2 shows a mild inward rectification when recorded in a symmetrical \( \text{K}^+ \) gradient (fig. 2E).\(^{37}\) Mild inward rectification is also typical to TWIK-1 and THIK-1.\(^{25,28}\) TWIK-2 is additionally characterized by a time-dependent inactivation.\(^{37}\) The various 4TMS–2P channels will differentially tune the resting potential or the action potential duration because of these particular rectification, time-, and voltage-dependent properties.

Mechano-gated TREK-1 and TREK-2 \( \text{K}^+ \) Channels are Opened by Inhatalonal Anesthetics

Human TREK-1 is highly expressed in brain and ovary and to a lesser extent in kidney and small intestine.\(^{15,17,54,55}\) In human brain, TREK-1 shows the greatest expression in the caudate nucleus, the putamen, the spinal cord, and the dorsal root ganglia (fig. 3).\(^{17,55}\) At the protein level, TREK-1 is present at both synaptic and
nonsynaptic sites in mouse brain. Signi-ificant ex-
pression is also detected in both small and medium sensory neurons of mouse dorsal root ganglia. Human TREK-2 (78% of homology with TREK-1) is abundantly expressed in kidney and pancreas and more moderately in testis, brain, colon, and small intestine. In human brain, TREK-2 shows the strongest expression in the caudate nucleus, the cerebellum, the corpus callosum, and the putamen (fig. 3). Some tissues only express TREK-1 (ovary) or TREK-2 (pancreas, colon). Other tissues do not express these channels or only to very modest levels (heart, skeletal muscle, lung, blood leukocytes, and spleen). Finally, some tissues present overlapping expression (brain, kidney, small intestine).

TREK-1 and TREK-2 channels are mechano-gated \( K^+ \) channels opened by membrane stretch. Mechanical force is believed to be transmitted directly to the channel via the lipid bilayer. Lowering intracellular pH shifts the pressure–activation relation of TREK-1 and TREK-2 toward positive values and ultimately leads to channel opening at atmospheric pressure. Acidosis essentially converts a TREK mechano-gated channel into a constitutively active background channel.

### Table 1. Nomenclature of Mammalian 2P Domain \( K^+ \) Channels

<table>
<thead>
<tr>
<th>Original Abbreviations</th>
<th>Original Names</th>
<th>Hugo Nomenclature</th>
<th>Human Chromosomal Localization</th>
</tr>
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<tbody>
<tr>
<td>TWIK-1</td>
<td>Tandem of P domains in a weak inward rectifying ( K^+ ) channel-1</td>
<td>KCNK1</td>
<td>1q42–q43</td>
</tr>
<tr>
<td>TWIK-2</td>
<td>Tandem of P domains in a weak inward rectifying ( K^+ ) channel-2</td>
<td>KCNK6</td>
<td>19q13.1</td>
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<td>KCNK-7</td>
<td></td>
<td>KCNK7</td>
<td>11q13</td>
</tr>
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<td>TREK-1</td>
<td>TWIK-1-related ( K^+ ) channel-1</td>
<td>KCNK2</td>
<td>1q41</td>
</tr>
<tr>
<td>TREK-2</td>
<td>TWIK-1-related ( K^+ ) channel-2</td>
<td>KCNK10</td>
<td>14q31</td>
</tr>
<tr>
<td>TRAAK</td>
<td>TWIK-related arachidonic acid–stimulated ( K^+ ) channel</td>
<td>KCNK4</td>
<td>11q13</td>
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<td>TASK-1</td>
<td>TWIK-related acid-sensitive ( K^+ ) channel-1</td>
<td>KCNK3</td>
<td>2p23</td>
</tr>
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<td>TASK-3</td>
<td>TWIK-related acid-sensitive ( K^+ ) channel-3</td>
<td>KCNK9</td>
<td>8q24.3</td>
</tr>
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<td>TASK-2</td>
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<td>KCNK5</td>
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<tr>
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<td>KCNK16</td>
<td>6p21</td>
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<tr>
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<td>TWIK-related alkaline pH activated ( K^+ ) channel-2</td>
<td>KCNK17</td>
<td>6p21</td>
</tr>
<tr>
<td>THIK-1</td>
<td>Tandem pore domain halothane inhibited ( K^+ ) channel-1</td>
<td>KCNK13</td>
<td>14q24.1–14q24.3</td>
</tr>
<tr>
<td>THIK-2</td>
<td>Tandem pore domain halothane inhibited ( K^+ ) channel-2</td>
<td>KCNK12</td>
<td>2p22–2p21</td>
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</tbody>
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K⁺ channel.¹⁷,⁵⁹ TREK-1 is also gradually and reversibly opened by heat. An increase in temperature of 10°C enhances TREK-1 current amplitude by approximately sevenfold.²² Finally, TREK-1, TREK-2, and TRAAK are reversibly opened by polyunsaturated fatty acids and lysophospholipids, including arachidonic acid and lysophosphatidylcholine (fig. 4).¹⁷,²⁹,⁴⁴,⁴⁵,⁶⁰ Deletional analysis demonstrates that the carboxy terminus, but not the amino terminus and the extracellular M1P1 loop, is critical for activation of TREK-1 by stretch, arachidonic acid, lysophospholipids, intracellular acidosis, and temperature.²²,²⁹,⁵⁹ TREK-1 and TREK-2 activation are reversed by protein kinase A stimulation.¹⁷,²⁰,²²,²⁹,⁶⁰ Protein kinase A–mediated phosphorylation of Ser333 in the carboxy terminus mediates TREK-1 closing.²⁹ TREK-1 and TREK-2 are insensitive to most of the classical K⁺ channel blockers, including tetraethylammonium (TEA⁺; 10 mM), 4-aminopyridine (4-AP; 3 mM), Ba²⁺ (1 mM), glibenclamide (10 μM), charybdotoxin (1 μM), and apamin (10 μM). TREK-1 is reversibly blocked by Gd³⁺ (30 μM), amiloride (2 mM), and chlorpromazine (10 μM).²⁹,⁴⁵,⁶⁰

TREK-1 and TREK-2 are opened by chloroform, diethyl ether, halothane, and isoflurane in transfected mammalian cells (figs. 4 and 5A).¹⁵,¹⁷,²⁹ Opening of these channels by anesthetics induces cell hyperpolarization (fig. 5B). Interestingly, the other structurally and functionally related 2P domain K⁺ channel, TRAAK, is insensitive to volatile anesthetics.¹⁵ Human TREK-1 is most sensitive to chloroform (2.3-fold increase in current amplitude at 1 mM), whereas halothane is the strongest opener of human TREK-2 (2.3-fold increase at 1 mM).¹⁵ In excised outside-out patches, the 48 pS TREK-1 channel is reversibly opened in a dose-dependent manner by chloroform and halothane (fig. 5C).¹⁵ No channel activity is observed in the absence of anesthetic, suggesting that it converts inactive channels to active ones. Deletion of the amino terminus does not affect anesthetic-induced TREK-1 opening.¹⁵ In contrast, deletion of the carboxy terminus at Thr 322 completely suppresses responses to both chloroform and halothane.¹⁵ These results demonstrate that the carboxy terminus, but not the amino terminus, of TREK-1 is critical for anesthetic activation.

TREK-1 and TREK-2 share all the functional properties of the anesthetic-sensitive background K⁺ channels in Lymnaea pacemaker neurons and the S channel in Aplysia sensory neurons (fig. 1B).⁹,¹¹,¹² Both endogenous
and cloned background $K^+$ channels are opened by volatile anesthetics in excised patches, suggesting a direct mechanism of action (fig. 5C).\textsuperscript{12,15} Moreover, the lack of effect of volatile anesthetics on TRAAK, another mechano-gated polyunsaturated fatty acid-sensitive 2P domain $K^+$ subunit, suggests that an indirect membrane effect is unlikely.\textsuperscript{15} Pure optical isomers of the volatile anesthetic isoflurane show clear stereoselectivity in activating background $K^+$ currents in pacemaker neurons of the \textit{Lymnaea}.\textsuperscript{15} The $+$ isomer is more potent than the $-$ isomer in hyperpolarizing neurons, suggesting that volatile anesthetics act by direct binding to the protein rather than a nonspecific perturbation of lipids.\textsuperscript{13} Although the stimulation by inhalational anesthetics seems to be direct, one cannot fully rule out possible indirect effects.\textsuperscript{11,12,15} Indeed, it has been shown in \textit{Lymnaea} neurons that, although the activation of IKan by volatile anesthetics is independent of the lipoxygenase and cytochrome P450 pathway, it might involve the cytochrome P450 pathway.\textsuperscript{11} Moreover, TREK-1 is not sensitive to volatile anesthetics when expressed in \textit{Xenopus} oocytes.\textsuperscript{16} These negative results may indicate that either a specific membrane environment or critical cofactors, which are absent in \textit{Xenopus} oocytes but present in mammalian cells, may be required.

\textbf{Acid-sensitive Background $K^+$ Channels TASK-1 and TASK-3 Are Opened by Volatile Anesthetics}

Human TASK-1 is particularly abundant in the pancreas and the placenta.\textsuperscript{21} Lower levels of expression are found in brain, lung, prostate, heart, kidney, uterus, small intestine, and colon. High concentrations of TASK-1 are found in cerebellar and olfactory granule cells, olfactory tubercles, scattered neurons through all layers of cerebral cortex, intralaminar thalamic nuclei, pontine nuclei, and the locus coeruleus of the rat.\textsuperscript{8,21} Brainstem and spinal cord motoneurons display the strongest expression of TASK-1.\textsuperscript{8} Motor nuclei with high concentrations of TASK-1 include facial, hypoglossal, ambigual, and motor trigeminal, as well as the vagal motor nucleus. TASK-1 is also particularly abundant in rat carotid body cells.\textsuperscript{61} In human brain, the strongest expression is found in the cerebellum, thalamus, and pituitary gland (fig. 3).\textsuperscript{55} TASK-1 is also particularly abundant in human dorsal root ganglia.\textsuperscript{55} Human TASK-3, which is 62% identical to TASK-1, is largely and selectively expressed in the cerebellum.\textsuperscript{52,55}

Fig. 5. TREK-1 is opened by general anesthetics. (A) Chloroform (0.8 ms) stimulates whole cell TREK-1 currents recorded in transfected epithelial cells. (B) Chloroform (0.8 ms) reversibly hyperpolarizes a cell expressing TREK-1. (C) Increasing concentrations of halothane reversibly open TREK-1 channels in an excised outside-out patch. (Adapted with permission from Patel et al.\textsuperscript{49})
cated between residues 242 and 248 (VLRFMT) is critical for anesthetic sensitivity.15

A background K⁺ current sets the resting membrane potential in type I carotid body chemoreceptor cells.61,66 Reversible inhibition of this background K⁺ current by hypoxia or acidosis induces membrane depolarization. Depolarization of type I cells leads to opening of voltage-gated Ca²⁺ channels, an increase in intracellular Ca²⁺, and release of neurotransmitters, including dopamine.67 The released neurotransmitters stimulate sinus nerve endings and trigger the reflex increase in respiration. The endogenous background K⁺ channel in type I cells shares the biophysical and pharmacologic properties of TASK-1.61 It is reversibly inhibited by mild external acidosis, time- and voltage-independent, resistant to TEA⁺ and 4-AP, but blocked by Ba²⁺, Zn²⁺, bupivacaine, and quinidine. Moreover, the type I cell background K⁺ current is enhanced by halothane but is insensitive to chloroform.61 Opening of TASK-1-like background K⁺ channels in type I carotid body cells may be partially responsible for the suppression of hypoxic ventilatory drive during general anesthesia.

In rat somatic motoneurons, locus coeruleus neurons, and cerebellar granule neurons, inhalational anesthetics similarly activate a background TASK-1-like conductance, causing membrane hyperpolarization and suppressing action potential discharge (figs. 7A and B).8,65 These effects occur at clinically relevant anesthetic concentrations with the steep dose dependence expected for anesthetic effects of these compounds.8 External acidosis to pH 6.5 completely blocks the current activated by anesthetics (fig. 7B, inset).8,65 In motoneurons and cerebellar granule neurons, opening of TASK-1 channels may contribute to anesthetic-induced immobilization, whereas in the locus coeruleus, it may support analgesic and hypnotic actions.8

Application of 1 mM halothane reversibly potentiates human TASK-3 current amplitude by 66%.26 The onset of halothane stimulation in *Xenopus* oocyte is rapid (τ: 62 s), whereas full recovery takes as long as 5 min. By contrast, the neurosteroidal anesthetic alfaxalone inhibits TASK-3.26 Pentobarbital and ketamine do not significantly affect TASK-3 at a concentration of 100 μM.26

**Spinal Cord and Dorsal Root Ganglion Background K⁺ Channel TASK-2 Is Opened by Inhalational Anesthetics**

Human TASK-2 is found in kidney, pancreas, lung, and placenta.66 Although TASK-2 expression is weak in whole brain, it can be detected by polymerase chain reaction in rat spinal cord.16 TASK-2 is found throughout the spinal cord in both ventral and dorsal sections.16 Moreover, TASK-2 is expressed in high concentrations in

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**Fig. 6.** TASK-1 is opened by halogenated inhalational anesthetics. (A) Halothane (1 mM) stimulates TASK-1 current in a transfected cell voltage clamped at 0 mV. (B) Halothane (1 mM)-stimulated I-V curves recorded in both physiological and symmetrical K⁺ gradients. (C) Halothane (1 mM) stimulates TASK-1 opening in an excised inside-out patch. (Adapted with permission from Patel et al.15)

**Fig. 7.** (A) Halothane (0.3 mM) hyperpolarizes neurons of the rat locus coeruleus. These recordings were performed in the continued presence of bicuculline and strychnine to rule out the possible effects of γ-aminobutyric acid and glycine inhibition. In addition, ZD7288 was included in the pipette to block hyperpolarization-activated cationic current (Ih). The halothane-induced hyperpolarization is reversed by extracellular acidosis to pH 6.5. (B) pH sensitivity of the halothane-induced K⁺ current in locus coeruleus neurons. The I-V curve obtained from subtracting the halothane current in pH 6.5 from that in pH 7.3 follows the Goldman–Hodgkin–Katz equation. The histogram in the inset illustrates the current amplitude at −60 mV in control pH 7.3 and during acidosis at pH 6.5. (Adapted with permission from Sirois et al.8)
human spinal cord as well as in dorsal root ganglia (fig. 3).\textsuperscript{55} TASK-2 produces non-inactivating, outwardly rectifying K\textsuperscript{+} currents with activation potential thresholds that closely follow the K\textsuperscript{+} equilibrium potential.\textsuperscript{16,46} TASK-2 activation is time-dependent with a fast time constant of approximately 60 ms at 0 mV. TASK-2 currents are blocked by quinine and quindine but not by the classical K\textsuperscript{+} channel blockers TEA\textsuperscript{+}, 4-AP, Cs\textsuperscript{+}, and Ba\textsuperscript{2+}.\textsuperscript{46} TASK-2 is inhibited by external acidosis with a half-inhibition at pH 7.8.\textsuperscript{16,46} Application of volatile anesthetics causes a concentration-dependent increase in TASK-2 currents in a range overlapping minimum alveolar concentrations.\textsuperscript{16} TASK-2 is more sensitive to halothane than isoflurane.\textsuperscript{16} Unlike TASK-1, TASK-2 is also stimulated by chloroform (fig. 4). Site-directed mutagenesis has been used to delete the carboxy terminus of TASK-2.\textsuperscript{16} The truncated TASK-2 channel does not express a spontaneous or volatile anesthetic-evoked activity, further demonstrating the critical role of the carboxy terminus in the function of 2P domain K\textsuperscript{+} channels.\textsuperscript{15,16,29}

\textbf{Volatile Anesthetic-inhibited 2P Domain K\textsuperscript{+} Channels}

TWIK-2 is a background K\textsuperscript{+} channel that is highly expressed in both visceral and vascular smooth muscle.\textsuperscript{57} Human TWIK-2 is absent in the brain and in the cerebellum (fig. 3).\textsuperscript{37–39,55} However, a moderate to strong expression is found in the human spinal cord and in the dorsal root ganglia.\textsuperscript{55} Chloroform (300 \textmu M) and halothane (750 \textmu M) reversibly inhibit TWIK-2 by 32 and 27%, respectively.\textsuperscript{57}

THIK-1 expression is ubiquitous, with a substantial expression in some restricted areas of the rat brain (fig. 3).\textsuperscript{48} The strongest concentrations are found in the olfactory bulb granule cell layer, the lateral septal nucleus dorsal, the ventromedial hypothalamic nucleus, the thalamus reticular and reunions nuclei, and, finally, the parabrachial nuclei.\textsuperscript{48} THIK-1 is a weak inward rectifier that is stimulated by arachidonic acid but inhibited by halothane, with an IC\textsubscript{50} value of 2.83 mm (fig. 4).\textsuperscript{48} Interestingly, 1 mm chloroform fails to affect THIK-1.\textsuperscript{48}

Human TALK-1 is exclusively expressed in the pancreas.\textsuperscript{25} Human TALK-2 is similarly found in high concentrations in the pancreas but is also present in liver, placenta, heart, and lung.\textsuperscript{25} TALK-1 and TALK-2 are background K\textsuperscript{+} currents that are activated by alkaline pH but are insensitive to arachidonic acid. Both channels are inhibited by 800 \textmu M chloroform (−21 and −44%, respectively) and 800 \textmu M halothane (−27 and −56%, respectively) (fig. 4).\textsuperscript{25,47} Interestingly, TALK-1 is not sensitive to 800 \textmu M isoflurane, whereas TALK-2 is stimulated (+58%).\textsuperscript{25}

\textbf{Inhibition of Background K\textsuperscript{+} Channels by Local Anesthetics}

Bupivacaine, tetracaine, and lidocaine inhibit several mammalian 2P domain K\textsuperscript{+} channels, including TASK-1, TASK-3, TREK-1, and TWIK-1.\textsuperscript{26–29} The presence of the uncharged form of the local anesthetic is important for channel inhibition. TASK-1 inhibition is greater at alkaline pH values (28% inhibition with 10 \mu M bupivacaine at pH 8.4).\textsuperscript{27} The potency of inhibition is directly correlated with the octanol:buffer distribution coefficient of the local anesthetic. The IC\textsubscript{50} values for TASK-1 are 709 \mu M mepivacaine, 222 \mu M lidocaine, 51 \mu M \textit{R(+)}-ropivacaine, 53 \mu M \textit{S(−)}-ropivacaine, 668 \mu M tetracaine, 41 \mu M bupivacaine, and 39 \mu M etidocaine.\textsuperscript{27} The Hill coefficient of the dose-effect curves is close to 1, suggesting that a single local anesthetic molecule binds to each 2P domain K\textsuperscript{+} channel. The stereoisomers of ropivacaine are equipotent, demonstrating that the inhibition is not stereoselective.\textsuperscript{27} Local anesthetics significantly depolarize cells expressing TASK-1. The membrane depolarization may enhance the binding of local anesthetics to the open and inactivated states of the voltage-dependent Na\textsuperscript{+} channels.\textsuperscript{27} Therefore, the inhibition of background 2P domain K\textsuperscript{+} channels by local anesthetics should contribute to enhance the conduction block of peripheral nerves.

\textbf{Conclusions and Perspectives}

These recent findings provide strong evidence that 2P domain K\textsuperscript{+} channels are sensitive molecular targets for volatile anesthetics. Together with the known modulation by neurotransmitter receptors,\textsuperscript{2,3} opening of these channels will contribute to the hyperpolarizing action of general anesthetics.\textsuperscript{15}

Opening of the 2P domain K\textsuperscript{+} channels is agent-specific. For instance, TREK-1, TREK-2, and TASK-2 are opened by chloroform; TASK-1, THIK-1, and TRAAK are unaffected; and TWIK-2, TALK-1, and TALK-2 are inhibited.\textsuperscript{15,17,25,37,48} Interestingly, TALK-2 is inhibited by chloroform and halothane while it is stimulated by isoflurane.\textsuperscript{25} The volatile anesthetic-inhibited 2P domain K\textsuperscript{+} channels, including TWIK-2, THIK-1, TALK-1, and TALK-2, are mostly nonneuronal (THIK-1 is restricted to some brain areas) and strongly expressed in peripheral organs.\textsuperscript{25,37,48} TREK-1, TREK-2, and TASK-1 are more sensitive to halothane than isoflurane.\textsuperscript{15,17} This difference in potency between the two volatile anesthetics indicates that opening of 2P domain K\textsuperscript{+} channels will probably be prevalent during halothane-induced anesthesia. Clearly, further work is necessary to map the putative anesthetic binding site and understand the role of the carboxy terminus in the mechanism of channel activation.\textsuperscript{15}

Opening of 2P domain K\textsuperscript{+} channels will have profound hyperpolarizing effects at both presynaptic and
postsynaptic levels. Because of the leak behavior of the 2P domain K\(^+\) channels, even moderate stimulation, as observed for clinical doses of volatile anesthetics, will have a major effect on the membrane potential.\(^{30,31}\) The discovery of this class of anesthetic-sensitive K\(^+\) channels with distinct patterns of expression may provide a basis for how inhalational anesthetics depress the central nervous system.\(^{15,17,55}\) In the human brain, opening of TREK-1 and TREK-2 in the caudate nucleus and the putamen, opening of TREK-2 and TASK-3 in the cerebellum, and opening of TREK-2 in the corpus callosum may be functionally important during general anesthesia by volatile anesthetics (fig. 3).\(^{15,17,55}\) Opening of TREK-1, TASK-1, and TASK-2 in the sensory neurons of human dorsal root ganglia may block sensory inputs and contribute to loss of consciousness.\(^{15,17,55}\) Finally, opening of TREK-1 in motoneurons by inhalational anesthetics may depress mobility (fig. 3).\(^{15,55}\)

Local anesthetics inhibit background K\(^+\) channels and induce cell depolarization.\(^{27}\) These results suggest that closing of 2P domain K\(^+\) channels by local anesthetics could contribute to peripheral analgesia by augmenting conduction blockade, whereas opening by volatile anesthetics may contribute to general anesthesia.\(^{15,27}\) These recent results contribute to the understanding of the molecular and cellular mechanisms of action of anesthetics.

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10. MacIver MB, Kending JJ: Anesthetic effects on resting membrane potential of dorsal root ganglia may block sensory inputs and conduction-blockade whereas opening by volatile anesthetics may depress mobility (fig. 3).\(^{15,55}\) Local anesthetics inhibit background K\(^+\) channels and induce cell depolarization.\(^{27}\) These results suggest that closing of 2P domain K\(^+\) channels by local anesthetics could contribute to peripheral analgesia by augmenting conduction blockade, whereas opening by volatile anesthetics may contribute to general anesthesia.\(^{15,27}\)

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