

# The neuronal background $K_{2p}$ channels: focus on TREK1

Eric Honoré

**Abstract** | Two-pore-domain  $K^+$  ( $K_{2p}$ ) channel subunits are made up of four transmembrane segments and two pore-forming domains that are arranged in tandem and function as either homo- or heterodimeric channels. This structural motif is associated with unusual gating properties, including background channel activity and sensitivity to membrane stretch. Moreover,  $K_{2p}$  channels are modulated by a variety of cellular lipids and pharmacological agents, including polyunsaturated fatty acids and volatile general anaesthetics. Recent *in vivo* studies have demonstrated that TREK1, the most thoroughly studied  $K_{2p}$  channel, has a key role in the cellular mechanisms of neuroprotection, anaesthesia, pain and depression.

## P domain

A short amino acid segment between two transmembrane helices that dips into the membrane without fully crossing it.

Background (also called baseline or leak)  $K^+$  channels are transmembrane  $K^+$ -selective ionic pores that are constitutively open at rest and are central to neural function. In the marine snails *Aplysia* and *Lymnaea*, the serotonin-sensitive S-type and the anaesthetic-sensitive K(An) channels are classical examples of such background  $K^+$  channels<sup>1–4</sup>. The resting activity of these  $K^+$  channels drives the membrane potential (through hyperpolarization) closer to the  $K^+$  equilibrium potential of about  $-90$  mV, and therefore tends to reduce excitability. Downmodulation of the S-type background  $K^+$  channel activity in *Aplysia* is involved in synaptic sensitization<sup>5</sup>. Conversely, in *Lymnaea*, stimulation of the inhibitory synaptic anaesthetic-sensitive background  $K^+$  current IK(An) hyperpolarizes and reversibly suppresses electrical activity in anaesthetic-sensitive pacemaker neurons<sup>3,4</sup>. Background  $K^+$  channels and their regulation by membrane-receptor-coupled second messengers, as well as pharmacological agents, are therefore important in tuning neuronal resting membrane potential, action potential duration, membrane input resistance and, consequently, regulating transmitter release<sup>1,3</sup>.

Background  $K^+$  channels are composed of  $K_{2p}$  channel subunits that have previously been called KCNKx subunits or tandem of P domains in a weak inwardly rectifying  $K^+$  channel (TWIK) subunits (FIG. 1a,b). Mechano-gated and arachidonic acid-activated TWIK-related  $K^+$  1 (TREK1) and TREK2 are the hypothetical functional homologues of the *Aplysia* S-type background  $K^+$  channel<sup>6,7</sup>. Recently, genetic inactivation of TREK1 in the mouse has revealed the potential involvement of this  $K_{2p}$  channel in a range of neuronal disease states, including

pain, ischaemia, epilepsy and depression<sup>8–10</sup>. Moreover, TREK1 displays unique pharmacological properties, such as modulation by lipids and volatile and gaseous general anaesthetics<sup>11,12</sup>.

In this article, I will discuss the functional properties of the mammalian neuronal  $K_{2p}$  background  $K^+$  channels, with a special focus on TREK1, the most extensively studied  $K_{2p}$  channel. Human *TREK1* is highly expressed in the brain, where it is particularly abundant in GABA ( $\gamma$ -aminobutyric acid)-containing interneurons of the caudate nucleus and putamen<sup>13</sup>. *TREK1* is also expressed in the prefrontal cortex, hippocampus, hypothalamus, midbrain serotonergic neurons of the dorsal raphe nucleus and sensory neurons of the dorsal root ganglia (DRG)<sup>8,14</sup>. TREK1 is also found in peripheral tissues such as the gastrointestinal tract<sup>14–16</sup>.

TREK1 is a signal integrator responding to a wide range of physiological and pathological inputs. The complex gating properties of TREK1 and its modulation by cellular lipids, membrane-receptor-coupled second messengers and pharmacological agents will be described. I will then discuss the role of TREK1 in neuronal disease states before focusing on the involvement of TREK1 in the presynaptic control of neurotransmission. Finally, the questions and future challenges that face the field of  $K_{2p}$  channels will be outlined.

The aim of this review is to summarize the biophysical, pharmacological and regulatory properties of  $K_{2p}$  channels, describing the well-established results, but also indicating the main controversies in this field. Current working hypotheses and the most generally accepted functional models for TREK1 gating will be discussed.

Institut de Pharmacologie Moléculaire et Cellulaire, CNRS UMR 6097, Université de Nice-Sophia Antipolis, 660 route des Lucioles, 06560 Valbonne, France. e-mail: honore@ipmc.cnrs.fr doi:10.1038/nrn2117

**Selectivity filter**

The sequence that determines K<sup>+</sup> selectivity of K<sup>+</sup> channels. The primary sequence of the P loop of most K<sup>+</sup> channels has the signature sequence Thr–Val–Gly–Tyr–Gly.

**Permeability ratio**

The relative permeability of an ion channel for a particular monovalent cation. A given ion channel can allow the passage of related ionic species, although not all with the same ease.

**Mammalian K<sup>+</sup> channel subunits.**

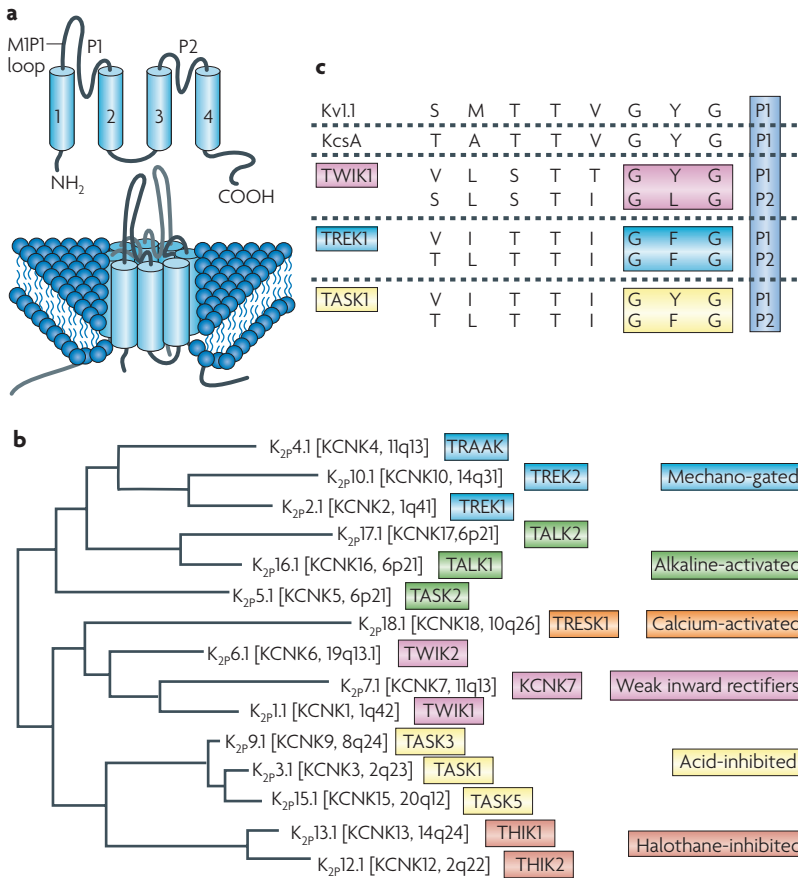
Mammalian K<sup>+</sup> channel subunits can contain two, four or six/seven transmembrane segments. Members of the two and six/seven transmembrane segment classes are characterized by the presence of a single pore-forming (P) domain, whereas the more recently discovered class of four transmembrane segment subunits contain two P domains that are arranged in tandem<sup>17–21</sup> (BOX 1; FIG. 1a). In one-pore-domain K<sup>+</sup> (K<sub>1p</sub>) channels, four matching P loops are assembled in homo- or heterotetramers (all subunits have a similar P domain sequence, which contains the residues YYG or FFG), whereas in the dimeric K<sub>2p</sub> channels, the first pore (P1) and P2 domains can have different sequences as exemplified by TWIK1 or TWIK-related acid-sensitive K<sup>+</sup> 1 (TASK1) (REFS 22,23) (FIG. 1c). Many K<sub>2p</sub> channels have a phenylalanine or a leucine in the GXG motif (where X represents any amino

acid) of the selectivity filter in the P2 domain instead of a tyrosine<sup>18,19,23</sup> (FIG. 1c). Therefore, in K<sub>2p</sub> channels, the pore is predicted to have a two-fold symmetry rather than the classical four-fold arrangement of other K<sup>+</sup> channels. Although the selectivity of K<sub>2p</sub> channels for K<sup>+</sup> over Na<sup>+</sup> is high (permeability ratio (P<sub>Na</sub>/P<sub>K</sub>) < 0.03), these structural differences suggest a more varied permeation and gating compared with K<sub>1p</sub> channels<sup>17,23</sup>.

**Members of the K<sub>2p</sub> channel subunit class.** The class of mammalian K<sub>2p</sub> channel subunits now includes 15 members (FIG. 1b). Although these subunits display the same structural arrangement, with four transmembrane segments, two P domains, an extended M1P1 extracellular loop and intracellular amino (N) and carboxyl (C) termini, they share low sequence identity outside the P regions<sup>17,24</sup> (FIG. 1b,c). The K<sub>2p</sub> channel subunits are subdivided into six main structural classes (BOX 1; FIG. 1b): TWIK1, TWIK2 and KCNK7 channels (functional expression of KCNK7 has not yet been reported); TREK1, TREK2 and TWIK-related arachidonic acid-stimulated (TRAAK) channels; TASK1, TASK3 and TASK5 channels (functional expression of TASK5 has not yet been reported); tandem-pore-domain halothane-inhibited K<sup>+</sup> 1 (THIK1) and THIK2 channels (functional expression of THIK2 has not yet been reported); TWIK-related alkaline-pH-activated K<sup>+</sup> 1 (TALK1), TALK2 and TASK2 channels; and the TWIK-related spinal cord K<sup>+</sup> (TRESK) channel, which is regulated by intracellular calcium (for reviews, see REFS 17–20,23). Evidence for heteromultimerization has been provided for TASK1 and TASK3 (REFS 25,26). At least two splice variants differing at their extreme N terminus have been identified for TREK1 (REFS 15,27,28). Various proteins that interact and modulate the function and localization of K<sub>2p</sub> channels have been recently identified (BOX 2).

**K<sub>2p</sub> permeation and voltage-dependency.** Unlike the yeast K<sub>2p</sub> channel Tok1, which contains eight transmembrane segments and two P domains in tandem<sup>29–32</sup>, mammalian K<sub>2p</sub> channels can pass large inward K<sup>+</sup> currents in elevated concentrations of extracellular K<sup>+</sup> at negative membrane potentials<sup>33–38</sup>. The rectification of a constitutively open K<sup>+</sup>-selective pore (leak channel) is a direct function of the difference in concentration of K<sup>+</sup> across the membrane, as expected from the Goldman–Hodgkin–Katz (GHK) constant field theory<sup>39</sup> (Supplementary information S1 (figure)). The GHK equation predicts an increase in conductance when ions flow across the membrane from the more concentrated side<sup>39</sup>. The equation also assumes that permeant ions do not interact with each other. However, K<sub>2p</sub> channels, as previously demonstrated for the classical K<sub>1p</sub> channels, fail to respect this rule of ionic independence, which indicates that the pore can simultaneously accommodate multiple ions and that their movement is influenced by each other<sup>40</sup>.

The GHK equation also anticipates that leak channels lack voltage and time dependency — that is, K<sup>+</sup> flow should remain stable over time<sup>39</sup>. However, several mammalian K<sub>2p</sub> channels, including TREK1, show both voltage- and time-dependent gating<sup>7,28,41,42</sup>. Indeed, most



**Figure 1 | Diversity and structural properties of the human K<sub>2p</sub> channels.** **a** | Predicted dimeric topology of two-pore-domain K<sup>+</sup> (K<sub>2p</sub>) channels. Each subunit is made up of four transmembrane segments and two pore-forming (P) domains that are arranged in tandem (top). Two subunits, which are either identical or different in sequence, associate to form a functional K<sub>2p</sub> channel (bottom). **b** | Phylogenetic tree of human K<sub>2p</sub> channels. The nomenclature, chromosomal localization and functional characteristics of each channel subunit are indicated. The highest region of homology between these subunits is found in the P regions. Six structural and functional subgroups are identified by different colours. **c** | The K<sup>+</sup> channel pore signature sequence is illustrated for the one-pore-domain (K<sub>1p</sub>) channel subunits of Kv1.1 and KcsA, and for the K<sub>2p</sub> channel subunits of TWIK1, TASK1 and TREK1. The residues phenylalanine (F) or leucine (L), rather than tyrosine (Y) are found in the P2 domain of K<sub>2p</sub> subunits. A, alanine; G, glycine; I, isoleucine; S, serine; T, threonine; V, valine.

**Box 1 | Structural and functional classes of K<sup>+</sup> channel subunits**

The versatility of neuronal electrical activity is largely regulated by the expression of different structural and functional classes of K<sup>+</sup> channels. More than 80 genes coding for the main K<sup>+</sup> channel  $\alpha$ -subunits have been identified in the human genome. The two transmembrane segment-containing one-pore-forming K<sup>+</sup> channel subunits encode the inward rectifiers. Some of these channels are constitutively active at rest, while the activity of others is influenced by modulators such as G proteins (G-protein-coupled inwardly rectifying K<sup>+</sup> channels), nucleotides (KATP) and polyamines (inward rectifier K<sup>+</sup> channels). Their conductance increases on hyperpolarization and, consequently, the inward K<sup>+</sup> currents recorded at potentials below the equilibrium potential are much larger than the outward K<sup>+</sup> currents recorded at depolarized potentials. Although the amplitude of the outward currents flowing through the inward rectifiers is limited, they profoundly influence the resting membrane potential. Inward rectifiers allow long action potentials to be generated, as they close upon depolarization.

The outward rectifiers encoded by the 6/7 transmembrane segment-containing, one pore-forming subunits open upon depolarization (voltage-gated K<sup>+</sup> (Kv) channels) and/or after intracellular Ca<sup>2+</sup> increase (BK and SK channels). Depolarization is sensed by the positively charged fourth transmembrane segment of Kv channels, which is coupled to the activation gates. Opening of the Kv channels is time-dependent, contributes to repolarization and terminates the action potential.

Soon after the identification of the *Saccharomyces cerevisiae* Tok1 K<sup>+</sup> channel, K<sub>2p</sub> channel subunits comprising four transmembrane segments and two P domains in tandem were cloned in mammals, *Drosophila melanogaster*, *Caenorhabditis elegans* and several plant species<sup>29–33,35,85,86</sup>. Mammalian K<sub>2p</sub> channels<sup>17–21</sup> show either a weak inward rectification (as is the case for TWIK1)<sup>33</sup>, an open rectification (as for TASK1)<sup>34</sup>, or an outward rectification (as for TREK1)<sup>6,41</sup>. Some channels, including TASK1 or TASK3, are constitutively open at rest<sup>34,87–90</sup>, whereas other channels, including TREK1, require physical or chemical stimulation to open<sup>6,47,50,58,59</sup>. A key feature of the K<sub>2p</sub> channels is that they open over the whole voltage range, and therefore qualify as background K<sup>+</sup> channels<sup>17,19,21,91</sup>.

K<sub>2p</sub> channels, including TASK1 and TREK1, present an instantaneous current component and a second time-dependent component in response to depolarization<sup>41–43</sup>. Furthermore, TREK1 shows a strong outward rectification in a symmetrical K<sup>+</sup> gradient instead of the linear current to voltage relationship predicted by the GHK equation<sup>28,41</sup> (**Supplementary information S1** (figure)). The outward rectification of TREK1 is attributed to an external Mg<sup>2+</sup> block, which is present at negative membrane potentials, and to an intrinsic voltage-dependent mechanism<sup>28,41</sup>. Transfection of TREK1 (either splice variant) in HEK cells surprisingly produces two populations of channels with different single-channel conductances (about 40 pS and 100 pS in a symmetrical K<sup>+</sup> gradient)<sup>27</sup>. Therefore, K<sub>2p</sub> channels diverge from the constant-field GHK current formulation and are characterized by complex permeation and gating mechanisms<sup>28,44</sup>.

**Regulation of voltage- and time-dependent gating.** The complex gating of K<sub>2p</sub> channels is regulated by various receptors and second messenger pathways. Deletional and chimeric analyses have shown that the C-terminal domain of TREK1 regulates the voltage- and time-dependent gating<sup>41</sup>. Phosphorylation by protein kinase A (PKA) of Ser333 in the distal part of the C-terminal domain has been proposed to be responsible for the interconversion between the voltage-dependent and the leak phenotype of rat TREK1 (REFS 28,45) (FIG. 2). However, in a significant number of recordings in cells expressing the TREK1 Ser333Ala mutant (which mimics the dephosphorylated state of the channel),

an intermediate phenotype between leak and voltage dependency was demonstrated<sup>28</sup>. This indicates that there must be additional mechanisms controlling TREK1 voltage-dependent gating. Furthermore, the activation kinetics and the voltage dependency of the mouse TREK1 Ser333Ala mutant do not differ from those of the wild-type channel<sup>41</sup>. These studies indicate that phosphorylation of Ser333 by PKA actually controls the number of active channels, rather than modulating mouse TREK1 voltage dependency<sup>6,41</sup>. Additionally, agonist-induced phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P<sub>2</sub>) hydrolysis shifts the voltage sensitivity of TREK1 channels towards depolarized potentials (see below), thus indicating a complex and dynamic regulation of TREK1 voltage-dependency<sup>46</sup>. The controversy about the role of the PKA site Ser333 in the regulation of TREK1 voltage dependency might actually result from the use of different species (rat TREK1 versus mouse TREK1), different experimental protocols (single-channel versus whole-cell recording) and different expression systems (transfected COS cells versus RNA-injected *Xenopus* oocytes)<sup>28,41</sup>.

**Polymodal activation of TREK1**

TREK1 can be activated by mechanical stimulation, intracellular acidosis and warm temperature, demonstrating that K<sub>2p</sub> channels are characterized by unconventional gating mechanisms<sup>6,15,47–49</sup> (FIG. 2).

**Mechanoactivation.** Patch-clamp studies have shown that membrane stretch reversibly induces TREK1 channel opening in both cell-attached and excised inside-out configurations<sup>6,50</sup>. Furthermore, opening of TREK1 occurs independently of intracellular Ca<sup>2+</sup> and ATP levels, suggesting a direct mechanism of activation<sup>6</sup>. In the inside-out patch configuration, positive pressure is significantly less effective than negative pressure at opening TREK1 channels, which indicates that a specific membrane deformation (convex curving) preferentially opens these channels<sup>6</sup> (**Supplementary information S2** (figure)). The relationship between channel activity and pressure is sigmoidal, with half-maximal activation at about –50 mm Hg<sup>7</sup>. At the whole-cell level, when the osmolarity of the external solution is increased, the basal TREK1 current amplitude is strongly reduced, which suggests that cellular volume also regulates channel activity (presumably by influencing tension in the cell membrane)<sup>6,47</sup>.

The number of active TREK1 channels is enhanced after treatment of cell-attached patches with agents that disrupt the actin cytoskeleton or after patch excision<sup>6,7,51</sup>. This suggests that mechanical force is likely to be transmitted to the channel through the membrane bilayer, with the cytoskeleton acting as a tonic repressor to limit channel activation by membrane tension<sup>6,24,51</sup>. Conversely, overexpression of *TREK1* has been shown to markedly alter the cytoskeletal network and induce the formation of membrane protrusions that are rich in actin and ezrin (a protein that links the cytoskeleton to the membrane)<sup>51</sup>. Thus, there is a dynamic interaction between TREK1 and the actin cytoskeleton that will influence both neuronal electrogenesis and synaptogenesis<sup>51</sup>.

**Rectification**

The property whereby current through a channel does not flow with the same ease from the inside as from the outside.

**Inward rectifiers**

Channels that allow long depolarizing responses, as they close during depolarizing pulses and open with steep voltage dependence upon hyperpolarization. They are called inward rectifiers because current flows through them more easily into than out of the cell.

**Outward rectifiers**

Channels that allow current to flow more easily out of the cell. Voltage-gated K<sup>+</sup> channels are outward rectifiers that shape the action potential duration.

**Intracellular acidosis**

A decrease in intracellular pH that occurs, for example, during brain ischaemia.



Box 2 | **K<sub>2p</sub> channel protein partners**

Interaction with auxiliary regulatory subunits further increases the molecular and functional diversity of K<sup>+</sup> channels. Several K<sub>2p</sub> channel protein partners that modulate channel activity, transport and degradation have recently been identified<sup>92</sup>.

A kinase anchoring protein 150 (AKAP150) interacts with TREK1 and changes the regulatory properties of the channel, as outlined in the main text<sup>52</sup>. In addition, a number of proteins interact with other K<sub>2p</sub> channels.

Enzymes in the plasma membrane that conjugate the small ubiquitin-like modifier (SUMO) assemble with TWIK1 (KCNK1, K<sub>2p1.1</sub>)<sup>93</sup>. Covalent modification at Lys274 by SUMO inhibits TWIK1 channel activity. Conversely, removal of this peptide by SUMO protease activates TWIK1. After the removal of SUMO, TWIK1 becomes a K<sup>+</sup>-selective, pH-sensitive, openly rectifying K<sup>+</sup> channel<sup>93</sup>. However, recent unpublished data (F. Lesage, unpublished observations) fail to confirm this regulation of TWIK1 by sumoylation. In both transfected COS cells and mRNA injected *Xenopus* oocytes, a weak inward rectifier K<sup>+</sup> channel activity was reported for TWIK1 (REF. 33). This current is recorded in the whole-cell configuration and without the addition of SUMO proteases<sup>33</sup>. The reasons for such major discrepancies between these studies remain unclear and this controversy has yet to be resolved.

EFA6, an exchange factor for the small G protein ADP-ribosylation factor 6 (ARF6), is another protein partner of TWIK1 (REF. 94). EFA6 interacts with TWIK1 only when it is bound to ARF6. Because ARF6 modulates endocytosis at the apical surface of epithelial cells, the ARF6–EFA6–TWIK1 association is probably important for TWIK1 internalization and recycling<sup>94</sup>.

The EF-hand superfamily protein p11 (S100A10, annexin 2 light chain) directly interacts with the carboxy (C)-terminal domain of TASK1 (REF. 95). Conflicting results concerning the exact site of interaction and the functional effect of P11 on TASK1 have been reported: P11 either promotes the expression of TASK1 at the plasma membrane, or it acts as a 'retention factor' that causes localization of TASK1 to the endoplasmic reticulum<sup>95,96</sup>.

Interaction of the scaffolding protein 14-3-3 with the C-terminal domain of TASK1 overcomes retention of the channel in the endoplasmic reticulum that is mediated by dibasic signals in TASK1 binding to β-coatamer protein<sup>97</sup>. Therefore, 14-3-3 promotes forward transport of TASK1 to the surface of the membrane<sup>97</sup>.

Vpu1, a human immunodeficiency virus (HIV)-1-encoded membrane protein that enhances the release of progeny virions from infected cells, interacts with TASK1 and induces its degradation<sup>98</sup>.

TREK1 channels show pronounced desensitization within 100 ms of membrane stretch<sup>7</sup>. This phenomenon is independent of the cytoskeleton and remains after patch excision, suggesting that it is dependent on the membrane and/or the channel itself. Mechanosensitive TREK1 currents can be assigned to a four-state cyclic kinetic model that includes three closed states and one open state, without the need to introduce adaptation of the stimulus, which therefore indicates the presence of an inactivation mechanism that is intrinsic to the channel<sup>7</sup>. Progressive deletion of the C-terminal domain of TREK1 gradually renders the channels more resistant to stretch, with a faster inactivation demonstrating that this domain is central to channel mechano-gating<sup>6,7,50</sup>.

**Sensitivity to internal pH.** Lowering the internal pH (pH<sub>i</sub>) shifts the pressure-activation relationship of TREK1 towards positive pressure values (the opposite effect to that of C-terminal deletion) and ultimately leads to channel opening at atmospheric pressure<sup>48,50</sup>. Moreover, TREK1 inactivation is gradually inhibited by intracellular acidosis<sup>7</sup>. Acidosis converts a TREK1 mechano-gated channel into a constitutively active, leak K<sup>+</sup> channel<sup>48,50</sup>. A negatively charged residue (Glu306) in

the proximal C-terminal domain acts as a proton sensor<sup>48</sup> (FIG. 3). Removing this negative charge by protonation is central to the regulation of TREK1 gating by pH<sub>i</sub><sup>48</sup>.

**Temperature sensitivity.** A progressive rise in temperature induces a gradual and reversible stimulation of TREK1 activity<sup>47,49</sup>. The maximal temperature sensitivity of TREK1 is observed between 32°C and 37°C, with a 0.9-fold increase in current amplitude per degree centigrade<sup>47</sup>. Patch excision results in the loss of the response of TREK1 to heat, whereas stretch still maximally opens channels<sup>47,49</sup>. Therefore, thermal activation of TREK1 crucially requires cell integrity, which suggests the existence of an indirect mechanism.

**Modulation of TREK1 by cellular lipids**

Besides its activation by physical stimuli, TREK1 is also upmodulated by various chemical stimuli such as cellular lipids<sup>21,24</sup>. Recent evidence suggests that both physical and chemical activations of TREK1 may be functionally linked.

**Phospholipids.** The cationic molecules polylysine or spermine, which have a high affinity for anionic phospholipids, inhibit TREK1 currents when these molecules are administered intracellularly on excised inside-out patches<sup>46</sup> (FIG. 3). However, channel activity can be restored and even stimulated by applying PtdIns(4,5)P<sub>2</sub> on the intracellular side of the channel<sup>43,46</sup>. Other inner leaflet phospholipids such as phosphatidylinositol, phosphatidylethanolamine or phosphatidylserine also increase the activity of TREK1 (REF. 43). The presence of a large polar head is not an absolute requirement, as phosphatidic acid, which only contains a phosphate group at position 3 of the glycerol, also stimulates TREK1 channel activity<sup>43</sup>. However, diacylglycerol cannot increase this activity, which indicates that the presence of a negative phosphate group is crucial<sup>43,46</sup>.

A cluster of five positive charges in the proximal C-terminal domain of TREK1, which encompass the proton sensor Glu306, is central to the effect of phospholipids<sup>43</sup> (FIG. 3). This cationic region is required for the interaction between the C-terminal domain of TREK1 and the inner leaflet of the plasma membrane<sup>43</sup>. The positively charged nature of this region is increased at acidic pH<sub>i</sub> (or by a Glu306Ala mutation), which probably favours a stronger electrostatic interaction with the inner leaflet phospholipids<sup>43</sup>. The proximal C-terminal domain is also involved in the interaction of TREK1 with the A kinase anchoring protein 150 (AKAP150) and contains a serine residue at position 300 that can be phosphorylated by protein kinase C (PKC)<sup>52,53</sup>.

Agonist-induced PtdIns(4,5)P<sub>2</sub> hydrolysis inhibits TREK1 activity by shifting the voltage-dependency of its activation towards more depolarized voltages<sup>46</sup> (FIG. 3). Conversely, stimulation of channel activity as a result of a shift in the voltage dependency of TREK1 currents towards more hyperpolarized voltages occurs in response to the addition of PtdIns(4,5)P<sub>2</sub> (REFS 43,46).

**Cell-attached patch configuration**

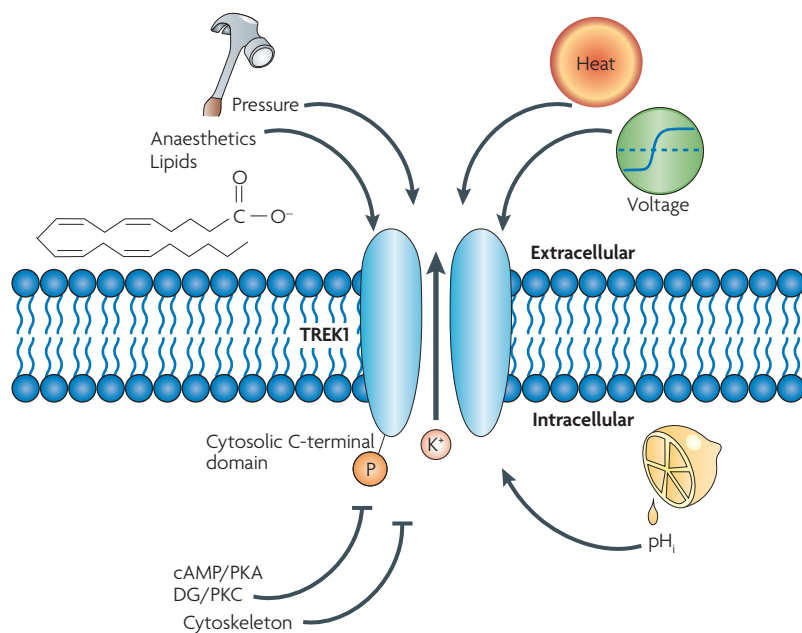
Recording configuration in which the patch of membrane at the tip of the recording electrode is not excised but remains attached to the cell. This configuration allows the measurement of the current flowing through the ion channels embedded in the electrically isolated membrane patch.

**Inside-out patch configuration**

Recording configuration in which the patch of membrane at the tip of the patch-clamp electrode is excised from the cell. The intracellular side of the channel is exposed to the bathing solution.

**Desensitization**

Decrease in the activity of a protein during maintained stimulation.



**Figure 2 | Polymodal activation of TREK1 by physical and chemical stimuli.** TREK1 is opened by stretch, heat, intracellular acidosis, depolarization, lipids and volatile general anaesthetics, and is closed by protein kinase A (PKA) and protein kinase C (PKC) phosphorylation pathways. TREK1 is tonically inhibited by the actin cytoskeleton. The cytosolic carboxy (C)-terminal domain has a key role in the regulation of TREK1 activity. Phosphorylation of Ser333 by PKA and phosphorylation of both Ser333 and Ser300 by PKC in this region inhibit TREK1 opening. cAMP, cyclic AMP; DG, diacylglycerol;  $pH_i$ , internal pH.

**Polyunsaturated fatty acids.** The TREK1 channel is reversibly opened by polyunsaturated fatty acids, such as arachidonic acid<sup>6</sup>. This activation is observed in excised patch configurations and in the presence of cyclooxygenase and lipoxygenase inhibitors, which indicates that the effect is direct<sup>24</sup>. Large chain length (docosahexaenoic acid C22:6 being the most potent polyunsaturated acid tested), a high degree of unsaturation (at least one double bond) and a negative charge are vital for channel stimulation<sup>6</sup>.

The bilayer–couple hypothesis, which has been put forward to explain the alteration in the shape of erythrocytes in the presence of amphipaths, assumes that the effects of these molecules derive entirely from interactions within the bilayer<sup>54,55</sup> (**Supplementary information S2** (figure)). Anionic amphipaths, including arachidonic acid, preferentially insert into the outer leaflet, presumably because of the natural asymmetric distribution of negatively charged phosphatidylserines in the inner leaflet<sup>54,55</sup>. This differential insertion produces a convex curvature of the membrane. By contrast, positively charged amphipaths are expected to preferentially insert into the inner leaflet of the bilayer and thereby generate a concave curvature<sup>54,55</sup>. Assuming that TREK1 is preferentially opened by negative (producing a convex curvature of the membrane) rather than positive mechanical pressure, it is anticipated from the bilayer–couple hypothesis that anionic amphipaths, such as trinitrophenol, will open the channel, whereas cationic amphipaths, including

**Inner leaflet**  
The inner layer of phospholipids in the plasma membrane.

**Polar head**  
Hydrophilic charged groups such as choline, ethanolamine, serine or inositol, bound to glycerol phosphate in membrane phospholipids.

**Amphipaths**  
A molecule with both hydrophobic and hydrophilic surfaces.

chlorpromazine, will close it; indeed, this has been experimentally observed<sup>6,24</sup>.

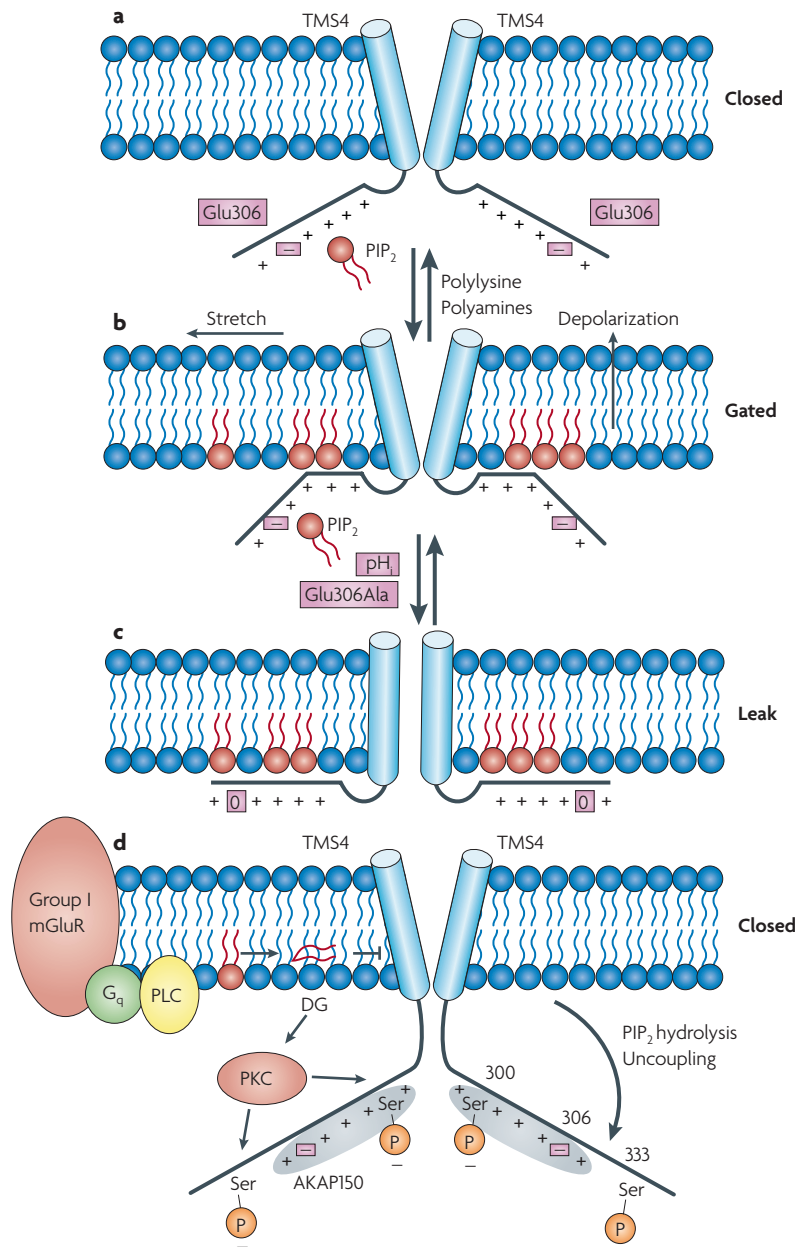
Deletional analysis demonstrates that the C terminus of TREK1 is crucial for the response to arachidonic acid, as previously demonstrated for the response of the channel to membrane stretch<sup>6</sup>. This suggests that activation of TREK1 by polyunsaturated fatty acids and stretch might be related (**Supplementary information S2** (figure)). However, the possible existence of a specific binding site for polyunsaturated fatty acids in the C-terminal domain of TREK1 cannot be entirely ruled out<sup>6,21,24</sup>. Interestingly, when the C terminus of TREK2 is replaced with that of TASK3, mechanosensitivity is preserved, but activation by arachidonic acid is lost<sup>56</sup>. Moreover, the TRAAK/TASK3 chimera remains sensitive to both stretch and arachidonic acid, demonstrating that different mechanisms are clearly at work for the activation of TREK1, TREK2 and TRAAK by membrane stretch and/or polyunsaturated fatty acids<sup>57</sup>.

**Lysophospholipids.** Unlike phospholipids, extracellular lysophospholipids, including lysophosphatidylcholine, open TREK1 (REF. 58). At low doses, arachidonic acid and lysophosphatidylcholine induce additive activation. The effect of lysophospholipids is dependent on the length of the carbonyl chain and the presence of a large polar head, but is independent of the global charge of the molecule<sup>58</sup>. The conical shape of extracellular lysophospholipids is the key parameter that allows them to stimulate TREK1. By contrast, intracellular lysophospholipids inhibit TREK1 activation<sup>24</sup>. The opposite membrane curvature produced by external (convex deformation) and internal (concave deformation) lysophospholipids may be responsible for this differential effect (**Supplementary information S2** (figure)).

TREK1 is also strongly activated by lysophosphatidic acid (LPA), but only when it is applied on the intracellular side of the channel following patch excision in the inside-out patch configuration<sup>59</sup>. LPA reversibly converts the voltage-,  $pH_i$ - and stretch-sensitive  $K^+$  channel TREK1 into a leak conductance channel<sup>59</sup>. Thus, TREK1 is a stretch- and lipid-sensitive  $K^+$  channel. The mechanical and chemical activations of TREK1 are proposed to be functionally coupled (FIG. 3; **Supplementary information S2** (figure)).

### Membrane receptors and second messengers

TREK1 is downmodulated by the stimulation of both  $G_s$ - and  $G_i$ -coupled membrane receptors. Recent studies have identified the second messenger pathways involved in this regulation. When co-expressed in transfected COS cells with the  $G_s$ -coupled 5-hydroxytryptamine 4 (5-HT<sub>4</sub>) receptor, serotonin inhibits TREK1 opening<sup>6,15</sup> (FIG. 4a). This effect is mimicked by a membrane-permeant derivative of cyclic AMP (cAMP) and is controlled by PKA-mediated phosphorylation of Ser333 in the C-terminal domain of TREK1 (REF. 6) (FIG. 4a). In the presence of AKAP150, inhibition of TREK1 by  $G_s$ -coupled receptors is enhanced, which suggests that AKAP150 might cluster TREK1 with PKA to facilitate PKA-mediated phosphorylation of TREK1 (REF. 52) (FIG. 3d).



**Figure 3 | Modulation of TREK1 by phosphatidylinositol-4,5-bisphosphate.** **a** | Intracellular polylysine or polyamines inhibit TREK1 activity by disrupting the interaction between the carboxy (C)-terminal domain of TREK1, which is positively charged, and the native negatively charged phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P<sub>2</sub>) in the inner leaflet of the bilayer. **b** | Intracellular exogenous PtdIns(4,5)P<sub>2</sub> (red; PIP<sub>2</sub>) promotes TREK1 opening. When the C-terminal domain is partially coupled to the membrane, TREK1 channel activity can be increased by stretch, intracellular acidosis and depolarization. **c** | Protonation of Glu306 within the C terminus of TREK1 increases the affinity of this domain for inner leaflet phospholipids. When the negative charge of Glu306 is titrated at acidic pH or when it is mutated by amino acid substitution (Glu306Ala), TREK1 becomes constitutively active. **d** | Stimulation of G<sub>q</sub>-coupled receptors, including the metabotropic glutamate receptors mGluR1 and mGluR5, activates phospholipase C (PLC) leading to hydrolysis of PtdIns(4,5)P<sub>2</sub> and inhibition of TREK1 activity. Several mechanisms occur: hydrolysis of PtdIns(4,5)P<sub>2</sub> and uncoupling of the C-terminal domain of TREK1 from the membrane; a direct inhibition of TREK1 by diacylglycerol (DG); and phosphorylation of Ser300 and Ser333 by protein kinase C (PKC). Negatively charged Glu306 (pink minus sign) and positively charged residues (black plus sign) in the PtdIns(4,5)P<sub>2</sub>-interacting domain are shown. A kinase anchoring protein 150 (AKAP150; grey) also interacts with this region. pH<sub>i</sub>, internal pH; TMS4, fourth transmembrane segment. Panels **a–c** reproduced, with permission, from *EMBO J*, REF. 43 © (2005) Macmillan Publishers Ltd.

Stimulation of G<sub>q</sub>-coupled receptors, including metabotropic glutamate receptors mGluR1 or mGluR5, inhibits TREK1 (REFS 46,53,60) (FIG. 3). Several pathways are involved: first, phospholipase C hydrolyses PtdIns(4,5)P<sub>2</sub> and provokes a shift in the voltage-dependency of TREK1 activation towards more depolarized voltages<sup>46</sup>; second, TREK1 may be directly inhibited by diacylglycerol<sup>60</sup>; and, finally, PKC sequentially phosphorylates Ser333 and Ser300 (located in the AKAP150 binding site)<sup>53</sup>. AKAP150 reverses the downmodulation of TREK1 by G<sub>q</sub>-coupled receptor stimulation (or stimulation with the phorbol ester phorbol-12-myristate-13-acetate); this suggests that it might prevent the access of PKC to the Ser300 phosphorylation site<sup>52</sup>.

Finally, nitric oxide donors, as well as 8-bromo-cGMP, increase TREK1 currents by protein kinase G-mediated phosphorylation of Ser351 (REF. 61). This effect is apparently very labile, as it can only be detected using the perforated whole-cell patch-clamp configuration<sup>61</sup>.

### Pharmacology of TREK1

TREK1 is unusual in terms of its pharmacology, as it is resistant to all the classical blockers of K<sub>IP</sub> channels, including tetraethylammonium and 4-aminopyridine<sup>6,15</sup>. However, it is inhibited by various other pharmacological agents, including the antidepressant selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine<sup>8,62</sup>. The effect of SSRIs seems to be direct, as the channels have been shown to be inhibited in the outside-out patch configuration<sup>62</sup>.

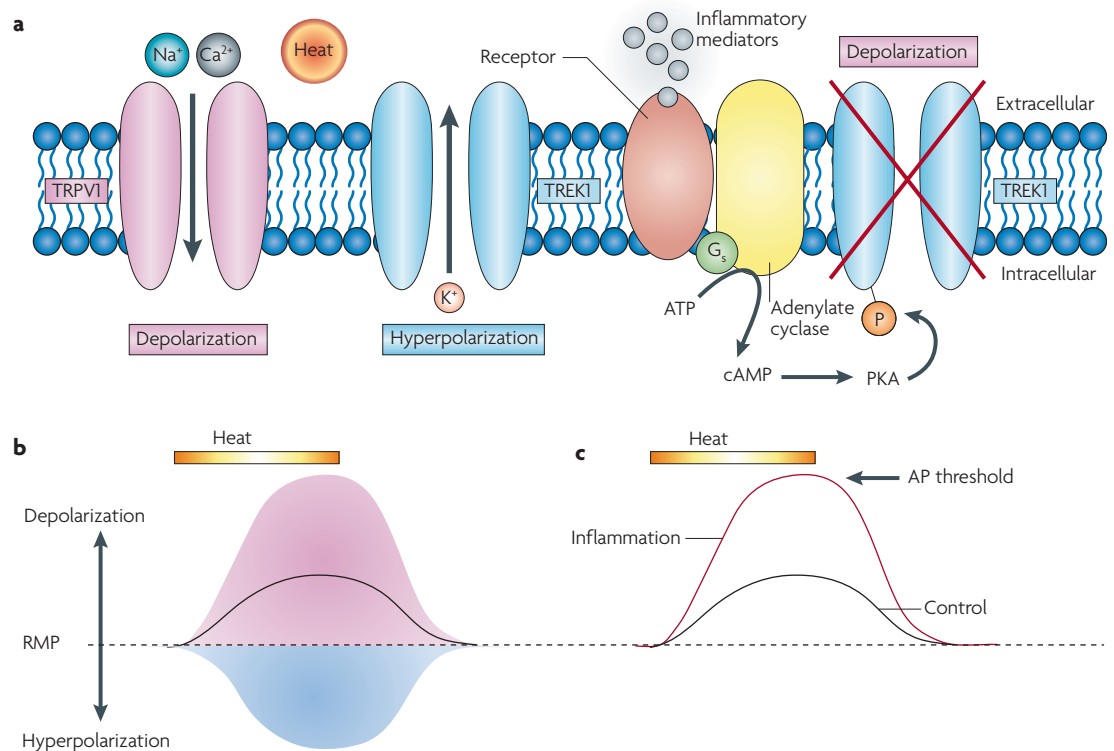
TREK1 is opened by another important class of pharmacological agents, the volatile general anaesthetics<sup>6,11,44,63,64</sup> (FIG. 5). Clinical doses of chloroform, diethyl ether, halothane and isoflurane open TREK1 (REF. 11). Nitrous oxide, xenon and cyclopropane, which are gaseous anaesthetics known for their potent analgesic action in addition to their euphoric and neuroprotective effects, similarly stimulate TREK1 at clinical doses<sup>12</sup>, as does chloral hydrate<sup>65</sup>. Stimulation of TREK1 activity by these anaesthetics occurs in excised patches, which suggests a direct effect. Again, the C-terminal domain of TREK1 also has a major role in its modulation by anaesthetics<sup>11,12,65</sup>.

### Insights from *Trek1*-knockout mice

In order to study the physiopathological role of TREK1 *in vivo*, its gene has been disrupted by homologous recombination in the mouse. *Trek1*<sup>-/-</sup> mutant mice are healthy, fertile and do not display any visible morphological abnormalities. However, using this knockout mouse model, recent studies indicate a central role for TREK1 in anaesthesia, neuroprotection, pain perception and depression.

**TREK1 and general anaesthesia.** The opening of TREK1 by volatile general anaesthetics induces cell hyperpolarization<sup>11</sup>. *Trek1*<sup>-/-</sup> mice show a marked decrease in sensitivity to chloroform, halothane, sevoflurane and desflurane<sup>10,11,44,63</sup>. A concentration of halothane that is sufficient to anaesthetize 100% of a population of wild-type mice has no effect in the knockout mice<sup>10</sup>. Although the neuronal pathways that





**Figure 4 | TREK1 is involved in polymodal pain perception.** **a** | TREK1 is a temperature-sensitive and mechano-gated K<sup>+</sup> channel that is co-expressed with the capsaicin-activated non-selective ion channel transient receptor potential subfamily V (vanilloid), member 1 (TRPV1) in small diameter sensory neurons (left). *Trek1*<sup>-/-</sup> mice show an increased thermal and mechanical hyperalgesia in inflammatory conditions. Inflammatory mediators, including prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), induce the inhibition of TREK1 via the cyclic AMP (cAMP)/protein kinase A (PKA) pathway. Ser333 in the carboxy (C)-terminal domain of TREK1 is phosphorylated by PKA (right). **b** | Heat stimulation simultaneously opens the depolarizing cationic non-selective channel TRPV1 (pink shading) and the hyperpolarizing K<sup>+</sup> channel TREK1 (blue shading). The resulting effect of heat stimulation on the membrane potential of dorsal root ganglia sensory neurons is shown by the black trace. The initial resting membrane potential (RMP) is shown by a black dashed line. **c** | Inhibition of TREK1 by membrane receptors and second messenger pathways during inflammation (shown by a red trace) is predicted to enhance the depolarizing effect of TRPV1, causing it to reach the action potential (AP) firing threshold, thus increasing the excitability of sensory neurons and pain perception.

are responsible remain to be determined, these data demonstrate that the opening of TREK1, along with the modulation of other targets including the GABA<sub>A</sub> receptors, contributes to the cellular mechanisms of general anaesthesia<sup>10,11,44,63</sup> (FIG. 5).

**TREK1, lipids and neuroprotection.** TREK1 is resistant to hypoxia and opens during chemical ischaemia<sup>66,67</sup>. *Trek1*<sup>-/-</sup> mice are more sensitive to both ischaemia and epilepsy than wild-type mice<sup>10,63</sup>. The polyunsaturated fatty acid linolenate or lysophospholipids administered either intracerebroventricularly or intravenously are neuroprotective against global ischaemia and kainate-induced seizures<sup>68-71</sup>, yet such neuroprotection is absent in *Trek1*<sup>-/-</sup> mice, which indicates that protection by polyunsaturated fatty acids is mediated by TREK1 opening<sup>10,63</sup>.

During brain ischaemia, arachidonic acid is released, the pHi falls and neurons swell. These pathological alterations might contribute to the opening of TREK1. The subsequent hyperpolarization of both presynaptic neurons (which would limit the opening of voltage-

dependent Ca<sup>2+</sup> channels) and of postsynaptic neurons (which would increase the block of NMDA (N-methyl-D-aspartate) receptors by Mg<sup>2+</sup>) will protect neurons against glutamate excitotoxicity<sup>63</sup> (FIG. 5). It is interesting to note that various other neuroprotective agents, including riluzole, nitrous oxide and xenon, are also potent openers of TREK1 (REFS 12,72).

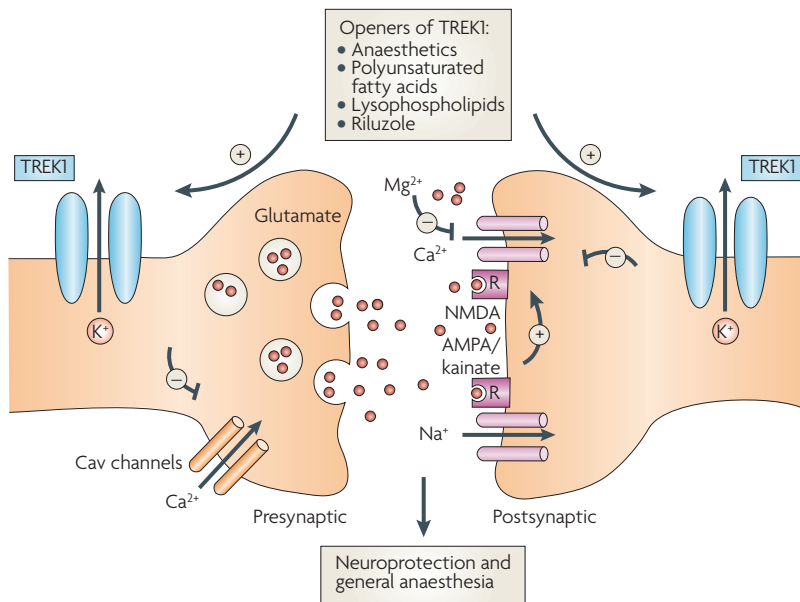
**TREK1 and pain perception.** TREK1 is colocalized with the capsaicin-activated (the active ingredient in chili peppers) non-selective transient receptor potential channel, subfamily V (vanilloid), member 1 (TRPV1) in both small and medium-sized sensory neurons of mouse DRG cells<sup>9,16,47</sup> (FIG. 4). TREK1 can be opened by nociceptive stimuli, including pressure and heat<sup>6,7,47</sup>. *Trek1*<sup>-/-</sup> mice are more sensitive than wild-type mice to painful heat stimulation with an intensity near the threshold between non-painful and painful heat<sup>9</sup>. Moreover, experiments using single polymodal C-fibres demonstrate that DRG neurons from *Trek1*<sup>-/-</sup> mice have increased sensitivity to heat stimulation at 30–45°C (REF. 9). However, no difference is observed in the sensitivity to cold induced

**Outside-out patch configuration**

A variant of the patch-clamp technique, in which a patch of plasma membrane is excised from the cell. The outside of the membrane is exposed to the bathing solution.

**Polymodal C-fibres**

Non-myelinated axons characterized by a slow conduction. Polymodal nociceptors are activated by high intensity mechanical, chemical and thermal stimuli, involving non-myelinated C-fibres conducting delayed pain.



**Figure 5 | Role of TREK1 in general anaesthesia and neuroprotection.** TREK1 is expressed in both pre- and postsynaptic neurons. Opening of TREK1 in response to anaesthetics, polyunsaturated fatty acids, lysophospholipids and neuroprotective agents such as riluzole, and the consequent hyperpolarization of presynaptic neurons, leads to the closure of voltage-dependent calcium (Cav) channels. The decrease in intracellular calcium reduces the release of neurotoxic glutamate. At the postsynaptic level, hyperpolarization caused by TREK1 opening increases the voltage-dependent  $Mg^{2+}$  blockage of the NMDA (N-methyl-D-aspartate) receptor (R) and therefore reduces neurotransmission and glutamate excitotoxicity. The postsynaptic hyperpolarization will also tend to antagonize the depolarizing effect of the AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)/kainate receptor activation that is required to remove the  $Mg^{2+}$  blockage of the NMDA receptor.

by a drop of acetone to the dorsal surface of the paw, suggesting that TREK1 is probably not involved in cold sensing<sup>9</sup>.

Touching the skin with von Frey hairs of increasing stiffness revealed that *Trek1*<sup>-/-</sup> mice are more sensitive to mechanical stimulus than are wild-type mice<sup>9</sup>. Thus, *Trek1* deletion results in allodynia, suggesting that this  $K_{2p}$  channel is probably important for tuning the mechanosensitivity of nociceptors. Chronic pain syndromes involve the sensitization of nociceptors and thermal receptors by inflammatory mediators. Interestingly, inflammation-induced mechanical and thermal hyperalgesia is lower in *Trek1*<sup>-/-</sup> mice than in wild-type mice, suggesting that TREK1 is, at least in part, involved in the peripheral sensitization of nociceptors during inflammation<sup>9</sup> (FIG. 4).

DRG neurons express various TRP ion channels that sense hot, warm and cold temperatures<sup>73,74</sup>. For example, TRPV3 and TRPV4 sense warm (> 30°C) and TRPV1 senses hot (> 43°C) temperatures<sup>73,74</sup>. The  $Q_{10}$  (the ratio of reaction rates for a 10°C increase in temperature) of TRPV1 gating is estimated to be about 10–20, while a  $Q_{10}$  of about 5–7 has been reported for TREK1 (REFS 47,49). These results suggest that TREK1, although less sensitive than TRP channels to temperature, modulates the excitability of nociceptors, probably by opposing the depolarization that results from the opening of non-selective TRP channels, including TRPV1 (FIG. 4b–c).

These findings make TREK1 an attractive pharmacological target for the development of new types of analgesic drugs.

**TREK1 and depression.** Neither reflex (cornea, pinna and righting reflexes) nor cognitive functions are significantly altered in *Trek1*<sup>-/-</sup> mice<sup>8,10</sup>. However, TREK1 is reported to have an important functional role in mood regulation<sup>8</sup>. In the Porsolt forced swim test (FST)<sup>75</sup>, *Trek1*<sup>-/-</sup> mice swam for much longer than wild-type mice before feeling despair and giving up<sup>8</sup>. Administration of the antidepressants fluoxetine or paroxetine in the FST reduce the immobility time of wild-type mice (that is, they have an antidepressant action), but fail to affect *Trek1*<sup>-/-</sup> mice<sup>8</sup>. Various other behavioural tests used to assay for the antidepressant effects of drugs confirmed the ‘antidepressant’ state of the *Trek1*<sup>-/-</sup> mice<sup>8</sup>.

TREK1 is expressed in the serotonergic neurons of the midbrain dorsal raphe nucleus<sup>8</sup> (FIG. 6). Importantly, combined treatment with fluoxetine and the tryptophan hydroxylase inhibitor p-chlorophenylalanine methyl ester, which deplete serotonin from the nerve terminals, completely eliminates the antidepressant phenotype of the *Trek1*<sup>-/-</sup> mice<sup>8</sup>. Moreover, the firing rate of neurons from the dorsal raphe nucleus is more than twofold higher in *Trek1*<sup>-/-</sup> mice compared with wild-type mice<sup>8</sup>. These results indicate that TREK1 has a major role in mood regulation<sup>75</sup>.

In the neurons of the dorsal raphe nucleus, 5-HT<sub>1A</sub> autoreceptor stimulation reduces neuronal firing and, consequently, serotonin neurotransmission<sup>75</sup> (FIG. 6). Inhibition of adenylate cyclase and activation of G-protein-coupled inwardly rectifying  $K^+$  channels are involved in this negative feedback<sup>75</sup>. The decrease in cAMP concentration (as a result of reduced adenylate cyclase activity) in the serotonergic neurons might also lead to TREK1 channel opening because of a consequent reduction in phosphorylation of Ser333 by PKA<sup>28,76</sup>. According to this model, the knockout of *Trek1* would reduce the serotonin negative feedback on presynaptic neurons, resulting in increased serotonin neurotransmission and the antidepressant phenotype<sup>75</sup> (FIG. 6). Although both TREK1 and TRAAK are expressed in dorsal raphe serotonergic neurons, the mood of only the *Trek1*<sup>-/-</sup> mice is altered<sup>8</sup>, suggesting that the specific functional properties of TREK1, such as its regulation by cAMP and PKA (TRAAK is not modulated by the cAMP/PKA pathway) are probably involved<sup>6,15</sup>. Direct inhibition of TREK1 by clinical doses of fluoxetine and related agents (as outlined above) might also contribute to enhanced presynaptic excitability and, along with inhibition of serotonin reuptake, will increase serotonin neurotransmission to produce an antidepressant effect<sup>8,62,75</sup>. Specific TREK1 antagonists might therefore be useful agents for the treatment of depression.

**Presynaptic modulation**

TREK1 is expressed both pre- and postsynaptically<sup>47,71</sup>. Therefore, regulation of TREK1 opening in presynaptic neurons is anticipated to affect neurotransmitter release.

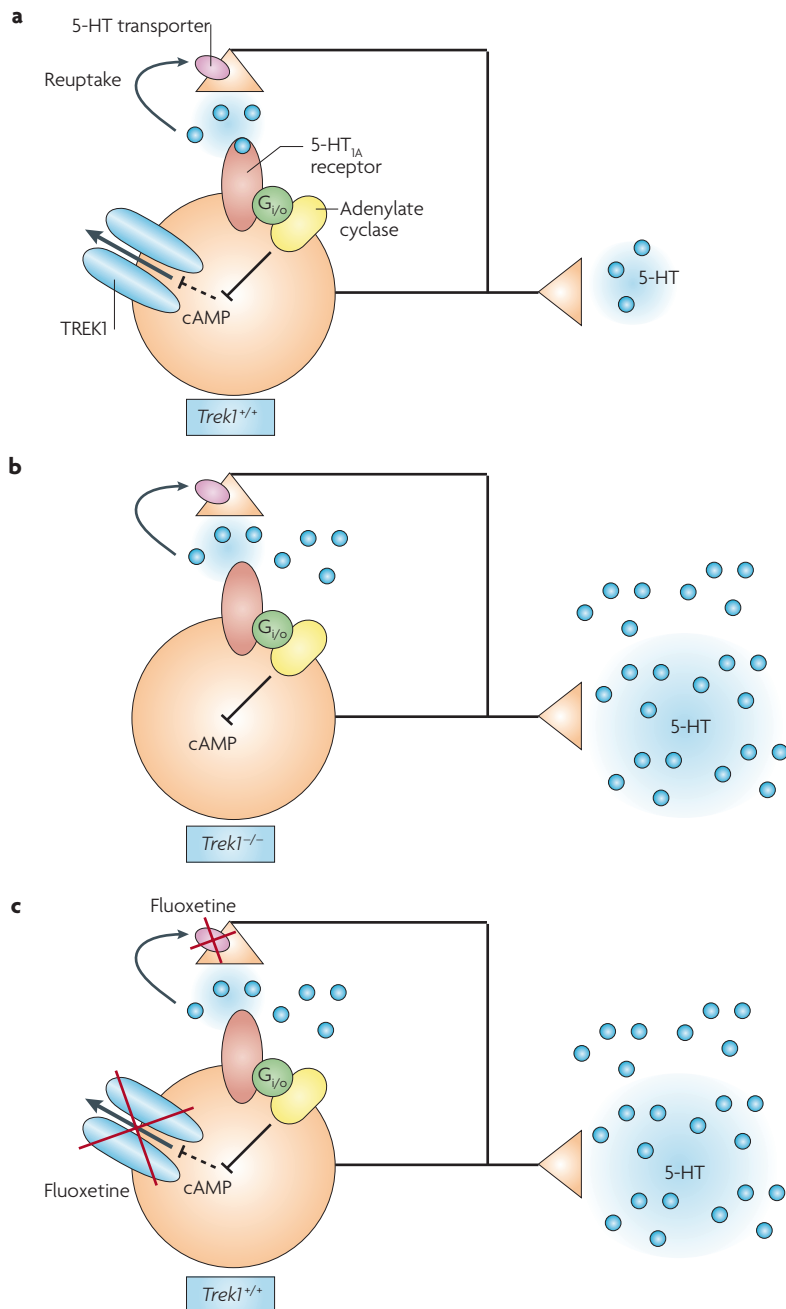
**Allodynia**

The perception of a stimulus as painful when previously the same stimulus was reported to be non-painful.

**Porsolt forced swim test**

A method to estimate behavioural despair in a stressful and inescapable situation. Mice rapidly adopt a characteristic immobile posture when they are forced to swim in a water tank. Immobility is considered to be a state of ‘lowered mood’ in which the animal has given up hope of finding an exit and is resigned to the stressful situation.





**Figure 6 | Role of TREK1 in feedback inhibition of serotonergic dorsal raphe neurons and the response to antidepressants. a** | Stimulation of the serotonin 5-HT<sub>1A</sub> receptor (red) inhibits adenylate cyclase (yellow) via the G<sub>vo</sub> protein (green). Consequent lowering of the level of intracellular cyclic AMP (cAMP) will contribute to enhanced TREK1 (blue) opening due to a decrease in the protein kinase A-mediated phosphorylation. TREK1 opening leads to cell hyperpolarization, reduction in the firing rate and, therefore, decreased serotonin release from dorsal raphe neurons. Serotonin is removed from the synaptic space by serotonin transporters expressed in the dorsal raphe neurons. Serotonin is involved in the regulation of several brain functions, including depression, mood, emotion, aggression, sleep, appetite, anxiety, memory and perception. **b** | In dorsal raphe neurons from *Trek1*<sup>-/-</sup> mice, feedback hyperpolarization is predicted to be reduced, thereby increasing serotonin release. **c** | Increased levels of serotonin in these pathways, brought about by reducing serotonin reuptake with serotonin uptake inhibitors, including fluoxetine, is one therapeutic approach to treating depression. Additionally, direct inhibition of TREK1 by selective serotonin reuptake inhibitors will also contribute to increased excitability of dorsal raphe neurons and serotonin release.

TREK1 and TREK2 are the hypothetical functional homologues of the *Aplysia* presynaptic S-type K<sup>+</sup> channel that is involved in behavioural sensitization<sup>6</sup>. This molluscan S channel is a resting, outwardly rectifying, weak voltage- and time-dependent, calcium-independent, 45–55 pS K<sup>+</sup> channel that shares all the properties of TREK1, including sensitivity to volatile anaesthetics and activation by membrane stretch<sup>77</sup>. In *Aplysia*, sensitization of the gill-withdrawal reflex by noxious stimulus to the tail is caused by presynaptic facilitation of transmission (that is, an increase in the release of neurotransmitter) between the sensory and the motor neurons of the reflex<sup>77</sup>. Serotonin is released by facilitating interneurons and inhibits a resting K<sup>+</sup> conductance (mediated by S-type K<sup>+</sup> channels) in presynaptic sensory terminals through phosphorylation of the K<sup>+</sup> channels by the cAMP/PKA pathway<sup>2</sup>. Inhibition of the S channels enhances the duration of the action potential, allowing more calcium to flow into the terminal, and thereby increasing neurotransmitter release<sup>77</sup>. These studies in *Aplysia* provided the first evidence for heterosynaptic facilitation and for a direct role of a second messenger pathway, involving phosphorylation of ion channels, in the regulation of synaptic transmission<sup>1,2,78</sup>. Conversely, the neuropeptide FMRFamide released by inhibitory interneurons opens the S channels through the arachidonic acid pathway, decreases the duration of the action potential, reduces transmitter release from the sensory neuron terminals and leads to presynaptic and behavioural inhibition (that is, decrease in the gill-withdrawal reflex)<sup>79,80</sup>.

Both the *Aplysia* S-type K<sup>+</sup> channel and mammalian TREK1 are involved in controlling the excitability of presynaptic neurons through the pathway mediated by serotonin, cAMP and PKA<sup>2,75</sup>. However, in the dorsal raphe neurons, serotonin probably opens TREK1 through the G<sub>vo</sub> pathway, whereas serotonin closes the S-type K<sup>+</sup> channel through the G<sub>s</sub> pathway in molluscan sensory neurons. The role of the serotonin-sensitive TREK-like channels in presynaptic modulation is, therefore, conserved during evolution, which itself implies a key functional role for these background K<sup>+</sup> channels.

### Conclusion and perspectives

*Trek1*-knockout mice provide very strong evidence for the important functional role of this K<sup>+</sup> channel in both the CNS and PNS<sup>8–10</sup>. This ‘unconventional’ K<sup>+</sup> channel, with its complex gating and regulation by membrane receptors and second messengers, is central to ischaemic and epileptic neuroprotection, pain sensing and depression. Furthermore, TREK1 is opened by neuroprotective agents and volatile and gaseous anaesthetics, whereas it is inhibited by clinical doses of antidepressant drugs, suggesting that this channel is an important pharmacological target<sup>44,63,64,75</sup>.

TREK1 activity is stimulated by membrane stretch, heat, intracellular acidosis and cellular lipids. Therefore, TREK1 qualifies as a polymodal sensory ion channel, which integrates multiple physical and chemical stimuli. The C-terminal domain of this channel has a major role in the transduction of these stimuli into channel opening. The proposed model states that a tight dynamic

interaction of this domain with the inner leaflet of the plasma membrane is central to the mechanism of channel gating and regulation by membrane receptors and second messenger pathways.

These studies have contributed to a better understanding of the molecular basis of mechanotransduction<sup>81,82</sup>. TREK1 was the first mammalian mechano-gated ion channel to be cloned, expressed and characterized<sup>6,15</sup>. Moreover, work on TREK1 has demonstrated that lipid modulation and stretch activation are closely linked. Interestingly, recent evidence has shown that lipids are also intimately involved in the opening and closing of other mechanosensitive channels in fungal, plant and animal species<sup>83</sup>. It is also of interest to note that the cytosolic C-terminal charged cluster RKKEE of the bacterial stretch- and lipid-sensitive channel MscL also functions as a pH sensor, indicating that such mechanisms may be conserved throughout evolution<sup>84</sup>. The working hypothesis proposed for TREK1 gating and modulation by pH and lipids (FIG. 3) could thus be applicable to other types of mechanosensitive ion channels implicated in various sensory functions, including touch sensitivity and hearing<sup>7,43</sup>.

Although major progress has been made in the characterization of this K<sub>2p</sub> channel, several important questions remain. What makes TREK1 mechanosensitive, and how is the mechanical force transmitted to the channel? Where is the activation gate, and what controls inactivation? The role of the cytoskeleton in modulating TREK1 mechanosensitivity is also unclear; so too is the effect of TREK1 on the actin cytoskeleton. What makes the channel sensitive to temperature is unknown, as is the location of the voltage sensor, and it is not yet understood how phosphorylation of Ser300 and Ser333 regulates TREK1 opening. What is the mechanism of TREK1 activation by gaseous and volatile anaesthetics? This article has focused on TREK1, but what is the physiological role of the functional homologues TREK2 and TRAAK? Is there an involvement of these K<sub>2p</sub> channels in human genetic diseases? As additional K<sub>2p</sub> channel transgenic animals become available, the roles of other members of this intriguing family of ion channels in physiology, pharmacology and pathology should soon become clearer. At the pharmacological level, future studies will be needed to identify high-affinity channel blockers and openers that might prove useful for the treatment of a range of neuronal disease states.

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#### Competing interests statement

The author declares no competing financial interests.

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