REVIEW

Tandem pore TWIK-related potassium channels and neuroprotection

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Abstract

TWIK-related potassium channels (TREK) belong to a subfamily of the two-pore domain potassium channels family with three members, TREK1, TREK2 and TWIK-related arachidonic acid-activated potassium channels. The two-pore domain potassium channels is the last big family of channels being discovered, therefore it is not surprising that most of the information we know about TREK channels predominantly comes from the study of heterologously expressed channels. Notwithstanding, in this review we pay special attention to the limited amount of information available on native TREK-like channels and real neurons in relation to neuroprotection. Mainly we focus on the role of free fatty acids, lysophospholipids and other neuroprotective agents like riluzole in the modulation of TREK channels, emphasizing on how important this modulation may be for the development of new therapies against neuropathic pain, depression, schizophrenia, epilepsy, ischemia and cardiac complications.

Key Words: *TREK channels; TREK-1; TREK-2; TRAAK; neuroprotection; free fatty acids; lysophospholipids; riluzole*

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Introduction

Several good reviews have partially dealt with the relationship between TWIK-related potassium channel (TREK) channels and neuroprotection (Lesage and Lazdunski, 2000; Patel and Honore, 2001; Patel et al., 2001; Kim, 2003; Lesage, 2003; Franks and Honore, 2004; Honore, 2007; Lotshaw, 2007; Mathie and Veale, 2007; Bayliss and Barrett, 2008; Dedman et al., 2009; Gurney and Manoury, 2009; Sabbadini and Yost, 2009; Enyedi and Czirjak, 2010; Es-Salah-Lamoureux et al., 2010; Mathie et al., 2010; Noël et al., 2011; Lamas, 2012; Ehling et al., 2015; Djillani et al., 2019). We believe that there is now enough information to dedicate a complete review to this important topic.

Neuroprotective factors are a heterogeneous group of substances with protective activity on the damaged or undamaged nervous system. Different classes of compounds exert neuroprotective actions to the central nervous system. Endogenous molecules like certain amino acids (*e.g.*, taurine), endorphins, fatty acids and estrogens (Lauritzen et al., 2000; Wu et al., 2009; Galano et al., 2011; Spence and Voskuhl, 2012), and also synthetic compounds like memantine, riluzole or nifedipine (Jain, 2000; Vallazza-Deschamps et al., 2005; Cheah et al., 2010) have been proved neuroprotective. The action mechanism of these molecules is very diverse but in most cases implies the activation or inhibition of G-protein coupled metabotropic receptors and voltage- and ligand-gated ion channels. Among these, potassium channels are common targets for neuroprotective molecules. Particularly the family of two-pore domain potassium (K2P) channels, being key mediators of the resting membrane potential and therefore having a direct control over the excitability of the plasma membrane, emerged as the final effectors of numerous neuroprotective compounds (Mathie and Veale, 2007; Es-Salah-Lamoureux et al., 2010).

TREK is one of the six subfamilies in which K2P channels are divided. Although probably better known by their mechanical sensitivity, soon after the discovery of TREK channels (Fink et al., 1996) it was clear that besides many physical and chemical stimuli (Fink et al., 1998; Patel et al., 1998; Bang et al., 2000; Lesage et al., 2000b), the three members of this subfamily (TREK1, TREK2 and TWIK-related arachidonic acid-activated potassium channels (TRAAK)) were modulated by several neuroprotective substances.

In the present review, we focus on how TREK channels are affected by different neuroprotective factors. In particular, we look into the well-studied effect that fatty acids, lysophospholipids and riluzole exert on these channels. We also discuss the potential of TREK channels as therapeutic targets for the treatment of different neuronal and cardiac diseases.

Free Fatty Acids

Polyunsaturated fatty acids (PUFAs) like arachidonic (AA), linolenic (LLA) or docosahexaenoic (DHA) acids, but not saturated fatty acids (**Figure 1** and **Table 1**), are known to be potentially useful for the treatment of several cardiac and cerebral pathologies. They prevent cellular death in *in vivo* and *in vitro* models of global ischemia, neurotoxicity (induced by kainate or by a magnesium-depleted glycine-supplemented medium) and status epilepticus (Lauritzen et al., 2000; Blondeau et al., 2002). The main mechanism of action implies their interaction (blockade) with glutamatergic neurotransmission, where the activation of TREK channels expressed pre and postsynaptically in glutamatergic synapses might be responsible for such a blockade by hyperpolarizing both pre and postsynaptic membranes (Lauritzen et al., 2000; Hennebelle et al., 2014). Notwithstanding, PUFAs can have multiple effects on other

channels, receptors or transporters like voltage-sensitive potassium, sodium and calcium channels, glutamate transporters or N-methyl-D-aspartic acid receptors for example (Boland and Drzewiecki, 2008; Yazdi et al., 2016; Elinder and Liin, 2017).

Before K2P channels were discovered, Kim et al. (1995) reported a family of new potassium channels (named KAA or KFA) with at least three components, being their main characteristic a strong activation by AA and other unsaturated free fatty acids. Besides their activation by PUFAs, these channels share several key features with the TREK subfamily, like activation by membrane stretch, marked open-channel noise, large conductance at negative voltages and insensitivity to classical potassium channel blockers, thus suggesting a common molecular background (Bang et al., 2000).

TWIK-related potassium channel 1

Heterologously expressed channels

Single channel: In COS cells (cell line derived from kidney tissue), AA activates heterologously expressed TREK1 channels strongly and dose-dependently, when recorded in outside-out and inside-out patches (Maingret et al., 2000a). A similar result was obtained with two other polyunsaturated fatty acids (docosahexaenoate and oleate) in the outside-out configuration, strongly suggesting a direct effect on the channel or the membrane (Patel et al., 1998; Maingret et al., 2000a, b; Honore et al., 2002; Kang and Kim, 2006; Sandoz et al., 2006). Importantly, the effect of AA was maintained in COS-expressed channels at 37°C in cell-attached and inside-out patches (Kang et al., 2005). Consistently, the activity of TREK1 channels recorded in a macropatch, using the cell-attached patch configuration, was slowly and weakly activated by AA (Maingret et al., 2000a) but controversially, very strong activation of human TREK1 (hTREK1) channels recorded in similar conditions has also been reported (Miller et al., 2003). On the contrary, palmitate and arachidate, saturated fatty acids, had no effect on COS-expressed TREK1 channels in outside-out patches (Patel et al., 1998).

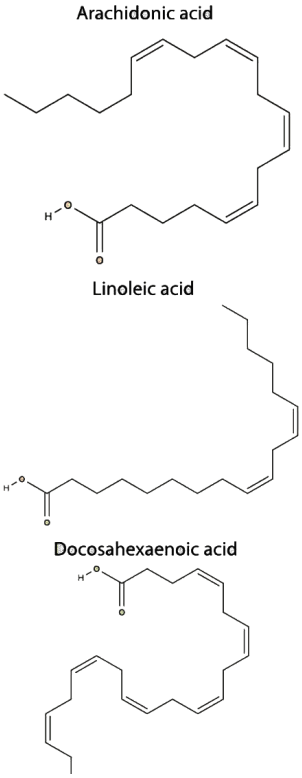

Figure 1 Major polyunsaturated fatty acids activating TWIK-related potassium channels.
See Table 1 for more details.

Macroscopic currents: Whole-cell TREK1 currents (expressed in COS, HEK cells (human embryonic kidney cells) or in oocytes) were strongly, reversibly and dose-dependently potentiated by AA, being the AA-sensitive current outwardly rectifying but without apparent voltage threshold (Patel et al., 1998; Maingret et al., 1999b, 2000a; Meadows et al., 2000; Honore et al., 2002; Miller et al., 2003; Takahira et al., 2005; Chemin et al., 2007; Cohen et al., 2009; Mazella et al., 2010; Moha ou Maati et al., 2011; Moha Ou Maati et al., 2012; Djillani et al., 2017; Soussia et al., 2018; Woo et al., 2018). Other PUFAs, like DHA and LLA acids, also activated heterologously expressed TREK1 channels (Moha ou Maati et al., 2011). Like in single-channel recordings, saturated fatty acids (myristate, palmitate, stearate, arachidate) had no effect on the TREK1 channels expressed in COS cells (Maingret et al., 2000a).

Natively expressed channels

Single channel: Rat atrial myocytes express a non-inactivating potassium current called IKAA which, being strongly activated by AA, has been ascribed to the activation of TREK1 channels. Putative TREK1 single-channel currents showed outwardly rectifying current-voltage (IV) curves both in physiological and in symmetrical potassium concentrations, when recorded in inside-out patches (Terrenoire et al., 2001). Similar results using AA were obtained in cultured supraoptic cells, striatal, ventricular cardiomyocytes and dorsal root ganglion (DRG) neurons in inside-out patches (Han et al., 2003; Heurteaux et al., 2004; Alloui et al., 2006; Kang and Kim, 2006; Li et al., 2006; La and Gebhart, 2011) both at room temperature and at 37°C (Kang et al., 2005).

Table 1 Reported effect of different fatty acids on channels of the TREK subfamily

Fatty acid	Type	TREK1	TREK2	TRAAK
Stearic acid	Saturated	NE: 20 μM^N (Moha ou Maati et al., 2011)	NE: 20 μM^N (Gnatenco et al., 2002)	NE: 10 μM^H (Fink et al., 1998)
Oleic acid	Mono unsaturated	NA	A: 20 μM^H (Bang et al., 2000)	A: 20 μM^H (Fink et al., 1998)
Linolelaidic acid	Polyunsaturated	NE: 20 μM^N (Moha ou Maati et al., 2011)	NA	NA
Docosahexaenoic acid	Polyunsaturated	A: 10 μM^H (Moha ou Maati et al., 2011)	A: 20 μM^H (Bang et al., 2000)	A: 20 μM^H (Fink et al., 1998)
Arachidonic acid	Polyunsaturated	A: 10 μM^H (Patel et al., 1998)	A: 10 μM^N (Ferroni et al., 2003)	A: 20 μM^H (Takahira et al., 2005)
Linoleic acid	Polyunsaturated	A: 20 μM^N (Moha ou Maati et al., 2011)	A: 20 μM^H (Bang et al., 2000)	A: 20 μM^H (Fink et al., 1998)
Linolenic acid	Polyunsaturated	A: 10 μM^H (Moha ou Maati et al., 2011)	A: 20 μM^H (Bang et al., 2000)	A: 20 μM^H (Fink et al., 1998)

The tested concentration is indicated. A: Activation; N: tested on native channels; NA: not addressed; NE: no effect; H: tested on heterologously expressed channels; TRAAK: TWIK-related arachidonic acid-activated potassium channels; TREK: TWIK-related potassium channels.

Protection of cerebellar granule cells by AA, DHA and LLA acids, in a model of excitotoxicity, has been attributed to the activation of putative TREK1/TRAAK channels. This effect was dependent on the equilibrium potential for potassium suggesting that PUFAs exert their effect by hyperpolarizing the neuronal membrane (Lauritzen et al., 2000). Activation of potassium channels (in outside-out patches) with properties similar to those shown by heterologously expressed TREK1/TRAAK channels was also shown in this work.

Similarly, bovine TREK1 (bTREK1) channels natively expressed in bovine adrenal zona fasciculata cells were activated by AA and linoleic acid (LA), but not by linolelaidic acid (Danthi et al., 2003). Furthermore, TREK1-like currents were activated by AA in rat urinary bladder smooth muscle cells, where only this member of the TREK subfamily is expressed (Fukasaku et al., 2016).

Macroscopic currents: Using whole-cell patch-clamp recordings, Danthi et al. (2003) showed that polyunsaturated AA and LA acid increased de activity of bTREK1 in bovine adrenal cells dramatically, dose-dependently and reversibly but slowly (several minutes). The current activated by AA is strongly outward-rectifying and reverses at the equilibrium potential for potassium. Although reduced, this rectification persists at symmetrical concentrations of potassium (Danthi et al., 2003). AA also enhances whole-cell TREK1-like currents in DRG neurons, hippocampal astrocytes, CA3 hippocampal neurons in slices and corticotrope cells (Alloui et al., 2006; Seifert et al., 2009; Mazella et al., 2010; Lee et al., 2011). On the contrary, neither the trans-polyunsaturated (linolelaidic acid) nor saturated fatty acids (steric acid) affected native TREK currents in adrenal cells (Danthi et al., 2003).

TWIK-related potassium channel 2

Heterologously expressed channels

Single channel: AA dose-dependently increased the activity of COS-expressed TREK2 channels when applied in inside- and outside-out patches. Similar results were obtained with other unsaturated free fatty acids like LA and oleic acid, and also with DHA, eicosapentaenoic and LLA acids when applied to inside-out patches (Bang et al., 2000; Kim et al., 2001b; Chemin et al., 2003; Kang and Kim, 2006). Studies reported two TREK2 phenotypes (TREK2-S and TREK2-L) with different conductances when expressed in COS, HEK, HeLa (human cell line derived from a cervical cancer) cells and *Xenopus* oocytes, being both phenotypes strongly activated by AA in inside-out patches and cell-attached patches (Kang et al., 2007; Simkin et al., 2008). AA also increased the activity of TREK2 channels at 37°C in cell-attached and inside-out patches (Kang et al., 2005). On the contrary, saturated fatty acids, like stearic and palmitic, did not affect TREK2 channels either in inside- or outside-out patches (COS-expressed) (Bang et al., 2000).

Macroscopic currents: Heterologously expressed TREK2 channels (COS and HEK) are strongly and reversibly activated by AA and other PUFAs (DHA and LA) (Lesage et al., 2000b; Gu et al., 2002; Takahira et al., 2005; Woo et al., 2016, 2018). In contrast, saturated fatty acids (palmitic) do not affect TREK2 channels expressed in COS cells (Lesage et al., 2000b).

Natively expressed channels

Single channel: Single channel recording revealed a potassium channel with electrophysiological and pharmacological characteristics nearly identical to those shown by expressed TREK2 channels in cerebellar granule, supraoptic, the pancreatic cell line MIN6 and DRG neurons in culture (Han et al., 2002, 2003; Kang et al., 2004; Kang and Kim, 2006; La and Gebhart, 2011). In inside-out and cell-attached patches the activity of these channels was strongly enhanced by AA (Han et al., 2002, 2003; Kang et al., 2004, 2005), but also by LLA and LA (Han et al., 2002; Kang et al., 2005). In addition, the two phenotypes of TREK2 channels (TREK2-S and TREK2-L) were activated by AA in cerebellar neurons (Kang et al., 2007). Native TREK2 currents were also identified in astrocytes and activated by a variety of PUFAs including AA, LA, LLA and oleic acid, but not by saturated fatty acids such as palmitic or stearic acids (Gnatenco et al., 2002).

Macroscopic currents: Whole-cell TREK2-like currents were identified upon application of AA in rat type-1 cortical astrocytes in culture (Ferroni et al., 2003). The activation of the AA-sensitive current was rather slow and its IV curve displayed a marked outward rectification that became apparent at potentials more negative than –60 mV, showing very little inward currents, a characteristic property of TREK channels. Moreover, this rectification was clearly reduced in symmetrical concentrations of potassium (Ferroni et al., 2003; Kucheryavykh et al., 2009). Similar results were obtained in the insulin-secreting pancreatic cell line MIN6 and in hippocampal and cortical astrocytes (Kang et al., 2004; Seifert et al., 2009; Woo et al., 2016). Native slowly developing outward currents (perforated-patch) induced by LA in cultured mouse superior cervical ganglion (mSCG) neurons were also attributed to the slow activation of TREK2 channels and they were robustly inhibited by fluoxetine, an inhibitor of TREK subfamily channels (Cadaveira-Mosquera et al., 2011).

TWIK-related arachidonic acid-activated potassium channels

Heterologously expressed channels

Single channel: The activity of TRAAK channels recorded in COS cells was strongly stimulated by AA both in inside-out and outside-out patches, contributing to the hypothesis of a direct effect of polyunsaturated fatty acids on TRAAK channels from mouse and human (Fink et al., 1998; Lesage et al., 2000a; Kim et al., 2001a; Kang and Kim, 2006). Same results were obtained with other fatty acids like LLA and LA in both configurations (Kim et al., 2001a). AA also increased the activity of TRAAK channels at 37°C in cell-attached and inside-out patches (Kang et al., 2005).

Macroscopic currents: When discovering and describing for the first time TRAAK channels, Fink et al. (1998) reported that the current produced by these channels was strongly, slowly and reversibly stimulated by AA, a polyunsaturated fatty acid, in a dose-dependent manner. Similar results were found in different species and different heterologous systems (COS, HEK) (Fink et al., 1998; Maingret et al., 1999a, 2000a; Lesage et al., 2000a; Meadows et al., 2001; Takahira et al., 2005; Brohawn et al., 2012). Interestingly, although the control IV curves recti-

fied and did not show much inward current, application of AA clearly increased the inward current at hyperpolarized potentials indicating an enhancing effect at all potentials tested (Fink et al., 1998; Lesage et al., 2000a; Soussia et al., 2018). However, a strong outward rectification was also reported for the AA-sensitive current under similar conditions (Maingret et al., 1999a, b; Lesage et al., 2000a). Besides AA, most polyunsaturated fatty acids (LA, LLA, eicosapentaenoic acid, DHA) enhanced TRAAK currents expressed in COS cells (Fink et al., 1998; Lesage et al., 2000a). A similar enhancing effect was shown for monounsaturated fatty acids like oleic acid (Fink et al., 1998). On the contrary, saturated fatty acids (palmitate, stearate, arachidate, myristate) did not affect TRAAK currents (Fink et al., 1998; Lesage et al., 2000a; Maingret et al., 2000a).

Natively expressed channels

Single Channel: Before TRAAK channels were discovered, a family of potassium channels with a very similar response to AA and other saturated and unsaturated fatty acids was reported in cultured mesencephalic and hypothalamic neurons (Kim et al., 1995). The activation of these channels could be recorded in whole-cell, inside-out and outside-out preparations with equivalent conductance values. These currents were blocked by barium but not by other classical potassium channel blockers and they were sensitive to stretch and pH but essentially voltage-independent. All these properties pointed to TRAAK channels as the background of these AA activated currents (Fink et al., 1998; Bang et al., 2000). TRAAK-like channels are activated in supraoptic and DRG neurons when AA is applied to the intracellular side of inside-out macropatches, and similar results were obtained with other unsaturated fatty acids like LA and oleic acid (Han et al., 2003; La and Gebhart, 2011).

Action mechanism

Deletion of the N-terminus (Chemin et al., 2005a) or the C-terminus (up to Thr322) of TREK1 channels does not affect either basal or AA activated TREK1 currents, but additional truncation of the C-terminal to Arg311 reduced the activation of the current by AA, and truncation at Val298 completely abolished AA stimulation (Patel et al., 1998; Maingret et al., 2000a). These experiments strongly suggest that the region between Val298 and Thr322 in the C terminal of the channel is critical for AA stimulation. Interestingly, the same region is also essential for the activation of TREK1 channels by mechanical stimuli and intracellular acidification (Patel et al., 1998; Maingret et al., 1999b; Woo et al., 2018). On the same line, mutation of residue E306A increased the basal activity and also affected the modulation of TREK1 by AA (Honore et al., 2002). In this same study it is suggested that protonation of residue E306 mechanically couples the channel to the lipid bilayer allowing AA and mechanical stimuli to open the channel more easily (Honore et al., 2002). The activation of TREK1 channels by AA, recorded in a macropatch using the cell-attached patch configuration, was very slow (around 10 minutes) and weak suggesting a direct effect on the channel or by partitioning into the membrane (Maingret et al., 2000a). The inhibition of the formation of active AA metabolites did not preclude the activation of TREK1 currents in adrenal or corticotrope cells supporting the thesis of a direct effect (Danthi et al., 2003; Lee et al., 2011).

The activating effect of AA on TREK2 can be abolished by removing or replacing the C-terminus with that of TASK3 or by mutating the residue E332A, suggesting a strong role for this portion of the channel on the modulation by AA (Kim et al., 2001a, b; Kang et al., 2005; Woo et al., 2018). Interestingly, the sequential removal of the C-terminus also gradually diminished the activation of TREK2 by AA and the activation disappeared when the entire C-terminus was detached (Kim et al., 2001b). However, removal of the N-terminus does not interfere with the action of AA (Simkin et al., 2008). It has also been reported that the activation of native TREK2-like currents in astrocytes is independent of the AA metabolism or protein kinase C activation but rather due to a direct interaction of AA with the extracellular side of the membrane, as intracellular application did not increase the current (Ferroni et al., 2003).

Unlike TREK1 and TREK2, alteration of the C-terminus of TRAAK channels did not affect their responsiveness to AA, suggesting a different mechanism among channels within this subfamily. Consistently, TRAAK C-terminus shares only 50% identity with TREK channels, while in TREK1 and TREK2 channels this region is nearly identical (Kim et al., 2001a; Honore et al., 2002). The inhibition of several AA-dependent metabolic pathways did not preclude the effect of AA on TRAAK channels, AA metabolites did not affect TRAAK currents and the activation could be reproduced in outside- and inside-out patch, all this supporting the hypothesis of a direct action of AA on TRAAK channels (Fink et al., 1998; Han et al., 2003). It is unlikely that AA affects TRAAK channels by membrane deformation because negative pressure still activates these channels in the presence of lipid-free bovine serum albumin (COS cells; inside-out), which is known to bind fatty acids and remove them from the membranes (Maingret et al., 1999a). Interestingly, mechanical stimulation of TRAAK channels greatly increases their responsiveness to AA, indicating a synergistic effect of these two stimuli (Kim et al., 2001a).

Lysophospholipids

Lysophospholipids are intermediate molecules in the pathway of the synthesis and degradation of the phospholipids constituting the plasma membrane. These bioactive molecules (**Figure 2**) are also released in response to tissue damage and ischemia, where they induce neuroprotection by interacting with a variety of G-protein coupled receptors as well as ion channels, including the TREK subfamily (Chemin et al., 2005b; Hernandez-Araiza et al., 2018) (**Table 2**).

TWIK-related potassium channel 1

Heterologously expressed channels

Single channel: The activity of TREK1 channels recorded in a macropatch using the cell-attached patch configuration is rapidly activated by lysophosphatidylcholine (LPC), which however does not activate TREK1 channels either in inside- or outside-out patch configurations (Maingret et al., 2000a) suggesting an indirect effect. Unexpectedly LPC inhibited the activity of TREK1 channels when induced by AA in the inside-out configuration (Maingret et al., 2000a). Similarly, lysophosphatidic acid (LPA) increased TREK1 currents in inside-out macropatches (dose-dependently and reversibly) but had no effect when applied in outside-out or whole-cell

recordings (Chemin et al., 2005a; Parrill, 2005). These results indicate that the effect of lysophospholipids on TREK channels is very dependent on the recording technique and warns of the extreme care that must be taken when interpreting negative results under some experimental conditions.

Macroscopic currents: LPC, lysophosphatidylinositol (LPI), platelet-activating factor and Lyso-platelet-activating factor strongly activated TREK1 channels and induced a dose-dependent outward current in COS cells transfected with TREK1 channels and voltage-clamped at 0 mV. Interestingly the effect of LPC was noticeably faster in comparison to that of AA (Maingret et al., 2000a). It is important to note that current activation induced by LPC did not decayed with time (up to 15 minutes), but see below (Maingret et al., 2000a; Cohen et al., 2009). The IV curve shows that the LPC-sensitive current has a strong outward rectification in physiological potassium concentrations, retaining this outward rectification at negative potentials even in equimolar concentrations of potassium (Maingret et al., 2000a).

On the contrary, choline, phosphatidylcholine (two acyl chains) and LPA (lacking the head group), lysophosphatidylserine and lysophosphatidylethanolamine failed to increase TREK1 currents (Maingret et al., 2000a). LPA had a similar lack of effect in COS-expressed TREK1 current recorded in whole-cell, but see above (Chemin et al., 2005a). In fact, LPA strongly and reversibly reduced TREK1 currents expressed in oocytes and inhibited the TREK1 currents induced by AA and LPC, with all these effects involving the activation of the Phospholipase C pathway and requiring the C-terminus of the channel protein (Cohen et al., 2009).

Natively expressed channels

Single channel: LPC activates the IKAA current, which was attributed to the activation of TREK1 channels, in atrial myocytes recorded under the cell-attached configuration (Terrenoire et al., 2001). Another study performed in striatal neurons found that TREK1-like single channel currents are strongly activated by LPA probably through an interaction with the interior of the membrane (Chemin et al., 2005a).

Macroscopic currents: Both LPC and LPI were shown to transiently activate bTREK1 channels in bovine adrenal zona fasciculata cells (Danthi et al., 2003). This transient activation is in contrast with the sustained response of TREK1 channels by LPC and LPI in heterologous systems (Maingret et al., 2000a; Danthi et al., 2003). Activation of TREK1 channels by LPC was much faster than that evoked by AA, and when these two compounds are applied together, a mixed response (rapid increase followed by a sustained response) develops, suggesting that TREK1 activation by fatty acids and lipophospholipids happens through different mechanisms (Danthi et al., 2003). Indeed, it was found that the Glu306 residue of the carboxyl-terminal domain, which mediates TREK1 activation by AA, is not responsible of the channel activation by LPA, which seems to be dependent on an interaction with the M2-M3 intracellular loop (Chemin et al., 2005a).

TWIK-related potassium channel 2

Compared to TREK1, very few data have been published describing the effect of lysophospholipids on TREK2 channels. COS-expressed TREK2 channels are activated by LPA in inside-out macropatches (Chemin et al., 2005a) and whole-cell hTREK2 currents expressed in COS cells are strongly activated by LPI and LPC (Lesage et al., 2000b).

TWIK-related arachidonic acid-activated potassium channels

Data on lysophospholipids and TRAAK channels are also scarce. COS-expressed TRAAK channels are strongly activated by LPA

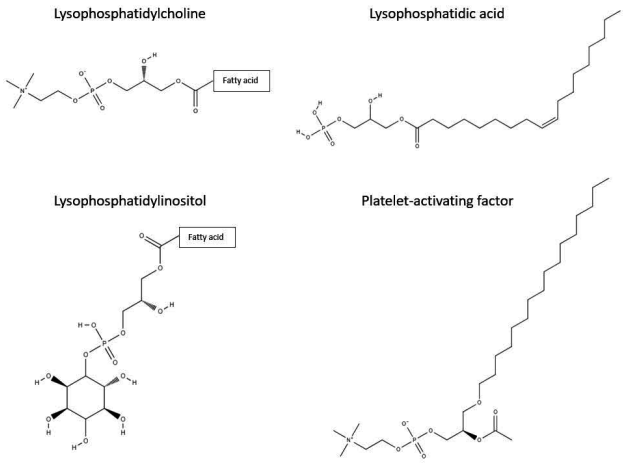

Figure 2 Major lysophospholipids activating TWIK-related potassium channels.
See Table 2 for more details.

Table 2 Reported effect of different phospholipids on channels of the TREK subfamily

Phospholipid	TREK1	TREK2	TRAAK
LPC	A: 10 μM^H (Maingret et al., 2000a)	A: 10 μM^H (Lesage et al., 2000b)	A: 10 μM^H (Maingret et al., 2000a)
LPI	A: 10 μM^H (Maingret et al., 2000a)	A: 10 μM^H (Lesage et al., 2000b)	A: 10 μM^H (Maingret et al., 2000a)
LPA	A: 5 μM^N (Chemin et al., 2005a)	A: 5 μM^H (Chemin et al., 2005a)	A: 5 μM^H (Chemin et al., 2005a)
LPS	NE^H (Maingret et al., 2000a)	NA	NE^H (Maingret et al., 2000a)
LPE	NE^H (Maingret et al., 2000a)	NA	NE^H (Maingret et al., 2000a)
PC	NE^H (Maingret et al., 2000a)	NA	NE^H (Maingret et al., 2000a)
PAF	A: 10 μM^H (Maingret et al., 2000a)	NA	A: 10 μM^H (Maingret et al., 2000a)

The tested concentration is indicated. A: Activation; N: tested on native channels; NA: not addressed; NE: no effect; H: tested on heterologously expressed channels; LPA: lysophosphatidic acid; LPC: lysophosphatidylcholine; LPE: lysophosphatidylethanolamine; LPI: lysophosphatidylinositol; LPS: lysophosphatidylserine; PAF: platelet-activating factor; PC: phosphatidylcholine; TRAAK: TWIK-related arachidonic acid-activated potassium channels; TREK: TWIK-related potassium channels.

in inside-out macropatches (Chemin et al., 2005a). In addition, LPC, platelet-activating factor, Lyso-platelet-activating factor and LPI stimulated heterologously expressed TRAAK channels in a similar manner than reported for TREK1 channels in whole-cell recordings (Maingret et al., 2000a). However, phosphatidylcholine, LPA, lysophosphatidylethanolamine, lysophosphatidylserine and choline were ineffective on heterologously expressed macroscopic TRAAK currents (Maingret et al., 2000a).

Action mechanism

The activation of TREK1 and TRAAK by lysophospholipids strongly depends on the size of the polar head and the length of the acyl chain, however it seems to be independent of the charge of the molecule (Maingret et al., 2000a). It has been suggested that the shape rather than the charge may be the clue, being the conical form of lysophospholipids the main factor (Patel et al., 2001). Importantly, the effect of LPC on TREK1 and TRAAK channels can be inhibited by chlorpromazine, gadolinium and by amiloride, and could be reversed by 8-cyclic adenosine monophosphate (cAMP) and phorbol myristate acetate, suggesting the involvement of protein kinases A and/or protein kinase C (Maingret et al., 2000a). However, in adrenal native cells recorded in the whole-cell mode, LPC still induced a strong activation of bTREK1 currents in the absence of intracellular nucleotides or in the presence of adenosine monophosphate-adenylyl-imidodiphosphate, suggesting that kinases and adenosine triphosphate (ATP)ases are not involved in the response (Danthi et al., 2003).

Deletion of the N-terminus of TREK1 channels (in COS, whole-cell) does not affect the activation of TREK1 currents by LPC, however deletion of the C-terminus abolished it (Maingret et al., 2000a). The amino terminal domain of TREK1 expressed in COS cells is also unnecessary for the activation of the channel by LPA in inside-out patches (Chemin et al., 2005a).

Riluzole and Other Neuroprotective Agents

Riluzole (RIL) is a neuroprotective agent with anticonvulsant, sedative and antiischemic properties, currently used for the treatment of amyotrophic lateral sclerosis (ALS) and other nervous system injuries (Cheah et al., 2010; Weiss et al., 2010; Weiss and Saint, 2010; Bellingham, 2011). RIL activates all channels of the TREK subfamily (Duprat et al., 2000; Lesage et al., 2000b). However, this compound is far from being a selective drug, and exerts effects on a good number of ion channels, like sodium, potassium, calcium channels, as well as ligand-gated ion channels like γ-aminobutyric acid $(GABA)_A$, glycine or glutamate receptors (Huang et al., 1997; Grunnet et al., 2001; Mohammadi et al., 2001; Reboreda et al., 2003; Lamanauskas and Nistri, 2008; Lamas et al., 2009). On the other hand, other known neuroprotectors and mood stabilizers also interact with TREK channels (Meadows et al., 2001) (**Figure 3** and **Table 3**).

TWIK-related potassium channel 1

Heterologously expressed channels

Single channel: In outside-out patches, RIL enhances the activity of single TREK1 channels suggesting a direct effect (Duprat et al., 2000). Also the newly developed TREK1 enhancer ML67-33 works in inside and outside-out macropatches suggesting that second messengers are not necessary (Bagriantsev et al., 2013).

Macroscopic currents: Riluzole induces a dual effect on TREK1 macroscopic currents, starting with a rapid and strong stimulation of the current which is followed by a current decay and finishing with a strong inhibition, ultimately leading to a final outward current in the presence of RIL that is smaller than the control current (Duprat et al., 2000). Note that most of these experiments are carried out in COS, HEK or oocyte-expressed channels fixed at 0 mV, so that a stable TREK current is present before RIL is applied (Duprat et al., 2000; Meadows et al., 2000; Moha ou Maati et al., 2011).

Sipatrigine is a well-known neuroprotective and anticonvulsive substance blocking voltage dependent sodium and calcium channels and inhibiting glutamate release. On the contrary to RIL, sipatrigine emerged as a potent antagonist of hTREK1 channels, being this effect dose-dependent, reversible and followed by a small rebound (Meadows et al., 2001). Sipatrigine is a derivative of lamotrigine, which shows stronger anticonvulsant properties, but lower neuroprotective activity. Interestingly, lamotrigine has no effect on hTREK1 currents (Meadows et al., 2001; Kim et al., 2017).

Other synthetic compounds have been developed in order to specifically modulate TREK channels. Recently, GI-530159, a novel activator for TREK1 channels, has been described to strongly and directly activate TREK1 channels stably expressed on HEK293 cells, reporting a half maximal effective concentration of around 900 nM (Loucif et al., 2018). This compound also activates TREK2 channels, but not TRAAK channels (Loucif et al., 2018). Similarly, BL-1249 is described to directly activate TREK1 channels (Veale et al., 2014), however this compound not only activates the other two members of the TREK subfamily, but also other channels including TASK3 (K2P channel), calcium-activated BK channels, $K_V7.2$, $K_V7.3$ and also sodium channels ($Na_V1.7$) (Loucif et al., 2018). Previously, ML67-33, a dihydroacridine analogue, was also reported as a selective activator of the three channels of the TREK subfamily, showing no effect over other K2P (TASK1, TASK2, TASK3, TRESK) or on KCNQ2 channels (Bagriantsev et al., 2013). ML67-33 appears to directly enhance channel activity, as its effect is fast and it can be reproduced in inside- and outside-out (Bagriantsev et al., 2013). It should be tested whether ML67-33 allows discriminating the contribution of TREK currents from that of the M-current (KCNQ2/3) in setting the resting membrane potential (RMP) of neurons that express both currents.

Remarkably, a specific inhibitor for TREK1 channels with no effect on the other two members of the TREK subfamily has been described. Spadin, which is a 17-amino acid peptide derived from the endogenous peptide sortilin, induces a decrease in TREK1 currents by promoting the internalization of the channel (Mazella et al., 2010). The specificity and rapid action of spadin on TREK1 channels, as well as the positive outcome obtained from preclinical assays in animal models of depression, positions this compound as a potential drug for the treatment of this disease and other TREK1-related conditions (Djillani et al., 2019).

Natively expressed channels

Macroscopic currents: Natively expressed I_{AC} potassium currents in bovine adrenal cells are thought to flow through bTREK1; this current is transiently enhanced by RIL in most

cells recorded, although sustained and intermediate responses have also been reported (Enyeart et al., 2002). IV curves of I_{AC} currents showed a rectification similar to that obtained for macroscopic TREK1 channels (Enyeart et al., 2002). In addition, a TREK1-like current in the mouse nodose ganglion neurons in culture was activated by RIL (I_{RIL}) (Cadaveira-Mosquera et al., 2012; Fernández-Fernández et al., 2018). This activation was often transient, occurred in all the three different cell subtypes of this ganglion and it was strongly blocked by fluoxetine and spadin. Similar results were found with the two more selective TREK-current enhancers ML67-33 and BL-1249 (Fernández-Fernández et al., 2018). The current activated by RIL in mouse nodose ganglion neurons was clearly outwardly rectifying in standard but linearized in symmetrical potassium (Fernández-Fernández et al., 2018). In DRG neurons expressing TREK1 channels, GI-530159 induced the hyperpolarization of the RMP, therefore leading to a decrease in action potential firing (Loucif et al., 2018). The concentration of GI-530159 tested indicates that this decrease in excitability is likely mediated by the direct activation of TREK1 channels, thus supporting a putative therapeutic effect that targeting these channels with GI-530159 or other synthetic activators of TREK1 may have for the treatment of DRG-mediated forms of pain.

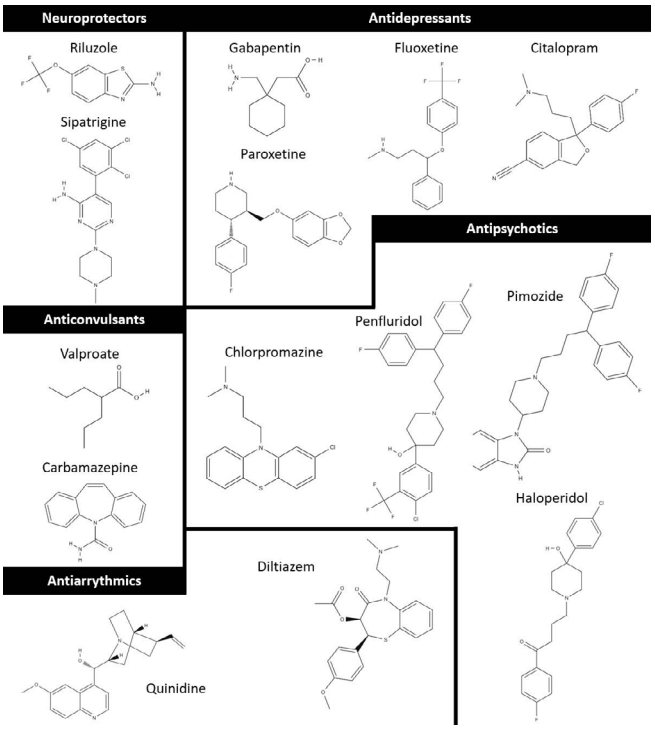

Figure 3 Major therapeutics modulating TWIK-related potassium channels.
See Table 3 for more details.

TWIK-related potassium channel 2

Heterologously expressed channels

Single channel: In COS cells expressing TREK2 channels, single-channel recordings were studied in the cell-attached modality. Under such conditions, RIL enhanced TREK2 channel activity by two-fold, an effect that was mimicked by the application of the flavonoids baicalein and wogonin (Kim et al., 2011).

Macroscopic currents: The neuroprotective drug RIL also have a dual modulation on expressed (COS cells) TREK2 channels; at first the current is strongly enhanced but, after reaching a peak, I_{RIL} progressively decays and finally even the basal TREK2 current was inhibited (Lesage et al., 2000b). TREK2 channels expressed in HEK293 cells are also activated by GI-530159, BL-1249 and ML67-33 (Bagriantsev et al., 2013; Loucif et al., 2018), thus so far there is no specific activator that allows to differentiate between TREK1 and TREK2 channels.

Natively expressed channels

Single channel: The open probability of single TREK2-like

Table 3 Reported effect of different therapeutics and mood stabilizers on channels of the TREK subfamily

Therapeutic	Indication	TREK1	TREK2	TRAAK
Riluzole	Neuroprotector (amyotrophic lateral sclerosis)	A: 100 μM^H (Moha ou Maati et al., 2011)	A: 300 μM^N (Cadaveira-Mosquera et al., 2011)	A: 100 μM^H (Fink et al., 1998)
Sipatrigine	Neuroprotector	I: 10 μM^H (Meadows et al., 2001)	NA	I: 10 μM^H (Meadows et al., 2001)
Fluoxetine	Antidepressant	I: 10 μM^H (Kim et al., 2017)	I: 100 μM^N (Cadaveira-Mosquera et al., 2011)	NE: 10 μM^H (Heurteaux et al., 2006b)
Norfluoxetine	Antidepressant	I: 3 μM^H (Kennard et al., 2005	I: 3 μM^H (Dong et al., 2015)	NA
Paroxetine	Antidepressant	I: 20 μM^H (Kim et al., 2017)	I: 20 μM^H (Kim et al., 2017)	NE: 10 μM^H (Heurteaux et al., 2006b)
Citalopram	Antidepressant	I: 100 μM^H (Kim et al., 2017)	I: 100 μM^H (Kim et al., 2017)	NA
Gabapentin	Antidepressant	A: 100 μM^H (Kim et al., 2017)	NE: 100 μM^H (Kim et al., 2017)	NA
Lamotrigine	Anticonvulsant	NE: 10 μM^H (Meadows et al., 2001)	NE^H (Kim et al., 2017)	NE: 10 μM^H (Meadows et al., 2001)
Valproate	Anticonvulsant	A: 100 μM^H (Kim et al., 2017)	NE: 100 μM^H (Kim et al., 2017)	NA
Carbamazepine	Anticonvulsant	A: 100 μM^H (Kim et al., 2017)	NE: 100 μM^H (Kim et al., 2017)	NA
Lithium chloride	Bipolar disorder	A: 1 mM^H (Kim et al., 2017)	NE: 1 mM^H (Kim et al., 2017)	NA
Chlorpromazine	Antipsychotic	I: 30 μM^H (Kim et al., 2017)	I: 100 μM^H (Kim et al., 2017)	NE: 1 μM^H (Maingret et al., 2000a)
Haloperidol	Antipsychotic	I: 10 μM^H (Thümmler et al., 2007)	I: 10 μM^H (Thümmler et al., 2007)	NE: 10 μM^H (Thümmler et al., 2007)
Pimozide	Antipsychotic	I: 10 μM^H (Thümmler et al., 2007)	I: 10 μM^H (Thümmler et al., 2007)	I: 10 μM^H (Thümmler et al., 2007)
Sulpiride	Antipsychotic	NE: 10 μM^H (Thümmler et al., 2007)	NE: 10 μM^H (Thümmler et al., 2007)	NE: 10 μM^H (Thümmler et al., 2007)
Diltiazem	Antiarrythmic	I: 1 mM^H (Takahira et al., 2005)	I: 1 mM^H (Takahira et al., 2005)	NE: 1 mM^H (Takahira et al., 2005)

When reported, the tested concentration is indicated. A: Activation; H: tested on heterologously expressed channels; I: inactivation; N: tested on native channels; NA: not addressed; NE: no effect; TRAAK: TWIK-related arachidonic acid-activated potassium channels; TREK: TWIK-related potassium channels.

channels in mSCG cultured neurons, clearly increased in cell-attached patches when RIL was included inside the patch pipette. Interestingly this increase was almost abolished when RIL was accompanied by fluoxetine (Cadaveira-Mosquera et al., 2011).

Macroscopic currents: Our group has characterized a riluzole-activated outward TREK2-like current at –30 mV in cultured mSCG neurons using the perforated-patch technique, the effect of riluzole was weaker when fixing the membrane at –60 mV (close to the RMP of these cells) (Cadaveira-Mosquera et al., 2011; Rivas-Ramirez et al., 2015). Very often I_{RIL} also showed a transient behavior and it was outwardly rectifying at physiological but not at symmetrical potassium concentrations (Cadaveira-Mosquera et al., 2011; Rivas-Ramirez et al., 2015).

TWIK-related arachidonic acid-activated potassium channels

Heterologously expressed channels

Single channel: Outside-out patches of TRAAK channels expressed in COS cells showed for the first time the strong activation produced by RIL on TREK subfamily channels (Fink et al., 1998). **Macroscopic currents:** Macroscopic currents obtained from TRAAK-transfected COS cells were strongly enhanced by RIL and this I_{RIL} was strongly rectifying in the outward direction (Fink et al., 1998). The effect of RIL on TRAAK channels is rapid, reversible, dose-dependent and, unlike the other two members of the family, it is a sustained response. I_{RIL} mediated by TRAAK channels is instantaneous and non-inactivating in response to depolarizing voltage-steps (Duprat et al., 2000). Sipatrigine also inhibited TRAAK currents but to a lesser extent than TREK1 channels (Meadows et al., 2001). Much like with TREK1 currents, lamotrigine did not affect TRAAK currents (Meadows et al., 2001). TRAAK currents are also strongly activated by the synthetic enhancer ML67-33 (Bagriantsev et al., 2013).

Action mechanism

Riluzole enhances the activity of TREK1 and TRAAK in outside-out patches, suggesting that the activation may be due to a direct effect of the drug on TREK channels (Fink et al., 1998; Duprat et al., 2000). However, the secondary inhibition produced by RIL on TREK1 and TREK2 currents seem to be due to the intracellular increase of cAMP concentration. Accordingly, the permeant derivative of cAMP (CPT-cAMP) reversibly inhibits macroscopic TREK1 currents expressed in COS cells and impedes the activation of the current by RIL (Duprat et al., 2000; Moha ou Maati et al., 2011). Similarly, heterologously expressed bovine bTREK1 currents and native I_{AC} currents present in adrenal cells (carried by native TREK1 channels) were inhibited by 8-pp-cAMP (Enyeart et al., 2002). In adrenal cells, it has been suggested that the transient responses to RIL are obtained when using pipettes of high series resistances (slower dialysis), while sustained responses were observed with low series resistances (Enyeart et al., 2002). However, native neurons from the mSCG and from the mouse nodose ganglion showed the same kinetic variability in response to RIL when recorded with the perforated-patch variant of the patch-clamp, suggesting that the difference is not due to the washout of any intracellular component (Cadaveira-Mosquera et al., 2011; Fernández-Fernández et al., 2018).

The C-terminal region of TREK1 channels have two phosphorylation sites for protein kinase A and a mutant lacking these two sites is insensitive to cAMP although only one of them seems to be related with the inhibition of the current by cAMP (Patel et al., 1998). Mutation of the Ser334 removes the sensibility of TREK1 to cAMP and the current can be activated by RIL even in the presence of cAMP. Interestingly, under these conditions I_{RIL} is sustained and consistently RIL stimulates the activity of unitary TREK1 channels without signs of inactivation when using excised outside-out patches instead of whole-cell recordings (Duprat et al., 2000). In summary, RIL inhibits the phosphodiesterase E provoking an increase of the cAMP concentration leading to the activation of protein kinase A, which phosphorylates TREK1 channels reducing their activity (Duprat et al., 2000).

Neuroprotection, Resting Membrane Potential and Excitability

Although K2P channels are generally accepted to be "background" or "resting" potassium channels, very few studies dealt with the effect of these channels on the RMP and excitability. In general, TREK currents in response to voltage steps are (1) almost instantaneous, (2) do not inactivate and (3) seem not to have a voltage threshold, suggesting that they contribute on setting the RMP. In physiological concentrations of potassium, both macroscopic and single-channel TREK currents show a strong outward rectification with almost no current being observed in the inward direction, and the activity of these channels at room temperature and atmospheric pressure is very low (Maingret et al., 1999b; Cadaveira-Mosquera et al., 2011). This means that currents through these channels may be rather small around the RMP (Lamas, 2012). Similarly, it is commonly assumed that different neuroprotective substances exert their beneficial action on the central nervous system by hyperpolarizing the potential of the membrane, but most studies do not show real evidence that can prove this hypothesis.

In their pioneer study, Fink et al reported that the oocytes expressing TREK1 channels had values of RMP clearly more negative than their non-injected counterparts (approx. –80 *versus* –40 mV, respectively) (Fink et al., 1996; Meadows et al., 2000; Koh et al., 2001). Similar results were reported in other heterologous systems (Punke et al., 2003; Gruss et al., 2004; Harinath and Sikdar, 2005). Taken this into consideration, as neuroprotective agents usually activate TREK currents, they should also hyperpolarize the RMP and perhaps reduce the neuron excitability (number of action potential fired in response to depolarizing current injections). Accordingly, the hyperpolarization of the RMP and the reduction in firing of action potentials observed in cerebellar granule and corticotrope cells after application of AA has been ascribed to the activation of TREK1 channels (Lauritzen et al., 2000; Lee et al., 2011). Interestingly, a TREK1-like current, which is a component of the classic I_{SO} expressed in thalamocortical neurons, has been suggested to participate in setting the RMP and to contribute to the characteristic switch from burst to tonic firing in these neurons (Bista et al., 2012). Likewise, RIL activated a TREK1-like current in mouse nodose ganglion neurons in culture, and hyperpolarized these neurons by about 10 mV when recorded in the perforated-patch mode (Fernández-Fernández et al., 2018).

Unexpectedly, although the neuroprotective action of linolenic acid on spinal cord ischemia is lost in the TREK1 knockout (KO) mouse; striatal and DRG neurons showed the same RMP than their savage counterparts in TREK1 KO mice (Heurteaux et al., 2004; Alloui et al., 2006). This result implies that RMP and neuroprotection may not be so tightly related, and that TREK1 could not be so determinant in maintaining the RMP in native cellular systems when compared with the effect on heterologous systems. Nevertheless, caution must be taking when conclusions are to be drawn from studies using KO mice, as compensatory up-regulation might be masking a positive effect of the experimental manipulation (for example with an overexpression of closely related channels *e.g.*, TREK2 or TRAAK).

Consistent with a key role of lysophospholipids in the pathophysiology of brain injury and ischemia, LPC and LPA exert differential effects on TREK1 currents depending on its interaction with the intra- or the extracellular domains of the channel. The intracellular release of lysophospholipids evokes the activation of TREK1 currents, which will therefore induce neuronal hyperpolarization thus protecting the neuron from reaching a hyperexcitable state. However, when LPA is applied extracellularly, it inhibits TREK1 channels throughout an indirect participation of intracellular pathways (Cohen et al., 2009). This effect might underlie part of the deleterious effects that extracellular agents, including lysophospholipids, released during an ischemic insult exert on neuronal tissue.

The expression of TREK2 channels in COS cells produced a time-independent and non-inactivating potassium current, whose IV curve showed a reversal potential of about –9 mV in non-transfected COS cells but close to –75 mV when cells were transfected with TREK2 channels (Bang et al., 2000). Consistently, the RMP of oocytes injected with TREK2 is hyperpolarized from –20 to –80 mV approximately (Kim et al., 2005). In the same direction, activation of TREK2-like currents by AA in cortical astrocytes induced a hyperpolarization from –30 to –70 mV approximately, while the saturated arachidic acid did not induced any current at all (Ferroni et al., 2003). Activation of TREK2-like channels in native entorhinal cortical neurons, upon the activation of $GABA_B$ receptors, has been reported to decrease their excitability by inhibiting action potential firing, hyperpolarizing the RMP and diminishing the membrane resistance (Deng et al., 2009). In agreement, inhibition of a TREK2-like current by neurotensin in stellate neurons strongly increased the firing of action potentials (Xiao et al., 2014). Activation of TREK2 by norepinephrine in entorhinal cortex hyperpolarized the membrane and decreased excitability, reducing the frequency of action potential firing (Xiao et al., 2009). Also RIL activated a TREK2-like current in mSCG neurons producing a hyperpolarization of the membrane (about 10 mV at –30 mV), the inhibition of the same current by fluoxetine provoked a depolarization of the resting membrane and a reduction of the latency to the first action potential triggered by a depolarizing current injection (Cadaveira-Mosquera et al., 2011; Rivas-Ramirez et al., 2015).

Much like with TREK1, it was a surprise that the knockdown of TREK2 channels using small interfering RNA does not affect the RMP of native entorhinal neurons (Deng et al., 2009), and stellate cells from TREK2-KO mice have resting potentials comparable to those from wild neurons (Xiao et al., 2014). On the contrary, the knockdown of TREK2 by small interfering RNA hyperpolarized isolectin B4-binding neurons ($IB4^+$) C-nociceptors in culture by 10 mV (Acosta et al., 2014).

When expressed in oocytes or COS cells, TRAAK channels generate macroscopic outwardly rectifying IV relationships in standard concentrations of potassium (Fink et al., 1998; Ozaita and Vega-Saenz de Miera, 2002). Consistently, oocytes expressing these channels have RMP close to –80 mV (*i.e.*, close to the equilibrium potential for potassium) while controls showed a characteristic and more depolarized RMP around –40 mV (Fink et al., 1998; Ozaita and Vega-Saenz de Miera, 2002). These currents have no voltage activation threshold, they are time independent and non-inactivating (Lesage et al., 2000a; Ozaita and Vega-Saenz de Miera, 2002). Human TRAAK channels expressed in oocytes generate a hyperpolarization of the RMP of about 30 mV (–40 to –70 mV approximate) and similar results were reported in HEK293 cells (Meadows et al., 2001).

When dealing with the importance of TREK channels on the RMP it should be taken into account that most experiments are carried out at room temperature (about 24°C). We know now that all three members of this family have a very low activity at room temperature but strongly increase their activity when the temperature is increased to values close to the physiological range (Kang et al., 2005; Viatchenko-Karpinski et al., 2018), advising to repeat most relevant experiments at more physiological temperatures. In fact, chicken atrial myocytes have RMPs around –22 mV at room temperature but around –70 mV at 35°C, and interestingly this effect of temperature was mimicked by the application of AA and ascribed to the activation of native TREK1/2-like channels (Zhang et al., 2008). On the other hand, TREK IV curves in symmetrical potassium are quite similar (strong outward rectification), although due to different reasons, to those showed for the M-current (KCNQ channels). The M-current has been proposed to exert a stabilizing effect on the RMP rather than having a major role in setting it (Lamas et al., 2002; Cadaveira-Mosquera et al., 2011). This may be the reason for TREK channels to have a robust effect when these are heterologously expressed in cellular lines and oocytes or when they are activated/eliminated in cells with relatively low resting potentials, but not so strong in neurons with more negative (close to the equilibrium potential for potassium) RMP.

How the Stimulation/Inhibition of a Potassium Current Can Be Neuroprotective?

Stimulation

Hypoxia, ischemia and other cell insults produce a rise in intracellular free fatty acids, cell swelling and intracellular acidosis. All these factors are well known modulators of TREK channels. In fact, ischemia is accompanied of an important efflux of potassium which cannot be eliminated by blockers of ATP-sensitive or calcium-activated potassium channels (Maingret et al., 1999b).

The increase of the activity of several potassium channel types is known to protect against cardiac and brain ischemia by reducing the expression of c-fox, c-jun and other ischemia induced gene expression, besides protecting neuronal cells against degeneration (Heurteaux et al., 1993). Consistently both polyunsaturated fatty acids and lysophospholipids increase the activity of all three members of the TREK subfamily. Further-

more, RIL enhances the activity of the three members of this family, but for TREK1 and TREK2 this effect is transient and followed by a strong inhibition. How this dual action relates with the neuroprotective role of RIL remains unknown but the inhibitory phase of this modulation was eliminated by the metabolic inhibitor dinitrophenol suggesting that the effect of RIL in ischemic conditions may be sustained (Duprat et al., 2000).

The neuroprotective properties of potassium channel activators can come from several routes (Heurteaux et al., 1993):

1. Membrane potential hyperpolarization: fixing the RMP close to the equilibrium potential for potassium reduces cell excitability and calcium entry, precluding apoptosis. Hyperpolarization of smooth muscle cells seems to be the reason for these activators having vasorelaxant and antihypertensive properties.

2. Increasing action potential repolarization speed: shortening of the action potential reduces the calcium entry and ATP consumption. The reduction of the action potential plateau protects cardiomyocytes against ischemia.

3. Reducing glutamatergic tone: activation of potassium channels in glutamatergic synapses reduces calcium entry at both pre- and postsynaptic levels and precluding neuronal death. On the one hand, the opening of presynaptic potassium channels would hyperpolarize the presynaptic terminal avoiding the entry of calcium and consequently the release of glutamate. On the other hand, the opening of postsynaptic potassium channels would hyperpolarize the postsynaptic neuron, thus maintaining the blockade of the N-methyl-D-aspartic acid channel by Mg^{2+} and therefore avoiding the excessive entry of calcium that could lead to neuronal death.

Inhibition

It is somehow counterintuitive the fact that the inhibition of a potassium channel could result in neuroprotection, however sipatrigine is a well-known neuroprotective substance and a potent inhibitor of TREK1 and TRAAK channels (Meadows et al., 2001). Two explanations could account for this neuroprotective effect of the inhibition of potassium channels:

1. A hypothesis has been proposed in which the potassium channels inhibited by sipatrigine could be more expressed in inhibitory (*e.g.*, GABAergic) neurons, resulting in a secondary decrease of general neuronal activity (Meadows et al., 2001).

2. Another possibility is that the depolarization induced by the reduction of potassium channels inactivates Ca and/or Na channels, reducing neuronal activity (Meadows et al., 2001). It should be taken into consideration that the effect of a depolarization on the firing of a neuron greatly depends on the range of voltages reached, generally a small depolarization increases the excitability but larger depolarizations may result in the inactivation of the system.

Pathophysiology Related to TREK Channels

Neuropathic pain

Neuropathic pain is a chronic condition characterized by a constant sensation of pain in a tissue not affected by injure or disease. It is hypothesized that neuronal hyperexcitability underlies this form of pain, although the exact mechanisms remain obscure (Ratte and Prescott, 2016). Several lines of evidence suggest that TREK channels might be directly involved in the pathophysiology of neuropathic pain. In particular, it has been shown that knocking down TREK1, TRAAK or both, increases pain responses to thermal and mechanical stimuli (Alloui et al., 2006; Noël et al., 2009; Vivier et al., 2017). In this direction, TREK1 channels were found to be 9-fold overexpressed in the DRG of a mouse model of neuropathic pain (induced through the chronic constriction injury mode). TREK1 overexpression might be a neuroprotective response by increasing background potassium currents, which would suppress neuronal states of hyperexcitability. Considering this, TREK1 channels appear as promising targets for the treatment of neuropathic pain, and selective TREK1 enhancers are being developed and tested for their analgesic properties (Vivier et al., 2017). Indeed, the analgesic actions of morphine have been shown to be at least partly mediated by the direct activation of TREK1 channels by this opioid (Devilliers et al., 2013). Moreover, it has been recently demonstrated that RIL alleviates neuropathic pain induced by oxaliplatin, a common drug used for the treatment of colon cancer, through the activation of TREK1 channels (Poupon et al., 2018).

It has also been suggested that TREK2 activation could reduce the sensitivity of DRG c-fibers to pain and that TREK2 hyperpolarizes $IB4^+$ C-nociceptors and reduces neuropathic spontaneous pain in animal models (Acosta et al., 2014; Dadi et al., 2017). Surprisingly, analgesics like acetaminophen, ibuprofen and nabumentone did not affect TREK2 channels expressed in HEK cells (Park et al., 2016).

Depression

Fluoxetine, known commercially as Prozac©, is the prototypic drug for the treatment of common depression. Fluoxetine is classically described as a selective serotonin reuptake inhibitor but it has other unspecific actions and among them it acts as a potent inhibitor (IC_{50} (half maximal inhibitory concentration) 19 μM) of human TREK1 channels (Kennard et al., 2005; Moha ou Maati et al., 2011; Sandoz et al., 2011; Kim et al., 2017; Soussia et al., 2018), being this the first description of an ion channel directly involved in the pathophysiology of depression. Importantly, genetic variations of TREK1 have been related with the resistance to antidepressant treatments (Perlis et al., 2008). It is not clear though how fluoxetine might exert part of its antidepressant actions through the inhibition of TREK1 channels. One possibility is that the direct inhibition of TREK1 activity by fluoxetine could increase the firing of dorsal raphe neurons, where TREK1 channels are highly expressed (Talley et al., 2001). This increase of excitability would therefore potentiate the release of 5-hydroxytryptamine by these neurons, thus exerting antidepressant actions on postsynaptic targets. Furthermore, it has been suggested that the inhibitory effect of fluoxetine on TREK1 channels is due to the dissociation of the C-terminal domain from the membrane (Sandoz et al., 2011). Interestingly, fluoxetine is unable to inhibit TREK1 and TREK2 currents when they are activated by AA ("up" state) (Soussia et al., 2018).

Fluoxetine and norfluoxetine also inhibit TREK1-like channels in corticotrope cells and thalamocortical neurons (Lee et al., 2011; Bista et al., 2012) and TREK1-like native currents induced by RIL, ML67-33 and BL-1249 in mouse nodose ganglion neurons in culture (Fernández-Fernández et al., 2018). Other selective serotonin reuptake inhibitors, like paroxetine,

sertraline, fluvoxamine, citalopram, also inhibit human TREK1 (but not TRAAK) currents (Kim et al., 2017). Accordingly, the TREK1 (but not TRAAK) KO mouse shows a depression- and stress-resistant phenotype acting like wild animals treated with fluoxetine in behavioral tests (Heurteaux et al., 2006b). Interestingly, conventional selective serotonin reuptake inhibitors exert no effect on the TREK1 KO, suggesting that their actions are directly mediated by TREK1 channels.

In addition, sortilin deficient mice show resistance to depression and increased activity of serotoninergic neurons, probably by altering the expression and function of TREK1 channels and, as a consequence, a depolarization of the RMP and an increased firing was found in cortical cultured neurons from sortilin KO mice (Moreno et al., 2018). Spadin, a sortilin derived peptide, and other spadin analogs, are specific blockers of heterologously expressed mouse and human TREK1 channels (without effects on TREK2, TRAAK, TASK1, TRESK, hERG or KCNQ1/KCNE1 currents). These compounds stimulate neurogenesis at the hippocampus and have been proposed as potential drugs for the treatment of depression (Mazella et al., 2010; Moha ou Maati et al., 2011; Moha Ou Maati et al., 2012; Djillani et al., 2017; Moreno et al., 2018). Spadin and its analogs are more potent against TREK1 when stimulated by AA than in basal conditions, indicating an open-channel blockade (Djillani et al., 2017, 2019). Spadin strongly blocked a TREK1-like current induced by AA in CA3 hippocampal neurons, both in slices and in culture, and this effect was absent in TREK1 KO mice (Mazella et al., 2010). Moreover, spadin also inhibited a TREK1-like component of I_{SO} in thalamocortical neurons (Bista et al., 2012) and a TREK1-like current induced by RIL in mouse nodose ganglion neurons (Fernández-Fernández et al., 2018). Mice treated with spadin showed a rapidly induced antidepressant (but not anxiolytic) phenotype as confirmed with several behavioral tests; the results were similar to those obtained in TREK1 KO mice or in wild mice treated with fluoxetine and probably due to the increase in the activity of serotoninergic neurons of the dorsal raphe nucleus (Mazella et al., 2010).

TREK2 channels have not been so related with depression but several antidepressant drugs (amitriptyline), fluoxetine, paroxetine, citalopram, escitalopram (selective serotonin reuptake inhibitors)), also inhibited these channels when expressed in HEK cells (Park et al., 2016; Kim et al., 2017). Additionally a TREK2-like I_{RIL} in sympathetic neurons (mSCG) has been shown to be strongly inhibited by fluoxetine using perforated-patch recordings (Cadaveira-Mosquera et al., 2011). In this preparation, fluoxetine also strongly inhibited the currents activated by intracellular acidification, membrane stretch and LA. When included in the pipette solution, fluoxetine abolished the activation produced by RIL on single TREK2-like channels recorded in mSCG cell-attached patches (Cadaveira-Mosquera et al., 2011).

Contrary to what happens with TREK1 and TREK2, it has been shown that fluoxetine is not able to inhibit TRAAK channels in their basal state ("up" state), but it does when they are activated by AA ("down" state) (Dong et al., 2015; Soussia et al., 2018). It is interesting that TREK1 is inhibited by antidepressants whereas it is activated by mood stabilizers used for the treatment of bipolar disorder (LiCl, gabapentin, valproate, carbamazepine), while TREK2 is inhibited by antidepressant but is not modulated by mood stabilizers (Kim et al., 2017). This differentiation might highlight a specific role of TREK2 channels in the development of depression.

Schizophrenia

Schizophrenia is a complex mental illness and the drugs that are currently used are not very efficient for the treatment of cognitive problems or for the depression that normally accompanies this disease (Thümmler et al., 2007; Miyamoto et al., 2012).

Initially chlorpromazine, probably the first treatment against schizophrenia, was reported to inhibit TREK1 currents (Patel et al., 1998; Kim et al., 2017). Later it was demonstrated that most of the substances used in the treatment of schizophrenia (fluphenazine, chlorpromazine, haloperidol, flupenthixol, loxapine, clozapine, pimozide) inhibit TREK1 and TREK2, but not TRAAK channels, in a reversible and concentration-dependent way (COS-expressed channels, whole-cell, inside-out patches). On the contrary, the substituted benzamides (sulpiride, tiapride) did not affect TREK1 (Chemin et al., 2005a; Thümmler et al., 2007; Kim et al., 2017). In addition, TREK1-like currents activated by AA were inhibited by chlorpromacine, penfluridol or pimozide (Lee et al., 2011).

Epilepsy

TREK1 is strongly expressed both pre and postsynaptically in the cortex and hippocampus, places particularly sensitive to epileptic seizures (Hervieu et al., 2001; Lamas, 2012). TREK1 KO mice are particularly prone to epileptic states induced in response to kainic acid (Heurteaux et al., 2004). The neuroprotection conferred by TREK1 was evident when comparing the death rate of mutant animals (> 75%) with that of wild-type littermates (3% death rate). In the same study, the neuroprotective effect of TREK1 channels was further enhanced after the administration of the PUFA LLA and LPC. In another study, the expression of a mutated form of the TREK1 channel, which remains constitutively active by evading its down-regulation by protein kinases, made hippocampal cultured cells a 50% less susceptible to suffer from status epilepticus (Dey et al., 2014). These studies demonstrate a key neuroprotective role of TREK1 channels during epilepsy, and suggest that they might constitute promising therapeutic targets for the treatment of this common neurological disorder. In fact, the epileptogenicity of caffeine and theophylline has been suggested to be due to the blockade of TREK1 channels (Harinath and Sikdar, 2005).

Although much less studied, an increase in TREK2 expression at the hippocampus following epileptogenic insults has been related with a putative neuroprotection in a rat epilepsy model (Haenisch et al., 2016).

On the contrary KO mice for TRAAK channels do not show an increased sensitivity to provoked epilepsy when compared with wild-type counterparts, and both LA and LPC were still effective in protecting the mutant animals against epileptic seizures (Heurteaux et al., 2004).

Ischemia

Cerebral ischemia is caused when blood supply to the brain is obstructed either focally or globally causing irreversible neuronal death in the affected brain area. According to the World Health Organization, it causes around 17 million deaths

annually worldwide. It has been speculated that activation of TREK channels may provide a neuroprotective effect on cerebral ischemia, but the mechanism is not well understood and data against this hypothesis also exist. Interestingly, all the three members of the TREK subfamily have been shown to increase their expression in cortex and hippocampus in a model of acute cerebral ischemia (middle cerebral artery occlusion) (Li et al., 2005). Ischemia induced in cultured astrocytes (hypoxia) also triggered an increase in TREK1 channel expression in their membranes (Wu et al., 2013). Suppression of this channel expression resulted in a reduced ability of astrocytes to clear glutamate upon the simulated ischemic insult, which leaded to a higher rate of apoptosis in the cultured astrocytes. Also HEK cells expressing TREK1 channels were much more resistant than wild cells in a model of isquemia (glucose and oxygen deprivation); this protection was increased adding AA and it was abolished by spadin (Moha ou Maati et al., 2011). Similarly, TREK2 channel expression was also found increased in cultured cortical astrocytes after the induction of an *in vitro* model of brain ischemia (Kucheryavykh et al., 2009). These data suggest that the increase in TREK expression is a defense mechanism against ischemia.

TREK1 KO mice are more susceptible to cerebral and spinal ischemia than wild-type littermates (Heurteaux et al., 2004). Ischemia induced the release of AA and a decrease in the intracellular pH, both factors being strong activators of the TREK subfamily, saving TRAAK channels, which prefer an increase in pH. Besides, LA and LPC have been shown to protect against ischemia by activating TREK1 channels; as a proof these drugs only protected wild type mice but not the TREK1 KO (Heurteaux et al., 2004).

Looking from another point of view, unsaturated (linolenic, docohexanoic), but not saturated fatty acids (palmitic), induced basilar artery relaxation and hence improved oxygenation, an effect that was absent in TREK1 KO mice (Blondeau et al., 2007). Interestingly, the carotid artery was unresponsive to those fatty acids probably because it does not express TREK1 channels (Blondeau et al., 2007). Surprisingly, it has also been reported that the regulation of arterial diameter is not affected in mice lacking TREK1 channels (Namiranian et al., 2010, 2011), the reason for this discrepancy is unknown but very often the effect of knocking down a channel does not produce the expected effect.

On the contrary, a reduction of Po2 strongly and reversibly reduced the current through heterologously expressed hTREK1 channels and AA acid was unable to revert this effect, suggesting that the neuroprotective role of TREK1 activation on ischemic processes had to be re-examined (Miller et al., 2003). It may be relevant to point here that TREK1 and TREK2 have been reported to be depressed by hypoxia through a pathway involving AMPK, suggesting an important role of these channels in oxygen sensing in neurons of the carotid body (Kreneisz et al., 2009). These results have originated some controversy as other groups were unable to reduce TREK currents by provoking hypoxia (Buckler and Honore, 2005; Caley et al., 2005). It has also been reported a beneficial effect of suppressing the expression of another member of the TREK subfamily, TRAAK, during temporary focal cerebral ischemia (Laigle et al., 2012). This effect of TRAAK inhibition appears contradictory in view of previous studies showing a neuroprotective action of RIL, an activator of TRAAK channels, against focal brain ischemia (Heurteaux et al., 2006a), but indeed, TRAAK deficient mice do not display an increased sensitivity to ischemia (Heurteaux et al., 2004). One explanation could be that the beneficial effects of RIL might be attributable to its action on other ion channels (Bellingham, 2011). However, pointing in the same direction is the fact that the neuroprotector sipatrigine is an inhibitor of TREK1 and TRAAK channels (Meadows et al., 2001), again suggesting that in some scenarios TREK1 and TRAAK inhibition might be neuroprotective. Furthermore, it should be taken in mind that the effect of RIL on TREK1 and TREK2 is biphasic, a strong activation followed by an inhibition, so that it may be difficult to ascertain which of these effects confers neuroprotection. In any case, the beneficial effect of TRAAK channel inhibition could be related to the fact that its deletion has been associated with a subsequent increase in the levels of the amino acid taurine, which exerts neuroprotective actions against neuronal death (Saransaari and Oja, 2000; Laigle et al., 2012). Another explanation might be that in areas more susceptible to ischemia damage like the hippocampus, the reticular thalamic nucleus and the neostriatum, TREK1 channels are mainly expressed in inhibitory interneurons (Hervieu et al., 2001), where its blockade would lead to the interneuron depolarization thus generating an overall inhibition of the neuronal network.

More research should be performed concerning the potential of channels from the TREK subfamily as therapeutic targets for different neurological pathologies, and more particularly to clarify how its activation or inhibition might be beneficial to the treatment of cerebral ischemia. At present, the simplest view would be that during cerebral ischemia a large amount of AA is released, the intracellular pH falls and the neurons swell, all these changes are strong stimulators of TREK1 channel activity that would cause hyperpolarization, lower calcium intake and would reduce glutamatergic excitotoxicity.

Cardiac pathophysiology

There is compelling evidence supporting a key role of channels from the TREK subfamily in a variety of cardiac conditions (Wiedmann et al., 2016), and particularly in atrial fibrillation and heart failure. TREK1 and TREK2, but not TRAAK channels, are inhibited by antiarrhythmic drugs like diltiazem (Takahira et al., 2005), a non-dihydropyridine also indicated for the treatment of hypertension and angina pectoris. TREK channels are also modulated by other cardiac-related drugs like mibefradil (Chemin et al., 2005a) and quinidine (Bodnar et al., 2015). One study recently reported that TREK1 is the most expressed TREK channel in the murine and human heart (Schmidt et al., 2017). These authors found a reduction of TREK1 channels in patients suffering left ventricular dysfunction. Correspondingly, it is well established the expression of TREK1 channels in atrial and ventricular myocytes, where they might have a key role counteracting the excitatory action of stretch-activated cation currents that underlie the generation of ventricular arrhythmias (Li et al., 2006). In this scenario, TREK1 channels would represent the molecular correlate of the stretch-activated K^+ (SAK) currents opposing stretch-activated cation currents (Xian Tao et al., 2006; Decher et al., 2017). Recently, a protective role of TREK1 channel inhibition has been reported for

channels specifically expressed in cardiac fibroblasts, which could contribute to the development of cardiac dysfunction in response to pressure overload (Abraham et al., 2018).

Besides the presence of TREK channels in the membrane of cardiac myocytes, they could also have a neuroprotective role by modulating the excitability of intracardiac ganglion neurons, where a prominent heterogeneous potassium current modulating its resting potential and rhythmic activity has been described but remains to be fully characterized (Xi-Moy and Dun, 1995; Zhang and Cuevas, 2005).

Conclusions

TREK channels are promising therapeutic candidates for the treatment of several pathologies of the nervous and cardiovascular systems. Besides their notable modulation by temperature and mechanical forces, TREK channels are also regulated by a wide array of compounds with neuroprotective properties including fatty acids, lysophospholipids and different synthetic therapeutics like riluzole. In the last fifteen years, as reviewed in the present manuscript, there has been a huge increase of data describing how these neuroprotectors influence TREK channels. However, several gaps of information remain, which must be addressed in order to fully understand the potential of targeting these channels for the treatment of different disorders. In particular, a more complete picture of how their stimulation or inhibition might be beneficial for certain conditions is essential. Furthermore, understanding which are the specific brain areas affected by TREK channel dysfunction is fundamental for the development of novel TREK-based drugs for the treatment of specific syndromes.

In summary, TREK channels constitute fundamental elements of the cell physiology by fine-tuning the plasma membrane excitability. Their role as neuroprotectors makes them promising drug targets for the treatment of numerous brain and cardiac diseases including depression, neuropathic pain, epilepsy, ischemia, arrhythmia, *etc.* Future studies must focus on the design of specific activators and inhibitors for TREK1, TREK2 and TRAAK, which will likely open a new horizon in the therapy of these common conditions.

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References

Abraham DM, Lee TE, Watson LJ, Mao L, Chandok G, Wang HG, Frangakis S, Pitt GS, Shah SH, Wolf MJ, Rockman HA (2018) The two-pore domain potassium channel TREK-1 mediates cardiac fibrosis and diastolic dysfunction. J Clin Invest 128:4843-4855.

Acosta C, Djouhri L, Watkins R, Berry C, Bromage K, Lawson SN (2014) TREK2 expressed selectively in IB4-binding C-fiber nociceptors hyperpolarizes their membrane potentials and limits spontaneous pain. J Neurosci 34:1494-1509.

Alloui A, Zimmermann K, Mamet J, Duprat F, Noel J, Chemin J, Guy N, Blondeau N, Voilley N, Rubat-Coudert C, Borsotto M, Romey G, Heurteaux C, Reeh P, Eschalier A, Lazdunski M (2006) TREK-1, a K^+ channel involved in polymodal pain perception. EMBO J 25:2368-2376.

Bagriantsev SN, Ang KH, Gallardo-Godoy A, Clark KA, Arkin MR, Renslo AR, Minor DL Jr (2013) A high-throughput functional screen identifies small molecule regulators of temperature- and mechano-sensitive K2P channels. ACS Chem Biol 8:1841-1851.

Bang H, Kim Y, Kim D (2000) TREK-2, a new member of the mechanosensitive tandem-pore K^+ channel family. J Biol Chem 275:17412-17419.

Bayliss DA, Barrett PQ (2008) Emerging roles for two-pore-domain potassium channels and their potential therapeutic impact. Trends Pharmacol Sci 29:566-575.

Bellingham MC (2011) A review of the neural mechanisms of action and clinical efficiency of riluzole in treating amyotrophic lateral sclerosis: what have we learned in the last decade? CNS Neurosci Ther 17:4-31.

Bista P, Meuth SG, Kanyshkova T, Cerina M, Pawlowski M, Ehling P, Landgraf P, Borsotto M, Heurteaux C, Pape HC, Baukrowitz T, Budde T (2012) Identification of the muscarinic pathway underlying cessation of sleep-related burst activity in rat thalamocortical relay neurons. Pflug Arch Eur J Phy 463:89-102.

Blondeau N, Widmann C, Lazdunski M, Heurteaux C (2002) Polyunsaturated fatty acids induce ischemic and epileptic tolerance. Neuroscience 109:231-241.

Blondeau N, Petrault O, Manta S, Giordanengo V, Gounon P, Bordet R, Lazdunski M, Heurteaux C (2007) Polyunsaturated fatty acids are cerebral vasodilators via the TREK-1 potassium channel. Circ Res 101:176-184.

Bodnar M, Schlichthorl G, Daut J (2015) The potassium current carried by TREK-1 channels in rat cardiac ventricular muscle. Pflug Arch Eur J Phy 467:1069-1079.

Boland LM, Drzewiecki MM (2008) Polyunsaturated fatty acid modulation of voltage-gated ion channels. Cell Biochem Biophys 52:59-84.

Brohawn SG, del MJ, MacKinnon R (2012) Crystal structure of the human K2P TRAAK, a lipid- and mechano-sensitive K^+ ion channel. Science 335:436-441.

Buckler KJ, Honore E (2005) The lipid-activated two-pore domain K^+ channel TREK-1 is resistant to hypoxia: implication for ischaemic neuroprotection. J Physiol 562:213-222.

Cadaveira-Mosquera A, Ribeiro SJ, Reboreda A, Perez M, Lamas JA (2011) Activation of TREK currents by the neuroprotective agent riluzole in mouse sympathetic neurons. J Neurosci 31:1375-1385.

Cadaveira-Mosquera A, Perez M, Reboreda A, Rivas-Ramirez P, Fernandez-Fernandez D, Lamas JA (2012) Expression of K2P channels in sensory and motor neurons of the autonomic nervous system. J Mol Neurosci 48:86-96.

Caley AJ, Gruss M, Franks NP (2005) The effects of hypoxia on the modulation of human TREK-1 potassium channels. J Physiol 562:205-212.

Cheah BC, Vucic S, Krishnan AV, Kiernan MC (2010) Riluzole, neuroprotection and amyotrophic lateral sclerosis. Curr Med Chem 17:1942-1199.

Chemin J, Girard C, Duprat F, Lesage F, Romey G, Lazdunski M (2003) Mechanisms underlying excitatory effects of group I metabotropic glutamate receptors via inhibition of 2P domain K^+ channels. EMBO J 22:5403-5411.

Chemin J, Patel A, Duprat F, Zanzouri M, Lazdunski M, Honore E (2005a) Lysophosphatidic acid-operated K^+ channels. J Biol Chem 280:4415-4421.

Chemin J, Patel AJ, Duprat F, Lauritzen I, Lazdunski M, Honoré E (2005b) A phospholipid sensor controls mechanogating of the K^+ channel TREK-1. EMBO J 24:44-53.

Chemin J, Patel AJ, Duprat F, Sachs F, Lazdunski M, Honore E (2007) Up- and down-regulation of the mechano-gated K(2P) channel TREK-1 by PIP (2) and other membrane phospholipids. Pflug Arch Eur J Phy 455:97-103.

Cohen A, Sagron R, Somech E, Segal-Hayoun Y, Zilberberg N (2009) Pain-associated signals, acidosis and lysophosphatidic acid, modulate the neuronal K(2P)2.1 channel. Mol Cell Neurosci 40:382-389.

Dadi PK, Vierra NC, Days E, Dickerson MT, Vinson PN, Weaver CD, Jacobson DA (2017) Selective small molecule activators of TREK-2 channels stimulate dorsal root ganglion c-fiber nociceptor two-pore-domain potassium channel currents and limit calcium influx. ACS Chem Neurosci 8:558-568.

Danthi S, Enyeart JA, Enyeart JJ (2003) Modulation of native TREK-1 and Kv1.4 K^+ channels by polyunsaturated fatty acids and lysophospholipids. J Membr Biol 195:147-164.

Decher N, Kiper AK, Rinne S (2017) Stretch-activated potassium currents in the heart: Focus on TREK-1 and arrhythmias. Prog Biophys Mol Biol 130:223-232.

Dedman A, Sharif-Naeini R, Folgering JH, Duprat F, Patel A, Honore E (2009) The mechano-gated K(2P) channel TREK-1. Eur Biophys J 38:293-303.

Deng PY, Xiao Z, Yang C, Rojanathammanee L, Grisanti L, Watt J, Geiger JD, Liu R, Porter JE, Lei S (2009) GABA(B) receptor activation inhibits neuronal excitability and spatial learning in the entorhinal cortex by activating TREK-2 K^+ channels. Neuron 63:230-243.

Devilliers M, Busserolles J, Lolignier S, Deval E, Pereira V, Alloui A, Christin M, Mazet B, Delmas P, Noel J, Lazdunski M, Eschalier A (2013) Activation of TREK-1 by morphine results in analgesia without adverse side effects. Nat Commun 4:2941.

Dey D, Eckle VS, Vitko I, Sullivan KA, Lasiecka ZM, Winckler B, Stornetta RL, Williamson JM, Kapur J, Perez-Reyes E (2014) A potassium leak channel silences hyperactive neurons and ameliorates status epilepticus. Epilepsia 55:203-213.

Djillani A, Pietri M, Mazella J, Heurteaux C, Borsotto M (2019) Fighting against depression with TREK-1 blockers: Past and future. A focus on spadin. Pharmacol Ther 194:185-198.

Djillani A, Pietri M, Moreno S, Heurteaux C, Mazella J, Borsotto M (2017) Shortened spadin analogs display better TREK-1 inhibition, in vivo stability and antidepressant activity. Front Pharmacol 8:643.

Dong YY, Pike AC, Mackenzie A, McClenaghan C, Aryal P, Dong L, Quigley A, Grieben M, Goubin S, Mukhopadhyay S, Ruda GF, Clausen MV, Cao L, Brennan PE, Burgess-Brown NA, Sansom MS, Tucker SJ, Carpenter EP (2015) K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac. Science 347:1256-1259.

Duprat F, Lesage F, Patel AJ, Fink M, Romey G, Lazdunski M (2000) The neuroprotective agent riluzole activates the two P domain K(+) channels TREK-1 and TRAAK. Mol Pharmacol 57:906-912.

Ehling P, Cerina M, Budde T, Meuth SG, Bittner S (2015) The CNS under pathophysiologic attack--examining the role of K(2)p channels. Pflug Arch Eur J Physiol 467:959-972.

Elinder F, Liin SI (2017) Actions and mechanisms of polyunsaturated fatty acids on voltage-gated ion channels. Front Physiol 8:43.

Enyeart JJ, Xu L, Danthi S, Enyeart JA (2002) An ACTH- and ATP-regulated background K^+ channel in adrenocortical cells is TREK-1. J Biol Chem 277:49186-49199.

Enyedi P, Czirjak G (2010) Molecular background of leak K^+ currents: two-pore domain potassium channels. Physiol Rev 90:559-605.

Es-Salah-Lamoureux Z, Steele DF, Fedida D (2010) Research into the therapeutic roles of two-pore-domain potassium channels. Trends Pharmacol Sci 31:587-595.

Fernández-Fernández D, Cadaveira-Mosquera A, Rueda-Ruzafa L, Herrera-Perez S, Veale EL, Reboreda A, Mathie A, Lamas JA (2018) Activation of TREK currents by riluzole in three subgroups of cultured mouse nodose ganglion neurons. PLoS One 13:e0199282.

Ferroni S, Valente P, Caprini M, Nobile M, Schubert P, Rapisarda C (2003) Arachidonic acid activates an open rectifier potassium channel in cultured rat cortical astrocytes. J Neurosci Res 72:363-372.

Fink M, Duprat F, Lesage F, Reyes R, Romey G, Heurteaux C, Lazdunski M (1996) Cloning, functional expression and brain localization of a novel unconventional outward rectifier K^+ channel. EMBO J 15:6854-6862.

Fink M, Lesage F, Duprat F, Heurteaux C, Reyes R, Fosset M, Lazdunski M (1998) A neuronal two P domain K^+ channel stimulated by arachidonic acid and polyunsaturated fatty acids. EMBO J 17:3297-3308.

Franks NP, Honore E (2004) The TREK K2P channels and their role in general anaesthesia and neuroprotection. Trends Pharmacol Sci 25:601-608.

Fukasaku M, Kimura J, Yamaguchi O (2016) Swelling-activated and arachidonic acid-induced currents are TREK-1 in rat bladder smooth muscle cells. Fukushima J Med Sci 62:18-26.

Galano A, Tan DX, Reiter RJ (2011) Melatonin as a natural ally against oxidative stress: a physicochemical examination. J Pineal Res 51:1-16.

Gnatenco C, Han J, Snyder AK, Kim D (2002) Functional expression of TREK-2 K^+ channel in cultured rat brain astrocytes. Brain Res 931:56-67.

Grunnet M, Jespersen T, Angelo K, Frøkjær-Jensen C, Klaerke DA, Olesen SP, Jensen BS (2001) Pharmacological modulation of SK3 channels. Neuropharmacology 40:879-887.

Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP (2004) Two-pore-domain K^+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Mol Pharmacol 65:443-452.

Gu W, Günter S, Jochen RH, Hartmut E, Chiristine KS, Andreas KS, Christian D, Ortrud KS, Jürgen D (2002) Expression pattern and functional characteristics of two novel splice variants of the two-pore-domain potassium channel TREK-2. J Physiol 539:657-668.

Gurney A, Manoury B (2009) Two-pore potassium channels in the cardiovascular system. Eur Biophys J 38:305-318.

Haenisch S, von Ruden EL, Wahmkow H, Rettenbeck ML, Michler C, Russmann V, Bruckmueller H, Waetzig V, Cascorbi I, Potschka H (2016) miRNA-187-3p-mediated regulation of the KCNK10/TREK-2 potassium channel in a rat epilepsy model. ACS Chem Neurosci 7:1585-1594.

Han J, Truell J, Gnatenco C, Kim D (2002) Characterization of four types of background potassium channels in rat cerebellar granule neurons. J Physiol 542:431-444.

Han J, Gnatenco C, Sladek CD, Kim D (2003) Background and tandem-pore potassium channels in magnocellular neurosecretory cells of the rat supraoptic nucleus. J Physiol 546:625-639.

Harinath S, Sikdar SK (2005) Inhibition of human TREK-1 channels by caffeine and theophylline. Epilepsy Res 64:127-135.

Hennebelle M, Champeil-Potokar G, Lavialle M, Vancassel S, Denis I (2014) Omega-3 polyunsaturated fatty acids and chronic stress-induced modulations of glutamatergic neurotransmission in the hippocampus. Nutr Rev 72:99-112.

Hernandez-Araiza I, Morales-Lazaro SL, Canul-Sanchez JA, Islas LD, Rosenbaum T (2018) Role of lysophosphatidic acid in ion channel function and disease. J Neurophysiol 120:1198-1211.

Hervieu GJ, Cluderay JE, Gray CW, Green PJ, Ranson JL, Randall AD, Meadows HJ (2001) Distribution and expression of TREK-1, a two-pore-domain potassium channel, in the adult rat CNS. Neuroscience 103:899-919.

Heurteaux C, Bertaina V, Widmann C, Lazdunski M (1993) K^+ channel openers prevent global ischemia-induced expression of c-fos, c-jun, heat shock protein, and amyloid beta-protein precursor genes and neuronal death in rat hippocampus. Proc Natl Acad Sci U S A 90:9431-9435.

Heurteaux C, Laigle C, Blondeau N, Jarretou G, Lazdunski M (2006a) Alpha-linolenic acid and riluzole treatment confer cerebral protection and improve survival after focal brain ischemia. Neuroscience 137:241-251.

Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M, Lang-Lazdunski L, Widmann C, Zanzouri M, Romey G, Lazdunski M (2004) TREK-1, a K^+ channel involved in neuroprotection and general anesthesia. EMBO J 23:2684-2695.

Heurteaux C, Lucas G, Guy N, El Yacoubi M, Thümmler S, Peng XD, Noble F, Blondeau N, Widmann C, Borsotto M, Gobbi G, Vaugeois JM, Debonnel G, Lazdunski M (2006b) Deletion of the background potassium channel TREK-1 results in a depression-resistant phenotype. Nat Neurosci 9:1134-1144.

Honore E (2007) The neuronal background K2P channels: focus on TREK1. Nat Rev Neurosci 8:251-261.

Honore E, Maingret F, Lazdunski M, Patel AJ (2002) An intracellular proton sensor commands lipid- and mechano-gating of the K^+ channel TREK-1. EMBO J 21:2968-2976.

Huang CS, Song JH, Nagata K, Yeh JZ, Narahashi T (1997) Effects of the neuroprotective agent riluzole on the high voltage-activated calcium channels of rat dorsal root ganglion neurons. J Pharmacol Exp Ther 282:1280-1290.

Jain KK (2000) Evaluation of memantine for neuroprotection in dementia. Expert Opin Investig Drugs 9:1397-1406.

Kang D, Kim D (2006) TREK-2 (K2P10.1) and TRESK (K2P18.1) are major background K^+ channels in dorsal root ganglion neurons. Am J Physiol Cell Physiol 291:C138-146.

Kang D, Choe C, Kim D (2004) Functional expression of TREK-2 in insulin-secreting MIN6 cells. Biochem Biophys Res Commun 323:323-331.

Kang D, Choe C, Kim D (2005) Thermosensitivity of the two-pore domain K^+ channels TREK-2 and TRAAK. J Physiol 564:103-116.

Kang D, Choe C, Cavanaugh E, Kim D (2007) Properties of single two-pore domain TREK-2 channels expressed in mammalian cells. J Physiol 583:57-69.

Kennard LE, Chumbley JR, Ranatunga KM, Armstrong SJ, Veale EL, Mathie A (2005) Inhibition of the human two-pore domain potassium channel, TREK-1, by fluoxetine and its metabolite norfluoxetine. Br J Pharmacol 144:821-829.

Kim D (2003) Fatty acid-sensitive two-pore domain K^+ channels. Trends Pharmacol Sci 24:648-654.

Kim D, Sladek CD, Aguado-Velasco C, Mathiasen JR (1995) Arachidonic acid activation of a new family of K^+ channels in cultured rat neuronal cells. J Physiol 484:643-660.

Kim EJ, Kang D, Han J (2011) Baicalein and wogonin are activators of rat TREK-2 two-pore domain K^+ channel. Acta Physiol (Oxf) 202:185-192.

Kim EJ, Lee DK, Hong SG, Han J, Kang D (2017) Activation of TREK-1, but Not TREK-2, Channel by Mood Stabilizers. Int J Mol Sci 18:2460.

Kim JS, Park JY, Kang HW, Lee EJ, Bang H, Lee JH (2005) Zinc activates TREK-2 potassium channel activity. J Pharmacol Exp Ther 314:618-625.

Kim Y, Bang H, Gnatenco C, Kim D (2001a) Synergistic interaction and the role of C-terminus in the activation of TRAAK K^+ channels by pressure, free fatty acids and alkali. Pflugers Arch 442:64-72.

Kim Y, Gnatenco C, Bang H, Kim D (2001b) Localization of TREK-2 K^+ channel domains that regulate channel kinetics and sensitivity to pressure, fatty acids and pHi. Pflugers Arch 442:952-960.

Koh SD, Monaghan K, Sergeant GP, Ro S, Walker RL, Sanders KM, Horowitz B (2001) TREK-1 regulation by nitric oxide and cGMP-dependent protein kinase. An essential role in smooth muscle inhibitory neurotransmission. J Biol Chem 276:44338-44346.

Kreneisz O, Benoit JP, Bayliss DA, Mulkey DK (2009) AMP-activated protein kinase inhibits TREK channels. J Physiol 587:5819-5830.

Kucheryavykh LY, Kucheryavykh YV, Inyushin M, Shuba YM, Sanabria P, Cubano LA, Skatchkov SN, Eaton MJ (2009) Ischemia increases TREK-2 channel expression in astrocytes: relevance to glutamate clearance. Open Neurosci J 2:40-47.

La JH, Gebhart GF (2011) Colitis decreases mechanosensitive K2P channel expression and function in mouse colon sensory neurons. Am J Physiol Gastrointest Liver Physiol 301:G165-G174.

Laigle C, Confort-Gouny S, Le Fur Y, Cozzone PJ, Viola A (2012) Deletion of TRAAK potassium channel affects brain metabolism and protects against ischemia. PLoS One 7:e53266.

Lamanauskas N, Nistri A (2008) Riluzole blocks persistent Na^+ and Ca^{2+} currents and modulates release of glutamate via presynaptic NMDA receptors on neonatal rat hypoglossal motoneurons in vitro. Eur J Neurosci 27:2501-2514.

Lamas JA (2012) Mechanosensitive K2P channels, TREKking through the autonomic nervous system. In: Mechanically Gated Channels and Their Regulation (Kamkin A, Lozinsky I, eds), pp 35-68. Dordrecht, Netherlands: Springer Science + Business Media.

Lamas JA, Reboreda A, Codesido V (2002) Ionic basis of the resting membrane potential in cultured rat sympathetic neurons. Neuroreport 13:585-591.

Lamas JA, Romero M, Reboreda A, Sanchez E, Ribeiro SJ (2009) A riluzole- and valproate-sensitive persistent sodium current contributes to the resting membrane potential and increases the excitability of sympathetic neurones. Pflugers Arch 458:589-599.

Lauritzen I, Blondeau N, Heurteaux C, Widmann C, Romey G, Lazdunski M (2000) Polyunsaturated fatty acids are potent neuroprotectors. EMBO J 19:1784-1793.

Lee AK, Smart JL, Rubinstein M, Low MJ, Tse A (2011) Reciprocal regulation of TREK-1 channels by arachidonic acid and CRH in mouse corticotropes. Endocrinology 152:1901-1910.

Lesage F (2003) Pharmacology of neuronal background potassium channels. Neuropharmacology 44:1-7.

Lesage F, Lazdunski M (2000) Molecular and functional properties of two-pore-domain potassium channels. Am J Physiol Renal Physiol 279:F793-801.

Lesage F, Maingret F, Lazdunski M (2000a) Cloning and expression of human TRAAK, a polyunsaturated fatty acids-activated and mechano-sensitive K(+) channel. FEBS Lett 471:137-140.

Lesage F, Terrenoire C, Romey G, Lazdunski M (2000b) Human TREK2, a 2P domain mechano-sensitive K^+ channel with multiple regulations by polyunsaturated fatty acids, lysophospholipids, and Gs, Gi, and Gq protein-coupled receptors. J Biol Chem 275:28398-28405.

Lesage F, Guillemare E, Fink M, Duprat F, Lazdunski M, Romey G, Barhanin J (1996) TWIK-1, a ubiquitous human weakly inward rectifying K^+ channel with a novel structure. EMBO J 15:1004-1011.

Li XT, Dyachenko V, Zuzarte M, Putzke C, Preisig-Muller R, Isenberg G, Daut J (2006) The stretch-activated potassium channel TREK-1 in rat cardiac ventricular muscle. Cardiovasc Res 69:86-97.

Li ZB, Zhang HX, Li LL, Wang XL (2005) Enhanced expressions of arachidonic acid-sensitive tandem-pore domain potassium channels in rat experimental acute cerebral ischemia. Biochem Biophys Res Commun 327:1163-1169.

Lotshaw DP (2007) Biophysical, pharmacological, and functional characteristics of cloned and native mammalian two-pore domain K^+ channels. Cell Biochem Biophys 47:209-256.

Loucif AJC, Saintot PP, Liu J, Antonio BM, Zellmer SG, Yoger K, Veale EL, Wilbrey A, Omoto K, Cao L, Gutteridge A, Castle NA, Stevens EB, Mathie A (2018) GI-530159, a novel, selective, mechanosensitive two-pore-domain potassium (K2P) channel opener, reduces rat dorsal root ganglion neuron excitability. Br J Pharmacol 175:2272-2283.

Maingret F, Fosset M, Lesage F, Lazdunski M, Honore E (1999a) TRAAK is a mammalian neuronal mechano-gated K^+ channel. J Biol Chem 274:1381-1387.

Maingret F, Patel AJ, Lesage F, Lazdunski M, Honore E (1999b) Mechano- or acid stimulation, two interactive modes of activation of the TREK-1 potassium channel. J Biol Chem 274:26691-26696.

Maingret F, Patel AJ, Lesage F, Lazdunski M, Honore E (2000a) Lysophospholipids open the two-pore domain mechano-gated K(+) channels TREK-1 and TRAAK. J Biol Chem 275:10128-10133.

Maingret F, Lauritzen I, Patel AJ, Heurteaux C, Reyes R, Lesage F, Lazdunski M, Honore E (2000b) TREK-1 is a heat-activated background K(+) channel. EMBO J 19:2483-2491.

Mathie A, Veale EL (2007) Therapeutic potential of neuronal two-pore domain potassium-channel modulators. Curr Opin Investig Drugs 8:555-562.

Mathie A, Rees KA, El Hachmane MF, Veale EL (2010) Trafficking of neuronal two pore domain potassium channels. Curr Neuropharmacol 8:276-286.

Mazella J, Petrault O, Lucas G, Deval E, Beraud-Dufour S, Gandin C, El-Yacoubi M, Widmann C, Guyon A, Chevet E, Taouji S, Conductier G, Corinus A, Coppola T, Gobbi G, Nahon JL, Heurteaux C, Borsotto M (2010) Spadin, a sortilin-derived peptide, targeting rodent TREK-1 channels: a new concept in the antidepressant drug design. PLoS Biol 8:e1000355.

Meadows HJ, Benham CD, Cairns W, Gloger I, Jennings C, Medhurst AD, Murdock P, Chapman CG (2000) Cloning, localisation and functional expression of the human orthologue of the TREK-1 potassium channel. Pflugers Arch 439:714-722.

Meadows HJ, Chapman CG, Duckworth DM, Kelsell RE, Murdock PR, Nasir S, Rennie G, Randall AD (2001) The neuroprotective agent sipatrigine (BW619C89) potently inhibits the human tandem pore-domain K(+) channels TREK-1 and TRAAK. Brain Res 892:94-101.

Miller P, Kemp PJ, Lewis A, Chapman CG, Meadows HJ, Peers C (2003) Acute hypoxia occludes hTREK-1 modulation: re-evaluation of the potential role of tandem P domain K^+ channels in central neuroprotection. J Physiol 548:31-37.

Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA (2012) Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol Psychiatry 17:1206-1227.

Moha ou Maati H, Peyronnet R, Devader C, Veyssiere J, Labbal F, Gandin C, Mazella J, Heurteaux C, Borsotto M (2011) A human TREK-1/HEK cell line: a highly efficient screening tool for drug development in neurological diseases. PLoS One 6:e25602.

Moha Ou Maati H, Veyssiere J, Labbal F, Coppola T, Gandin C, Widmann C, Mazella J, Heurteaux C, Borsotto M (2012) Spadin as a new antidepressant: absence of TREK-1-related side effects. Neuropharmacology 62:278-288.

Mohammadi B, Krampfl K, Moschref H, Dengler R, Bufler J (2001) Interaction of the neuroprotective drug riluzole with GABAA and glycine receptor channels. Eur J Pharmacol 415:135-140.

Moreno S, Devader CM, Pietri M, Borsotto M, Heurteaux C, Mazella J (2018) Altered Trek-1 function in sortilin deficient mice results in decreased depressive-like behavior. Front Pharmacol 9:863.

Namiranian K, Brink CD, Goodman JC, Robertson CS, Bryan RM Jr (2011) Traumatic brain injury in mice lacking the K channel, TREK-1. J Cereb Blood Flow Metab 31:e1-6.

Namiranian K, Lloyd EE, Crossland RF, Marrelli SP, Taffet GE, Reddy AK, Hartley CJ, Bryan RM Jr (2010) Cerebrovascular responses in mice deficient in the potassium channel, TREK-1. Am J Physiol Regul Integr Comp Physiol 299:R461-469.

Noël J, Sandoz G, Lesage F (2011) Molecular regulations governing TREK and TRAAK channel functions. Channels (Austin) 5:402-409.

Noël J, Zimmermann K, Busserolles J, Deval E, Alloui A, Diochot S, Guy N, Borsotto M, Reeh P, Eschalier A, Lazdunski M (2009) The mechano-activated K^+ channels TRAAK and TREK-1 control both warm and cold perception. EMBO J 28:1308-1318.

Ozaita A, Vega-Saenz de Miera E (2002) Cloning of two transcripts, HKT4.1a and HKT4.1b, from the human two-pore K^+ channel gene KCNK4: Chromosomal localization, tissue distribution and functional expression. Mol Brain Res 102:18-27.

Park H, Kim EJ, Han J, Kang D (2016) Effects of analgesics and antidepressants on TREK-2 and TRESK currents. Korean J Physiol Pharmacol 20:379-385.

Parrill AL (2005) Structural characteristics of lysophosphatidic acid biological targets. Biochem Soc Trans 33:1366-1369.

Patel AJ, Honore E (2001) Properties and modulation of mammalian 2P domain K^+ channels. Trends Neurosci 24:339-346.

Patel AJ, Lazdunski M, Honore E (2001) Lipid and mechano-gated 2P domain K^+ channels. Curr Opin Cell Biol 13:422-428.

Patel AJ, Honore E, Maingret F, Lesage F, Fink M, Duprat F, Lazdunski M (1998) A mammalian two pore domain mechano-gated S-like K^+ channel. EMBO J 17:4283-4290.

Perlis RH, Moorjani P, Fagerness J, Purcell S, Trivedi MH, Fava M, Rush AJ, Smoller JW (2008) Pharmacogenetic analysis of genes implicated in rodent models of antidepressant response: association of TREK1 and treatment resistance in the STAR(*)D study. Neuropsychopharmacology 33:2810-2819.

Poupon L, Lamoine S, Pereira V, Barriere DA, Lolignier S, Giraudet F, Aissouni Y, Meleine M, Prival L, Richard D, Kerckhove N, Authier N, Balayssac D, Eschalier A, Lazdunski M, Busserolles J (2018) Targeting the TREK-1 potassium channel via riluzole to eliminate the neuropathic and depressive-like effects of oxaliplatin. Neuropharmacology 140:43-61.

Punke MA, Licher T, Pongs O, Friederich P (2003) Inhibition of human TREK-1 channels by bupivacaine. Anesth Analg 96:1665-1673.

Ratte S, Prescott SA (2016) Afferent hyperexcitability in neuropathic pain and the inconvenient truth about its degeneracy. Curr Opin Neurobiol 36:31-37.

Reboreda A, Sanchez E, Romero M, Lamas JA (2003) Intrinsic spontaneous activity and subthreshold oscillations in neurones of the rat dorsal column nuclei in culture. J Physiol 551:191-205.

Rivas-Ramirez P, Cadaveira-Mosquera A, Lamas JA, Reboreda A (2015) Muscarinic modulation of TREK currents in mouse sympathetic superior cervical ganglion neurons. Eur J Neurosci 42:1797-1807.

Sabbadini M, Yost CS (2009) Molecular biology of background K^+ channels: insights from K2P knockout mice. J Mol Biol 385:1331-1344.

Sandoz G, Bell SC, Isacoff EY (2011) Optical probing of a dynamic membrane interaction that regulates the TREK1 channel. Proc Natl Acad Sci U S A 108:2605-2610.

Sandoz G, Thummler S, Duprat F, Feliciangeli S, Vinh J, Escoubas P, Guy N, Lazdunski M, Lesage F (2006) AKAP150, a switch to convert mechano-, pH- and arachidonic acid-sensitive TREK K(+) channels into open leak channels. EMBO J 25:5864-5872.

Saransaari P, Oja SS (2000) Taurine and neural cell damage. Amino Acids 19:509-526.

Schmidt C, Wiedmann F, Kallenberger SM, Ratte A, Schulte JS, Scholz B, Muller FU, Voigt N, Zafeiriou MP, Ehrlich JR, Tochtermann U, Veres G, Ruhparwar A, Karck M, Katus HA, Thomas D (2017) Stretch-activated two-pore-domain (K2P) potassium channels in the heart: Focus on atrial fibrillation and heart failure. Prog Biophys Mol Biol 130:233-243.

Seifert G, Huttmann K, Binder DK, Hartmann C, Wyczynski A, Neusch C, Steinhauser C (2009) Analysis of astroglial K^+ channel expression in the developing hippocampus reveals a predominant role of the Kir4.1 subunit. J Neurosci 29:7474-7488.

Simkin D, Cavanaugh EJ, Kim D (2008) Control of the single channel conductance of K2P10.1 (TREK-2) by the amino-terminus: role of alternative translation initiation. J Physiol 586:5651-5663.

Soussia IB, Choveau FS, Blin S, Kim EJ, Feliciangeli S, Chatelain FC, Kang D, Bichet D, Lesage F (2018) Antagonistic effect of a cytoplasmic domain on the basal activity of polymodal potassium channels. Front Mol Neurosci 11:301.

Spence RD, Voskuhl RR (2012) Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. Front Neuroendocrinol 33:105-115.

Takahira M, Sakurai M, Sakurada N, Sugiyama K (2005) Fenamates and diltiazem modulate lipid-sensitive mechano-gated 2P domain K(+) channels. Pflugers Arch 451:474-478.

Talley EM, Solorzano G, Lei Q, Kim D, Bayliss DA (2001) CNS distribution of members of the two-pore-domain (KCNK) potassium channel family. J Neurosci 21:7491-7505.

Terrenoire C, Lauritzen I, Lesage F, Romey G, Lazdunski M (2001) A TREK-1-like potassium channel in atrial cells inhibited by beta-adrenergic stimulation and activated by volatile anesthetics. Circ Res 89:336-342.

Thümmler S, Duprat F, Lazdunski M (2007) Antipsychotics inhibit TREK but not TRAAK channels. Biochem Biophys Res Commun 354:284-289.

Vallazza-Deschamps G, Fuchs C, Cia D, Tessier LH, Sahel JA, Dreyfus H, Picaud S (2005) Diltiazem-induced neuroprotection in glutamate excitotoxicity and ischemic insult of retinal neurons. Doc Ophthalmol 110:25-35.

Veale EL, Al-Moubarak E, Bajaria N, Omoto K, Cao L, Tucker SJ, Stevens EB, Mathie A (2014) Influence of the N terminus on the biophysical properties and pharmacology of TREK1 potassium channels. Mol Pharmacol 85:671-681.

Viatchenko-Karpinski V, Ling J, Gu JG (2018) Characterization of temperature-sensitive leak K(+) currents and expression of TRAAK, TREK-1, and TREK2 channels in dorsal root ganglion neurons of rats. Mol Brain 11:40.

Vivier D, Soussia IB, Rodrigues N, Lolignier S, Devilliers M, Chatelain FC, Prival L, Chapuy E, Bourdier G, Bennis K, Lesage F, Eschalier A, Busserolles J, Ducki S (2017) Development of the first two-pore domain potassium channel TWIK-related K(+) channel 1-selective agonist possessing in vivo antinociceptive activity. J Med Chem 60:1076-1088.

Weiss S, Benoist D, White E, Teng W, Saint DA (2010) Riluzole protects against cardiac ischaemia and reperfusion damage via block of the persistent sodium current. Br J Pharmacol 160:1072-1082.

Weiss SM, Saint DA (2010) The persistent sodium current blocker riluzole is antiarrhythmic and anti-ischaemic in a pig model of acute myocardial infarction. PLoS One 5:e14103.

Wiedmann F, Schmidt C, Lugenbiel P, Staudacher I, Rahm AK, Seyler C, Schweizer PA, Katus HA, Thomas D (2016) Therapeutic targeting of two-pore-domain potassium (K(2P)) channels in the cardiovascular system. Clin Sci (Lond) 130:643-650.

Woo J, Jun YK, Zhang YH, Nam JH, Shin DH, Kim SJ (2018) Identification of critical amino acids in the proximal C-terminal of TREK-2 K(+) channel for activation by acidic pHi and ATP-dependent inhibition. Pflugers Arch 470:327-337.

Woo J, Shin DH, Kim HJ, Yoo HY, Zhang YH, Nam JH, Kim WK, Kim SJ (2016) Inhibition of TREK-2 K(+) channels by PI(4,5)P2: an intrinsic mode of regulation by intracellular ATP via phosphatidylinositol kinase. Pflugers Arch 468:1389-1402.

Wu JY, Wu H, Jin Y, Wei J, Sha D, Prentice H, Lee HH, Lin CH, Lee YH, Yang LL (2009) Mechanism of neuroprotective function of taurine. Adv Exp Med Biol 643:169-179.

Wu X, Liu Y, Chen X, Sun Q, Tang R, Wang W, Yu Z, Xie M (2013) Involvement of TREK-1 activity in astrocyte function and neuroprotection under simulated ischemia conditions. J Mol Neurosci 49:499-506.

Xi-Moy SX, Dun NJ (1995) Potassium currents in adult rat intracardiac neurones. J Physiol 486:15-31.

Xian Tao L, Dyachenko V, Zuzarte M, Putzke C, Preisig-Muller R, Isenberg G, Daut J (2006) The stretch-activated potassium channel TREK-1 in rat cardiac ventricular muscle. Cardiovasc Res 69:86-97.

Xiao Z, Deng PY, Rojanathammanee L, Yang C, Grisanti L, Permpoonputtana K, Weinshenker D, Doze VA, Porter JE, Lei S (2009) Noradrenergic depression of neuronal excitability in the entorhinal cortex via activation of TREK-2 K^+ channels. J Biol Chem 284:10980-10991.

Xiao Z, Cilz NI, Kurada L, Hu B, Yang C, Wada E, Combs CK, Porter JE, Lesage F, Lei S (2014) Activation of neurotensin receptor 1 facilitates neuronal excitability and spatial learning and memory in the entorhinal cortex: beneficial actions in an Alzheimer's disease model. J Neurosci 34:7027-7042.

Yazdi S, Stein M, Elinder F, Andersson M, Lindahl E (2016) The molecular basis of polyunsaturated fatty acid interactions with the shaker voltage-gated potassium channel. PLoS Comput Biol 12:e1004704.

Zhang H, Cuevas J (2005) σ Receptor activation blocks potassium channels and depresses neuroexcitability in rat intracardiac neurons. J Pharmacol Exp Ther 313:1387-1396.

Zhang H, Shepherd N, Creazzo TL (2008) Temperature-sensitive TREK currents contribute to setting the resting membrane potential in embryonic atrial myocytes. J Physiol 586:3645-3656.

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