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Two-pore domain potassium (K2P) channels are expressed in cells throughout the body and give rise to leak potassium currents which control the excitability of these cells. Although not inhibited by classical potassium channel-blocking drugs, such as tetraethylammonium and 4-aminopyridine, K2P channels are regulated by a diverse array of pharmacological mediators. There are six main families of K2P channels and among these certain members of the TREK family (ie, TREK-1 and TREK-2) are activated by general anesthetic agents such as halothane, xenon and nitrous oxide. In addition, all members of the TREK family are activated by neuroprotective agents such as riluzole, polyunsaturated fatty acids and lysophospholipids, suggesting that these channels play an important role in neuroprotection. TREK channels are also inhibited by chlorpromazine, local anesthetics and the antidepressant fluoxetine. Furthermore, all members of the TASK family are inhibited by cannabinoids and local anesthetics, and TASK-3 is selectively inhibited by ruthenium red. Thus, the diversity and physiological importance of K2P channels suggest that the development of selective compounds to target these proteins has therapeutic potential for CNS disorders such as stroke, depression and epilepsy.

Keywords Antidepressant, cannabinoid, ciclosporin, fluoxetine, general anesthetic, lysophospholipid, neuro-protection, polyunsaturated fatty acid, ruthenium red, two-pore domain potassium channel

Introduction

Two-pore domain potassium (K2P) channels give rise to leak potassium currents and are expressed throughout the CNS [1,2] and in most other organs in the body [3•,4•,5•]. They contribute to the resting membrane potential of neurons and regulate their excitability. While K2P channels are generally open at all voltages, they also display some voltage dependency [6]. There are 15 members of the human K2P channel superfamily, which can be divided into six main families based on their structural and functional properties: TREK, TASK, TWIK, TALK, THIK and TRESK (Figure 1) [3•,4•,7–9]. Furthermore, K2P channels are regulated by a diverse array of pharmacological agents, physiological mediators and neurotransmitter-activated pathways [3•,5•,7].

Currently, there are no compounds specifically designed to inhibit K2P channels; however, a large number of existing compounds act on these channels to alter their activity. In some instances, the action of these compounds may underlie or contribute to their therapeutic activity. The physiological consequences of such activity may lead to the generation of compounds that selectively inhibit K2P channels for a particular therapeutic advantage. K2P channels can also be regulated indirectly (ie, by G-protein-coupled receptor pathways and kinases), and thus compounds which interact with these indirect pathways also have important physiological actions mediated via K2P channels. However, it is beyond the scope of this review to also consider these indirect regulatory pathways (see reference [10] for examples). This review focuses on compounds that directly modulate K2P channel activity, assesses the physiological consequences of such actions and discusses whether these (or any related, more selective, second-generation) compounds provide further support for the potential targeting of K2P channels in CNS diseases such as stroke, epilepsy and depression.

General blockers of K2P channels

An interesting pharmacological feature of K2P channels is that they are highly insensitive to both of the classical drugs used to block voltage-gated potassium channels: tetraethylammonium (TEA) ions and 4-aminopyridine (4-AP). However, K2P channels can be blocked by barium ions and, in some cases, by quinidine and quinine.

Quinidine and quinine

Quinidine, a stereoisomer of the naturally occurring product quinine, is used as a class I anti-arrhythmic agent in the heart and affects many ion channels, including sodium, calcium and potassium channels. While quinidine blocks the TASK-1 and TASK-3 K2P channels modestly (approximately 30% at 100 μM) [11–13], its effects on TREK-1 channels are more varied. An early study of TREK-1 channels expressed in Xenopus oocytes showed that the channels were unaffected by either quinidine or quinine [14]. However, later research with COS cells (transformed monkey kidney fibroblasts) suggested that quinidine could block TREK-1 channels [15]. Similarly, both quinine and quinidine block TWIK-2 channels but only when recordings are made in physiological potassium solutions – no blockade has been observed in symmetrical potassium solutions [16]. These latter observations highlight the importance of understanding the pharmacology of K2P channels; the effectiveness of certain compounds is dependent upon the experimental approach, and certain compounds (presumably those that interact with the permeation pathway) are influenced by the concentration and the net direction of movement of the permeating ion. Of the other K2P channels, TRESK [17,18] and TRAAK [19] are inhibited by both quinidine and quinine. However, the situation for TALK channels is more complicated. While both TALK-1 and TALK-2 channels are inhibited by quinidine (1 mM), quinine strongly inhibited TALK-1 channels and activated TALK-2 channels [20,21].
The 15 members of the K2P channel superfamily are shown according to their six main groups. The K2P nomenclature as approved by the International Union of Basic and Clinical Pharmacology is shown in parentheses (see reference [4•] for further details). Note that the KCNK-7, THIK-2 and TASK-5 subtypes are functionally silent when expressed in isolation. It is generally useful for a compound to selectively act on either a particular K2P channel family or an individual family member. The most extensively researched families of K2P channels are the TREK and TASK families, and as such this review focuses on compounds in relation to these two families. However, where effects of compounds have also been observed in other K2P channel families these will also be mentioned.

The TREK family of K2P channels

The TREK family (TREK-1, TREK-2 and TRAAK) is the most widely studied of the K2P channels and appears to show the largest diversity of regulation by pharmacological agents [22]. A number of compounds have been identified which either upregulate or downregulate TREK channel activity, and among these several compounds have shown important therapeutic actions, for example, as general anesthetic and neuroprotective agents.

General anesthetic agents

General anesthetics can be divided into three broad classes: intravenous agents (such as barbiturates, propofol and etomidate), volatile anesthetics (such as halothane, chloroform and isoflurane) and gaseous anesthetics (such as xenon, nitrous oxide and cyclopropane). While intravenous agents appear to have little effect on K2P channels and likely mediate their anesthetic activity through enhancement of GABAA receptor activity, the volatile anesthetics have a range of stimulatory and inhibitory effects on K2P channels in addition to their actions on GABAA receptors [23••,24-26].

TREK-1 and TREK-2 (but not TRAAK) channels are activated by general anesthetics [19,23••], and progressive deletion of the C terminus of TREK-1 suggests that this region is important for their anesthetic activity [23••]. In addition, the reduced sensitivity to volatile anesthetics in TREK-1 knockout animals [27••] suggests that the action of volatile anesthetics on TREK-1 channels is of considerable physiological importance.

Interestingly, gaseous anesthetics appear to selectively target and enhance the activity of TREK-1 channels (and presumably the related TREK-2 channels) with little action on other K2P channels [26,28••]. The effect of these agents on TREK-1 activity was completely abolished by a single amino-acid point mutation (ie, E306A) in the C terminus of TREK-1 [28••], again confirming the importance of this region in transducing the effect of many regulatory compounds on TREK-1 [29•]. The activation of TREK-1 channels by gaseous anesthetic agents may also contribute to their neuroprotective effects (see below and reference [26]).

Trichloroethanol (TCE; a metabolic by-product of chloral hydrate and which is responsible for the pharmacological actions of chloral hydrate) has been shown to regulate TREK channels [30]. In addition, TCE (5 mM) activated both human (h)TREK-1 and hTRAAK channels [30]. This latter finding is particularly surprising because TRAAK channels, unlike other TREK and TASK family members, are insensitive to inhalation anesthetics and thus was the first indication that an anesthetic could have an effect on TRAAK channels.

Arguably, general anesthetics are among the most 'promiscuous' of all compounds which act on K2P channels. In addition to their action on TREK channels, certain general anesthetics also act on TASK channels to enhance their activity (see below for further information). Furthermore,
TRESK channels are extremely sensitive to volatile anesthetics such as isoflurane, halothane, sevoflurane and desflurane. While the effect is species dependent [31], hTRESK channels are more strongly enhanced by volatile anesthetics compared with other K2P channels [32]. As volatile anesthetics produce surgical immobility via a spinal cord-mediated action, this finding suggests a role for hTRESK channels in anesthetic mechanisms. On the other hand, a number of K2P channels are inhibited by general anesthetic agents, for example, halothane inhibits members of the TWIK and THIK families [16,25]. Furthermore, halothane demonstrates various actions on the TALK family, as it inhibits TALK-1 and TALK-2 [20], and activates TASK-2 [33].

Neuroprotective agents

A number of neuroprotective compounds regulate the activity of TREK channels, including riluzole (Rilutek) a potent neuroprotective drug used to treat amyotrophic lateral sclerosis [34]. In preclinical trials, riluzole demonstrated efficacy in preventing spinal cord injury and improving recovery from ischemia in the rat retina [35,36]. Riluzole (10 to 100 μM) enhanced the activity of both TREK-1 and TRAAK channels through a direct interaction with the specific channel [37]. However, prolonged application of riluzole has a biphasic effect on TREK-1 channels (but not TRAAK channels) with a secondary inhibition of current also observed. This is an indirect effect that occurs via the inhibitory action of cAMP on TREK-1 channels, due to the blockade of PDE breakdown of cAMP by riluzole [37]. It is not clear which of the two effects will dominate in vivo. Furthermore, sipatrigine (BW-619-C89; discontinued from development for the treatment of stroke [33]) demonstrated protection against neuronal ischemia [40]. Therefore, and somewhat surprisingly, some neuroprotective agents can both enhance and inhibit the activity of TREK and TRAAK channels.

Polyunsaturated fatty acids (PUFAs), such as linoleic acid (found in high quantities in vegetable oils), have also demonstrated protection against neuronal ischemia [40]. Arachidonic acid (AA) and other PUFAs activate all three members of the TREK family [15,41,42]. This activation initially protects the neurons; however, high levels of AA can occur during seizures and in ischemia [43], resulting in neuronal cell death [44-46].

A potent protective role of lysophospholipids has also been demonstrated in global cerebral ischemia and glutamate excitotoxicity in rats [26,47]. Lysophosphatidic acid (LPA) is a bioactive lipid with both extra- and intracellular targets, and important roles in physiology and pathophysiology. Lysophospholipids also activate TREK channels [19,48] and converts them into pure leak potassium conductances, with LPA demonstrating an EC_{50} value of approximately 2.5 μM [49].

Because PUFAs and extracellular lysophospholipids are neuroprotective and activate TREK and TRAAK channels, they appear to have an important physiological role in neuroprotection [40]. The role of the TREK-1 channel in PUFAs- and LPA-induced neuroprotection was demonstrated by comparing TREK-1 wild-type mice with TREK-1 knockout mice [27]. Importantly, PUFAs- and LPA-induced neuroprotection was not observed in the TREK-1 knockout mice. In addition, the combined effect of riluzole and linoleic acid post-ischemia has demonstrated beneficial effects to both individual neuron survival and overall animal survival [50].

At a molecular level, the effects of neuroprotective agents are dependent upon an intracellular glutamate residue at position 306 (E306), which acts as a key sensor for transduction (similarly to general anesthetics). What is not clear, however, is where on the channels these neuroprotectants bind or whether there are multiple binding sites for the different activators of TREK channels. Indeed, the effect of LPA (but not PUFAs) has been suggested to be mediated through a change in the curvature of the membrane [49], rather than direct binding to the channel itself.

Antipsychotic and antidepressant agents

TREK channels are inhibited by the antipsychotic agent chlorpromazine [14] and the antidepressant fluoxetine (IC_{50} = 19 μM, or 9 μM for norfluoxetine) [51]. Fluoxetine blockade of TREK-1 channels does not require the C terminus of the channel (in contrast to the activation observed with the general anesthetics and AA [23,28]); however, it appears to interact with the transduction pathway through E306, and thus acts as an allosteric blocker of channel activity [28,51]. Both chlorpromazine and fluoxetine are lipophilic and it has been suggested that they enter the lipid membrane and act as a cationic amphiphil to change the curvature of the membrane and inhibit TREK-1 channel current [15]. In other words, chlorpromazine may act in the opposite manner to LPA (which enhances current). It was originally thought that neither chlorpromazine nor fluoxetine produced their effects through an interaction with TREK channels, and that their actions may contribute to some of the side effects observed, such as an exacerbation of convulsion tendency. However, a recent study using TREK-1 knockout mice reported that these animals displayed an antidepressant phenotype, suggesting that the action of fluoxetine and other antidepressant agents on TREK-1 channels may contribute, at least in part, to their therapeutic benefit in the treatment of depression [52].

Local anesthetic agents

A number of amide-linked local anesthetic agents (such as lidocaine, mepivacaine [AP Pharma Inc; Figure 2], tetracaine, ropivacaine and bupivacaine) inhibit various K2P channels, with little or no effect occurring with ester-linked local anesthetics [53,54]. The increase in membrane excitability following K2P channel blockade may contribute to the cardiotoxic and excitotoxic side effects of local anesthetics. For example, bupivacaine, in comparison with other local anesthetics, is markedly cardiotoxic and inhibits TREK-1, TASK-1 and TASK-2 channels [53,54] - all of which are highly expressed in the heart and CNS. Another possible K2P channel-related side effect of local anesthetics is
tinnitus, as a number of local anesthetic-sensitive K2P channels are highly expressed in the cochlea [55]. Similar to general anesthetic agents, local anesthetics demonstrate activity on a number of other K2P channels, and in all cases these actions have also been inhibitory [31,53,54].

**Other agents that act on TREK channels**

A number of other therapeutically important agents have demonstrated activity on the TREK family of K2P channels, including theophylline [56], caffeic acid derivatives [57•], flufenamic acid [58,59], diltiazem [59] and mibebradil [49•,60].

**Theophylline**

Theophylline and caffeine belong to the family of xanthine alkaloids, which are used therapeutically as bronchodilators and mild stimulants. It has been suggested that the epileptogenicity of excess caffeine and theophylline may be related to their inhibition of K2P channels, in particular the TREK-1 channels [56].

**Caffeic acid derivatives**

Caffeic acid is a carboxylic acid found in many fruits, vegetables and beverages (including coffee, although there is no other connection between caffeic acid and caffeine). Certain caffeic acid derivatives (such as cinnamyl 1-3,4-dihydroxy-cyanocinnamate; 5 to 10 μM) markedly enhance the activity of TREK-1 channels [57•], although caffeic acid itself is without effect. It appears that caffeic acid derivatives bind to an external site to produce their effects on TREK-1 channels [57•] in contrast with other agents that act via an intracellular site (ie, AA).

**Flufenamic acid**

Fenamates belong to the family of NSAIDs, and demonstrate analgesic, antipyrexic and anti-inflammatory properties. Fenamates stimulate the activity of a large conductance potassium channel in the rabbit and bovine corneal epithelium [58,59]. Importantly, this potassium channel was characterized as a mechan gated K2P channel belonging to the TREK/TRAANK family. A number of fenamates, such as flufenamic acid, niflumic acid and mafenamic acid (all at 100 μM), were tested on recombinant members of the TREK/TRAANK family of channels [61]. As was observed in the corneal epithelium, fenamates augmented TREK-1, TREK-2 and TRAAK channel currents, which may contribute to their pain-relieving and anti-inflammatory properties.

**Diltiazem and mibebradil**

The l-type calcium channel blocker diltiazem [59] and the t-type calcium channel blocker mibebradil [49•,60] inhibit members of the TREK family. In addition, diltiazem inhibits the background potassium conductance in the corneal epithelium. When administered to recombinant clones, diltiazem inhibited TREK-1 and TREK-2 channels (with a complete blockade at 1 mM), but had no effect on TRAAK channels [59].

**The TASK family of K2P channels**

The TASK family of K2P channels (including TASK-1, TASK-3 and the non-functional TASK-5) underlie leak potassium conductances in many CNS neurons. These channels are regulated by a number of signaling pathways in the neurons and by various pharmacological mediators, although there is currently a distinct lack of compounds that are selective for a particular channel type.

**Ruthenium red and zinc**

Ruthenium red inhibits a number of different channels and, as such, is not considered to be a selective antagonist for a particular K2P channel. Nevertheless, it has demonstrated selective inhibition of TASK-3 channels (IC50 = 0.7 μM) compared with TASK-1 and the heterodimeric TASK-1/TASK-3 channels [62••]. As such, ruthenium red is useful as a diagnostic tool to distinguish between TASK channel types once it has been established that a TASK channel underlies the observed current. Interestingly, identification of the ruthenium red-binding region on the TASK-3 channel highlights the possibility of selectively targeting this site through rational drug design. Ruthenium red binds to a glutamate residue (E70) on the M1/P1 loop of TASK-3 (the large extracellular loop between the first transmembrane domain and the first pore region). The equivalent residue at position 70 is a lysine (potassium) in TASK-1 channels [62••]. The presence of the same residue also explains the relative selectivity of zinc for TASK-3 over TASK-1 (IC50 = 20 μM) [63] and the ability of other divalent (ie, magnesium and calcium) and polyvalent ( spermine) cations to specifically block TASK-3 channels [64]. Interestingly, heterodimeric TASK-1/TASK-3 channels are insensitive to ruthenium red, suggesting that two E residues at the E70 position are required per channel for effective binding of the compound [62••]. These data support the M1/P1 loop as a potential site of action for the design of compounds which selectively act on particular TASK channel subtypes.

**Cannabinoids**

Anandamide (Yissum Research Development Co of the Hebrew University of Jerusalem/Kadmus Pharmaceuticals Inc; Figure 3) is a naturally occurring endogenous cannabinoid neurotransmitter found in the brain and other organs of the body, which binds to and activates the CB1 and CB2 cannabinoid receptors. Anandamide and other cannabinoid agonists reproduce the effects of the psychoactive component of cannabis, Δ9-tetrahydrocannabinol. Endocannabinoid agonists, including anandamide, methanandamide and WIN-55212-2 (R(+-)2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]1,4-benzoazinyl)-(1-naphthalenyl)methanone mesylate), significantly inhibit TASK-1 channels [65] with little effect on other K2P channels. In addition, methanandamide is equally effective at blocking TASK-3 channels [2,66]. While WIN-55212-2 was being developed as a potential treatment for emesis, pain and inflammation by Sanofi Winthrop Inc [67], no development has been reported on...
this compound since 1996 and it is now assumed to be used as a research tool. The effect of cannabinoids on TASK-1 and TASK-3 channels occurs independently of the cannabinoid receptors [65], and direct inhibition of these channels may explain some of the physiological and behavioral effects observed with these agonists, such as hypothermia, hypokinesia, analgesia and catalepsy. In support of this hypothesis, the analgesic, sedative and hypothermic effects of WIN-55212-2 were reduced in TASK-1 knockout mice [68].

**General anesthetic agents**

Halothane and isoflurane were originally considered potent activators for a variety of TASK family members [23,69,70], and this effect was particularly strong in brainstem motoneurons and thalamocortical neurons [71,72] – the regions of the brain that are fundamentally important in mediating the loss of motor control and consciousness during general anesthesia. However, it has since been demonstrated that while high concentrations of isoflurane potentiate TASK-3 channels, TASK-1 channels are inhibited [73]. Moreover, TASK-1/TASK-3 heterodimeric channels behave in a similar manner to TASK-3 channels as they are potentiated by isoflurane. Thus, together with other agents such as ruthenium red and zinc, isoflurane is particularly useful for discriminating between homodimeric and heterodimeric TASK channels in native neurons [2,73].

**Local anesthetic agents**

In addition to inhibiting TREK channels, local anesthetic agents are also inhibitors of TASK channels. Bupivacaine potently inhibits both TASK-1 and TASK-3 channels (IC\textsubscript{50} \approx 40 \textmu M) [11,12,53,54]. Lidocaine is approximately 5- to 10-fold less effective than bupivacaine at inhibiting TASK-1 and -3 channels (IC\textsubscript{50} \approx 220 \textmu M) [11,12].

**Other compounds which act on TASK channels**

**Treprostinil**

Treprostinil is a stable analog of prostacyclin and is used to treat the symptoms of primary pulmonary hypertension [74]. This compound (IC\textsubscript{50} = 1.2 \textmu M) has demonstrated activation of TASK-1 channels present in pulmonary artery smooth-muscle cells via a protein kinase A-dependent pathway [75]. An important mechanism underlying the prostanoïd-induced relaxation of pulmonary arteries might be elucidated from these data.

**Doxapram**

The analeptic agent doxapram, a respiratory stimulant used to treat ventilatory failure, inhibits TASK-1, TASK-3 and TASK-1/TASK-3 channels (EC\textsubscript{50} = 410 nM, 37 \textmu M and 9 \textmu M, respectively) [76]. TASK-1 and TASK-3 channels are expressed in the carotid bodies and brainstem, and a potassium conductance with TASK-1-like properties has been identified in the carotid cell bodies [13]. Doxapram is known to stimulate chemoreceptors in the carotid bodies, suggesting that K2P channels (in particular TASK-1 channels) have a role in chemosensing.

**Other blockers of K2P channels and native leak potassium channels**

**Calcineurin inhibitors**

The most recently cloned member of the K2P channel superfamily, TRESK, was thought to be expressed solely in the spinal cord [17], but it has since been localized to various regions of the brain [32,77] and dorsal root ganglia of mice [78]. One interesting property of TRESK channels is that they are activated in response to increased cytoplasmic calcium levels by the calcium/calmodulin-dependent protein phosphatase calcineurin [79]. A docking site similar to the NFAT (nuclear factor of activated T-cells) site has been identified on TRESK channels, suggesting that calcineurin may have a direct action on TRESK [77]. In addition, common immunosuppressants, such as ciclosporin A (100 nM) and tacrolimus (200 nM), are specific inhibitors of calcineurin and have been shown to ablate TRESK channel activation [77,79].

**Ecstasy**

In cultured hippocampal neurons of rats, ecstasy (3,4-methyleneoxy-N-methylamphetamine [MDMA]) inhibits background potassium conductance (Figure 4), which leads to increased neuronal excitability and enhanced synaptic strength [80]. Hippocampal neurons express a large number of K2P channels to varying degrees [1], with TASK-3 and TREK-1 channels most highly expressed. It is not clear which K2P channels are the primary targets for MDMA; however, it has been suggested that this drug has no effect on recombinant TREK-1 and TASK-1 channels [7].

**BL-1249**

BL-1249 (5,6,7,8-tetrahydro-naphthalen-1-yl)-2-[(1H-tetrazol-5-yl)-phenyl]-amine is a putative activator of the potassium channels which are found in smooth-muscle cells of the bladder, and has demonstrated bladder-relaxant properties [81]. BL-1249 (EC\textsubscript{50} = 1.5 \textmu M) produced a concentration-dependent membrane hyperpolarization, with a reversal potential of -80 mV, similar to the activation of potassium conductance [81]. This BL-1249-induced current was blocked by barium ions, and was insensitive to TEA and 4-AP, data characteristic of K2P channels. High levels of TREN-2 mRNA were identified in human bladder myocytes using real-time PCR, and the kinetics and pharmacological properties of these channels correlated well with those of the BL-1249-evoked potassium currents [81].

**Conclusion and future prospects**

K2P channels are expressed throughout the nervous system and have a role in controlling both the neuronal resting membrane potential and the degree of neuronal excitability. As such, they are prime targets for the potential treatment of many CNS disorders. In contrast to voltage-gated potassium channels, K2P channels are insensitive to TEA and 4-AP; however, they are blocked by barium ions and in many
cases by quinidine, quinine and local anesthetic agents. Thus, while it is possible to identify a current as carried through K2P channels, in most cases it is difficult to assess which K2P channel (or which family of K2P channels) underlies a particular current.

The most commonly studied group of K2P channels are the TREK and TASK families, and there are a number of compounds which activate or inhibit these channels. Unfortunately, the large majority of these compounds have multiple actions on other channels and receptors. Therefore, while it is possible to identify the roles of individual K2P channels, there are currently no compounds available that are truly selective pharmacological agents. Nonetheless, for particular clinical issues, the regulation of K2P channel activity has important therapeutic applications. For example, considerable evidence suggests that TREK K2P channels are important for neuroprotection, and there is demonstrated potential for compounds that act to enhance their activity, such as riluzole [34], PUFAs (linoleic acid and AA [15,40-42]) and LPA [49]. Similarly, recent studies on the effects of antidepressant agents on K2P channels and the creation of a TREK-1 knockout mouse with an antidepressant phenotype suggest that this channel is a good future target for the development of drugs for the treatment of depression [52,82]. As such, continued research into the functional roles and physiological importance of K2P channels, together with the development of compounds that selectively target particular K2P channels, holds considerable therapeutic promise for CNS disorders.

Acknowledgements

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