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SYMPOSIUM REVIEW

The family of K_{2P} channels: salient structural and functional properties

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Abstract Potassium channels participate in many biological functions, from ion homeostasis to generation and modulation of the electrical membrane potential. They are involved in a large variety of diseases. In the human genome, 15 genes code for K^+ channels with two pore domains (K_{2P}). These channels form dimers of pore-forming subunits that produce background conductances finely regulated by a range of natural and chemical effectors, including signalling lipids, temperature, pressure, pH, antidepressants and volatile anaesthetics. Since the cloning of TWIK1, the prototypical member of this family, a lot of work has been carried out on their structure and biology. These studies are still in progress, but data gathered so far show that K_{2P} channels are central players in many processes, including ion homeostasis, hormone secretion, cell development and excitability. A growing number of studies underline their implication in physiological mechanisms, such as vascular and pulmonary hypertension, cardiac arrhythmias, nociception, neuroprotection and depression. This review gives a synthetic view of the most noticeable features of these channels.

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Abbreviations ER, endoplasmic reticulum; K_{ir} , inward rectifier potassium channel; KO, knock-out; K_{2P} channel, two-pore-domain potassium channel; K_v channel, voltage-gated K^+ channel; LP, lysophospholipid; PUFA, polyunsaturated fatty acid.

Introduction

Potassium channels are important for K^+ transport and cell volume regulation. By modulating the electrical membrane potential, they are also necessary for functions as diverse as neurotransmission, neuronal coding of

information, heart beating, muscle contraction and hormone secretion. With more than 78 genes encoding pore-forming subunits in the human genome, K^+ channels form the largest ion channel family. This family comprises three different structural subclasses related to

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voltage-gated K^+ (K_v) channels, inward rectifiers (K_{ir}) and two-pore domain K^+ (K_{2P}) channels (Goldstein *et al.* 2005; Gutman *et al.* 2005; Kubo *et al.* 2005; Wei *et al.* 2005; González *et al.* 2012). While the prototypical members of the K_v and K_{ir} subclasses were cloned on purpose using genetics and/or expression cloning, K_{2P} channels were identified by DNA database mining without clues about the electrophysiological and functional properties of their native correlates (Lesage *et al.* 1996). In heterologous systems, they were found to produce currents similar to native currents previously identified in cardiac and neuronal cells, including background K^+ currents, arachidonic acid-activated K^+ current and mechano-gated K^+ currents (for examples, see Franks & Lieb, 1988; Premkumar *et al.* 1990; Sackin, 1995; Kim *et al.* 1995). Fifteen genes (denoted *KCNKx*) encode K_{2P} channel pore-forming subunits. Alternative splicing and translation initiation, heteromerization and post-translational modifications further increase this diversity. These channels are regulated by a wide range of physical and chemical stimuli and are the targets of drugs such as anaesthetics, neuroprotective and antidepressive agents. The K_{2P} channels are involved in the development and excitability of many cell types. The characterization of their physiological and pathological functions is still ongoing, mainly using animal models. The scope of this review is to provide a synthetic overview of the most salient features of these channels. For in-depth information, the reader is referred to several exhaustive reviews (Enyedi & Czirják, 2010; Mathie *et al.* 2010; Noël *et al.* 2011; Lesage & Barhanin, 2011).

Structural features of the K_{2P} channels

Potassium channels contain a short signature sequence called the pore (P) domain. The assembly of four P domains forms the selectivity filter of an active channel (Doyle *et al.* 1998). All the subunits directly related to K_v and K_{ir} channels contain a single P domain and assemble as tetramers. TWIK1, the prototypical member of the K_{2P} channel class, was found by identifying a non-conventional P domain in an expressed sequence tag from human kidney (Lesage *et al.* 1996a). Cloning and sequencing of the corresponding full-length cDNA revealed the presence of two P domains (P1 and P2), while biochemical experiments showed that TWIK1 was able to form dimers containing four P domains, each P domain being flanked by two membrane-spanning helices (M1, M2, M3 and M4, respectively; Fig. 1A). The N- and C-termini of TWIK1 are cytoplasmic. Another unique feature is the presence of an extended extracellular loop between domains M1 and P1. This M1P1 loop is a coiled-coiled domain that interacts with the same structure of the other subunit of the dimer (Lesage *et al.* 1996b). It contains a cysteine residue (Cys69)

involved in the formation of a covalent bridge between two subunits (Lesage *et al.* 1996b). Purification and crystallization of TWIK1 (Miller & Long, 2012) and of the related TRAAK channel (Brohawn *et al.* 2012) have confirmed this organization, showing that the P domains are organized with a pseudo-fourfold symmetry (Fig. 1B). Both structures also showed that the M1P1 loop is highly structured into a helical cap that provides an

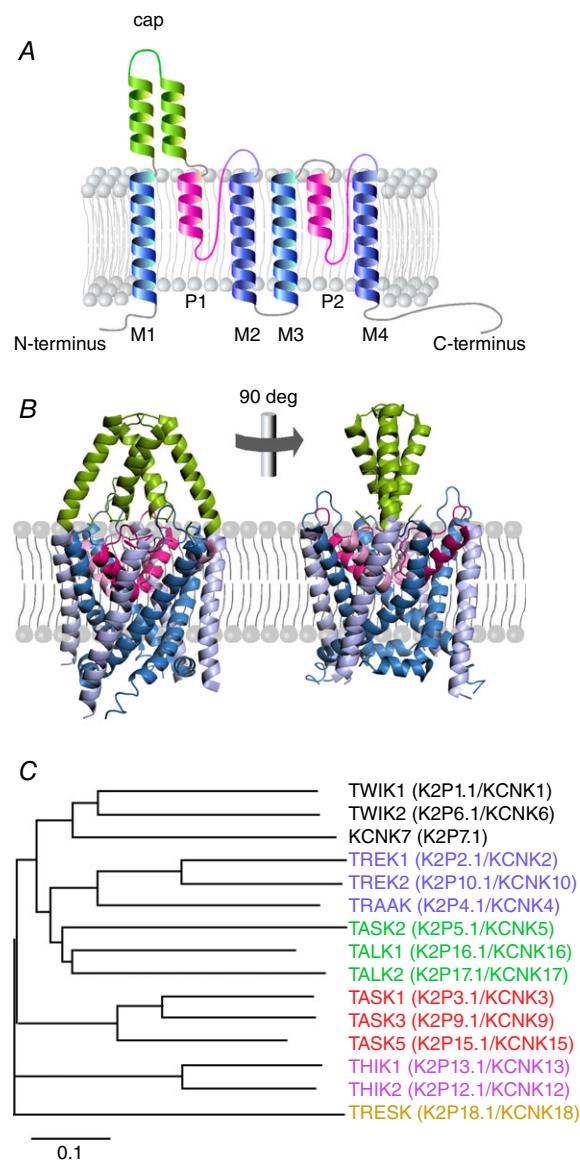


Figure 1. Structural organization of K_{2P} channels

A, schematic representation of K_{2P} subunit organization, with the two pore domains (in pink), the four transmembrane domains (in blue) and the extracellular cap (in green). B, three-dimensional reconstruction of TWIK1 deduced from the crystal structure (Miller & Long, 2012; Protein Data Bank identity code 3UKM). The different domains are represented with the same colour code as in A. C, dendrogram of the 15 K_{2P} subunits with their conventional and systematic names.

ion pathway, in which K^+ ions flow through side-portals. Disulfide-bridged cysteines are at the top of the cap and stabilize the structure. The crystals also revealed the existence of fenestrations that expose the inner pore of the channel to the lipid bilayer.

By sequence homology, 14 subunits related to TWIK1 were cloned that display the same overall organization. Based on sequence conservation and functional properties, these subunits were classified into the following six groups: TWIK for Two P-domain in a weakly inward rectifying K^+ channel; TREK (TWIK-related K^+ channel); TASK (TWIK-related acid-sensitive K^+ channel); TALK (TWIK-related alkaline-sensitive K^+ channel); THIK (Tandem pore domain halotane-inhibited K^+ channel); and TRESK (TWIK-related spinal cord K^+ channel; Fig. 1C). The only noticeable variations in the structural organization are the absence of a disulfide bond in the caps of TASK1 and TASK3 dimers and the presence of a long intracellular M2M3 loop in TRESK (Enyedi *et al.* 2012). While regulation by the cellular machinery involves the C-terminus of many K_{2P} channels, known regulations of TRESK take place in this M2M3 loop. Usually, a *KCNK* gene produces a unique K_{2P} subunit. However, the TREK/TRAAK subclass exhibits additional subunit diversity. Alternative transcription initiation leads to the production of TREK1 and TREK2 variants with a shortened cytoplasmic N-terminus, associated with a change of ionic selectivity for TREK1 (Thomas *et al.* 2008) and a change of unitary conductance for TREK2 (Simkin *et al.* 2008). In addition, alternative exon splicing produces variants of TREK1, TREK2 and TRAAK with variable levels of activity (Fink *et al.* 1996; Lesage *et al.* 2000a, b; Gu *et al.* 2002; Ozaita & Vega-Saenz de Miera, 2002; Veale *et al.* 2010; Rinné *et al.* 2014). Tissue-specific expression of some variants and the dominant-negative effect of one of them suggest that alternative splicing may be involved in the functional regulation of TREK/TRAAK channels.

Electrophysiological properties of the K_{2P} channels

Unlike K_v channels, K_{2P} channels have no voltage sensor and are not gated by the membrane potential (Fink *et al.* 1996; Lesage *et al.* 1996a; Duprat *et al.* 1997). Many of them produce almost instantaneous and non-inactivating currents over the whole range of the membrane potential. These properties mark them as background or leak K^+ channels, predicted to follow the Goldman–Hodgkin–Katz current equation for a K^+ -selective leak current. If TASK1 currents follow this equation perfectly (Duprat *et al.* 1997), others exhibit some variations, such as a slight outward (TREK1; Bockenhauer *et al.* 2001; Fink *et al.* 1996) or inward rectification (TWIK1 and TWIK2; Lesage *et al.* 1996a; Patel *et al.* 2000). Other unusual features are observed, such as a slow inactivating component that represents

about 50% of the TWIK2 current (Patel *et al.* 2000), different subconductance states for TREK1 and TREK2 (Fink *et al.* 1996; Patel *et al.* 1998; Lesage *et al.* 2000b; Kang *et al.* 2007; Simkin *et al.* 2008) and an asymmetrical gating behaviour for TRESK (Czirják *et al.* 2004). Regardless of these differences, K_{2P} channels are all insensitive or very weakly sensitive to the classical K^+ channel blockers, such as tetraethyl ammonium, Ba^{2+} , Cs^+ and 4-aminopyridine. This lack of specific pharmacology as well as their time and voltage independences explain why these currents have been overlooked despite their presence in many tissues and cells. However, even if these channels behave as leaks, they are finely regulated by many different stimuli (Table 1), and these regulations have proved to be very useful to correlate cloned and native channels.

Recent observations suggest that the gating mechanism in K_{2P} channels may be different from those of other K^+ channels. In K_{ir} and K_v channels, modulation of the activity occurs via the opening/closure of two distinct gates. The upper (or outer) gate takes place at the selectivity filter, whereas the lower (or inner) gate comprises the lower part of the inner membrane-spanning helices. Functional studies and crystal structure suggest that the access to the inner pore cavity is not modified by different stimuli that regulate K_{2P} channel activity, leading to a model in which the primary activation mechanisms reside close to or within the selectivity filter and do not involve gating at the lower cytoplasmic bundle crossing (Bagriantsev *et al.* 2011, 2012; Piechotta *et al.* 2011; Brohawn *et al.* 2012; Miller & Long, 2012).

Regulation of the K_{2P} channels by pH

Except for THIK1/2 and TRESK, K_{2P} channels are sensitive to pH. The TASK and TALK channels are inhibited by acidification of the extracellular medium. The pK_a value of this inhibition makes some channels active at neutral pH and inhibited by acid (pK_a of 7.3 for TASK1 and 6.7 for TASK3; Duprat *et al.* 1997; Kim *et al.* 2000; Rajan *et al.* 2000) and others active at alkaline pH and less active (TASK2), largely inhibited (TALK1) or totally inhibited (TALK2) at neutral pH (Reyes *et al.* 1998; Kang & Kim, 2004). The pH sensor is constituted primarily of a histidine residue in the P1 domain of TASK1 (Morton *et al.* 2003) and TASK3 (Kim *et al.* 2000; Rajan *et al.* 2000) and of a basic residue in the P2M4 loop of the TALKs (Niemeyer *et al.* 2006, 2007). In the TREK/TRAAK subfamily, the effect of the pH is more contrasted. The TREK1 and TREK2 channels are activated by internal acidification, whereas TRAAK is activated by internal alkalization. External acidification inhibits TREK1 and TRAAK but activates TREK2 (Duprat *et al.* 1997; Maingret *et al.* 1999b; Kim *et al.* 2001a, b; Sandoz *et al.* 2009). The sensor for activation of TREK1 and TREK2, but not TRAAK, by

Table 1. Natural and chemical effectors of K_{2p} channels, remarkable features and interacting partners

Name	Activators			Inhibitors		Remarkable features		Interacting partners	
TWIK1 K2P1.1 ¹	Gi-coupled receptor-mediated trafficking to the cell surface ²			Acid pH ¹ Protein kinase C ¹		Endosomal distribution ² / SUMO silencing ³ Dynamic ion selectivity ⁴ Heteromerization with other K _{2p} ^{5,6} Weak inward rectification ¹		EFA6/ARF6 _{GDP} ⁷ SUMO ? ³	
TWIK2 K2P6.1 ⁸⁻¹⁰						Slow inactivation ¹⁰			
KCNK7 K2P7.1 ¹¹						No current ¹¹			
TREK1 K2P2.1 ¹²	NO ¹³ Copper ¹⁴ Gβγ ¹⁵ ML67-33 ¹⁶ Substituted caffeate esters ¹⁷	Acid pH ^{18,19} Volatile anesthetics (halothane, isoflurane, chloroform) ^{19,20}	Mechanical stretch ^{19,21,22} PUFA ^{19,23,24} LP ²⁵ Temper- ature ^{26,27} Riluzole ^{19,28}	Zinc ¹⁴ Acid pH ²⁹ Fluoxetine ³⁰ Spadin ³¹	G _s , G _q (protein kin- ase A, pro- tein kinase C) ^{12,19}	Multiple unitary conductances ^{32,33} Alternative transcription initiation ^{34,35}	COP-I ³⁶ PrP _c ³⁷	AKAP150 ³⁸ Mtap2 ³⁹ Phospholipase D2 ⁴⁰	
TREK2 K2P10.1 ^{19,24}	Acid pH ⁴¹ Gi ¹⁹		Alkaline pH ⁴¹ Fluoxetine ⁴² Acid pH ⁴¹ Ruthenium Red ⁴⁴						
TRAAK1 K2P4.1 ²³	Alkaline pH ⁴³								
TASK1 K2P3.1 ⁴⁵	Alkaline pH ⁴⁵	Volatile anesthetics (halothane, isoflurane) ^{20,46}		Hypoxia ⁴⁷ Copper ¹⁴ Zinc ¹⁴ Ruthenium Red ⁴⁴	Acid pH _o ^{45,48,49} G _q ⁵⁰ Sanshool ⁵¹	Heteromerization TASK1/TASK3 ^{44,52} No Cys bond in the cap ^{45,48,49} Dynamic ion selectivity ⁵³ Relatively slow time-dependent activation ^{54,55}	p11 ⁵⁶ Syntaxin-8 ⁵⁷	14.3-3 ^{58,59} COP-I ^{58,59}	
TASK3 K2P9.1 ^{48,49}									
TASK5 K2P15.1 ^{60,61}						No current ^{60,61}			
TASK2 K2P5.1 ⁶²	Alkaline pH ⁶³	Alkaline pH _o ^{62,64}	Gβγ ⁶⁵		Relatively slow time-dependent activation ⁶²				
TALK1 K2P16.1 ⁶⁶	NO and reactive oxygen species ⁶⁷								
TALK2 K2P17.1 ⁶⁶									
THIK1 K2P13.1 ⁶⁸	Arachidonic acid ⁶⁸		Hypoxia ⁶⁹	Halothane ^{68,70}	No pH sensitivity ⁶⁸ ER retention ^{70,72}	Heteromerization THIK1/THIK2 ⁷¹			
THIK2 K2P12.1 ^{66,68}									
TRESK K2P18.1 ⁷³	Volatile anesthetics ⁷⁴ Calcium ⁷⁵ G _q ⁷⁵ Protein kinase C ⁷⁶		PUFA ⁷³ Sanshool ⁵¹		Asymmetrical gating behavior ⁷⁵ No pH sensitivity in the physiological range ⁷³		14.3-3 ⁷⁷ Calcineurin ⁷⁵ Tubulin ⁷⁸		

Abbreviations: PUFA, polyunsaturated fatty acid; LP, lysophospholipid; ER, endoplasmic reticulum; COP-I, coat protein 1; AKAP-150, A-kinase anchoring protein 150; Mtap2, microtubule-associated protein 2. Superscripts are as follows: 1, Lesage *et al.* (1996); 2, Feliciangeli *et al.* (2010); 3, Rajan *et al.* (2005); 4, Chatelain *et al.* (2012); 5, Hwang *et al.* (2014); 6, Plant *et al.* (2012); 7, Decressac *et al.* (2004); 8, Chavez *et al.* (1999); 9, Pountney *et al.* (1999); 10, Patel *et al.* (2000); 11, Salinas *et al.* (1999); 12, Fink *et al.* (1996); 13, Koh *et al.* (2001); 14, Gruss *et al.* (2004); 15, Woo *et al.* (2012); 16, Bagriantsev *et al.* (2013); 17, Rodrigues *et al.* (2014); 18, Maingret *et al.* (1999); 19, Lesage *et al.* (2000); 20, Patel *et al.* (1999); 21, Maingret *et al.* (1999); 22, Patel *et al.* (1998); 23, Fink *et al.* (1998); 24, Bang *et al.* (2000); 25, Maingret *et al.* (2000b); 26, Maingret *et al.* (2000a); 27, Kang *et al.* (2005); 28, Duprat *et al.* (2000); 29, Cohen *et al.* (2008); 30, Kennard *et al.* (2005); 31, Mazella *et al.* (2010); 32, Li *et al.* (2006); 33, Kang *et al.* (2007); 34, Thomas *et al.* (2008); 35, Simkin *et al.* (2008); 36, Kim *et al.* (2010); 37, Azzalin *et al.* (2006); 38, Sandoz *et al.* (2006); 39, Sandoz *et al.* (2008); 40, Comoglio *et al.* (2014); 41, Sandoz *et al.* (2009); 42, Kang *et al.* (2012); 43, Kim *et al.* (2001a); 44, Cziráj & Enyedi (2002); 45, Duprat *et al.* (1997); 46, Talley & Bayliss (2002); 47, Kemp *et al.* (2004); 48, Kim *et al.* (2000); 49, Rajan *et al.* (2000); 50, Chen *et al.* (2006); 51, Bautista *et al.* (2008); 52, Lauritzen *et al.* (2003); 53, Ma *et al.* (2012); 54, Lopes *et al.* (2000); 55, Meadows & Randall (2001); 56, Girard *et al.* (2002); 57, Renigunta *et al.* (2014); 58, O'Kelly *et al.* (2002); 59, Zuzarte *et al.* (2009); 60, Kim & Gnatenco (2001); 61, Ashmole *et al.* (2001); 62, Reyes *et al.* (1998); 63, Niemeyer *et al.* (2010); 64, Kang & Kim (2004); 65, Añazco *et al.* (2013); 66, Girard *et al.* (2001); 67, Duprat *et al.* (2005); 68, Rajan *et al.* (2001); 69, Campanucci *et al.* (2005); 70, Chatelain *et al.* (2013); 71, Blin *et al.* (2014); 72, Renigunta *et al.* (2014); 73, Sano *et al.* (2003); 74, Liu *et al.* (2004); 75, Cziráj *et al.* (2004); 76, Rahm *et al.* (2012); 77, Cziráj *et al.* (2008); 78, Enyedi *et al.* (2014).

internal pH is located in their C-termini (Maingret *et al.* 1999b; Kim *et al.* 2001b). The sensitivity to external pH requires a histidine residue in the M1P1 loop (Sandoz *et al.* 2009). Residues in the P2M4 loop, negatively charged in TREK1 and positively charged in TREK2, are responsible for the opposite effect of acidification on these channels, suggesting electrostatic attraction/repulsion, with the protonated side-chain of the histidine sensor leading to the opening or the closure of the pore. TWIK1 also displays a marked sensitivity to extracellular acidification, but with a very different effect. The channel reversibly shifts from a strict selectivity to K⁺ at neutral pH to a state permeable to Na⁺ at acidic pH, demonstrating that TWIK1 possesses a dynamic ion selectivity (Chatelain *et al.* 2012). A low K⁺ concentration has the same effect (Ma *et al.* 2011). This loss of K⁺ selectivity would cause paradoxical depolarization of human cardiac cells in pathological hypokalaemic conditions (Chen *et al.* 2014). Based on these findings, it was also reported that acidification affects the ion selectivity of TASK1 and TASK3 (Ma *et al.* 2012). These data show that external parameters can affect ion selectivity of K_{2P} channels. This finding expands the range of potential roles for K_{2P} channels that may also behave as excitatory channels when they are permeable to Na⁺.

Unique regulation of TWIK1

Dynamic ion selectivity of TWIK1 has been reported only very recently, although the channel was identified almost two decades ago (Lesage *et al.* 1996a). This lag was due to the difficulty in studying TWIK1 currents. Indeed, no native currents corresponding to TWIK1 have been characterized so far, and its weak activity was recorded only in a few heterologous expression systems. The identification of highly active K_{2P} channels soon after the discovery of TWIK1 overshadowed its study for a time. Two models were proposed to explain the lack of TWIK1 expression. In the first model, TWIK1 is present at the plasma membrane but silenced by the binding of a small ubiquitin-like modifier (SUMO) polypeptide to a non-conventional SUMO binding site (Rajan *et al.* 2005). When this site is inactivated by mutagenesis, the corresponding channel produces measurable currents. Following this line, the authors later reported that TWIK1 heteromerizes with TASK1/3 subunits and brings sumoylation sensitivity to the TWIK1/TASK heteromeric complexes (Plant *et al.* 2012). In the second model, low activity of TWIK1 is explained by its intracellular localization. The channel is rapidly and constitutively endocytosed from the plasma membrane and accumulates in recycling endosomes (Decressac *et al.* 2004; Feliciangeli *et al.* 2007, 2010). A mutant lacking the endocytosis signal redistributes at the plasma membrane, giving recordable current. This mutant allowed a reassessment of

the electrophysiological properties of TWIK1 (Chatelain *et al.* 2012). This work demonstrated that TWIK1 current is increased by mutations that target the pore of the channel without affecting the putative sumoylation site. Recent data show the existence of a hydrophobic barrier within the deep inner pore, the stochastic dewetting of which is a major barrier to ion conduction (Aryal *et al.* 2014).

Not so silent K_{2P} subunits

Beside TWIK1, other K_{2P} subunits (namely TASK5, KCNK7 and THIK2) have been coined 'silent' subunits because of their lack of expression in heterologous systems (Bichet *et al.* 2015). This raises the question of whether they are non-functional isoforms or functional subunits that require unidentified activators and/or protein partners. This second possibility has been strengthened by the recent demonstration that THIK2 could be turned on by overcoming two silencing mechanisms, retention in the endoplasmic reticulum (ER) and low activity at the plasma membrane (Chatelain *et al.* 2013; Renigunta *et al.* 2014b). Inactivation of the ER retention signal allowed the expression of THIK2 at the plasma membrane, enabling its electrophysiological characterization. THIK2 has electrophysiological and pharmacological properties very similar to those of THIK1, including inhibition by halothane and insensitivity to extracellular pH changes. Mutations equivalent to the pore mutations activating TWIK1 were able to activate THIK2, suggesting that THIK2 also contains a hydrophobic barrier in its deep pore (Chatelain *et al.* 2013). These results suggest that a similar approach may be successful to obtain functional expression of the 'silent' TASK5 and KCNK7 K_{2P} subunits.

Homo- and heteromerization of K_{2P} subunits

Further studies showed that THIK2 assembles with THIK1 to form an active channel (Blin *et al.* 2014). The resulting heterodimer reaches the cell surface and exhibits novel electrophysiological properties, providing evidence that interaction with another subunit can modulate K_{2P} channel activity. Whether such a mechanism also applies to silent TASK5 and KCNK7 subunits remains to be established. THIK1 and THIK2 are not the only K_{2P} subunits able to form active heterodimers. The best-documented case involves TASK1 and TASK3 (Czirják & Enyedi, 2002a; Berg *et al.* 2004). The resulting heterodimer retains some of the properties of each monomer and exhibits some others that are intermediate. There is a strong physiological relevance because native TASK heterodimers have been reported in different tissues, where they account for a significant part of the leak current (Enyedi & Czirják, 2010). As mentioned before,

TWIK1 may also interact with TASK1 and TASK3 subunits in the cerebellum (Plant *et al.* 2012). Recent data show that in astrocytes TWIK1 and TREK1 form heterodimers that mediate astrocytic passive conductance and cannabinoid-induced glutamate release (Hwang *et al.* 2014). This result suggests that TWIK1/TREK1 hetero-dimers are permeable to large molecules, such as glutamate. However, the molecular mechanisms underlying this unexpected property are not yet known.

Interacting partners of the K_{2P} channels

Heteromerization is a cost-effective means for a cell to acquire new functions by generating new channels with specific regulations and behaviours. Another way is the modulation of existing channels by auxiliary proteins that can affect different properties, such as channel trafficking or gating. This is well exemplified on TREK1 and TREK2. Indeed, binding of the A-kinase anchoring protein (AKAP)-150 to a major regulatory site adjacent to the M4 domain stimulates TREK1 and TREK2 activity (Sandoz *et al.* 2006), whereas interaction with microtubule-associated protein 2 (Mtap2) increases recruitment of the channels at the cell surface in a tubulin-dependent manner (Sandoz *et al.* 2008). Coat protein 1 (COP-I) also promotes TREK1 distribution at the cell surface (Kim *et al.* 2010) and so does its interaction with the neurotensin receptor (NTR) 3/sortilin, a protein located mostly in the trans-Golgi network and involved in intracellular trafficking (Mazella *et al.* 2010). On the contrary, the binding of spadin, a peptide derived from the maturation of NTR3/sortilin, causes TREK1 inhibition and internalization. Also, association of TREK1 with the prion protein PrPc has been reported, but its relevance has not been documented yet (Azzalin *et al.* 2006). Other K_{2P} channels are controlled by interaction with partner proteins. The presence of TASK1 and TASK3 at the plasma membrane is the result of a fine balance between the mutually exclusive binding of COP-I (retrieval to the ER) and 14-3-3 (forward signal; O'Kelly *et al.* 2002; Zuzarte *et al.* 2009). TASK1 also interacts with p11; however, the role of this interaction is not clear (Girard *et al.* 2002; Renigunta *et al.* 2006). Finally, endosomal SNARE protein syntaxin-8 interacts with TASK1 and promotes its internalization. TWIK1 interacts with a complex made of the small G-protein ARF6 and its nucleotide exchange factor EFA6, which are elements of the internalization machinery. TWIK1 binding to a complex comprising EFA6/ARF6_{GDP} would favour the exchange of GDP by GTP, the recruitment of coat proteins and the constitutive endocytosis of the channel (Decressac *et al.* 2004). In the case of TRESK, interaction with the calcium/calmodulin-dependent protein phosphatase calcineurin changes its regulation because it provides the

channel with sensitivity to intracellular Ca^{2+} (Czirják *et al.* 2004). The TRESK channel also interacts with 14-3-3 (Czirják *et al.* 2008) and tubulin (Enyedi *et al.* 2014).

Regulation of K_{2P} channels by G-protein-mediated pathways

Signalling pathways related to the activation of G-protein-coupled receptors by hormones and neurotransmitters affect K_{2P} channels in various ways. In some cases, G-protein activation affects cellular trafficking. For instance, activation of G_i -coupled receptors may increase TWIK1 current through relocation of endosomal channels to the cell surface (Feliciangeli *et al.* 2010). THIK2 ER retention signal contains a consensus protein kinase A site, suggesting that this signalling pathway could be involved in its exit from the ER and relocation to the plasma membrane (Chatelain *et al.* 2013). More often, G-protein activation directly affects the gating properties of K_{2P} channels. For instance, TRESK–calcineurin interaction causes dephosphorylation and activation of TRESK, hence coupling channel activity to the level of intracellular Ca^{2+} (Czirják *et al.* 2004). On the contrary, stimulation of G_q -coupled receptors leads to an inhibition of TASK channels (Chen *et al.* 2006). TREK1 and TREK2 are inhibited by stimulation of G_q -activated protein kinase C and G_s -activated protein kinase A (Fink *et al.* 1996; Lesage *et al.* 2000), although some studies also suggest an effect via the depletion of phosphatidylinositol 4,5-bisphosphate (PIP2) (Lopes *et al.* 2005). The C-termini of these channels have phosphorylation sites for each kinase, and phosphorylation by one kinase seems to favour the action of the other one (Murbartián *et al.* 2005; Kang *et al.* 2006). Another way for G-proteins to modulate K_{2P} activity is by interacting directly with the channels. It has been established that $G\beta\gamma$ can bind directly to the cytoplasmic C-termini of TASK2 and TREK1 with opposite results, i.e. inhibition of TASK2 (Añazco *et al.* 2013) and opening of TREK1 (Woo *et al.* 2012).

Effect of lipids and physical parameters

The K_{2P} channels are sensitive to different lipids. For instance, arachidonic acid and other polyunsaturated fatty acids (PUFAs) inhibit TRESK (Sano *et al.* 2003), whereas they activate TREK1 (Patel *et al.* 1998), TREK2 (Bang *et al.* 2000; Lesage *et al.* 2000) and TRAAK (Fink *et al.* 1998). Through the production of phosphatidic acid, phospholipase D2 potentiates the activity of TREK1 and TREK2, but not TRAAK (Comoglio *et al.* 2014). TREK/TRAAK channels are the only K_{2P} channels activated by a mechanical stretch of the membrane. The membrane-spanning helices (primarily M4) and the C-terminal region close to M4 play a pivotal role

in this regulation (Patel *et al.* 1998; Honoré *et al.* 2002). This mechanical sensitivity does not depend on a tether-mediated mechanism but comes directly from the lipid bilayer (Brohawn *et al.* 2014). TREK/TRAAK channels are very sensitive to temperature. A 10°C rise enhances TREK1 current amplitude by approximately sevenfold. In cells transfected with TREK2 or TRAAK, a rise from 24 to 42°C causes the whole-cell currents to increase about 20-fold (Maingret *et al.* 2000a; Kang *et al.* 2005).

Physiology and pathophysiology of K_{2P} channels

The role of the K_{2P} channels in the control of the membrane potential, and therefore of cellular excitability, mark them as potential players in a number of biological functions. The K_{2P} channels display very diverse expression patterns, from almost ubiquitous, such as TWIK1, to restricted to a subset of cells, such as TALK1, which is almost exclusively expressed in the exocrine pancreas. The field is active for development of drugs targeting K_{2P} channels (Bagriantsev *et al.* 2013; Rodrigues *et al.* 2014), and some specific inhibitors have been recently described, such as spadin, which inhibits TREK1 with an affinity in the nanomolar range (Mazella *et al.* 2010). Nonetheless, tools are still very limited, and this lack has hindered the investigations of the physiological roles of the K_{2P} channels by classical pharmacological approaches. As a consequence, most of the information has come from the study of transgenic animal models, essentially from mice with inactivated *KCNK* genes (Sabbadini & Yost, 2009). These mice do not show anatomical abnormalities and breed normally. The only exception is TASK2, for which two studies have reported a reduced viability due to increased mortality in the neonatal period (Gerstin *et al.* 2003; Warth *et al.* 2004). Subtle alterations in different physiological processes have been reported, some correlated and others causative of a disease (Table 2). Here, we will present only a few relevant examples of the studies that link K_{2P} channels to physiopathology. More detailed description can be found elsewhere (e.g. Bayliss & Barrett, 2008; Sabbadini & Yost, 2009; Enyedi & Czirják, 2010; Es-Salah-Lamoureux *et al.* 2010; Lesage & Barhanin, 2011).

Some phenotypes are directly linked to the regulation or the pharmacological properties of the inactivated channel. For example, knocking out volatile anaesthetic-activated K_{2P} channels TASK1/3 and TREK1 produces an anaesthetic-resistant phenotype (Heurteaux *et al.* 2004; Linden *et al.* 2006, 2007). TREK1 sensitivity to PUFAs forms a basis for the neuroprotective effects afforded by PUFAs against cerebral ischaemia (Heurteaux *et al.* 2004), because opening of the channel by PUFAs would lower cell excitability and excitotoxicity. Likewise, the higher

thresholds for thermal and mechanical nociception, as well as hyperalgesia in inflammatory conditions, observed in TREK1 knock-out (KO) mice seem to be associated with the sensitivity of TREK1 to temperature and mechanical stimulation (Alloui *et al.* 2006; Noël *et al.* 2009). Indeed, in nociceptor neurons of dorsal root ganglia both types of stimuli activate TREK1, causing hyperpolarization and attenuation of the signal. TREK2 and TRAAK are also involved in mechanical and thermal sensation, with specificities that make the three channels complementary (Pereira *et al.* 2014). TRESK is also abundant in dorsal root ganglia and other sensory ganglia; hence, it could potentially play a role in nociception. Blocking or silencing the channel was reported to modify nociceptor excitability (Tulleuda *et al.* 2011), but no phenotype could be observed in the TRESK KO mice (Dobler *et al.* 2007).

TASK1 and TASK3 are sensitive to pH and are expressed in several nuclei or carotid bodies with chemosensory functions. Therefore a role as sensors of P_{CO_2} by sensing acidosis was suspected early on. Using a pharmacological approach as well as single-channel current analysis, it was shown that TASK1, TASK3 and, mostly, TASK1/TASK3 heterodimers play an important role in chemoreception in the carotid bodies, the primary sensors of hypoxia and metabolic acidosis (Buckler *et al.* 2000; Kim *et al.* 2009). Data also support a role of TASK channels in the sensitivity of neuroepithelial bodies to P_{O_2} (Hartness *et al.* 2001). TASK1 and TASK3 are expressed in several nuclei of the brainstem that monitor P_{CO_2} , but studies, notably on KO models, argue against a role of these channels in central respiratory chemosensitivity (Mulkey *et al.* 2007).

The role of TALK channels was studied in conditions linked to alkalization. Data from KO mice suggest that TASK2 is engaged in bicarbonate reabsorption in the kidney and the accompanying Na^+ and water movements (Warth *et al.* 2004). Activation of the channel by HCO_3^- -mediated alkalization generates a K^+ flux that counterbalances the depolarization caused by the $Na^+-3 HCO_3^-$ cotransporter and hence enables the upholding of HCO_3^- flux (L'Hoste *et al.* 2007). A similar role has been suggested for TASK2, TALK1 and TALK2 in epithelial cells of the exocrine pancreas, based on their abundant expression in these cells (Fong *et al.* 2003). Also, TASK2 activation is necessary for volume regulation of native renal proximal tubule cells (Barriere *et al.* 2003). Finally, TASK2 is expressed in retrotrapezoid nucleus neurons, a population of which is involved in CO_2 and O_2 sensing, and TASK2 KO mice exhibit alteration in their breathing behaviour following hypoxia or exposure to low CO_2 (Gestreau *et al.* 2010). These data suggest a major role of the TASK2 channel in central O_2 chemosensitivity.

Even without stimulation, basal background conductance produced by K_{2P} channels plays a role in cellular excitability and development of different

Table 2. Pathophysiology of K_{2P} channels deduced from cell, and animal models and implications in human pathologies

Name	Physiology/Pathophysiology		Human pathologies	
TWIK1 K2P1.1 ¹	Phosphate and water reabsorption in kidney ²		Cancer ³ Paradoxical depolarization of cardiomyocytes in hypokalemia/arrhythmia ⁴	
TWIK2 K2P6.1 ⁵⁻⁷	Vascular ⁸ and pulmonary hypertension ⁹			
KCNK7 K2P7.1 ¹⁰	No altered phenotype ¹¹			
TREK1 K2P2.1 ¹²	Cytoskeletal organization during neuronal morphogenesis ¹³ Depression ¹⁴ Neuroprotection ¹⁵ Integrity of blood-brain barrier ¹⁶ Vasodilatation ^{17,18}	Modulation of thermal and mechanical nociception, and hyperalgesia in inflammation conditions ¹⁹⁻²¹	Cancer ²²	
TREK2 K2P10.1 ^{23,24}				
TRAAK1 K2P4.1 ²⁵	Brain metabolism ²⁶			
TASK1 K2P3.1 ²⁷	Adrenal gland zonation ²⁸ Modulation of auto-immune inflammation ²⁹	Aldosterone secretion ³⁰⁻³² Proliferation/apoptosis ³³	Pulmonary arterial hypertension ³⁴ Atrial fibrillation ³⁵	Cancer ^{36,37}
TASK3 K2P9.1 ^{38,39}	Sleep mechanisms and cognitive functions ⁴⁰ Neuronal migration during development ⁴¹ Depression ⁴²		Birk-Barel syndrome ⁴³	
TASK5 K2P15.1 ^{44,45}				
TASK2 K2P5.1 ⁴⁶	Bicarbonate reabsorption ⁴⁷ Volume control in kidney proximal tubule ⁴⁸ Volume regulation of T-cells ⁴⁹ Central chemoreception ⁵⁰		Cancer ⁵¹	
TALK1 K2P16.1 ⁵²				
TALK2 K2P17.1 ⁵²			Cardiac conduction disorder ⁵³	
THIK1 K2P13.1 ⁵⁴				
THIK2 K2P12.1 ^{52,54}				
TRESK K2P18.1 ⁵⁵	Temperature nociception ⁵⁶		Migraine ^{57,58}	

Superscripts are as follows: 1, Lesage *et al.* (1996); 2, Nie *et al.* (2005); 3, Beitzinger *et al.* (2008); 4, Ma *et al.* (2011); 5, Chavez *et al.* (1999); 6, Pountney *et al.* (1999); 7, Patel *et al.* (2000); 8, Lloyd *et al.* (2011); 9, Pandit *et al.* (2014); 10, Salinas *et al.* (1999); 11, Yost *et al.* (2008); 12, Fink *et al.* (1996); 13, Lauritzen *et al.* (2005); 14, Heurteaux *et al.* (2006); 15, Heurteaux *et al.* (2004); 16, Bittner *et al.* (2013); 17, Blondeau *et al.* (2007); 18, Garry *et al.* (2007); 19, Alloui *et al.* (2006); 20, Pereira *et al.* (2014); 21, Noël *et al.* (2009); 22, Voloshyna *et al.* (2008); 23, Lesage *et al.* (2000); 24, Bang *et al.* (2000); 25, Fink *et al.* (1998); 26, Laigle *et al.* (2012); 27, Duprat *et al.* (1997); 28, Heitzmann *et al.* (2008); 29, Bittner *et al.* (2009); 30, Davies *et al.* (2008); 31, Guagliardo *et al.* (2012); 32, Penton *et al.* (2012); 33, Lauritzen *et al.* (2003); 34, Ma *et al.* (2013); 35, Liang *et al.* (2014); 36, Mu *et al.* (2003); 37, Pei *et al.* (2003); 38, Kim *et al.* (2000); 39, Rajan *et al.* (2000); 40, Linden *et al.* (2007); 41, Bando *et al.* (2014); 42, Gotter *et al.* (2011); 43, Barel *et al.* (2008); 44, Kim & Gnatenco (2001); 45, Ashmole *et al.* (2001); 46, Reyes *et al.* (1998); 47, Warth *et al.* (2004); 48, Barriere *et al.* (2003); 49, Bobak *et al.* (2011); 50, Gestreau *et al.* (2010); 51, Alvarez-Baron *et al.* (2011); 52, Girard *et al.* (2001); 53, Friedrich *et al.* (2014); 54, Rajan *et al.* (2001); 55, Sano *et al.* (2003); 56, Chae *et al.* (2010); 57, Lafrenière *et al.* (2010); 58, Maher *et al.* (2013).

tissues. In the brain, TREK1 participates in serotonergic transmission, which is increased in TREK1 KO mice (Heurteaux *et al.* 2006). This affects behaviour, with KO mice displaying a depression-resistant phenotype in a large battery of assays for the evaluation of helplessness and despair. A similar phenotype was observed in mice treated with the TREK1 inhibitor spadin (Moha Ou Maati *et al.* 2012). These results mark TREK1 as a potential target for antidepressant development (Borsotto *et al.* 2015). Other effects of TREK1 inactivation have been observed, supporting other roles. For instance, recent data suggest that TREK1 is required for the integrity of the blood–brain barrier (Bittner *et al.* 2013, 2014). In TREK1 KO mice, leucocyte transmigration is increased in autoimmune encephalomyelitis, an experimental model of blood–brain barrier dysfunction related to inflammation. TREK1 inactivation is associated with aggravated symptoms and increased cellular infiltrates in the central nervous system, whereas TREK1 activation by riluzole or α -linolenic acid attenuates the severity of the symptoms in wild-type animals.

TASK channels are another example of leak K⁺ channels involved in both cellular excitability and development. In cerebellar granule cells, the spillover of synaptically released GABA gives rise to a persistent inhibitory conductance mediated by the GABA_A receptor. However, when this receptor is inactivated, no change is observed in the membrane potential because of a spontaneous compensation by overexpression of TASK1 and TASK3 (Brickley *et al.* 2001; Aller *et al.* 2005). In the cerebellum, TASK3 expression correlates with massive neuronal apoptosis during development (Lauritzen *et al.* 2003). On the contrary, TASK3 overexpression increases cell survival and causes cell proliferation of transformed fibroblasts (Mu *et al.* 2003). Together, these results suggest that TASK3 plays a dual role in proliferation or apoptosis depending on the context. Surprisingly, TASK3 KO mice display only minor impairment of locomotion. However, they present alterations such as impaired working memory and perturbation in the regulation of the circadian rhythm (Linden *et al.* 2007), which, together with the resistance of these mice to antidepressants, suggest an involvement of TASK3 in the mechanisms of depression (Gotter *et al.* 2011). In the hypothalamic orexin neurons, a role in glucose sensing was proposed for TASK channels (Burdakov *et al.* 2006); however, the function is preserved in TASK1/TASK3 double-KO mice (Guyon *et al.* 2009; González *et al.* 2009). In rat adrenal glomerulosa cells, TASK channels are responsible for the high resting conductance, with a major contribution of TASK3 (Czirják *et al.* 2000; Czirják & Enyedi, 2002b; Lotshaw, 2006). Knock-out of TASK1 or both TASK1 and TASK3 causes primary hyperaldosteronism (Heitzmann *et al.* 2008; Davies *et al.* 2008). In TASK1 KO mice, aldosterone overproduction is a consequence of an inappropriate

zonation of the adrenal gland (Heitzmann *et al.* 2008). Only immature mice and females are affected. This points out an unexpected role of TASK1 in the development and zonation of the adrenal cortex. It also shows that for this function, TASK3 cannot compensate for the absence of TASK1. The predominant role of TASK1 is also attested in human adrenal glands (Nogueira *et al.* 2010). In bovine tissue, the role in aldosterone secretion appears to be played by TREK1 (Enyeart *et al.* 2004). In the heart, TASK1 is predominantly expressed in the ventricle in rodents, and KO mice show a ventricular phenotype with prolonged QT interval, wide QRS and increased ventricular action potential duration (Decher *et al.* 2011; Donner *et al.* 2011). In humans, however, TASK1 is mostly found in the atria, leading to the proposal that it could be involved in atrial fibrillation. This possibility is strengthened by the fact that mutations found in patients with atrial fibrillation alter atrial TASK1 current in zebrafish (Liang *et al.* 2014). TWIK2 is highly expressed in the vascular system, and inactivation of its gene is associated with vascular and pulmonary hypertension (Lloyd *et al.* 2011; Pandit *et al.* 2014). In astrocytes (Wang *et al.* 2013), renal cells (Millar *et al.* 2006) and pancreatic β -cells (Chatelain *et al.* 2012), TWIK1 gene inactivation causes hyperpolarization of the resting membrane potential, which is explained by the dynamic ion selectivity of the channel.

K_{2P} channels in human pathologies

Dynamic ion selectivity of TWIK1 can account for the paradoxical depolarization of human cardiomyocytes observed in subphysiological K⁺, a phenomenon that may give rise to cardiac arrhythmias (Chen *et al.* 2014). A dominant-negative mutation in the gene encoding TRESK segregates with a phenotype of migraine with aura (Lafrenière *et al.* 2010). However, another loss-of-function mutation of TRESK could not be associated with the phenotype (Maher *et al.* 2013), suggesting a multigenic origin of this hereditary disease.

The relationship with a genetic disorder is more straightforward for other K_{2P} channels. In humans, whole-exome sequencing of multiple patients with pulmonary arterial hypertension has revealed a correlation between the pathology and several missense mutations, all of which abolish TASK1 activity (Ma *et al.* 2013). This fits well with the reports that TASK1 is sensitive to hypoxia and plays a role in the regulation of the pulmonary vascular tone (Gurney *et al.* 2003). Genome studies revealed that TASK3 is genetically imprinted, i.e. it is expressed only from the maternal allele, and that a missense mutation (G236R) is associated with the Birk–Barel syndrome, a maternally transmitted syndrome of mental retardation, hypotonia and unique dysmorphism with elongated face (Barel *et al.* 2008). The original study reported that the mutation produces a dominant-negative TASK3

subunit, resulting in non-functional TASK3 homodimers and TASK1/TASK3 heterodimers (Barel *et al.* 2008). However, others have described that the mutated subunit still produces current, although significantly decreased and with altered properties (Veale *et al.* 2014). In a patient with a severe cardiac phenotype of cardiac arrhythmia, in addition to a mutation in the cardiac sodium channel SCN5A, another mutation was identified in the M1P1 loop of TALK2 (G88R) that causes a gain of function and an increase of the channel conductance (Friedrich *et al.* 2014). This increased activity is likely to promote repolarization of the cardiac action potential and to shorten refractory period, which might therefore favour re-entry arrhythmias. This example illustrates the need for a tight control of K_{2P} channel activity within physiological margins. TASK3 is another example. In cell and animal models, TASK3 has been demonstrated to be involved in both cell apoptosis and survival. As mentioned above, the channel is associated both with massive apoptosis in the developing cerebellum and with survival and proliferation when overexpressed in fibroblasts (Mu *et al.* 2003; Lauritzen *et al.* 2003). This suggests that this channel could play different roles depending on its regulation and, therefore, that TASK3 could shift from one function to the other upon a change in its environment, with potential physiopathological consequences. Along this line, overexpression of the channel has been reported in many different types of human cancers (Mu *et al.* 2003).

In fact, all but three K_{2P} channels (TRAAK, TALK1 and TRESK) have their expression modified in different oncogenic processes (Williams *et al.* 2013). For instance, *TWIK1* is among the top 1% of genes with altered expression in different types of human cancers, either increased (bladder, lung and pancreas) or decreased (cancers of the central nervous system). Its expression varies in ovarian and prostate cancers, decreasing with tumour progression. Likewise, TREK exhibits modified expression in a variety of cancer types, such as lung or brain cancers. Although it was demonstrated in some cases that the activity of the channel is required in order to observe the oncogenic effect (Pei *et al.* 2003), more work is necessary to conclude whether altered expression is a cause or a consequence of the carcinogenesis.

Conclusions

Since the serendipitous identification of *TWIK1* in 1996, we have learned a lot about the diversity and nature of K_{2P} channels. Far from forming mere K^+ leaks in the plasma membrane, they have proved to be exquisitely regulated by a wide variety of mechanisms. The K_{2P} channels affect cell excitability and biology and are involved in the normal development and functioning of many tissues, including brain, heart, adrenal glands and kidneys. This field of research continues to evolve rapidly, constantly

improving our understanding of the physiological and pathological roles of the K_{2P} channels. New, fascinating questions emerge from recent data. The studies on 'silent' channels suggest that some of these K_{2P} channels may have a role in intracellular compartments (*TWIK1* in recycling endosomes and *THIK2* and *KCNK7* in the ER), and the presence of a hydrophobic barrier in the deep pore of some of them supports the existence of a new type of gate. How and by which stimuli this hydrophobic gate is controlled remain open questions. By suggesting that K^+ channels may fulfil inhibitory and excitatory roles traditionally attributed to distinct classes of ion channels, the recent demonstration that *TWIK1* exhibits dynamic ion selectivity opens new areas of research. Which K_{2P} channels exhibit this behaviour, which stimuli can influence their ionic selectivity, and what the impacts are on cell biology constitute fascinating interrogations. Finally, the therapeutic interest in these K_{2P} channels is important. Drugs targeting K_{2P} channels may be relevant for treating disorders as diverse as depression, pain, vascular and pulmonary hypertension and cancer.

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Additional information

Competing interests

None declared.

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