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INVITED REVIEW

The role of K_{2P} channels in anaesthesia and sleep

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Abstract Tandem two-pore potassium channels (K_{2P}s) have widespread expression in the central nervous system and periphery where they contribute to background membrane conductance. Some general anaesthetics promote the opening of some of these channels, enhancing potassium currents and thus producing a reduction in neuronal excitability that contributes to the transition to unconsciousness. Similarly, these channels may be recruited during the normal sleep-wake cycle as downstream effectors of wake-promoting neurotransmitters such as noradrenaline, histamine and acetylcholine. These transmitters promote K_{2P} channel closure and thus an increase in neuronal excitability. Our understanding of the roles of these channels in sleep and anaesthesia has been largely informed by the study of mouse K_{2P} knockout lines and what is currently predicted by in vitro electrophysiology and channel structure and gating.

Keywords K_{2P} channel · Anaesthesia · Sleep · Isoflurane · Halothane · Fluoxetine

Abbreviations

CNS	Central nervous system
GPCR	G-protein-coupled receptor
HCN	Hyperpolarisation-activated cyclic nucleotide-gated channels
K_{2P} or KCNK	Tandem two-pore potassium channel
KO	Knockout mouse model
NREMS	Non-rapid eye movement sleep
REMS	Rapid eye movement sleep
SSRI	Selective serotonin reuptake inhibitor
TWIK	Tandem of P-domains weak inward rectifying K+ channel (TWIK-1 (KCNK1), TWIK-2 (KCNK6), TWIK-3 (KCNK7))
TREK	TWIK-related K+ channel (TREK-1 (KCNK2), TREK-2 (KCNK10))
TASK	TWIK-related acid-sensitive K+ channel (TASK-1 (KCNK3), TASK-3 (KCNK9), TASK-5 (KCNK15))
TRAAK	TWIK-related arachidonic acid-activated K+ channel (KCNK4)
TALK	TWIK-related alkaline-sensitive K+ channel (TALK-1 (KCNK16), TALK-2 (KCNK17))
THIK	TWIK-related halothane-inhibited K+ channel (THIK-1 (KCNK13), THIK-2 (KCNK12))
TRESK	TWIK-related spinal cord K+ channel (KCNK18)

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K_{2P} channels, sleep and anaesthesia

The contribution of tandem two-pore potassium channels (K_{2P}s) to background potassium membrane conductance, coupled with their sensitivity to certain anaesthetics, suggests that they may play a role in the effects of anaesthetics on the mammalian conscious state, and by extension, to the mechanisms behind sleep-wake alternation [30]. Franks and Lieb [28] first identified a novel anaesthetic-activated potassium current in the pond snail which was subsequently confirmed to be mediated by a new class of channel, the K_{2P} family, cloned in mammals and snails some years later [4, 45, 50]. Our focus will be on K_{2P} channels with known anaesthetic sensitivities that are expressed in the CNS. The mammalian K_{2P} channel

family has 15 mammalian members, separated into six subfamilies by structure and function [33, 41, 54], starting with tandem of P-domains weak inward rectifying K+ channel (TWIK) and the derivatively named TASK, TREK, THIK, TRESK, TRAAK and TALK channels. Various K_{2P} channel subunits heterodimerise so, in addition to the electrophysiological properties and anaesthetic sensitivities of the 15 channel homodimers, there are an unknown number of heterodimers with distinct electrophysiological properties expressed throughout the CNS.

Anaesthetics, particularly halogenated volatile anaesthetics such as isoflurane and halothane, open various K_{2P} channels. What encourages us to think that this opening contributes to the transition into unconsciousness is that mouse K_{2P} knockouts (KOs) have altered behavioural responses after anaesthetics measured as reduction in locomotion, loss of righting reflex (an animal surrogate measure of transition into unconsciousness) and loss of limb withdrawal (deep surgical anaesthesia). Depending on the anaesthetic, this may be for several reasons: first, the K_{2P} channels are the direct target of anaesthetics; second, the channels are recruited downstream of anaesthetic targets; or third, the absence of the channels during development affects neuronal circuitry such that it is less responsive to anaesthesia. With regard to their recruitment downstream of anaesthetic targets, several K_{2P} channels are modulated by G-protein-coupled receptors (GPCRs) for histamine, noradrenaline, acetylcholine and others that make it probable that these channels mediate some of the effects of these neurotransmitters during the sleep-wake cycle. There may also be endogenous signalling molecules, as yet unknown, that directly affect the activity of these channels. Given, the widespread expression of K_{2P} channels in the CNS [78] and varied coupling to receptors, their distribution may help identify which K_{2P} members are involved in sleep circuitry and anaesthesia. CNS expression of the K_{2P} channel family varies both between subtypes (for example, TALK-1 appears to be limited to the pancreas and is not seen in the CNS) and also species [31]. There are some common themes, however: TASK-1, TASK-2, TREK-1, TWIK-1, TRAAK and THIK-1 are all strongly expressed in the cerebellum, hippocampal formation and dentate gyrus which suggest some redundancy in function [2, 78] and may reflect heterodimerisation in these regions [2]. Three of these channels (TREK-1, TASK-1 and TASK-3) are also co-expressed in the adult rodent thalamus, particularly in the intralaminar and reticular nuclei [2, 78], and there is evidence that their recruitment there may be relevant to sleep-wake transitions.

K_{2P} channels regulate diverse aspects of body physiology

Our understanding of how K_{2P} channels are involved in sleep and anaesthesia has relied heavily on mouse KO lines, and it is worth mentioning that these lines display additional phenotypes, reflecting the widespread role of K_{2P} channels in other processes, both in and beyond the brain. Examples include the salt-sensitive hyperaldosteronism observed in TASK-3 KO neonates and TASK-1 KO adults, reflecting the role of these channels in normal kidney function [6, 38]. Meanwhile, out of TASK-3 and TASK-1 knockouts, only TASK-1 KO mice have reduced blood pressure [63] and diminished responses to hypoxia and moderate normoxic hypercapnia [80]. Alterations such as these may interact with sleep-wake behaviour and responses to anaesthetics; for example, the attenuated ventilator response to hypoxia in TASK-1 knockout mice [80] may affect respiratory responses to anaesthesia and this should be borne in mind. Likewise, human variation in K_{2P} channels has already been implicated in several pathologies. Arguably, the most severe example is the single maternally imprinted mutation of TASK-3, which results in Birk-Barel syndrome, characterised by mental retardation and dysmorphism [7]. No other single human K_{2P} mutation has yet been linked to pathology, but single nucleotide polymorphisms (SNPs) and splice variants of K_{2P}s that have been associated with susceptibility to high blood pressure [42], preterm labour [83] and migraine [48, 65] amongst others. The relationships between K_{2P} channels and human sleep disorders or anaesthetic sensitivity have not yet been investigated.

K_{2P} channel involvement in pain and immobility

The loss of awareness produced by general anaesthetics is part of the functional spectrum of clinical anaesthesia which includes analgesia, anxiolysis, amnesia and suppression of somatic responses to injury that can be motor, cardiovascular and hormonal [71, 72]. Crucial to our discussion is evidence that K_{2P} channels play a role in several of these processes. TREK-1, TRAAK [3, 40, 64], TRESK [48] and TASK-1 [52] have all been implicated in the sensation of pain with knockout animals experiencing heightened pain sensitivity. Given that anaesthetics tend to open these channels, this would predict that the analgesic effect may involve activation of K_{2P} channels. TREK-1 in particular has been highlighted as an important component of pain perception [62] and is expressed in both small sensory neurons of the dorsal root ganglion [3] and in regions like the thalamus that process ascending nociceptive information. Likewise, these channels have been implicated in the suppression of motor function produced by anaesthetics [49, 75]. For example, TASK-like currents have been observed in brainstem motoneurons; the reduction in motoneuronal excitability that accompanies anaesthetic-induced immobility has been attributed to these currents [26, 76]. The involvement of K_{2P} channels in analgesia, muscle relaxation together with loss of awareness

should be borne in mind when interpreting 'loss of pain reflexes' or 'immobility' as an end point for knockout models.

Anaesthetic interaction with K_{2P} channels

The study of the structure of K_{2P} channels has demonstrated that certain intracellular portions of the channel are necessary for halogenated anaesthetics to produce an effect and has given insight into how K_{2P}s are recruited in cell membrane signalling via the activation of GPCRs. The name 'tandem two-pore' comes from a feature that distinguishes K_{2P}s from other potassium channels. Like all potassium channels, the potassium-selective pore of K_{2P}s is composed of four-pore-forming (P) domains which contain outer and inner transmembrane helices, a selectivity filter, a signature sequence and a pore helix [60]. In other potassium channels, each channel subunit is expressed with a single P-domain, so functional channels assemble as tetramers. K_{2P}s, however, are expressed as protomers with four transmembrane domains between which sit two P-domains [60]. The assembly of a functional channel, therefore, requires only a dimer. The N- and C-termini of these dimers are intracellular, and there is an additional feature unique to this member of the potassium channel superfamily: the extended ~55 amino acid extracellular loop between transmembrane domains 1 and 2. In the resolved TWIK-1 and TRAAK channel structures, these loops (which are actually two helices) form an 'A-frame' cap directly above the pore selectivity filter [12, 60]. This cap is far enough from the pore that it allows access to potassium ions, but its presence may explain why K_{2P} channels are resistant to certain pore-blocking toxins that affect other potassium channels [12, 60]. This cap feature may be common to all members of the K_{2P} family, though its significance is unknown.

Several K_{2P} channels are opened by anaesthetics. Two notable exceptions are TWIK channels which appear insensitive to anaesthetics and THIK channels which are closed by high concentrations of halothane. The gating of all potassium channels is thought to be mediated via two gating mechanisms at distinct sites: an activation site near the intracellular entrance to the channel and an extracellular slow inactivation site at the selectivity filter near the extracellular side [55]. Consistent with this, TASK channel activation by halogenated anaesthetics requires amino acid 159 located on the intracellular side of the transmembrane domain 3 [4, 18]. In addition to this, a six-amino-acid region between transmembrane domain 4 and the C-terminus has also been identified as necessary for TASK channel responses to halogenated anaesthetics [4, 77, 81]. It is unclear whether these six amino acids are directly involved in the activation gate via which anaesthetics open TASK channels or if they are in a site necessary for transduction of the binding signal to the gate [55]. Similarly, the C-terminal domain and site Glu306 is important for anaesthetic effects on TREK-1 [36, 68], although again, this does not confirm that this is where anaesthetics bind. How anaesthetics activate or inactivate other members of K_{2P} channels is currently not fully understood. However, it may be relevant that the two K_{2P} members not opened by anaesthetics, TWIK and THIK, lack conserved glycine residues found in other K_{2P} members and instead have a larger hydrophobic region. These glycine residues in transmembrane domain 2 have been proposed as a hinge for the activating gate in K_{2P}s and inwardly rectifying potassium channels [16]. Different hinging mechanisms for channel opening could distinguish those K_{2P}s that are activated by anaesthetics and those that are not. In addition, the structure of the anaesthetic-binding region in K_{2P}s may differ between species; while rodent and mollusk TASK channels respond differently to anaesthetic enantiomers, human TASK channels do not [4, 44].

GPCRs and K_{2P} channels

As previously mentioned, K_{2P} channels are regulated by a number of GPCRs, which are in turn involved in neurotransmitter systems associated with wakefulness, such as acetylcholine, histamine, serotonin, glutamate and noradrenaline [55]. Briefly, activation of Gαq proteins closes TASK and TREK family channels and opens TRESK channels. Meanwhile, Gi proteins appear to open TREK channels while Gs proteins close TREK channels [55]. Several wake-promoting transmitters such as histamine, acetylcholine, serotonin, glutamate and noradrenaline have receptors that are G-protein coupled, and we can posit that activation of these receptors while awake inhibits K_{2P} channels in distinct neuronal populations making these populations more excitable. For example, all of the abovementioned neurotransmitters have Gαq/11-coupled receptors in the CNS and these proteins inhibit TASK and TREK channels, which would subsequently lead to reduced potassium leak currents and more membrane depolarisation [26], particularly in the thalamus [20]. It is important to note that the effector pathways involving K_{2P} channels are likely to be complicated because K_{2P} channels can exist as heteromers. TASK channels can exist both as functionally distinct homodimers as well as TASK-1/TASK-3 heterodimers [1, 8, 11, 22, 43, 46], even in the same neuronal population. In addition, heterodimerisation between K_{2P} subfamilies TWIK and TASK occurs in cerebellar granule neurons [69], and heterodimerisation between THIK and TASK-1/TASK-3 channels has been predicted in the same population based on expression profiles [2]. Unravelling how these combinations are regulated in situ will advance our understanding of how K_{2P}s are involved in sleep-wake signalling.

Role of K_{2P} channels in sleep-wake regulation

K_{2P} channel expression in regions associated with sleep-wake transitions, such as the preoptic and superchiasmatic nuclei in the hypothalamus and thalamic relay nuclei [78], suggest that they may be involved in mechanisms promoting transition or maintenance of the two states [21]. Thalamic relay neuronal activity has two distinct activity states: <15 Hz burst activity during sleep and ~40 Hz tonic activity during wakefulness and rapid eye movement sleep (REMS). During normal sleep-wake activity, the switch between these two states is modulated by the ascending brainstem, including cholinergic projections, and other ascending modulatory influences such as serotonergic and glutamateric signalling [20]. These ascending inputs promote closure of K_{2P} channels such as TASK-1/TASK-3 and TREK; the subsequent depolarization of thalamic neurons causes a switch to tonic firing associated with wakefulness and REMS [10, 57–59]. This closure of K_{2P}s during tonic firing appears to rely crucially on Gαq signalling for the cholinergic input [13] and Gαq/11 signalling for serotonergic and glutamatergic inputs [20, 26]. Conversely, opening of K_{2P}s when the ascending input is withdrawn and their functional antagonism with hyperpolarisation-activated cyclic nucleotide gated channels (HCN) hyperpolarises thalamocortical neurons and promotes burst firing patterns associated with sleep [21, 82]. Reciprocal regulation of the K_{2P} and HCN current has likewise been observed with application of anaesthetics such as halothane, isoflurane and sevoflurane [14] which also promote hyperpolarisation of the thalamus. Although the main focus has been on the opening of TASK channels mediating this the anaesthetic-induced change in thalamic membrane potential, Budde et al. note a complex effect of halothane on the activation and inhibition of various thalamic K_{2P} channels such as TREK-1, TASK-1, TASK-3 and THIK-2 which overall result in a switch to burst firing [14]. Thalamocortical K_{2P} channels are recruited both during withdrawal of ascending input and after application of anaesthesia but whether or not this recruitment is sufficient to promote unconsciousness is controversial. The thalamus is strongly implicated in the transitions between conscious and unconscious states [82], but as we will discuss, none of the K_{2P} knockouts have so far displayed a compromised ability to transit in and out of consciousness per se. Nevertheless, altered sleep architecture and altered sensitivity to some anaesthetics in these animals suggest that thalamic K_{2P} involvement as well K_{2P}s in other regions are important.

So far, the only K_{2P} channel mouse knockout with a characterised sleep phenotype is the TASK-3-deficient line [17, 34, 53, 67]. TASK-1 knockout mice were assessed for sleep-wake behaviour and found to be indistinguishable from controls [57]. Whilst the proportion of time TASK-3 knockout mice spend in wakefulness, non-rapid eye movement sleep (NREMS) and REMS is similar to littermates, the distribution of these states and their EEG quality varies. The REMS episodes of TASK-3 mice show clear oscillatory fragmentation, and the mice have enhanced wake activity [67] as well as an overall increase in the amplitude of sleep architecture [34, 53]. The locomotor activity within the wake period of these mice is 2–3-fold increased above that of littermates [34, 53]; these results were replicated on independently generated TASK-3 KO lines. The two key phenotypes that have emerged from TASK-3 KOs, fragmented REMS and exaggerated wake activity, draw interesting parallels with the effects of drugs that suppress TASK-3 activity (Fig. 1). A recently developed TASK-3 antagonist, compound 23, produces a significant elevation in wake simultaneous with REMS and NREMS suppression in wild-type mice [17]; this effect on the sleep-wake is similar to the TASK-3 KO phenotype (Fig. 1). The elevation in wakefulness in both these cases may be mediated by disinhibition of cortico-thalamic processes, although why this effect is restricted to the light phase is not clear (in the case of the antagonist this is simply the phase in which the animals were dosed, so it may be a trivial parallel). An alternative explanation for the wake-promoting compound 23 effect and the TASK-3 knockout phenotype is that the inhibition of TASK-1/TASK-3 channels in arousal nuclei, such as the noradrenergic neurons in the locus coeruleus [52, 75], increases the excitability of these arousal nuclei and thereby promotes arousal. Given that locus coeruleus firing is associated with alert and attentive behaviour [9], an overactive locus coeruleus may produce hyperactivity in the 'active' nocturnal part of the sleep-wake cycle [34, 53]. Disinhibition of this arousal nucleus may also explain the REMS phenotype of the TASK-3 mice. During normal REMS, neurons in the locus coeruleus are silent [27], so an aberrantly active locus coeruleus may interfere with maintenance of this sleep state. Meanwhile, the REMS-suppressing effect of the TASK-3 antagonist appears to be TASK-3-specific because it cannot be replicated if the TASK-3 antagonist is administered to the TASK-3-deficient mice [17]; it is controversial whether this is because the baseline REMS is already impaired in these animals. Notably, the REMS-suppressing effect of the antidepressant fluoxetine on wild-type mice also cannot be replicated in TASK-3-deficient mice [34]. The majority of antidepressants are also REMS-suppressants, so it is interesting that the 'REMS-impaired' TASK-3-deficient mice have an 'antidepressant phenotype' [34]. In addition, TREK-1-deficient animals also show an antidepressant phenotype [39, 56], although there is some dispute over this [61]. Given that TREK-1 channels are robustly blocked under most experimental conditions by the application of the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, norfluoxetine, paroxetine and sipatrigin [24, 26, 84], it would be interesting to see if TREK-1-deficient animals have impaired REMS and are also resistant to the REMS-suppressing effects of fluoxetine. A recent review has questioned whether

antidepressant suppression of REMS preferentially suppresses some aspects of the sleep state (motor inhibition) over others [25]. Studying the apparent resistance of K_{2P} knockouts to SSRI effects on REMS may shed light on this question.

Role of K_{2P} channels in anaesthesia

General anaesthetics, whatever their various effects on analgesia, amnesia and muscle relaxation, all have in common their ability to suspend consciousness to some degree, depending on the drug dose administered. It is therefore crucial to study their relationship with putative targets in whole animal or clinical paradigms. The study of K_{2P} channels and anaesthesia has, so far, therefore consisted of two necessary branches of research: electrophysiology to determine which anaesthetics directly open/close K_{2P} channels, and the testing of anaesthetics on K_{2P} channel-deficient mouse strains to determine whether the end point of hypnosis, sedation or loss of pain reflexes can still achieved by the same dose of drug. There is a third emerging branch that investigates indirect modulation of K_{2P} s during anaesthesia. For example, the α2 adrenoceptor agonist and sedative drug dexmedetomidine is not likely to open K_{2P} channels, nor to act through Gq/11, the G-protein associated with TASK channels, and yet TASK-1-deficient mice are less sensitive to low sedative doses of dexmedetomidine [52], suggesting an indirect mechanism of action. Many K_{2P} channels are also closed by local anaesthetics [47], but as these drugs do not suspend consciousness, these interactions will not be discussed here.

Five of the six subfamilies of K_{2P} channels are directly sensitive to general anaesthetics, with the exception being weak inward-rectifier TWIK-1 and TWIK-2 channels. Notably, TWIK-1 channels can still be closed by local anaesthetics such as bupivacaine [31]. Because enhancement of background potassium current is a plausible mechanism for producing anaesthesia [30, 44], THIK channels that are inhibited by high concentrations of halothane are implausible candidates for mediating anaesthetic mechanisms. In contrast, based on in vivo mouse studies, TASK-1, TASK-3 and TREK-1 channels are strong candidates for a likely role in anaesthesia. Table 1 summarises the K_{2P} channel knockout lines and whether or not they have a reported change in anaesthetic sensitivity. It is important to note that these assessments were made in adult animals. Anaesthetic sensitivity changes with rodent age, with adult animals having a much lower minimum alveolar concentration for halogenated anaesthetics than juveniles [66]. This change in sensitivity may rely in part on significant K_{2P} channel CNS expression changes CNS during development [2, 5]. The various studies use different end points to assess different aspects of anaesthetic effects on the conscious state: reduction in movement (a surrogate measure of sedation), loss of righting reflex (a surrogate measure of unconsciousness in animals) and loss of paw or tail withdrawal to painful stimuli, which is normally assumed to be unconsciousness coupled with immobility. These different end points usually reflect the effects of increasing doses of drug, e.g. low doses of halothane are sedative and high doses cause loss of surgical reflexes, but do not necessarily mean an escalation of the same mechanism or recruitment of identical receptor populations in the CNS.

Despite the caveats of compensation, especially given that K_{2P} channels such as TASK-3 have been implicated in mouse CNS development [5], and TASK-1 KO mice have upregulated $GABA_A$ receptor function [51], K_{2P} channel-deficient mouse lines have yielded some interesting insights into anaesthetic processes. To date, there are mouse knockouts of TASK-1, TASK-2, TASK-3, TREK-1, TRAAK, KCNK7 and TRESK channels, as well as a TASK-1/TASK-3 double knockout [1, 11, 15, 32, 39, 49, 80, 86]. In addition, there is a TASK-1/TASK-3 channel knockout restricted to cholinergic cells that is substantially less sensitive to isoflurane and halothane-induced loss of righting reflex [49]. For anaesthesia using halogenated anaesthetics (isoflurane, halothane, sevoflurane, desflurane and chloroform), loss of specific K_{2P} channel expression generally results in a reduction, but not complete loss, of anaesthetic sensitivity. However, even within this class, there are differences. Halothane, for example, requires TASK-1 and TASK-3 for loss of pain reflex and TREK-1 for loss of righting reflex but does not require the TRESK channel [15, 39, 49, 52, 53, 67]. On the other hand, isoflurane-induced loss of pain reflex is diminished when both TASK-1 and TASK-3 are absent [49] but it is unclear whether single knockouts of TASK-3 channels have a diminished sensitivity for pain reflex [49, 67] or if TASK-1 channels are involved in isoflurane-induced loss of righting reflex [49, 67] the way that TREK-1 channels appear to be [39]. Other classes of anaesthetics have also been tested in K_{2P} knockouts, although not comprehensively. TASK-1 mice are more sensitive to $GABA_A$ receptor ligands and modulators propofol, pentobarbital, and benzodiazepines as it takes them longer to recover from the anaesthetised state [51]. This may be related to the increased expression of $GABA_A$ receptors in these animals. No such extended recovery time was seen in TREK-1 channel knockouts, which recover the same as controls from pentobarbital anaesthesia [39]. Propofol was tested on TASK-3 knockouts, but recovery time was not reported, so while the animals are certainly not less sensitive, it is not clear if they would take longer to recover from the anaesthetic dose [53]. Opposing changes in sensitivity to halogenated and non-halogenated anaesthetics such as those seen in TASK-1 channel knockouts highlights the importance of testing several classes of anaesthetics on each knockout model because generalising between channels or between anaesthetics is problematic. Given that knockout lines of six of the eight anaesthetic-sensitive K_{2P} channels are available,

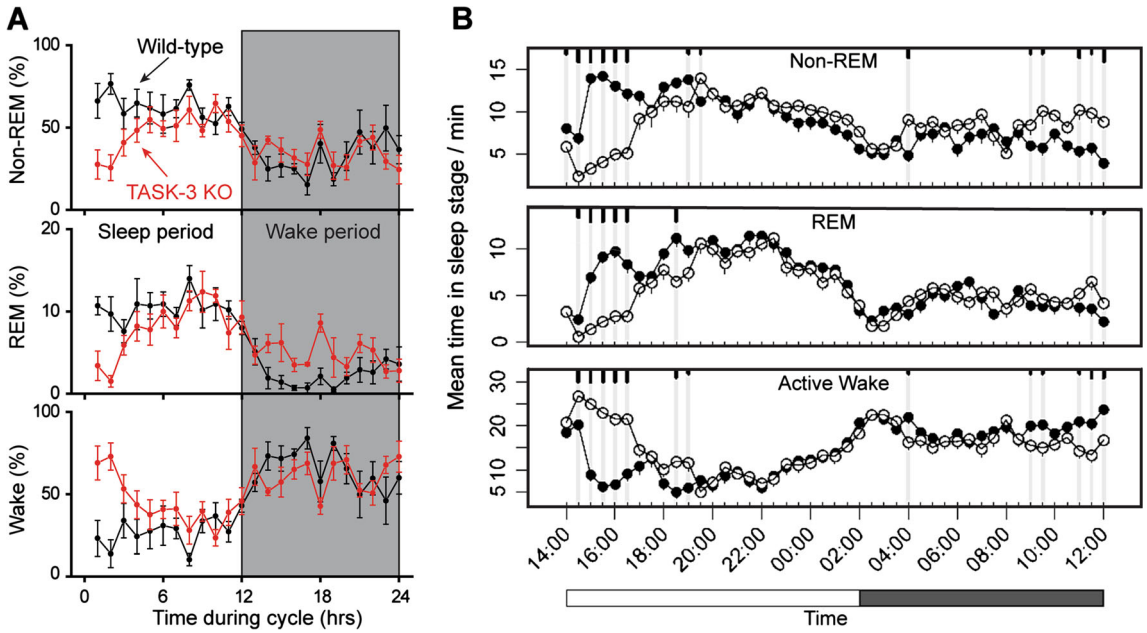

Fig. 1 Similarity between TASK-3 KO 'sleep phenotype' mice and how TASK-3 antagonist drugs affect the sleep-wake cycle in mice. **a** TASK-3 KO animals (*red traces*) have elevated wake in the light period with concurrent reductions in both REMS and NREMS compared to wild-type mice [67]. **b** Similarly, mice dosed with 100 mg/kg TASK-3 antagonist 'compound 23' (*open circles*) have elevated wake in the light period with concurrent reductions in REMS and NREMS compared to mice dosed with vehicle (*closed circles*) (modified from Coburn et al. [17])

comprehensive testing of propofol, pentobarbital, halothane, isoflurane and others using a range of anaesthetic end points to make the studies comparable might be informative. In any case, the K_{2P} knockout mouse studies have shown that K_{2P} are plausible targets for the actions of certain volatile and gaseous agents; however, they are not the only targets and other receptors and ion channels play a role—particularly certain populations of $GABA_A$ receptors [29, 73, 79, 85].

In the absence of a comprehensive testing paradigm, there are still published in vitro sensitivities that could be followed up in vivo. So far, the translation from electrophysiology to animal behaviour has been complex and likely to be affected by compensatory mechanisms during development. For example, TASK-2 channels are opened by clinically relevant concentrations of isoflurane in vitro [35], but TASK-2 deficient mice lose pain reflexes at the same dose of isoflurane anaesthesia as wild-types [32]. It is possible that TASK-2-deficient mice would show differences in loss of righting reflex and reduction in locomotion, but these have not been reported. Given the difficulty in predicting knockout sensitivity, it is crucial to test each drug by experiment. Another question that can now be addressed following the development of specific K_{2P} channel blockers [17, 19, 56, 70] is whether K_{2P} channel blockers can, to some degree, reverse general anaesthesia. As discussed above, TASK-3 channel antagonists are wake-promoting in rodents [17], so it is at least plausible that administration of such an agent during anaesthesia would produce some degree of reversal. So far, it appears that such agents do not reverse anaesthesia. In a recent study of rat respiration during isoflurane anaesthesia, administration of TASK antagonists, whilst stimulating breathing, did not affect anaesthetic depth [19]. Quantified support for this important observation is necessary, ideally using the same anaesthetic end points as those in the mouse knockout studies.

Conclusions and future directions

The focus on K_{2P}s as putative mediators of anaesthetics has been to understand how these drugs produce a loss of consciousness and painful sensation. There are two key motivations for this research: to understand how currently used anaesthetics exert their effects and to identify novel targets and develop better sedatives and anaesthetics. K_{2P} channels are likely to be necessary for the mechanism of action of halogenated anaesthetics and may or may not mediate the effects of some others. It is a curious phenomenon that in K_{2P} knockout mice loss of consciousness in response to one drug can remain intact while others are less potent. Work on these channels may also help us dissect out the pathways responsible for desirable effects of anaesthesia from their side effects. For example, TREK-1 may contribute to the neuroprotective effect of the anaesthetic xenon [23, 37]. Conversely, while TWIK-1 channels are so far not implicated in the transition to unconsciousness in the CNS, they may be recruited in phenobarbital-mediated hepatotoxicity [74] and as such are undesirable targets. It may be no coincidence that the K_{2P}

Table 1 Sensitivity of K_{2P} knockout mice to anaesthetics and sedatives

Channel KO	Reduction in movement	Loss of righting reflex	Loss of pain reflex
TASK-3	dex—no change hal (low dose)—↓	iso—no change prop—no change cyc—no change etom—no change hal—↓	iso—controversial; both no change and ↓ have been shown etom—no change hal—↓
TASK-1	win—no change zolp—no change barb—no change dex—↓ flur—↑ diaz—↑ gab—↑ (females only) prop— (males only) preg—↑ (males only)	iso—controversial. both no change and ↓ have been shown hal—no change prop—↑ (extended duration of LORR) barb—↑ (extended duration of LORR)	hal—↓ iso—no change
TASK-1/-3	hal (low dose) –↓	iso—no change hal—↓	iso—↓ hal—↓
TASK-1/TASK-3 in cholinergic cells only	hal (low dose) –↓	hal—no change	iso—↓ hal—↓
TASK-2	Not tested	Not tested	iso—no change hal—no change desf—no change
TREK-1	Not tested	iso—↓ hal—↓ sevo—↓ desf—↓ prop—no change	Not tested
TRESK	Not tested	Not tested	iso—no change hal—no change desf—no change sevo—no change*
KCNK7	Not tested	Not tested	iso—no change hal—no change desf—no change

Downwards arrows (↓) indicate that knockout animals were less affected by anaesthetic on that measure; conversely, upwards arrows (↑) indicate that knockout animals were more affected than controls by anaesthetic on measure indicated

iso isoflurane, *hal* halothane, *sevo* sevoflurane, *desf* desflurane, *chlor* chloroform, *prop* propofol, *etom* etomidate, *dex* dexmedetomidine, *cyc* cyclopropane, *barb* pentobarbital, *win* WIN55212-3, *flur* flurazepam, *diaz* diazepam, *zolp* zolpidem, *preg* pregnenalone, *gab* gaboxadol [15, 32, 36, 39, 49, 51–53, 86]

*Increased mortality after anaesthetic exposure

channels implicated in thalamocortical regulation, TASK and TREK, are also those deficient in anaesthetic-resistant knockout mouse lines. The same channels are sensitive to REMS manipulating fluoxetine, and the TASK-1 channel knockout is less sensitive to sedative doses of dexmedetomidine, suggesting it may also be a downstream effector of this distinct class of anaesthetic. Thus, drugs that manipulate sleep architecture such as fluoxetine and sedatives, such as low dose dexmedetomidine, may have common K_{2P} targets with general anaesthetics.

A key question is whether K_{2P} channels are recruited in physiological sleep-wake regulation. With regard to REMS and its pharmacological suppression, it is crucial to see if the interaction between K_{2P} channels and the REMS suppressor fluoxetine is limited to this molecule or whether it is a common mechanism of many other REMS suppressants. Because thalamocortical rhythms involve background potassium currents, K_{2P} channels may be necessary for physiological sleep-wake regulation [21]. Support for this comes from the altered sleep phenotype and inability to sustain coherent REMS oscillations in TASK-3 knockout mice [67]. On the other hand, sleep-wake transitions and time spent in arousal states are still intact in TASK-3 knockouts, but this may be because other thalamic (or non-thalamic) K_{2P}s can buffer the loss of TASK-3. This emphasis on K_{2P}s in the thalamocortical circuits would predict that channel knockouts of TASK-1 and TREK-1 and

possibly TREK-2 (all found in the thalamus) may have a similar sleep phenotype to TASK-3 knockouts and that double knockouts may produce a more severe phenotype. In addition, this hypothesis also predicts that selective disruption of thalamic K_{2P} channels in vivo may produce a similar sleep phenotype to that seen in the TASK-3 global knockout. In comparison to the study of K_{2P}s and sleep, the study of K_{2P} channels in anaesthesia has advanced much further. The emerging trend is that both TASK and TREK-1 channels are both necessary for the full effects of halogenated anaesthetics, but exactly which neuronal networks is only beginning to be revealed [63]. Much still remains to be understood about the roles these K_{2P} channels play in the regulation of the natural sleep-wake cycle.

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