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TASK, TREK & Co.: a mutable potassium channel family for diverse tasks in the brain

Introduction

Ion channels belonging to the family of two-pore domain potassium (K_{2P})-channels represent the molecular basis of the background conductance that is necessary for the stabilization of the negative resting membrane potential of nearly all cells (**Fig. 1**). Active K_{2P}-channels mediate a background (also known as leak) current that maintains a membrane potential close to the potassium equilibrium potential and thereby below the action potential threshold. This is how the electrical excitability of cells is typically restrained.

K_{2P}-channels could be identified in diverse animals (mammals, *Drosophila melanogaster, Caenorhabditis elegans*) but also plants [1]. One channel subunit consists of four transmembrane segments (M1–M4) and two pore-forming domains (P1, P2) that are arranged as a tandem (membrane topology: 4TM/2P; **Fig. 1**) thereby exemplifying the name given channel feature. In humans 15 genes encode for K_{2P}-channels that are subdivided in six subfamilies based on their sequence homologies and functional similarities (**Fig. 1; Table 1**). The name of the channel that has been discovered first, TWIK-1, is an acronym for *Tandem of P-domains in a weak inwardly rectifying K^+ channel* (KCNK1, $K_{2P}1$) [2]. In a heterologous expression system TWIK-1 is constantly active and displays no time and voltage dependency. There is an almost linear current–voltage relationship revealing some inward rectification at depolarized potentials which is due to the inhibition of those channels by intracellular magnesium ions. Later 14 further members of the K_{2P}-channel family have been discovered. Two subunits form one ion-conducting, functional channel which can be arranged by both homo- and heteromeres (2×4TM/2P; **Fig. 1**). Each monomer contributes two P-domains and two transmembrane segments, TM2 and TM4, to the channel pore. Interestingly, the potassium channel signature sequences (also known as GYG-motif) of the two P-domains are not identical [3, 4]. K_{2P}-channels define substantial passive (resting membrane potential, input resistance) and active (duration of action potentials, release of neurotransmitters) characteristics of neurons. The outward rectification valid for constitutively open potassium selective pores also describes the current–voltage relationship of several K_{2P}-channels, especially TASK-1, under asymmetric intra- and extracellular potassium concentrations (physiological situation; open channel rectification; **Fig. 1**). Although these channels do not possess a classical voltage sensor, nearly all of them display a voltage-dependent conductance increase upon depolarization and an instantaneous followed by a time-dependent current component. Thus, they should not be considered completely time and voltage independent.

Originally potassium leak channels were considered as rather boring open pores in the plasma membrane that are only slightly regulated. This view has changed completely after the identification of K_{2P}-channels as being their molecular correlates. All members of the K_{2P}-channel family are modulated by numerous neurotransmitters, physicochemical parameters and clinically relevant substances (**Figs. 1, 3**) [4, 6]. TREK-channels are regarded as prototypical here as their activity is regulated in multiple ways. TREK-1 and TREK-2 are activated by stretch or convex deformation of the plasma membrane, depolarization, heat, polyunsaturated fatty acids, arachidonic acid, phosphatidylinositol-4,5-bisphosphate (PIP_2) and inhalation narcotics [7, 8]. Then again these channels are inhibited by the activation of G-protein coupled membrane receptors (GPCR; $G\alpha_s$/adenylyl cyclase/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA); $G\alpha_q$/phospholipase C (PLC)/diacylglycerol (DAG)/protein kinase C (PKC)) [5]. The same complexity as for K_{2P}-channel modulation holds true for their physiological relevance (**Fig. 1**). Hence, these channels contribute to the registration of oxygen tension and proton concentration in tissue as well as to the sensory signal processing of odour stimuli in the *bulbus olfactorius*. Additionally, they are involved in the regulation of blood pressure, cardiac excitation, immune responses and apoptosis [9].

K_{2P}-channels are widely expressed in the central nervous system (CNS; **Fig. 1**) [10]. Regional differences can be found in terms of subtypes and species. Until now TALK-1 channels could not be detected in the CNS. Nevertheless, a general motif might be that TASK-1, TASK-2, TASK-3, TREK-1, TWIK-1, TRAAK and THIK-1 display strong expression in cer-

Note that a special issue on K_{2P}-channels was published in Pflügers Archiv—European Journal of Physiology in May 2015. This issue is considerably based on contributions from members of the DFG research group "K_{2P}-channels—from molecules to physiology and pathophysiology" (FOR1086).

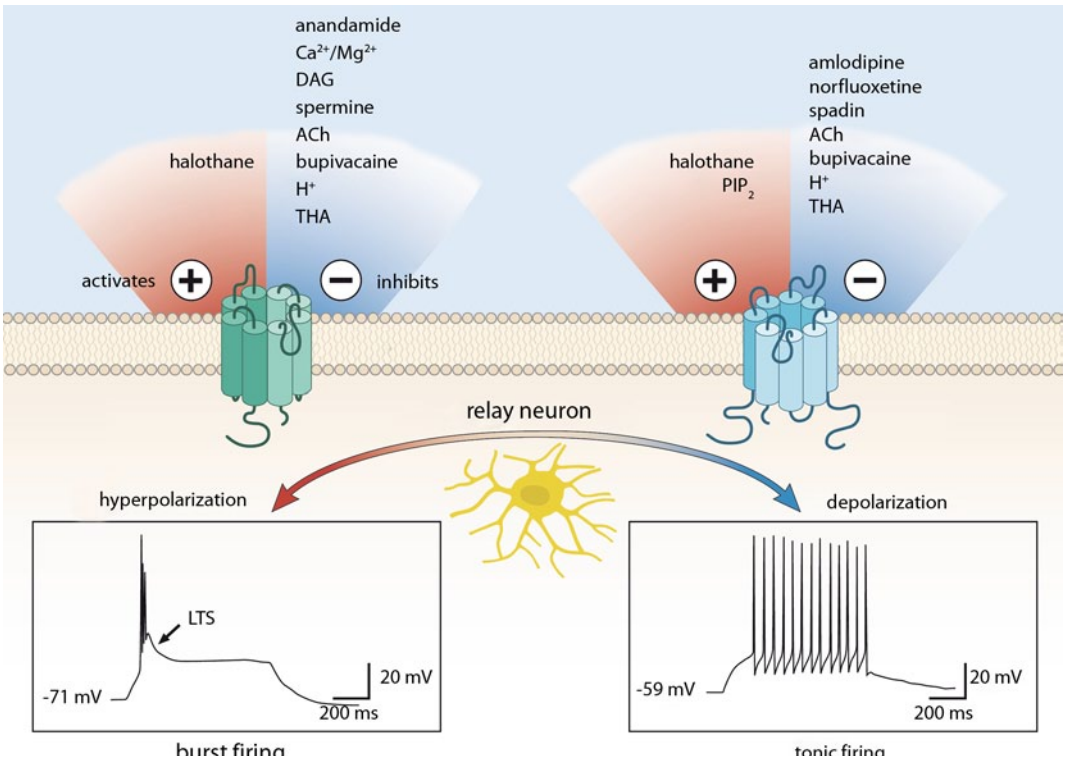

Fig. 1 ▲ Characteristics of K_{2P}-channels. Comprising presentation of the regulatory, biophysical, physiological and pathophysiological features of the K_{2P}-channel family. *Centre*: Regulatory mechanisms. The activity of K_{2P}-channels is influenced by different physiological stimuli. The channels are pH-, oxygen-, and/or temperature-sensitive depending on the subfamily. Other channels respond to mechanical stimuli (e.g. stretch of the cell membrane) and/or are regulated by the binding of polyunsaturated fatty acids and lysophospholipids. *Top right*: Biophysics. A functional K_{2P}-channel is composed of two subunits. Each subunit has four transmembrane domains (M1–M4) and two pore domains (P1, P2). A complex exchange of M2-domains (domain swap; not shown) between both subunits occurs. An active channel mediates a potassium outward current (for exceptions see excurse B). Some K_{2P}-channels can be described as open rectifier at physiological potassium-concentrations. At symmetrical K^+-concentrations their current linearly depends on the membrane potential. *Bottom right*: Expression. K_{2P}-channels are ubiquitously expressed in mammals. In the brain, TASK- and TREK-channels are particularly relevant while TASK-1-, TASK-2- and TREK-channels can be notably found in cardiomyocytes, in the kidney, and in endothelial cells, respectively. *Bottom*: Family members. The K_{2P}-channel family comprises 15 members which are subdivided into six subfamilies (TWIK, TASK, TREK, TALK, THIK, TRESK). *Bottom left*: Physiology. K_{2P}-channels carry a K^+-outward current which contributes to the stabilization of the resting membrane potential, and which supports a hyperpolarization thereby opposing a depolarization. Thus, K_{2P}-channels are conducive to the regulation of excitability in electrically excitable cells. *Top left*: Pathophysiology. A contribution of K_{2P}-channels was shown for different diseases. Among them multiple sclerosis, stroke, hypertension, sleep disorders and various oncological diseases. *MS* multiple sclerosis

ebellum, hippocampus and thalamus thereby pointing to a certain redundancy in terms of channel function and potential heterodimerizations (**Fig. 1**) in these regions. Especially rodent thalamus is characterized by the co-expression of TASK-1, TASK-3 and TREK-1 as well as their modulation by GPCR for acetylcholine (ACh), serotonin (5-HT) and noradrenaline (NA) [5, 11]. As the thalamus is of central importance for sensory information processing, regulation of the sleep-wake cycle and the generation of inhalation anaesthesia, this brain region was intensively examined in terms of physiology, pathophysiology and clinical relevance of K_{2P}-channels. Channel modulation through GPCR, protons and inhalation anaesthetics was of special interest in this context.

The thalamocortical system

In principal, three cell types compose the neuronal elements of the thalamic network (**Fig. 2**): First, excitatory thalamocortical relay neurons. Second, local GABAergic interneurons (which can be found only in distinct thalamic nuclei). Third, GABAergic neurons of the *nucleus reticularis thalami* (NRT). While relay neurons are mutually connected with specific cortical areas, locally branched interneurons and neurons of the NRT mediate inhibitory interactions in the thalamus [12]. In the visual system relay neurons of the *corpus geniculatum laterale pars dorsalis* (CGLd) receive synaptic inputs from retinal ganglion cells and forward the sensory information to the primary visual cortex. There are extensive synaptic connections between the NRT neurons and the sensory relay neurons that are both highly topographically organized. Interneurons that are rare (depending on the nucleus only up to 20 % of neurons), small (~ 10 µm diameter), and project only within a local area are poor-

ly understood hitherto. The three thalamic cell types are interconnected in synaptic loops that allow synchronized network activity.

The electrical activity pattern in the mammalian thalamocortical system is dependent on its present behavioural state [13]. Accordingly thalamocortical relay neurons display two different types of activity (**Fig. 3**). Synchronized, rhythmic bursts occur during slow wave sleep and find their expression in delta- and spindle waves in sleep electroencephalograms (EEGs). During these activity phases relay neurons are hyperpolarized in-between bursts. Similarly, the EEG is characterized by slow delta waves with high amplitude in certain phases of deep narcosis. During wakefulness and episodes of rapid-eye-movement (dream) sleep, tonic activity prevails in the thalamocortical system and is accompanied by high frequencies and low amplitudes in the EEG. When awake, sensory information is substantially encoded by the frequency of action potentials. The resting membrane potential of relay neurons is depolarized now [14].

The adjustment of both activity modes is subject to control by transmitter systems of the ascending reticular arousal system of the brain stem that adapts the thalamocortical system to the states of wakefulness and sleep [13]. In this process different types of neurons of the ascending brain stem system release ACh (cholinergic brain stem nuclei), NA (*Locus coeruleus*) and 5-HT (Raphe nuclei) during phases of wakefulness. The critical step leading to the depolarization of relay neurons is the reduction of a potassium leak conductance. However, the modulation of another membrane conductance also contributes to this depolarization. The activation of so-called HCN-channels (acronym for: hyperpolarization-activated and cyclic nucleotide-gated cation channels; also known as pacemaker channels) that are opened upon membrane hyperpolarization and generate a depolarizing cation current, is augmented by receptors for NA and 5-HT.

Beside the classical assignment of burst and tonic activity to phases of sleep and wakefulness, respectively, the thalamocortical system is characterized by the occurrence of irregular burst activity and slow rhythmic theta activity during wakefulness in apparently independent neurological and psychiatric states (e.g. absence epilepsy, neurogenic pain, tinnitus, cocaine addiction, depression, schizophrenia). These disorders are summarized as thalamocortical dysrhythmia syndromes. In this context, the hyperpolarization of relay neurons after deafferentation or by increased inhibition seems to be relevant [15, 16].

Traditionally CGLd relay neurons played a central role in identifying the potassium-leak channels. It could be demonstrated through the combination of electrophysiological and molecular biological techniques that TASK-1-, TASK-3-, and TREK-1-channels underlie this adjustable potassium-leak conductance in relay neurons [17–21]. Moreover, inhalation anaesthetics like halothane and isoflurane induce a hyperpolarization of relay neurons by activating K_{2P}-channels which is accompanied by increased burst activity [22]. Divalent cations (calcium ions, magnesium ions) and polyamines (spermine) inhibit TASK-3-channel-mediated current in relay neurons and induce a membrane depolarization associated with increased tonic activity [23]. Thus, a great potential for the pharmacological interference of the thalamic activity states can be assigned to those channels and their upstream modulation cascades, and relay neurons are accentuated as ideal research objects.

Muscarinic inhibition of K_{2P}-channels

Both in heterologous expression systems as well as in numerous central neurons, TASK- and TREK-channels are strongly inhibited through the activation of $G\alpha_q$/PLC-coupled receptors [5]. The signalling pathway linked to muscarinic ACh-receptors which are coupled to PLC via $G\alpha_q$ was under particularly intense investigations. For TREK-1 a complex regulation by PIP_2 was described that can explain a channel inhibition after enzymatic PLC activity. However, the downstream molecular mechanism leading to the closure of TASK-channels in native cells has been discussed controversially for a long time. In different experimental systems evidences were found for both a direct channel inhibition by $G\alpha_q$ as well as an indirect effect on channel proteins after PLC-activation and PIP_2-depletion. While the involvement of PLC could be clearly shown (in neurons and cardiomyocytes) over the last years, the inhibition of heterologously expressed TASK-channels following PIP_2-depletion was excluded by means of genetically modified, switchable phosphoinositide phosphatas-

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Abstract

Discovered during the 1990s and in the beginning regarded as passive membrane pores, the family of two-pore domain potassium (K_{2P})-channels initially received only little attention. Today the view on this channel family comprising 15 ubiquitously expressed members in mammals has greatly changed. K_{2P}-channels carry potassium outward current that counterbalances membrane depolarization and stabilizes the resting membrane potential. Thereby they are important regulators for the excitability and the firing behaviour especially in neurons. The long list of modulating mechanisms underlines the channels' relevance. K_{2P}-channels in the thalamus contribute to the regulation of the sleep-wake cycle. They also mediate the effect of volatile anaesthetics by supporting the thalamic activity mode that is also typical for sleep. This review summarizes our knowledge about K_{2P}-channel physiology in the brain, provides an idea of the role of these channels in neurological diseases and lists open questions as well as technical challenges in K_{2P}-channel research.

Keywords

K_{2P}-channels · Physiological relevance · Thalamocortical system · Muscarinic inhibition · Inhalational anaesthetics.

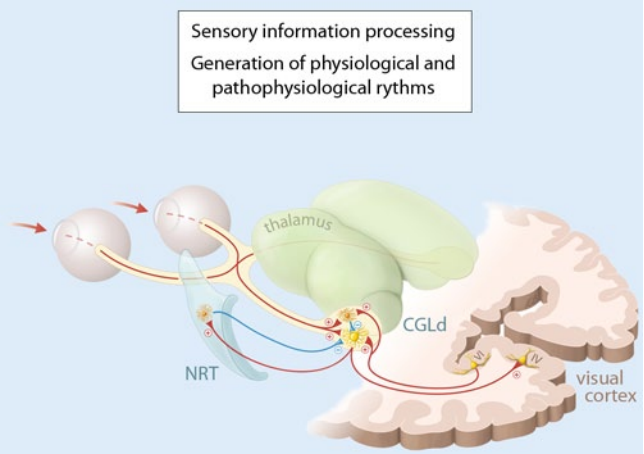

Fig. 2 ▲ The thalamocortical network on the example of the visual system. The optic nerve conducts visual information via excitatory synapses from the retina to relay neurons *(yellow)* and local interneurons *(orange)* of the visual nucleus (CGLd) of the thalamus. At hyperpolarized membrane potentials of the relay neurons, forwarding of visual signals to the cortex is restricted (e.g. during sleep). At depolarized membrane potentials, relay neurons transfer visual information for further processing via excitatory synapses to layer IV neurons of the primary visual cortex. Anatomically, the NRT is positioned like a shell around the thalamus and separates it from the cortex. All projections from the thalamus to the cortex and vice versa have collateral connections to the inhibitory neurons of the NRT *(orange)*. Thus, at least two feedback loops exist within the thalamocortical network. One loop originates from layer VI neurons of the cortex and projects via excitatory synapses back on relay and local interneurons of the CGLd while in the second loop, NRT-neurons inhibit relay neurons of the CGLd. For clearness corticothalamic connections from the cortex to the NRT are not depicted. –, GABAergic/inhibitory synapse; +, glutamatergic/excitatory synapse; *CGLd* corpus geniculatum laterale pars dorsalis, *IV* and *VI* cortical layers IV and VI, *NRT* nucleus reticularis thalami, *TC* thalamocortical relay neuron

es [24]. However, DAG could be identified as TASK-channel inhibitor in further experiments with heterologously expressed channels in which genetic sensors for PIP_2 and DAG have been used. These results could be recently confirmed in native neurons [21]. In this context, the signalling lipids, DAG and PIP_2 are obviously components of the membrane environment in which TASK- and TREK-channels are embedded. In relay neurons of the CGLd, TREK-channels are activated by PIP_2 and TASK-channels inhibited by DAG. After the activation of muscarinic ACh-receptors and enzymatic PLC-activity, PIP_2 and DAG are degraded and synthetized, respectively. Consequently both TASK- and TREK-channels close. The resulting depolarization of the cell membrane induces a switch from burst to tonic firing behaviour (◘ **Fig. 3**). These results characterize a complex interplay between two messenger molecules of the same signalling pathway. This interaction is the basis of a (conceivably strictly localized) fine tuning of TASK- and TREK-channel activity in the thalamus.

Neuroprotective potential of K_{2P}-channels

Owing to their hyperpolarizing influence on the membrane potential, a neuroprotective function is generally attributed to K_{2P}-channels. Nevertheless the exact physicochemical conditions and the cell type-specific channel expression determine whether K_{2P}-channels exert protective or harmful influences during a pathophysiological situation (excurse **A**: TREK-1-channels and neuroprotection: a paradox?) [25]. In this respect, 9 out of 15 K_{2P}-channels respond to changes of the extra- and/or intracellular pH value (◘ **Table 1**). Long lasting neuronal activity leads to an extracellular, transient alkalization succeeded by a persistent acidification. The intracellular pH value normally follows these changes with a certain delay. During ischemic events the extracellular pH might drop to values as low as 6.0 [26]. For the analysis of cytotoxic events during ischemia, the thalamus represents a suitable research object since several dorsal nuclei (including the CGLd) are part of a topographically organized system in the brain (together with the primary sensory cortical areas and the basal ganglia) which displays a preferential and selective sensitivity towards ischemia [27]. Vulnerable neurons respond to ischemia with a long lasting depolarization and cellular damage. Based on the functional expression of TASK-1, TASK-3- and TREK-1-channels in relay neurons, an extracellular acidification leads to a moderate depolarization of the cell membrane. Interactions with further pH-sensitive channels and subtype-specific effects were also shown to play a role. In relay neurons, at the same time, a decrease of the extracellular pH-value induces an inhibition of K_{2P}-channels and HCN-channels that normally hyperpolarize and depolarize the membrane, respectively. Together these effects result in a moderate net effect on the membrane potential [20]. Only the massive release of monoamines and the production of nitric oxide (NO) during ischemia cause a strong activation of HCN-channels and therefore a marked membrane depolarization [28]. In this context an increased spermine concentration might also play a role as, during ischemic events, it might raise to a level high enough to inhibit TASK-3-channels. Furthermore it could be demonstrated that TASK-1 and TASK-3 exert differential influences on brain damage after an insult. While TASK-1 has a neuroprotective effect and limits the infarct volume after the occlusion of the *arteria cerebri media* [29], TASK-3 has no considerable influence on the extent of the brain damage [30]. In another pathophysiological context, EAE, a model of multiple sclerosis, axonal damage is larger in the presence than in absence of TASK-1-channels [31].

Not only the external modulating influence but also the cell type-specific expression of K_{2P}-channels determines the direction of physiological effects. Thus, the application of 5-HT to interneurons of the entorhinal cortex, a key structure

Table 1 Modulation of K_{2P}-channels by protons and inhalational narcotics

Subfamily	Channel name	pH-dependency (effects compared to pH 7.4)	Modulation by inhalational narcotics
TWIK: *Tandem of P-domains in a weak inwardly rectifying K^+ channel*	TWIK-1, KCNK1, $K_{2P}1.1$	$pH_O\downarrow \Rightarrow$ Inhibition	No effects
	TWIK-2, KCNK6, $K_{2P}6.1$	–	
	TWIK-3, KCNK7, $K_{2P}7.1$	–	
TREK: *TWIK-related K^+ channel*/ TRAAK: *TWIK-related arachidonic acid-activated K^+ channel*	TREK-1, KCNK2, $K_{2P}2.1$	$pH_O\downarrow \Rightarrow$ Inhibition; $pH_i\downarrow \Rightarrow$ Activation	Chloroform, diethyl ester, halothane, isoflurane $\Rightarrow$ Activation
	TREK-2, KCNK10, $K_{2P}10.1$	$pH_O\downarrow \Rightarrow$ Activation; $pH_i\downarrow \Rightarrow$ Activation	
	TRAAK, KCNK4, $K_{2P}4.1$	$pH_O\uparrow \Rightarrow$ weak activation; $pH_i\uparrow \Rightarrow$ Activation	No effects
TASK: *TWIK-related acid-sensitive K^+ channel*	TASK-1, KCNK3, $K_{2P}3.1$	$pH_O\downarrow \Rightarrow$ Inhibition	Halothane, isoflurane $\Rightarrow$ Activation
	TASK-3, KCNK9, $K_{2P}9.1$	$pH_O\downarrow \Rightarrow$ Inhibition	
	TASK-5, KCNK15, $K_{2P}15.1$	–	–
TALK: *TWIK-related alkaline pH-activated K^+ channel*	TALK-1, KCNK16, $K_{2P}16.1$	$pH_O\uparrow \Rightarrow$ Activation	Chloroform, halothane $\Rightarrow$ Inhibition
	TALK-2, KCNK17, $K_{2P}17.1$	$pH_O\uparrow \Rightarrow$ Activation; $pH_i\uparrow \Rightarrow$ Activation	Chloroform, halothane $\Rightarrow$ Inhibition; Isoflurane $\Rightarrow$ Activation
	TASK-2, KCNK5, $K_{2P}5.1$	$pH_O\uparrow \Rightarrow$ Activation; $pH_i\uparrow \Rightarrow$ Activation	
THIK: *TWIK-related halothane-inhibited K^+ channel*	THIK-1, KCNK13, $K_{2P}13.1$	–	Halothane $\Rightarrow$ Inhibition
	THIK-2, KCNK12, $K_{2P}12.1$	–	
TRESK: *TWIK-related spinal cord K^+ channel*	TRESK, KCNK18, $K_{2P}18.1$	–	–

The original popular and the systemic nomenclature (HUGO, KCNKxx; *International Union of Pharmacology*, $K_{2P}x.x$) are given. (–) = no effects or not tested, (pH_O) = extracellular pH, (pH_i) = intracellular pH

in temporal lobe epilepsy, induces a depolarization that is based on the inhibition of TASK-3-channels. Consequently, the interneurons fire more action potentials, release GABA and thereby inhibit pyramidal neurons and epileptic activity which occurs in the presence of low extracellular magnesium concentrations [32]. Contrarily, in pyramidal cells of the hippocampus, a hyperexcitation and epileptic activity can be prevented by increased expression and activation of TREK-channels [33].

This observation is further complicated by the fact that some K_{2P}-channels dynamically change their ion selectivity and carry excitatory sodium currents as a consequence of changed extracellular proton or potassium concentrations (excurse **B**: Ion selectivity of TWIK-1-channels) [34, 35].

K_{2P}-channels as target structures of inhalation narcotics

The opening of potassium conductances represents a plausible mechanism for the generation of general anaesthesia. Most of the K_{2P}-channels are opened by inhalation gases (**Table 1**) [36]. Noticeable exceptions are THIK-channels that are closed by halothane [37] and TWIK-channels that are not sensitive towards these gases [38]. Therefore, it cannot be assumed that THIK- and TWIK-channels mediate the effects of inhalation anaesthetics. Nevertheless TASK-1-, TASK-3- and TREK-1-channels are ideally suitable to play an important role in the inhalation narcotics. Beside their activation by inhalation anaesthetics, this is due to their expression in the thalamus. Halothane and isoflurane activate pH-sensitive K_{2P}-channels in rat relay neurons while HCN-channels are inhibited at the same time [22]. This leads to a hyperpolarization of the membrane potential and increased burst activity. Eventually the halothane effect is accompanied by a strong decrease of the membrane resistance (shunting inhibition) and the interference with further membrane conductances by which neuronal activity is mostly suppressed. Thus, inhalation anaesthetics (activation of K_{2P}-channels + inhibition of HCN-channels $\Rightarrow$ narcosis) influence the activity of relay neurons in a way that is exactly the opposite to the effects of the transmitters of the ascending reticular arousal system (inhibition of K_{2P}-channels + activation of HCN-channels $\Rightarrow$ wakefulness). Clinical observations show that the minimal alveolar concentration of halogenated anaesthetics, necessary for the suppression of reactions to painful stimuli, is 30 % higher in juvenile compared to adult rats [39]. Changes in the postnatal expression profile of K_{2P}-channels might be the reason for these different sensitivities.

It is interesting to notice that local anaesthetics (like e.g. bupivacaine) inhibit TASK- and TREK-channels in clinically relevant concentrations [36].

TASK- and TREK-channels as signal integrators for the control of thalamic activity states

As stated above the molecular features of K_{2P}-channels in heterologous expression systems correlate very well with the functional characteristics of thalamic neurons. In sensory relay neurons of rodents, TASK- and TREK-channels are inhibited or activated by a number of neurotransmitters, divalent and polyvalent cations as well as clinically relevant substances, and thus they contribute to depolarization or hyperpolarization of the membrane potential (**Fig. 3**). As a result K_{2P}-channels represent central elements for the control of thalamic activity states and therefore of the sensory information processing, of the generation of natural sleep rhythms and general anaesthesia as well as of thalamocortical dysrhythmia.

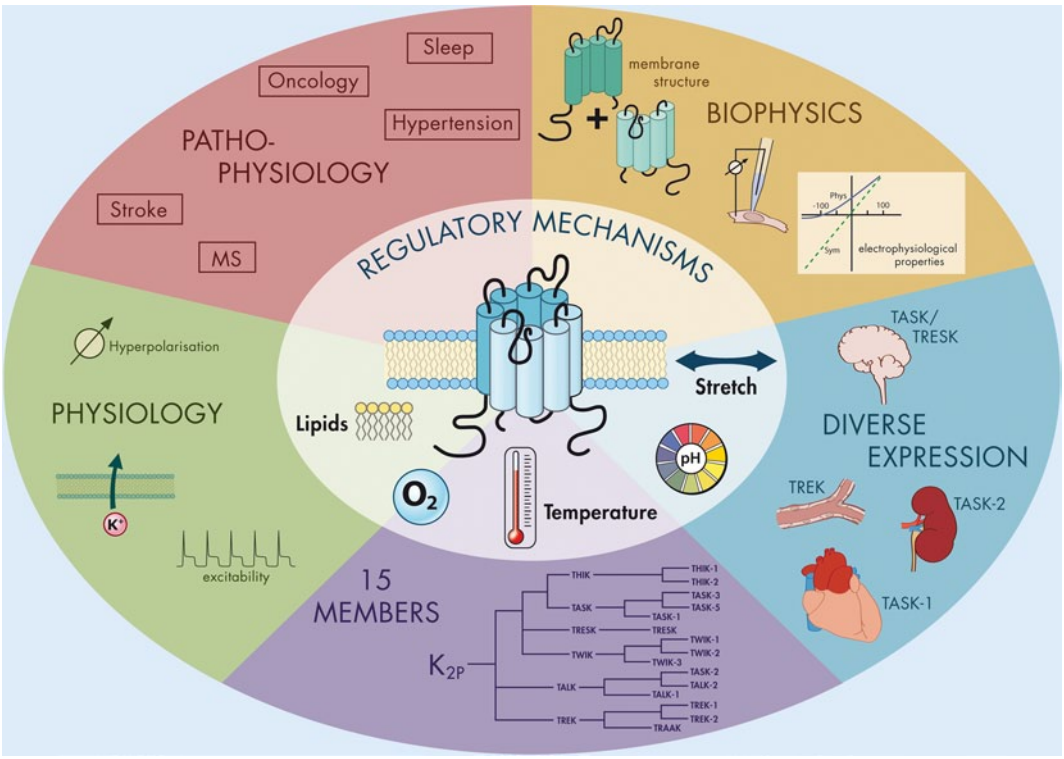

Fig. 3 ▲ Exogenous and endogenous modulation of TASK- and TREK-channels in thalamocortical relay neurons. Some substances specifically activate *(red)* and inhibit *(blue)* TASK- and/or TREK-channels. TASK-channels are activated by the inhalational anaesthetic halothane while they are inhibited by binding of anandamide, Ca^{2+}/Mg^{2+}, DAG and spermine. Phospholipids (like PIP_2), but also halothane, are activators of TREK-channels. Substances like amlodipine, norfluoxetine and spadin block TREK-channels. Both channels are inhibited by ACh, bupivacaine, THA as well as by high extracellular proton concentrations. Functionally, an activation of TASK- and TREK-channels results in a hyperpolarization whereas a channel blockade causes a depolarization of relay neurons. The membrane potential of those cells regulates their firing behaviour in a way that negative potentials below ~ – 70 mV favour rhythmic, burst-like action potential discharges (oscillatory firing behaviour) as a response to a depolarizing stimulus. Action potential bursts are superimposed to a Ca^{2+}-potential (LTS) which is generated by T-type-Ca^{2+}-channels *(arrow)*. During burst mode, the relay of sensory signals from the periphery to the cortex is strongly restricted. However, when starting from a positive membrane potential of about -55 mV, the neuronal response to a depolarizing stimulus changes. The cell fires in a tonic mode that is characterized by a series of single action potentials. In this mode, the firing frequency is proportional to the intensity of the evoking, excitatory stimulus thus allowing a 1:1-relay of sensory information to the cortex. *ACh* acetylcholine, *DAG* diacylglycerol, *LTS* low-threshold Ca^{2+} spike, *PIP_2* phosphatidylinositol-4,5-bisphosphate, *THA* tetrahexylammonium

Outlook

For a long time thalamus research mainly focused on the physiology of K_{2P}-channels in relay neurons thereby clearly describing the channels' relevance for behaviourally correlated activity patterns of the thalamocortical system. In comparison there is only very limited knowledge on the existence and physiological function of K_{2P}-channels in inhibitory neurons of the thalamus. As outlined above local interneurons are located in distinct nuclei of the thalamus. Due to their low numbers and small soma sizes, the electrophysiological investigation of those cells was markedly hindered for a long time. The generation of transgenic mouse lines that express green-fluorescent proteins (GFP) under a promotor specific for GABAergic neurons (GAD67) allowed the targeted electrophysiological and molecular biological investigations of local interneurons. Interestingly, preliminary single cell polymerase chain reaction (PCR) analyses on local interneurons could demonstrate the expression of transcripts from K_{2P}-channels of different subfamilies (TASK-subfamily: TASK-1, TASK-3, TASK-5; TREK-subfamily: TREK-1, TREK-2, TRAAK; TALK-subfamily: TASK-2; THIK-subfamily: THIK-1, THIK-2). Among them also so-called 'silent' members of the K_{2P}-channel family, THIK-2 and TASK-5, that, until now, is not shown to mediate current in heterologous expression systems. Recent studies in heterologous expression systems reveal that the apparent lack of THIK-2 channel activity on the cell surface is induced by the channels' retention in membranes of the endoplasmic reticulum as well as by their weak intrinsic activity [40]. It remains to be seen which physiological functions K_{2P}-channels and especially the 'silent' family members fulfil in local interneurons of the thalamus. It is conceivable that different physiological and also pathophysiological stimuli are necessary for the activation and expression of those channels on the cell sur-

Excurse A: TREK-1-channels and neuroprotection: a paradox?

In the past years, it could be demonstrated that the TREK-1-channel is involved in many different diseases of the CNS, and that its pharmacological modulation could be a potentially new therapeutic mode of action. Despite of certain common pathophysiological signalling pathways, in some diseases, a blockade of TREK-1 is neuroprotective (depression) whereas in other disease models (stroke, epilepsy, multiple sclerosis) an activation of TREK-1-channels has a positive effect. One reason for this could be the expression of TREK-1-channels on different cell types of the CNS and a differential temporal and functional regulation under acutely and chronically harmful conditions. Thus, TREK-1-deficient mice reveal larger infarct volumes compared to wild type controls. The activation of TREK-1-channels leads to neuroprotective effects via a direct neuronal reduction of glutamatergic excitotoxicity as well as via a regulation of the central blood flow [55, 56]. In EAE, TREK-1-channels on endothelial cells of the blood–brain barrier play a critical role for the migration of harmful immune cells into the CNS [57]. An activation of TREK-1-channels prevents the migration of immune cells thereby leading to an ameliorated disease course. The investigation of the exact functioning of TREK-1-channels under pathophysiological conditions is a major prerequisite for the development of potential pharmacological treatment strategies.

Excurse B: K_{2P}-channels are (not) always selective for potassium

The statement "K_{2P}-channels are potassium-selective ion channels" is not always correct. Recently it was found that there are exceptions. Human TWIK-1-channels (but not TWIK-1-channels of rats and mice) carry sodium instead of potassium ions when the extracellular potassium concentration decreases drastically [35]. A specific threonine residue (Thr118) within the selectivity filter of the pore allows this change in ion selectivity. This phenomenon might explain the occurrence of cardiac arrhythmias caused by hypokalaemia. Thus, the paradoxic depolarization of human cardiomyocytes at low extracellular potassium concentrations being hardly explainable with the Nernst-potential seems to be based on the influx of sodium ions via TWIK-1-channels [58]. Shortly after, this discovery was extended by the finding that TWK-1-channels mediate sodium current also upon extracellular acidification [34]. Since TWIK-1-channels contribute to the excitability of granule cells of the gyrus dentatus, similar considerations could be done on the generation of hyperexcitability and epilepsy in case of reduced extracellular potassium concentrations in the hippocampus. pH sensitivity is a classical hallmark of many members of K_{2P}-channel family reacting with a reduced potassium outward current upon extracellular acidification. The changed ion selectivity, however, is a more specific feature. After a pH drop the TWIK-1-channel changes into a state in which it, for minutes, non-selectively carries cations followed by a solely sodium conducting state [34]. Additionally, a pH-dependent change in ion selectivity was also found for TASK-1- and TASK-3-channels [35] suggesting that the pH-dependent change of ion selectivity is not restricted to the TWIK-subfamily. Typically the required acidic pH-values exist, for instance, inside recycling endosomes and under pathophysiological conditions of an inflammatory milieu. Why some K_{2P}-channels change their ion selectivity in dependence of potassium and proton concentrations, is unknown so far.

face. Thalamic relay neurons receive additional inhibitory inputs from GABAergic neurons of the NRT. First quantitative PCR studies on K_{2P}-gene expression in NRT neurons demonstrate a high expression level for TWIK-1 as well as weaker expression of TASK-1- and TREK-1-transcripts [10]. Immunohistochemically the expression of TREK-1-channels could be confirmed on GAD67-GFP-positive cells in the NRT of mice [11]. Functional analyses are still awaited for this type of thalamic cell type as well.

Non-neuronal cell types of the CNS possess functionally expressed K_{2P}-channels. TREK-1- and TREK-2-channels generate an outward current in hippocampal astrocytes of the mouse [41]. As such TREK-1-channels are shown to promote astrocytic glutamate release [42]. Immunhistochemical analyses of hippocampus biopsies taken from patients with temporal lobe epilepsy demonstrate increased TASK-1-expression on astrocytes and TASK-3-expression on astrocytes as well as on microglial cells while, on control tissue, both channels can be found predominantly on neurons [43]. In addition, myelin-producing oligodendrocytes express TASK-1-channels which, under hypoxic conditions, contribute to oligodendroglial cell damage [44]. Knowledge on the role of K_{2P}-channels on non-neuronal cells in the brain is very limited until now. In respect of the central role that glia cells play for the maintenance and functionality of neurons further investigations are indispensable.

A putative role of K_{2P}-channels for the generation of thalamocortical dysrhythmia needs to be further investigated in the future since new pharmacological target structures could be characterized in this respect. For the treatment of schizophrenia, potassium channel openers are already in use. How these pharmaceuticals act and whether they exert their effect via mediating enhanced potassium-currents in parts of the thalamus is not known until now. The inhibition of TREK-1- and TASK-3-channels as therapeutic strategy for the treatment of depression is also discussed [45–47] underlining a possible role of K_{2P}-channels in affective disorders. Thus, K_{2P}-channels seem to be potential target structures of pharmaceuticals whose application goes far beyond anaesthesia.

Currently the lack of suitable experimental tools hinders the establishment of K_{2P}-channels as therapeutics target structures. So far, only few cell type specific or inducible transgenic mouse lines are available that may provide insights into cell type-specific or development-dependent functions of K_{2P}-channels. Moreover, only a few selective channel modulators for pharmacological experiments and potential therapeutics are available. The majority of substances exerts an inhibitory effect, is semi-selective and thus allows no distinction between channel subtypes. Recently the first crystal structures of K_{2P}-channels (TWIK-1, TRAAK) were published [48–50]. These studies do not only improve our biophysical knowledge of these channels, but they also facilitate the generation of new specific modulators.

Nearly 20 years after the discovery of the channel family, many aspects of the K_{2P}-channel physiology are still not understood. After elucidation of the muscarinic inhibition of TREK-1-, TASK-1-, and TASK-3-channels, further studies will be necessary to explain the G-protein-mediated signalling pathways and their effects on different K_{2P}-channels. Furthermore, there are open questions concerning the physiology of channel subunit dimerization. Homo- as well as heterodimers can build a functional channel. In the last years, many dif-

ferent heterodimer combinations were found (THIK-1/THIK-2 [51]; TASK-1/TASK-3 [52]; TWIK-1/TASK-1 TASK-3 [53]; TWIK-1/TREK-1 [54]). The physiological relevance of variable channel subunit compositions, however, is mostly unknown.

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