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INVITED REVIEW

The role of two-pore-domain background K^+ (K_{2P}) channels in the thalamus

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Abstract The thalamocortical system is characterized by two fundamentally different activity states, namely synchronized burst firing and tonic action potential generation, which mainly occur during the behavioral states of sleep and wakefulness, respectively. The switch between the two firing modes is crucially governed by the bidirectional modulation of members of the K_{2P} channel family, namely tandem of P domains in a weakly inward rectifying K^+ (TWIK)-related acid-sensitive K^+ (TASK) and TWIK-related K^+ (TREK) channels, in thalamocortical relay (TC) neurons. Several physicochemical stimuli including neurotransmitters, protons, di- and multivalent cations as well as clinically used drugs have been shown to modulate K_{2P} channels in these cells. With respect to modulation of these channels by G-protein-coupled receptors, PLCβ plays a unique role with both substrate breakdown and product synthesis exerting important functions. While the degradation of PIP_2 leads to the closure of TREK channels, the production of DAG induces the inhibition of TASK channels. Therefore, TASK and TREK channels were found to be central elements in the control of thalamic activity modes. Since research has yet focused on identifying the muscarinic pathway underling the modulation of TASK and TREK channels in TC neurons, future studies should address other thalamic cell types and members of the K_{2P} channel family.

Keywords TASK channels · TREK channels · Muscarinic modulation · Thalamic firing modes · Thalamocortical network

Members of the K_{2P} channel family crucially contribute to the generation of the resting membrane potential in neurons [33]. In the thalamus, the functional expression of TASK and TREK channels has been shown. The occurrence of state-dependent activity modes in thalamic neurons critically depends on the level of the prevailing membrane potential [22]. Therefore, K_{2P} channels seem to represent the mechanistic basis for the occurrence of tonic and different forms of oscillatory activity in the thalamocortical network which are central to a number of neurocognitive functions (e.g., attention, cognition, perception, memory, and wakefulness/sleep) and apparently unrelated neurological and psychiatric conditions (e.g., depression, dystonia, neurogenic pain, Parkinson tremor, spasm, tinnitus, epilepsy) [55].

Activity modes and cellular components of the thalamocortical network

The thalamocortical network is the neuronal substrate for the generation and maintenance of two different behavioral state-dependent activity modes [22, 89]. States of wakefulness as well as rapid eye movement (REM) sleep are characterized by tonic generation of action potentials and high-frequency (~40 Hz) low-amplitude oscillations. States of slow wave sleep are characterized by highly synchronized oscillatory low-frequency (<15 Hz) and high-amplitude burst activity.

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Furthermore, a number of apparently unrelated neurological and psychiatric conditions (including neurogenic pain, tinnitus, abnormal movements, and epilepsy) are characterized by irregular random bursting and rhythmic low-frequency theta rhythmicity in the thalamus during wakefulness [55]. Especially, the highly synchronized rhythmic burst activity seen during ictal periods of childhood absence epilepsy (CAE) represents an example of the dysfunction of the thalamocortical system [13, 24, 78].

Based on their axonal projections, excitatory TC neurons connected to specific cerebral cortical areas and locally ramifying GABAergic interneurons can be distinguished within thalamic nuclei [85]. Furthermore, cells of the nucleus reticularis thalami (NRT) confine a shell-like area that surrounds mainly the anterior and lateral aspects of the dorsal thalamus and provide an additional source of inhibitory inputs. Within the visual pathway, TC neurons of the dorsal part of the lateral geniculate nucleus (dLGN), which receives afferents from the retina and projects to the primary visual cortex, probably represent the best-investigated thalamic cell type, while much less is known about local circuit interneurons [85]. The three main thalamic cell types are synaptically interconnected in functional loops which facilitate recurrent, synchronized network oscillations. TC neurons and NRT neurons, each of which possesses intrinsic pacemaker properties, are mutually interconnected via extensive synaptic contacts, thereby creating a recurrent intrathalamic loop (Fig. 1).

TC neurons are a population of excitatory cells with an intrinsic predisposition for oscillatory activity in the δ frequency range (0.5–4 Hz). The characteristic "rebound" spiking in TC neurons following inhibition, which is associated with a Ca^{2+}-dependent low-threshold spike (LTS) whose activation requires a conditioning membrane hyperpolarization, has been known for a long time [73]. The LTS is a long-lasting depolarization, carried by a low-threshold activated T-type Ca^{2+} current (I_T), which triggers a burst of conventional Na^+/K^+ action potentials (see Fig. 3, left voltage trace) and can drive oscillatory activity in the thalamocortical network [75]. Another membrane current, the hyperpolarization-activated cation current (also called pacemaker current), I_h, which is generated by hyperpolarization-activated and cyclic nucleotide-gated cation (HCN) channels, is of crucial importance for oscillatory activity in the thalamocortical system by determining the frequency of rhythmic burst generation [4].

In the rodent dLGN, about 20–25 % of the cells are local circuit interneurons, which release the inhibitory transmitter GABA [85]. Although these cells are endowed with critical oscillation-related membrane currents such as I_T and I_h, and reveal intrinsic oscillations, the role of thalamic interneurons in thalamocortical rhythmicity is not clear [100, 102, 103]. Because of limited synaptic connectivity with other thalamic elements (i.e., they receive little input from either TC neurons or NRT neurons), investigators have hypothesized that

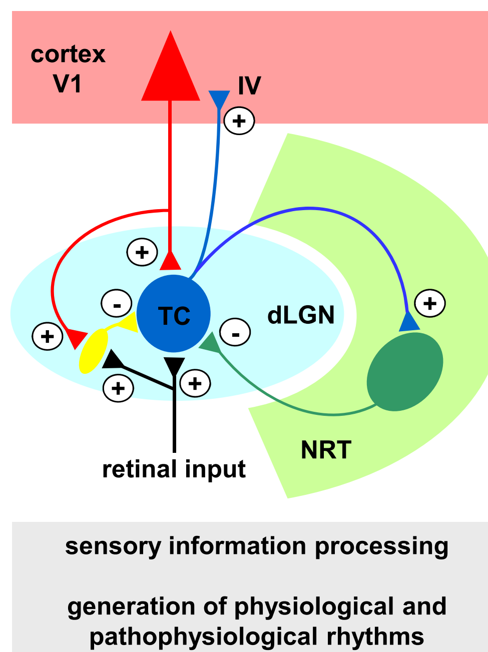

Fig. 1 Schematic representation of the visual thalamocortical pathway. The retina conveys visual stimuli to the dorsal part of the lateral geniculate nucleus of the thalamus (dLGN) which is reciprocally interconnected with the primary visual cortex (V1), specifically (with layer IV as the main input layer). Inhibition in this circuit is operated by interneurons located within the dLGN (in yellow) and by neurons of the NRT, with the latter also reciprocally connected to the dLGN. It should be noted that the corticothalamic projection includes excitatory collateral connections to the NRT which is not shown for clarity here

interneurons have no major role in generating recurrent thalamocortical oscillations but contribute primarily to the processing of sensory inputs [42].

The third neuronal component involved in thalamic rhythm generation is the entirely GABAergic population of NRT neurons which generate burst firing patterns from resting membrane potential preferentially in the spindle frequency domain (7–11 Hz) [41]. Compared with TC cells, the bursts generated by NRT neurons are not as stereotyped as in TC neurons and they are often of a longer duration and higher frequency.

Cholinergic inputs ascending from the brainstem represent one of the most prominent modulatory inputs (around 30 % of the total number of synapses) to dLGN TC neurons which mediate the switch between the two firing modes [60]. The central action of acetylcholine (ACh) is a depolarizing shift of the membrane potential of TC neurons, leading to cessation of rhythmic bursts and occurrence of tonic activity (see Fig. 3, right voltage trace). One crucial step of membrane depolarization is the decrease in leak K^+ current (I_{KL}), the molecular basis of which was enigmatic for a long time. Interestingly, the application of ACh to interneurons and NRT neurons results in a transient hyperpolarization and a marked inhibition of action potential output through the increase of K^+

conductances. The molecular nature of these conductances is still unknown.

Identification of K_{2P} channels in TC neurons

I_{KL} in the nervous system is often carried by two-pore-domain background K^+ (K_{2P}) channels which are regulated by a number of different G-protein-coupled receptor pathways [33, 39, 58]. Three major findings had suggested as early as 1999 that K_{2P} channels may be the molecular basis of I_{KL} in these cells [61]: (i) I_{KL} is decreased upon the activation of the muscarinic ACh receptor (MAChR) subtypes 1 (M_1AChR) and 3 (M_3AChR) [101]; (ii) I_{KL} is enhanced by halothane, which in turn may contribute to the induction and maintenance of generalized anesthesia in vivo [81]; and (iii) general inhalational anesthetics activate the K_{2P} channels TASK-1 and TREK-1 [74].

Since constitutively open K^+ channels should generate a constant outward current at potentials positive to the K^+ equilibrium potential (E_K), likewise I_{KL}, the functional expression of K_{2P} channels in TC neurons was assessed by applying classical ramp protocols [68] and analyzing the standing outward current (I_{SO}; see Fig. 2a). In this way, cells were voltage-clamped at a depolarized potential of around −30 mV to inactivate voltage-dependent membrane currents and to increase the amplitude of currents carried by K_{2P} channels. Thereafter, the membrane potential was rapidly (within 800 ms) ramped to a more negative potential of around −140 mV with a rate of hyperpolarization (7 ms/mV) that was sufficiently slow to allow the outward current to reach a steady state at each potential [64]. While this approach allows the analysis of constitutively open channels, the identification of the contribution of specific K_{2P} channels is complicated by the fact that the I_{SO} in rodent TC neurons results from the complex interplay of several inward (I_h; persistent Na^+ current, I_{NaP}) and K^+ current (inward rectifying K^+ channels, Kir; voltage-activated K^+ channels, Kv; K_{2P}) components. The mean amplitude of I_{SO} in dLGN TC neurons (P18-P23) found at depolarized membrane potentials (about −30 mV) in several studies was approximately +380 pA. Based on pharmacological approaches, it was found that Kir (blocked by Ba^{2+} or tertiapin Q), KCNQ (blocked by XE991), and non-inactivating components of voltage-dependent K^+ channels (blocked by tetraethylammonium (TEA) and 4-aminopyridine (4-AP)) contributed about 40, 25, and 180 pA to I_{SO}, respectively [5, 6, 30, 49, 64, 65, 71].

Initially, the contribution of TASK channels in TC neurons was assessed by probing the name-giving feature of these channels, the inhibition by H^+. Based on the effect of extracellular acidification, current through TASK channels was estimated to contribute about 35–40 % to I_{SO} in rodents (when HCN channels were blocked by ZD7288; Fig. 2a, b [30, 63, 64]). However, this TASK channel-specific property has been challenged recently as it was found that TREK-1 behaves like a TASK channel in that it is blocked by extracellular acidification [82]. Nevertheless, the pH-sensitive component is of exquisite importance in TC neurons since hyperpolarizing TASK and TREK channels on the one hand and depolarizing HCN channels on the other hand control the resting membrane potential by a mutual functional interaction [65]. Therefore, the most efficient way to regulate the membrane potential of

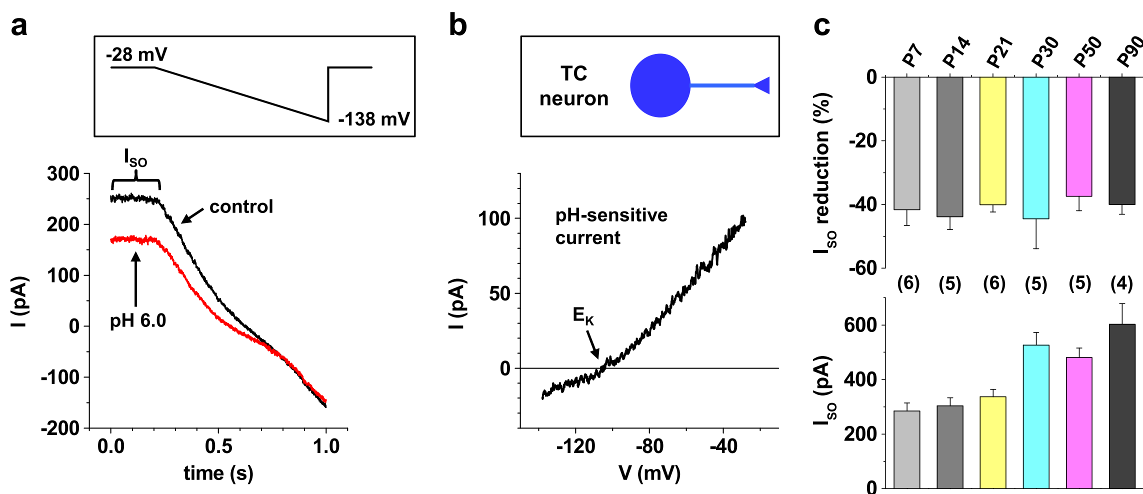

Fig. 2 H^+-inhibited K_{2P} channels in TC neurons. **a** The I_{SO} is significantly decreased by acidification of the extracellular environment (pH= 6), as shown in voltage clamp condition when TC neurons are clamped to −28 mV and the potential is rapidly (800 ms) ramped to −138 mV (Fig. 1a, *inset*). **b** The pH-sensitive current obtained by graphical subtraction of the control current (*black trace*) from the current obtained under acidified conditions (*red trace*) shows outward rectification and a reversal potential very similar to the calculated E_K (marked by the *arrow*). The *inset* refers to the schematic drawing of a TC neuron in Fig. 1 and indicates that all data were obtained from this thalamic cell type. **c** While I_{SO} increases during the postnatal development (lower panel), the percentage of the pH-sensitive component remains close to 40 % at all postnatal days taken into consideration (*upper panel*)

TC neurons is the converse modulation of TASK/TREK and HCN channels. It was speculated that another consequence of this interplay makes TC neurons potentially more resistant to insults accompanied by extracellular pH shifts in comparison to other CNS regions (but see below). Furthermore, the numerical balance between currents through K_{2P} and HCN channels seem to be highly important. During postnatal development, I_h amplitudes increase about 3.8 times from P7 to P108 in rat dLGN TC neurons [52]. In a similar way, the amplitude of I_{SO} (in the presence of ZD7288) increases during postnatal development (Fig. 2c, lower panel) with the pH-sensitive component of I_{SO} being constantly close to 40 % (Fig. 2c, upper panel; P. B. and T. B. unpublished data).

To what extent other ion channels may contribute to the increase in I_{SO} is not fully understood. Since at all ages analyzed the overall distribution patterns of G-protein-gated Kir channels (GIRK1-3) were found to be very similar, with high expression levels in the neocortex, cerebellum, hippocampus, and thalamus [36], the current through these channels may be constant at all ages and may not significantly contribute to the developmental increase. With respect to Kv channels, recent findings indicate that members of KCNQ channel family, the molecular substrate of the M-current (I_M), contribute to I_{SO} and the control of thalamic activity modes [6, 16]. The use of the KCNQ channel activator retigabine indicated a significant increase in I_M amplitude during postnatal development, thereby pointing to the possibility of an increasing influence of this current with age (M. C. and T. B., unpublished data). Although the exact proportions of all membrane currents involved in I_{SO} generation are not known for all ages yet, it appears that currents through TASK/TREK and HCN channels have converse contributions over the entire period of postnatal development.

The contribution of different K_{2P} channel subtypes in rodent TC neurons (P18-P23) was further assessed by probing the effects of a number of activators and blockers, some of them being highly subtype specific. It was concluded that TASK-1/TASK-3 (block by A293, bupivacaine, divalent cations, H^+, spermine, tetrahexylammonium (THA); activation by halothane) and TREK-1/TREK-2 channels (block by amlodipine, norfluoxetine, H^+, spadin, THA; activation by PIP_2) contribute about 70 and 30 pA to I_{SO}, respectively (Fig. 3; [5, 10, 22, 23, 30, 63–65]). It is interesting to note that TASK channels (as other K_{2P} channels) are poorly inhibited by extracellular TEA and have been therefore traditionally regarded as 'TEA insensitive' [57]. However, a more systematic analysis of the response to intracellularly applied quaternary ammonium ions revealed that TASK-3 and TREK-1 in heterologous expression systems are inhibited by THA with an IC_{50} value of about 0.3 and 1 μM, respectively [77], thereby allowing the use of low THA concentrations (10 μM) added to the pipette solution to identify functional channels in TC neurons [5]. The discovery of A293 [79] and spadin [59, 69] as selective TASK-1 and TREK-1 channel blockers, respectively, further allowed the quantification of the contribution of TASK and TREK channel subtypes to I_{SO} in TC neurons (see above).

Muscarinic modulation of K_{2P} channels in TC neurons

In expression systems as well as in native cells, TASK and TREK channels are robustly inhibited by the activation of receptors coupled to $G\alpha_q$ and PLCβ [5, 6, 10, 18, 19, 26, 48, 63, 83, 94]. However, the molecular mechanism downstream of PLC activation that leads to TASK channel closure in native neurons remained elusive for a long time. While TREK-1 seems to be subject to a complex up- and downregulation by PIP_2, there has been some disagreement on the regulation of TASK channels by PIP_2 depletion as a result of PLCβ enzymatic activity. Two alternative $G\alpha_q$-dependent mechanisms have been proposed. On the one hand, TASK channels seem to be directly inhibited by $G\alpha_q$ [19, 94]. On the other hand, TASK channels may be inhibited as a result of PIP_2 depletion by PLC activated downstream of $G\alpha_q$ [18, 56]. While there is experimental evidence for [18, 25, 26] and against [7, 19] a contribution of PLC, $G\alpha_q$-mediated inhibition of TASK channels by depletion of PIP_2 has recently been excluded by experiments on cloned channels in expression systems [54]. In peripheral arterial chemoreceptors, oleoacetylglycerol (OAG), an analog of diacylglycerol (DAG), inhibited a TASK-like K^+ channel [72], thereby suggesting that DAG may be the endogenous blocker of TASK channels. This alternative was recently verified by experiments that allowed to manipulate and monitor intracellular DAG concentration dynamics in living cells with a set of genetically encoded tools [97]. It was shown that the activation of PLC is essential for channel inhibition and that DAG is both sufficient for channel inhibition and required for TASK channel downregulation by $G\alpha_q$-coupled receptors. DAG analogs were also used to assess the DAG sensitivity of TASK channels in dLGN TC neurons [6]. Indeed, OAG induced a reversible reduction of I_{SO} under control condition in rats and mice which was significantly smaller in the presence of A293 or in TASK-1- and TASK-3-deficient mice. Furthermore, the membrane-permeable DAG analog 1,2-dioctanoyl-sn-glycerol (DiC8; 100 μM) reduced I_{SO} in TC neurons by about −16 % in wild-type mice. This effect was clearly smaller in TASK-1-deficient mice (−7.0 %) thereby further indicating that DAG is a potential endogenous inhibitor of neuronal TASK channels (M. C., M. L. and T. B., unpublished data). Thus, PLCβ plays an unusual and unique role in that the breakdown of substrate as well as the product of enzymatic activity exerts important signaling functions. While the degradation of PIP_2 leads to the closure of TREK channels, the production of DAG induces the inhibition of TASK channels.

Such a scenario allows the fine-tuned modulation of K_{2P} channels which may take place in different subcellular neuronal compartments.

Several ion channels contributing to I_{SO} in TC neurons can be expected to be modulated by the activation of MAChR. While the cholinergic modulation of Kir channels has long been appreciated [5, 6, 64], KCNQ channels are currently under investigation [11]. HCN channels represent further candidates, but little is known about their cholinergic modulation in the thalamus yet. The allosteric opening of HCN channels by PIP_2 has been described for all channel subtypes in expression systems, cardiac cells, and neurons, including thalamic intergeniculate leaflet neurons [76, 98, 104]. Consequently, the activation of PLC-coupled receptors leads to the inhibition of HCN channels via PIP_2 depletion [98]. Furthermore, the cholinergic inhibition of HCN channels by MAChR has been found in cardiac cells and motoneurons [21, 28]. However, no cholinergic modulation of I_h has classically been described for dLGN TC neurons [60]. The latter is in line with the finding that application of OxoM (10 μM) does not alter the half-maximal activation voltage (V_h) of I_h in rat TC neurons (control V_h=−87.0±1.1 mV; OxoM: V_h=−87.1±1.3 mV; n=6; P. B. and T. B., unpublished data). Nevertheless, a detailed analysis of the possible muscarinic modulation of HCN channels in thalamic neurons is still missing.

TASK and TREK channels as central elements for the control of thalamic activity modes

In sensory TC neurons, it has been shown that a number of neurotransmitters and neuromodulators, divalent and multivalent cations as well as clinically relevant drugs either inhibit or activate TASK and TREK channels and thereby depolarize and hyperpolarize their membrane potential, respectively (Fig. 3; only substances tested in TC neurons were considered here). In consequence, these channels represent central elements for the control of thalamic activity modes and thus sensory information processing, generation of natural sleep, and pathophysiological rhythms. Furthermore, TASK and TREK channels represent major targets for pharmacologically active drugs which offer routes to intervene in clinical conditions related to thalamic dysrhythmia as well as anesthesia.

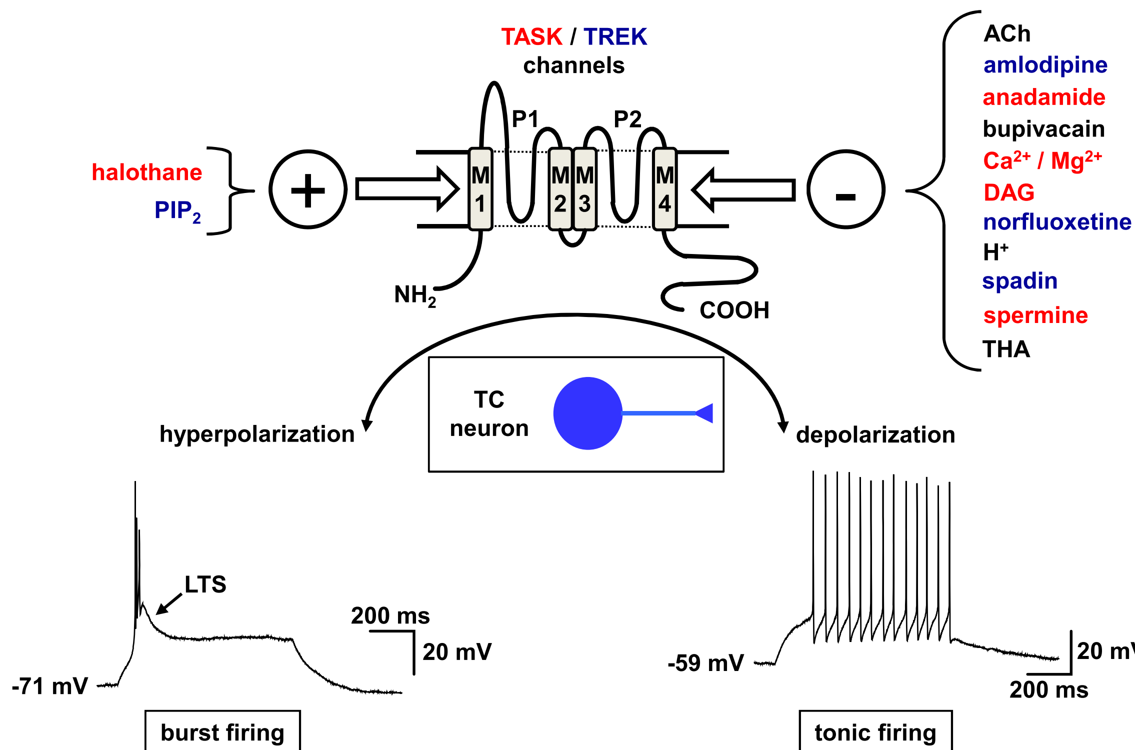

Fig. 3 Exogenous and endogenous modulation of TASK and TREK channels in TC neurons. Substances specifically influencing TASK and TREK channels are highlighted in *red* and *blue*, respectively. TASK channels are positively modulated (*plus sign*) by the volatile anesthetic halothane and inhibited (*minus sign*) by anandamide, Ca^{2+}/Mg^{2+}, diacylglycerol (DAG), and spermine. PIP_2 is a candidate to positively modulate TREK channels while spadin, norfluoxetine, and amlodipine inhibit these channels. Inhibition and activation of the two channels depolarize and hyperpolarize TC neurons, respectively. While the former is associated with tonic firing (*right voltage trace*), the latter is accompanied by bursting (*left voltage trace*). The *arrow* points to the low-threshold Ca^{2+} spike (LTS) which is generated by T-type Ca^{2+} channels. The *inset* refers to the schematic drawing of a TC neuron in Fig. 1 and indicates that all data were obtained from this thalamic cell type

Possible pathophysiological implications of K_{2P} channels in the thalamus

Given the high functional significance of K_{2P} channels in TC neurons, surprisingly little is known about the possible pathophysiological relevance of these channels in the thalamus. In this respect, conditions characterized by changes in extracellular and intracellular pH levels should be of interest since neuronal activity leads to transient extracellular alkalization followed by a persistent extracellular acidification [20]. In dLGN synchronous afferent stimulation, tonic activities as well as rhythmic burst discharges induce extracellular and intracellular increases in H^+ concentrations [67, 92]. Given that both TASK/TREK and HCN channels are inhibited by extracellular acidification, i.e., synchronously reducing a hyperpolarizing and a depolarizing influence, pH shifts induced by different forms of activity in dLGN are expected to have rather small effects on the overall firing pattern and resting membrane potential. This is of special interest for periods of generalized absence epilepsy, where highly synchronous burst pattern of large populations of TC neurons occur.

Periods of brain ischemia are characterized by a decrease in extracellular pH to values as low as 6.0 [86, 87]. CNS neurons, astrocytes, oligodendrocytes, and endothelial cells reveal rather different sensitivity to ischemic insults [15, 44]. The specific reasons for this differential vulnerability are still largely unknown, but seem to succumb to bioenergetic failure following increased Na^+ concentration in combination with dysregulation of cytosolic Ca^{2+} concentrations and mitochondrial Ca^{2+} uptake and dysfunction. Vulnerable neurons typically respond to ischemia with prolonged and strong membrane depolarization and subsequent cellular damage. As for pH changes induced by normal neuronal activity, the joined modulation of TASK and HCN may be assumed to prevent strong depolarization in response to acidification during ischemic insults and thus to lead to selective non-vulnerability of TC neurons. It seems, however, that stronger mechanisms dominate the reaction of TC neurons to acute hypoxia [34, 35, 88, 90]. Under hypoxic conditions, there is an enhanced release of monoamines and nitric oxide substances which strongly activate HCN channels in the thalamus. Therefore, acute hypoxia leads to membrane depolarization and altered electrical properties of TC neurons and makes the dLGN a part of a system-preferential, topographically organized brain injury after ischemia.

Activation of TASK and TREK channels has been found to increase the threshold for seizure induction in several models of epilepsy. The deletion of TASK-1/TASK-3 channels by genetic knockout reduces the sensitivity of mice to local anesthetic-induced seizures [29]. Furthermore, changes in TASK-1/TASK-3 channel expression from neurons to glia cells in the hippocampus of temporal lobe epilepsy patients and experimental animal model have been reported [53]. Also, TREK-1 is capable of silencing hyperactive neurons and of ameliorating status epilepticus [27]. Importantly, K_{2P} channels also influence a form of epilepsy which is critically involving the thalamocortical system, namely absence epilepsy. Absence seizures are characterized by spike-and-wave discharges (SWDs) and represent a state of hyper-synchronous activity in the thalamocortical system [13, 24, 78, 93]. In dLGN TC neurons, a number of different ion channels, including Ca^{2+} and HCN channels, revealed altered expression profiles in a rat model of human absence epilepsy, the WAG/Rij rats [8, 9, 12, 50, 51]. Given the functional interaction between K_{2P} and HCN channels in these neurons, TASK and TREK channels may be expected to show alterations in absence epilepsy. Although a detailed analysis of K_{2P} channel properties in rodent absence epilepsy models is still missing, TASK-3 has indeed been regarded as a promising candidate gene for absence epilepsy in humans. After localizing the human TASK-3 in the chromosomal region 8q24, a mutation analysis of the TASK-3 gene in absence epilepsy patients revealed one exon-2 polymorphism, which, however, was not associated with the disease [47].

Future aspects

In TC neurons, noradrenalin (NA) and glutamate (Glu) acting via α_1 adrenoceptors (α_1-AR) and metabotropic Glu receptors (mGluR), respectively, lead to blockade of a potassium conductance much resembling the one that is reduced by ACh: I_{KL} [60]. More recently, it has been shown that serotonin (5-HT) and Glu act via $G\alpha_q$-coupled intracellular signaling cascades to alter the physiology of TC neurons [23]. These findings converge towards a scenario where multiple membrane receptors modulate K_{2P} channels via $G\alpha_q$-dependent signaling. It is therefore of high interest to explore these pathways in TC neurons in more detail. Interestingly, it has been shown that successive stimulation of MAChR and 5-HT_2 receptors had an upper limit for the membrane potential depolarization which was achieved, e. g., the bigger the effect of a muscarinic agonist, the smaller the effect of a serotonergic agonist thereby pointing to a common limiting mechanism [23]. Thus, the strong convergence of transmitter/receptor systems on the $G\alpha_q$ family of G-proteins and downstream K_{2P} channels leads to the question of redundancy in their signaling in TC neurons. However, the finding (i) of differential subcellular location of specific membrane receptors, (ii) of the topographic organization of different input systems, (iii) of different state-dependent release of neurotransmitters, and (iv) of the formation of tight receptor/effector protein complexes in the forebrain indicate a separation of function between the different $G\alpha_q$-coupled receptor classes in the same neuronal population. Thus, spatial separation and state-dependent activation allow divergent action of several metabotropic receptor

classes, which seem to utilize the same pool of $G\alpha_q$ proteins and downstream signaling cascade in TC neurons. This assumption has to be addressed in future studies on channel-associated protein networks [84].

Besides $G\alpha_q$-coupled pathways, differently coupled membrane receptors may play a role in modulating K_{2P} channels in TC neurons. The fact that the action of ACh, 5-HT, and Glu on TC neuron physiology is not completely abolished in $G\alpha_q$/$G\alpha_{11}$-deficient mice opens up this possibility. An obvious pathway would be the $G\alpha_s$/adenylyl cyclyse/cAMP/PKA cascade [32, 40], which is involved in the modulation of several ion channels in TC neurons, including high-voltage activated (HVA) Ca^{2+} channels [50, 66], HCN channels [51, 52], and large conductance Ca^{2+}-activated K^+ (BKCa) channels [31]. This pathway may be of specific relevance for TREK channels which are known to be inhibited by PKA [43, 45].

A lot of research has focused on K_{2P} channels in TC neurons, and comparatively little is known about the existence and physiological roles of K_{2P} channels in local interneurons in the thalamus. These cells are absent or rare in most thalamic nuclei but represent up to 25 % of neurons in the dLGN in different species [85]. However, based on their small cell diameter, these cells are still rather difficult to investigate using electrophysiological methods. Earlier studies indicated that application of ACh hyperpolarized dLGN interneurons via M_2AChR through the increase of a K^+ conductance [2, 62, 99]. The generation of transgenic mice expressing green fluorescent protein (GFP) under the control of the GAD67 promoter greatly improved direct targeting of GABAergic neurons in the thalamus [70]. Indeed, an increase of I_{SO} was found in response to M_2/M_4AChR- but not M_1/M_3AChR-dependent stimulation in dLGN interneurons expressing GFP (M. L. and T. B., unpublished results). Furthermore, single-cell PCR revealed expression of several K_{2P} channel transcripts in these cells. In a total number of 17 identified dLGN interneurons, the following expression profiles were found: TASK-1, 18 %; TASK-2, 12 %; TASK-3, 35 %; TASK-5, 41 %; TREK-1, 29 %; TREK-2, 35 %; TWIK-related halothane-inhibited K^+ channel (THIK)-1, 35 %; THIK-2, 65 %; and TWIK-related arachidonic acid-stimulated K^+ channel (TRAAK), 18 % (P. E. and T. B., unpublished results). These data point to the possibility that different pathways are involved in the modulation of K_{2P} channels in dLGN interneurons and TC neurons. Noteworthy is the THIK-2 channel, which has been detected frequently in interneurons expressing GFP. These channels typically fail to be transported to the neuronal cell membrane and are, therefore, non-functional at their native state [17, 80]. It is of future interest to study the possible mechanisms that may enable functional THIK-2 expression at the membrane surface of dLGN interneurons. Modulation of THIK-1 channels has already been observed in mouse cerebellar Purkinje neurons by G-protein-coupled receptors namely MAChR [14], but the detailed mechanism is lacking.

Different K_{2P} channel gene transcripts have also been reported in NRT to various degrees: TASK-1 and TREK-1 are expressed at moderate levels while TWIK-1 at a high level [91]. Furthermore, immunohistochemical staining showed strong protein expression of TREK-1 in NRT neurons (Fig. 4). While the NRT is functionally required for sensory information processing, attentional demands, and oscillatory activity in the thalamocortical system, a dysfunction of the NRT has been associated with schizophrenia in human as well as in rodent. In both cases, affected individuals revealed deficits in attention, sensory gating, and a marked reduction in sleep spindles along with symptoms of psychosis in the case of human individuals [3, 37, 38]. At the cellular level, the symptoms of schizophrenia have been implicated to the decreased amount of thalamic burst firing which might have resulted from increased neuronal excitability secondary to a reported K^+ channel dysfunction. In line with that, various K^+ channel openers are prescribed in schizophrenic patients that may exert their antipsychotic effects by potentiating sustained

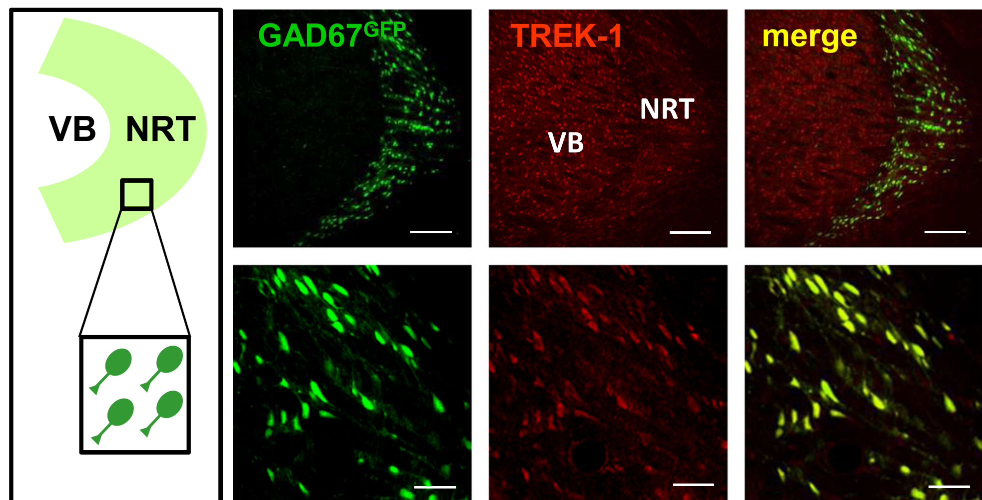

Fig. 4 TREK-1 expression in NRT and the ventrobasal thalamic complex (VB). TREK-1 (*middle column*) is expressed in TC neurons of VB- and GAD67-GFP-labeled neurons of the NRT (*left column*), as confirmed by the merged pictures in the *right column*. *Scale bars* represent 100 and 20 μm in the *upper* and *lower* row, respectively. The *inset* refers to the schematic drawing of the NRT in Fig. 1 and outlines the different spatial resolution of images in the *upper* and *lower* row

hyperpolarization due to increased K^+ conductance and subsequent enhancement of burst firing in the NRT and other thalamic areas [95]. Similarly, a number of K^+ channel genes have also been considered candidate for susceptibility to schizophrenia [46]; however, a direct casual role of K_{2P} channel genes has not been yet investigated. It is intriguing that K_{2P} channels may play an important role as they are directly involved in maintaining the resting membrane potential of neurons and thereby in regulating neuronal excitability, and in the case of TC neurons, their closure would lead to the change of firing pattern from burst to tonic condition. Therefore, drugs targeting and opening K_{2P} channels may be beneficial to schizophrenic individuals. Recently, TREK-1 channels have been suggested as a new potential target for the antidepressant action of spadin, a TREK-1 inhibitor, which also highlights the importance of K_{2P} channels in mood disorders [59, 69].

Another promising field of future research is the role of K_{2P} channels in thalamic dysrhythmia which describes a group of apparently unrelated neuropsychiatric conditions characterized by altered neural oscillations and their abnormal synchronization in the thalamocortical loop [55]. This phenomenon is for example common in patients suffering from peripheral and central neurogenic pain [96]. Pathological oscillations are based on hyperpolarization of the TC neurons (e.g., due to deafferentation or increased inhibition) which later entrains abnormal dynamics in the thalamocortical circuitry [96]. Recently, mice with a disrupted TREK-1 gene were shown to be more sensitive to painful sensations [1]. This may indicate that TREK-1 gene knockout animals can develop thalamic dysrhythmia which needs to be explored in the future. It remains still an open question how TREK-1 channels modulate pain perception. Thus, these channels appear as an interesting potential target for the development of new analgesics.

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