

Review

KCNQ potassium channels in sensory system and neural circuits

Jing-jing WANG, Yang Li*

Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

M channels, an important regulator of neural excitability, are composed of four subunits of the Kv7 (KCNQ) K⁺ channel family. M channels were named as such because their activity was suppressed by stimulation of muscarinic acetylcholine receptors. These channels are of particular interest because they are activated at the subthreshold membrane potentials. Furthermore, neural KCNQ channels are drug targets for the treatments of epilepsy and a variety of neurological disorders, including chronic and neuropathic pain, deafness, and mental illness. This review will update readers on the roles of KCNQ channels in the sensory system and neural circuits as well as discuss their respective mechanisms and the implications for physiology and medicine. We will also consider future perspectives and the development of additional pharmacological models, such as seizure, stroke, pain and mental illness, which work in combination with drug-design targeting of KCNQ channels. These models will hopefully deepen our understanding of KCNQ channels and provide general therapeutic prospects of related channelopathies.

Keywords: KCNQ channels; M channels; neural circuits; channelopathy; epilepsy; neuropathic pain; deafness; mental illness

Acta Pharmacologica Sinica (2016) 37: 25–33; doi: 10.1038/aps.2015.131; published online 21 Dec 2015

Introduction

More than 70 potassium channel genes have been found in human, and some of them have been shown to be associated with diseases. One of the first neurotransmitter-regulated channels to be identified, some 35 years ago, was the M channel. M channels are low-threshold K⁺ channels that were originally identified in the early 1980s in frog^[1] and rat sympathetic neurons. They were named as such because their activity was inhibited through stimulation of muscarinic acetylcholine receptors (mAChR)^[2]. This time- and voltage-dependent current regulates the firing rate of excitable cells after exposure to an excitatory stimulus. M channels are now known to be composed of subunits of the KCNQ (Kv7) K⁺ channel family. These channels are of particular interest in that they are activated by membrane potentials that are more negative than the action-potential threshold. Furthermore, neural KCNQ channels are drug targets for epilepsy treatments and are potential therapeutics that are used to treat a variety of neural disorders, including chronic and neuropathic pain, deafness, and mental illness.

Typically KCNQ channels consist of four subunits that encircle a central pore, which enables the selective passage of

potassium ions across the cell membrane. Each subunit consists of six transmembrane segments (S1–S6) with both N- and C-termini on the intracellular side of the membrane. The S4 segment contains the voltage-sensor of the channel; and the S5 and S6 segments, along with an intervening re-entrant loop (P-loop domain), form the pore region. Four P-loops combine to form the selectivity filter of the channel. All KCNQ channel members have a large C-termini which may form ‘receptor-somes’ or ‘channelosomes’^[2] for incorporation with multiple signaling pathways.

Distribution and function of KCNQ channels

KCNQ genes encode a growing family of six trans-membrane domains, which are single pore-loop, K⁺ channel α -subunits that have a wide range of physiological correlates. KCNQ1 (KvLTQ1) is co-assembled with the product of the KCNE1 (minimal K⁺-channel protein) gene in the heart to form a cardiac-delayed rectifier-like K⁺ current. Mutations in this channel can cause one form of inherited long QT syndrome (LQT1)^[3] as well as be associated with a form of deafness, thereby indicating that KCNQ1 has a role in K⁺ recycling in the inner ear^[4]. KCNQ1 can also co-assemble with KCNE3, and may be the molecular correlate of the cyclic AMP-regulated K⁺ current that is present in colonic crypt cells. KCNQ2 and KCNQ3 have 40% homology with KCNQ1, and KCNQ2 and KCNQ3 heteromultimers are thought to underlie the M-current^[5]; mutations

* To whom correspondence should be addressed.

E-mail liyang@simm.ac.cn

Received 2015-09-15 Accepted 2015-11-10

in these genes may cause benign familial neonatal convulsions (BFNC), a rare form of neonatal epilepsy in humans^[4, 6, 7]. The KCNQ4 gene is thought to encode the molecular correlate of $I_{K,n}$ in outer hair cells (OHCs) of the cochlea and $I_{K,L}$ in Type I hair cells of the vestibular apparatus^[4], mutations that lead to a form of inherited deafness. The expression of KCNQ4 in the CNS is restricted to certain structures in the brainstem, most notably to nuclei and tracts of the central auditory pathway and to trigeminal ganglia^[8]. The recently identified KCNQ4, which is also present in sensory neurons of the DRG as well as in the peripheral lanceolate endings and circular nerve fibers of hair follicles and in Meissner bodies, can modulate stimulus-excitation coupling^[9]. The KCNQ5 gene was identified in 2000, and is expressed in brain and skeletal muscle. Mutations in these genes may cause retinopathy^[4, 10]. KCNQ5 can co-assemble with KCNQ3, which suggests that it may also have a role in M-current heterogeneity^[11]. Using pre- and post-synaptic recordings combined with immunohistochemistry, KCNQ5 channels with unusually negative activation voltage were observed to be expressed in the calyx of Held, which is the presynaptic neuron of the medial nucleus of the trapezoid body (MNTB)^[12]. Moreover, immunocytochemistry analysis shows that KCNQ2/3 and KCNQ5 are expressed in DRG neurons^[13], where they might modulate pain sensitivity.

The gating of KCNQ channels

Neural KCNQ channels control somatic excitability, bursting and neurotransmitter release throughout the nervous system. Their activity is regulated by multiple signaling pathways. In superior cervical ganglion sympathetic neurons, muscarinic M1, angiotensin II AT₁, bradykinin B₂ and purinergic P2Y agonists suppress the M current (I_M). Probes of PLC activity show that agonists of all four receptors are able to induce robust phosphatidylinositol 4,5-bisphosphate (PIP₂) hydrolysis^[14, 15]. There are two basic types of G_{q/11}-mediated signaling mechanisms in SCG neurons. The first mechanism involves the stimulation of M₁ mACh and angiotensin II AT₁ receptors and the principally induced depletion of PIP₂^[16]. Perhaps due to the lack of spatial co-localization with inositol trisphosphate (IP₃) receptors, the stimulation of these receptors does not elicit $[Ca^{2+}]_i$ increases. Rather, membrane PIP₂ levels fall and the M channels are inhibited. The second mechanism is induced by bradykinin B₂ and purinergic P2Y receptors and is based upon the IP₃-mediated increase in intracellular Ca²⁺ that stimulate PIP₂ synthesis, thereby preventing its depletion^[17-19], and subsequent Ca²⁺ binding to calmodulin (CaM), which acts upon the channels^[19-21]. The Ca²⁺ signals that are produced by these receptors also augment PI4-kinase activity, thereby stabilizing PIP₂ levels. Ca²⁺/CaM activity could involve the reduction of the channels' affinity for PIP₂, which would then unbind from the channel proteins. Such competitive or allosteric regulation of the affinity of membrane transport proteins for regulatory PIP₂ molecules as a mechanism for modulation is widespread, and may act as a coincidence-detector motif for spatiotemporal targeting of receptor stimulation of the proper ion channel targets within the cell^[22-24].

When compared with other Kv channels, KCNQ channels have an extended intracellular carboxyl terminus that seems to be the target of several modulatory signals. Examples of this include modulation by Ca²⁺, using calmodulin as a channel Ca²⁺ sensor^[20, 21, 25], and regulation by plasma membrane phosphoinositides^[14, 21, 26], perhaps in concert with protein kinase C^[27]. Furthermore, Src tyrosine kinase suppresses^[28], while the cysteine-modifying reagent N-ethylmaleimide (NEM) augments^[29], the currents of KCNQ channels in a subunit-specific manner. This provides insights into the molecular mechanisms that regulate the gating of KCNQ channels.

The regulatory function of PIP₂ on KCNQ channels has been extensively investigated. Most recently, studies have indicated that there are multiple PIP₂ binding sites that are located at lipid-protein surfaces that are formed by the S6 segment, the S4-S5 linker, the S2-S3 linker, and the intracellular C-terminal of the KCNQ channel^[30]. PIP₂ could migrate between its binding sites, such as dynamic migration between the S4-S5 linker and S2-S3 linker, during the gating transitions between activation and de-activation^[31]. As shown in Figure 1, Chen *et al* reported that there is extensive dynamic migration of PIP₂ between the S4-S5 linker and the S2-S3 linker, which directly affects the rate of gating transition of the KCNQ2 channel. The

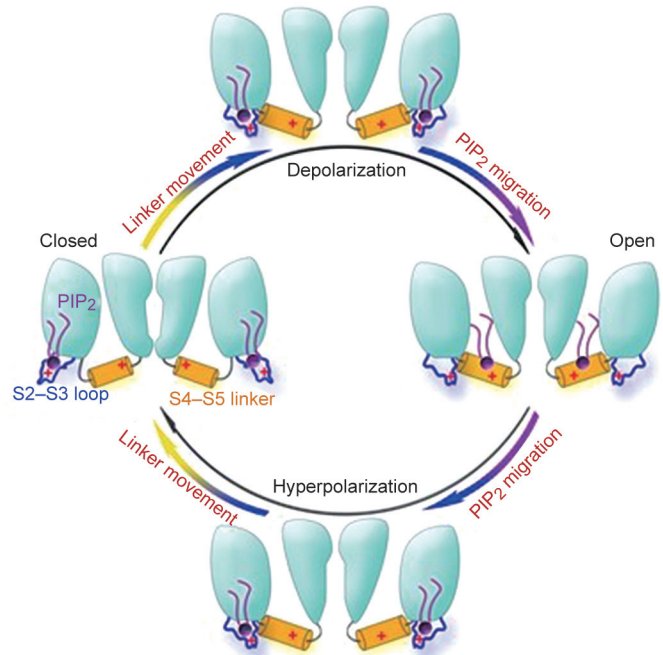


Figure 1. The hypothesized mechanism of PIP₂ migration within the KCNQ2 channel. In the closed state, PIP₂ molecules are bound to the S2-S3 loop of the KCNQ2 channel. Upon channel activation, the conformation of the S4-S5 linker is altered, thereby enabling the PIP₂ molecules to migrate from the S2-S3 loop to the S4-S5 linker. The binding of PIP₂ to the S4-S5 linker stabilizes the open conformation, which also means that PIP₂ has to dissociate from the linker to close the channel. The migration of PIP₂ from the S4-S5 linker to the S2-S3 loop facilitates PIP₂ dissociation from the linker and therefore strongly influences the deactivation kinetics of the channel.

recent discovery that A-kinase anchoring proteins (AKAPs) modulate voltage-gated neuronal M-type (KCNQ, Kv7) K⁺ channels highlights that AKAP79/150 has emerged as an integrative protein for diverse signals to achieve spatiotemporal resolution of directed cellular regulation. The highly dynamic feature of AKAP79/150 complexes include the dual fast and slow regulation of ion channels that alters PIP₂ sensitivity and CaM interactions with KCNQ channels^[32], which indicates the close regulation of function between the membrane and physiological input.

The role of KCNQ channels in neural circuits

Action potential firing over a wide frequency range depends upon multiple small currents that flow at subthreshold voltages, which speed or retard the approach to the action potential threshold and thereby influence the spike rate and pattern of firing. Spike after-potentials (*ie*, after-hyperpolarizations (AHPs) and after-depolarizations (ADPs)) play an important role in shaping neuronal firing patterns^[33–35]. The application of retigabine, a KCNQ channel modulator, completely abolished the bursts in an XE-991-sensitive manner. Furthermore, application of the KCNQ channel blockers linopirdine or XE-991 alone abolished the gamma frequency, but not the higher-frequency population spike firing that was observed during low Ca²⁺/high K⁺ bursts. These data suggest that KCNQ channels are likely to play a role in the regulation of synchronous population firing activity^[36].

These heterotetrameric KCNQ channels are thought to underlie the neuronal M-current, a non-inactivating, slowly deactivating, sub-threshold current that has long been known to exert a powerful stabilizing influence upon neuronal excitability^[37]. Small reductions in this current, either as a result of pharmacological inhibition, physiological modulation or mutation, can result in dramatic increases in neuronal excitability^[38]. Recent research supports this mechanism. The *in vitro* physiological characterization of PFC neurons in aged primates has indicated increases in the slow AHP, which is mediated in part by KCNQ channels^[39]. *In vivo* 7-channel recording in the dorsolateral PFC found that pyramidal cells synapse on spines of neurons in aged monkeys, where elevated cyclic-AMP signaling reduces persistent firing by opening HCN- and KCNQ-potassium channels^[12], which effectively inhibits synaptic input and modulates the strength of network connections between pyramidal cells with similar spatial tuning that would otherwise excite each other to maintain persistent firing across the delay period^[40]. At the same time, patching the calyx of Held, a giant glutamatergic terminal in the medial nucleus of the trapezoid body (MNTB) showed that KCNQ5 channels maintain a negative membrane potential, thus minimizing the substantial contributions from other outward currents and decreasing the probability of neurotransmitter release^[11]. The other likely sources that contribute to the resting conductance of the terminal are the HCN channels^[41, 42] and the persistent Na⁺ current (NaP)^[43]. These three channels (KCNQ, HCN, and NaP) together account for 98% of the resting conductance of the terminal. Electrophysiological

recordings from single afferents in *kcnq4*^{-/-} mice and mice that carry a KCNQ4 mutation found that DFNA2-type monogenic dominant human hearing loss exhibited an elevated mechanosensitivity and altered frequency response that results in rapid adaptation. Human subjects from independent DFNA2 pedigrees outperformed age-matched control subjects when tested for vibrotactile acuity at low frequencies^[9]. Increasingly, researchers are finding that KCNQ channels maintain the resting membrane potential and modulate the strength of the synapse.

In view of this central role of KCNQ channels in neural excitability, it is not surprising that some specific epilepsies are single-gene disorders that result from mutations in KCNQ channel genes^[44]. For example, benign familial neonatal convulsion (BFNC) is an autosomal dominant idiopathic epilepsy that is characterized by unprovoked partial or generalized clonic convulsions that sometimes occur with ocular symptoms and apnoea^[45]. BFNC was linked to two different loci (20q13.3 and 8q24) that are now known to encode the KCNQ2 and KCNQ3 potassium channel genes, respectively^[6, 7, 46]. There are approximately ten known mutations in KCNQ2^[6, 46], but only two in KCNQ3^[47]. These mutations include MISSENSE, FRAME-SHIFT, and SPLICE-SITE mutations and, in one family, the KCNQ2 gene is deleted from one chromosome^[46]. Currents from heteromeric KCNQ2/KCNQ3 channels were estimated to be reduced by only 25% in people who suffer from BFNC, which is sufficient to increase neuronal excitability to epileptogenic levels in early infancy^[48]. This small safety margin may be related to the physiological importance of increases in neuronal excitability that result from the neurotransmitter-mediated inhibition of KCNQ2/KCNQ3. The high degree of sensitivity that is required for this modification of excitability also has the result that slightly greater inhibition can result in epilepsy. The homozygous deletion of KCNQ2 in mice results in death a few hours after birth because of the inability to breathe properly, while heterozygous animals develop normally and lack spontaneous epileptic activity, but are more susceptible to pentylenetetrazole-induced seizures. For this reason, mice that are heterozygous (*kcnq2*^{+/-}) can serve as valuable models for studying the effects of KCNQ2-mediated reductions in currents.

KCNQ channels in hearing

Hearing impairment is a common sensory defect in humans. Non-syndromic hereditary forms in which the hearing loss is the only clinical sign have proven to be genetically heterogeneous. Two lines of evidence have implicated KCNQ1 in the function of the inner ear. First, mRNA for KCNQ1 and KCNE1 has been shown in the apical surface of marginal cells of the stria vascularis of the cochlea. Second, in the homozygous form of Jervell and Lange-Nielsen syndrome (JLNS), mutant KCNQ1 channels cause bilateral deafness. During auditory stimulation, K⁺ moves from the endolymph into hair cells. K⁺ then moves out of the basal portion of hair cells (possibly via KCNQ4-containing channels) into what is thought to be the cellular syncytium of supporting cells, which recycle

the K^+ back into the endolymph via the stria vascularis. The K^+ channels on the marginal cells regulate the flux are thought to contain KCNQ1 and KCNE1 proteins. Any reduction in the concentration gradient of K^+ results in the reduction of endolymph potential, and this can reduce sensitivity to auditory stimuli. A similar event is also thought to occur in the marginal cells of the vestibular epithelium. Mutations in both KCNQ1 (JLNS1) and KCNE1 (JLNS2) can result in hearing loss and vestibular disturbance; however, the latter is less phenotypically obvious in humans because we adapt well to the loss of vestibular function. Both frameshift and missense mutation, which results in nonfunctional, dominant negative and impaired assembly channels, have been described^[49-51].

KCNQ4 could almost be described as a “hearing K^+ channel” because it is almost exclusively expressed in the inner ear, the vestibular apparatus, and a number of nuclei in the central auditory pathway^[52]. All missense mutations and deletions that have been identified in KCNQ4 have been associated with DFNA2, a subtype of autosomal dominant non-syndromic sensorineural progressive hearing loss (ADNSHL) in which high frequencies are initially affected. This phenotype is consistent with the predominant pattern of KCNQ4 expression and native K^+ currents that are primarily mediated by homomeric KCNQ4 channels in the sensory outer hair cells (OHCs) of the basal turns of the cochlea^[8, 52, 53]. Missense mutations are generally associated with earlier onset and more severe hearing impairment than are deletions, which suggests that the phenotypic differences may be caused by distinct mechanisms of pathogenesis. The two deletions that have been identified so far truncate the protein before the first transmembrane domain^[54, 55], and hence, they can cause an expected reduction of 50% in channel activity. In contrast, missense mutations have been reported to exert a dominant-negative effect on wild type function that cause a higher reduction in channel activity^[52, 56]. Interestingly, most of the missense mutations occur within the P-loop domain in the pore region of the KCNQ4 channel^[52, 54, 57-60]. The mechanism that underlies the effect of dominant-inhibition has not yet been identified. The first study to identify a trafficking-dependent dominant mechanism for the loss of KCNQ4 channel function in DFNA2 was in a novel mutation c.886G>A, which leads to the p.G296S substitution in the pore region of the KCNQ4 channel. Expression and functional studies that are conducted in *Xenopus oocytes* and transfected NIH-3T3 cells reveal that the G296S mutant exerts a strong dominant-negative effect on wild type channel activity by causing a defect in trafficking of KCNQ4 channels to the cell surface membrane.

Using pre- and postsynaptic recordings combined with immunohistochemistry, the recent research has found that KCNQ5 channels with unusually negative activation voltages are expressed in the calyx of Held, which is presynaptic of the medial nucleus of the trapezoid body (MNTB)^[11, 61]. Given this voltage dependence, these channels account for most resting outward ionic current and determined presynaptic resting conductance and release probability. KCNQ5 has received relatively little attention so far because it is not associated

with muscarinic signaling and has not yet been identified as the basis for channelopathies^[37, 62, 63]. Nevertheless, similar to KCNQ4, its prominence in the auditory system suggests that it confers a particular advantage in maintaining high frequency synaptic signaling. This is congruent with the several molecular and biophysical specializations for preserving the timing of electrical signals that are associated with sound^[64].

KCNQ channels in vision

The retinal pigment epithelium (RPE) has a variety of functions that are critical to the integrity of the adjacent photoreceptors, including the phagocytosis of outer segments, the regeneration of photopigment, and the supply of nutrients and removal of waste^[65]. In addition, the RPE helps control the volume and ionic composition of fluid in the subretinal space, the extracellular compartment that is bound by the photoreceptor outer segments and the apical aspects of the RPE and Müller (radial glial) cells^[66]. Photoreceptor function critically depends upon the maintenance of subretinal K^+ concentration within narrow limits, which is achieved by K^+ transport mechanisms in the RPE and Müller cells. KCNQ mRNA and protein expression research has found that although KCNQ1, KCNQ4, and KCNQ5 transcripts are expressed in primate RPE, both KCNQ4 and KCNQ5 proteins are expressed in the monkey neural retina and in the RPE, while only KCNQ5 is expressed at a detectable level^[67]. Using patch-clamp electrophysiology, research has investigated the pharmacological sensitivity of the M-type current in isolated monkey RPE cells to elucidate the subunit composition of the channel and found that the M-type current in monkey RPE is likely mediated by channels that are encoded by KCNQ4 and KCNQ5 subunits^[68]. Mutations in KCNQ1 and KCNQ4 genes underlie a number of inherited diseases in humans, including cardiac arrhythmia and nonsyndromal deafness^[4]; however, no disease has been linked to mutations of KCNQ5. Interestingly, no visual disorder has been linked to KCNQ1 or KCNQ4 mutations that cause channelopathies in other tissues. This suggests that if they are expressed, KCNQ1 and KCNQ4 subunits likely have minor or redundant roles in RPE and neural retina physiology. Nevertheless, to date, KCNQ5 mutations are not known to be associated with human disease.

KCNQ channels in pain and touch sensation

Painful stimulation of the skin and viscera is detected by thinly myelinated A- and unmyelinated C-fibers. These first order neurons, with cell bodies that are located in the dorsal root ganglia (DRG), transmit painful stimuli to the substantia gelatinosa of the dorsal horn via the dorsal roots. Second order neurons in the lateral spinothalamic tracts convey impulses that are associated with pain up to the nuclei of the ventroposterior thalamus (ventroposterior medial nucleus, VPM, and ventroposterior lateral nucleus, VPL), where painful impulses are integrated. From the thalamus, third order neurons convey impulses up to the cerebral cortex, where subjective interpretation of pain is thought to occur. Molecular and electrophysiological techniques have provided evidence

for the expression of Kv7.2, 7.3 and 7.5 channels and functional Kv7.x based M-currents in the peripheral terminals, cell bodies, axons, and central terminals of sensory nerves^[69-71]. Activation of the peripheral KCNQ channels suffices to relieve inflammatory pain^[72]. KCNQ channels are also expressed in the dorsal horn of the spinal cord, and at key sites in the brain, such as the thalamus and cortex^[69-71]. Collectively, these data show that functional Kv7.x channels are expressed at all levels of the pain pathway and that these channels may represent excellent targets for the treatment of various pain states^[73].

Behavioral studies with KCNQ modulators, most of which are used in target validation studies and include retigabine (N-(2-amino-4-[fluorobenzylamino]-phenyl)carbamic acid; D-23129)^[13, 74] and flupirtine(N-[2-amino-6-[(4-fluorophenyl)methylamino]pyridin-3-yl]-carbamate)^[75-77], have also provided evidence to indicate that KCNQ channels may represent valid targets for novel analgesic, anti-hyperalgesic and anti-allodynic agents. In addition, an update concerning pre-clinical KCNQ drug discovery efforts will be expected, along with a summary of ongoing clinical trials with KCNQ channel.

KCNQ4 also presents in sensory neurons of the DRG, while in the periphery, KCNQ4 channels are expressed in lanceolate endings and circular nerve fibers of hair follicles and in Meissner bodies, at sites where they can modulate stimulus–excitation coupling. The electrophysiological recordings from single afferents from *Kcnq4*^{-/-} mice and mice that carry a KCNQ4 mutation that are found in DFNA2-type monogenic dominant human hearing loss showed an elevated mechanosensitivity and an altered frequency response during rapid adaptation. Human subjects from independent DFNA2 pedigrees outperformed age-matched control subjects when tested for vibrotactile acuity at low frequencies^[9].

KCNQ channels in olfactory sensation

The accessory olfactory bulb (AOB) is the first central nervous system (CNS) relay for processing pheromonal sensory information^[78]. It is an attractive region for study because of its simple structure, the observation that it consists of only three types of neurons (*ie*, one glutamate neuron (mitral cells) and two GABA neurons (granule cells and periglomerular cells)), and their implicated functions, such as information integration^[79, 80] or memory storage^[81]. Muscarinic receptor mRNAs are expressed in the AOB (strong M1 and M4 and weak M3). The cholinergic action increases spontaneous mIPSCs in the olfactory bulb^[82, 83]. The KCNQ channel is a potassium channel that is closed by muscarinic activity^[2]. Potassium channel closure excites the neuron by depolarizing its membrane as well as by making the membrane more susceptible to depolarizing inputs. Cholinergic modulation of spontaneous GABAergic currents (mIPSC) using whole-cell patch methods in AOB slices found that carbachol administration produced an increase in mIPSC frequency in mitral cells, but did not affect the responses of mitral cells to GABA that persists in the presence of combined glutamatergic receptor antagonists^[84]. The carbachol effect was reduced by the muscarinic receptor M1 and M4 antagonist pirenzepine, but not by the M2 and M4

antagonist himbacine. The KCNQ/Kv7 potassium channel openers retigabine and diclofenac blocked the carbachol action, while the KCNQ potassium channel blocker XE-911 increased mIPSC frequency, thereby suggesting that carbachol acts via the down-regulation of KCNQ channels to increase transmitter release^[85]. Furthermore, the relationship between muscarinic stimulation and KCNQ channel down-regulation is well-established^[2]. It is therefore probable that carbachol down-regulates the activity of KCNQ channels in granule cells dendrites and, through increased membrane depolarization, increases the open probability of membrane calcium channels, thereby resulting in an increase in synaptic vesicle release.

KCNQ channels in learning and memory

The activation of hippocampal mAChR by synaptically released acetylcholine facilitates the induction of synaptic plasticity and enhances cognitive function. The M1 subtype of mAChR is a prime candidate for mediating these cholinergic effects due to its ubiquitous expression in the cortex and hippocampus. Learning, working memory and induction of synaptic plasticity are all impaired in M1 receptor knockout mice^[86-88]. Furthermore, M1 mAChR specific agonists facilitate LTP induction^[89-91] and improve cognitive function in animal models^[92]. M1 mAChR that are expressed on CA1 pyramidal cells inhibit both small conductance Ca²⁺-activated K_{Ca} potassium channels (also known as SK channels)^[91, 93] and voltage-activated Kv7 potassium channels^[1, 94, 95]. The inhibition of K_{Ca} channels facilitates long-term potentiation (LTP) by enhancing Ca²⁺ influx through postsynaptic NMDA receptors (NMDAR)^[96]. The inhibition of KCNQ channels is also reported to facilitate LTP^[97, 98]. KCNQ channel inhibition promotes NMDAR opening during LTP induction by enhancing depolarization during and after bursts of postsynaptic action potentials.

Activity-dependent depression of the spike ADP generates long-lasting intrinsic plasticity in hippocampal CA3 pyramidal neurons. XE991 both enhanced the ADP and completely eliminated its conditioning-induced depression^[99]. XE991 also enhances learning and memory in healthy mice and reverts the cognitive impairment that is associated with acetylcholine depletion and neurodegeneration that is induced by kainic acid. Furthermore, behavioral training sessions regulate the M-current by transiently decreasing levels of KCNQ3 protein^[97]. This effect may be achieved by altering basal hippocampal synaptic activity and by diminishing the stimulation threshold for long-term changes in synaptic efficacy and learning-related gene expression.

Mice that express a KCNQ2 subunit with a dominant-negative pore mutation that can suppress M-channel activity by co-assembling with native KCNQ subunits developed epilepsy, behavioral hyperactivity, cognitive deficits, changes in brain morphology and markedly impaired hippocampus-dependent spatial memory in the Morris water maze, with signs of increased neuronal excitability, reduced spike-frequency adaptation, attenuated AHPs and reduced intrinsic subthreshold theta resonance^[38]. The results support the notion that M channels are critical determinants of cellular and neuronal

network excitability and that the attenuation of the M current has a profound effect on behavior and cognitive performance. Together, these results demonstrate that the inhibition of the M-current as a general strategy may be useful to enhance cognitive capacities in healthy and aging individuals as well as in those with neurodegenerative diseases.

Future directions

The identification of KCNQ channels and their relating channelopathies have been studied in recent decades. After 30 years of intense study, we have increased our knowledge of the physiological and pathological roles of KCNQ channels (Table 1). The potential therapeutic applications of Kv7 enhancers, as deduced from animal experimentation, have expanded from anti-nociceptive and anticonvulsant therapies to the treatment of migraine, anxiety, mania and addiction to psychostimulants^[100]. Although Kv7/M-channel dysfunction may not have any role in such disorders, the widespread distribution of these channels provides a means of general treatment by reducing overall neural excitability when Kv7 channel activity is enhanced^[37]. In the future, several questions will need to be resolved regarding the physiological assembly of KCNQ channels and their functional implications in complex neural circuits. First, we still lack sufficiently selective inhibitors and activators among the KCNQ family members. Although retigabine was approved for the treatment of epilepsy and XE991 has been widely used as a pharmacological tool, the selectivity of these drugs are still limited at the subtype level. Without a crystal structure of the KCNQ channel available, medium and high throughput screening with the aid of computer-based drug design are essential to exploit the versatility of drug-channel interactions. Second, the *in vivo* physiological assemble and functional localization of KCNQ channels requires further evidence. Although *in*

vitro heteromultimers KCNQ2 and KCNQ3 could assemble into M currents, we still lack enough tools to exploit the integrative assembling of KCNQ4 and KCNQ5 and their accessory partners. Based upon current research regarding the multiple physiological and pathological roles of the KCNQ channel, the development of additional pharmacological models such as seizure, stroke, pain and mental illness, combined with the development of drug targets for KCNQ channels, will enhance our knowledge of KCNQ channel and provide general therapeutic prospects of relating channelopathies.

Acknowledgements

This work was supported in part by the National Natural Science Foundation of China (31128009, 31171011, 31171066 and 91413122) and the Ministry of Science and Technology of China (2013CB910601).

References

- Brown DA, Adams PR. Muscarinic suppression of a novel voltage-sensitive K⁺ current in a vertebrate neurone. *Nature* 1980; 283: 673–6.
- Delmas P, Brown DA. Pathways modulating neural KCNQ/M (Kv7) potassium channels. *Nat Rev Neurosci* 2005; 6: 850–62.
- Tyson J, Tranebjaerg L, McEntagart M, Larsen LA, Christiansen M, Whiteford ML, *et al*. Mutational spectrum in the cardioauditory syndrome of Jervell and Lange-Nielsen. *Hum Genet* 2000; 107: 499–503.
- Robbins J. KCNQ potassium channels: physiology, pathophysiology, and pharmacology. *Pharmacol Ther* 2001; 90: 1–19.
- Wang HS, Pan Z, Shi W, Brown BS, Wymore RS, Cohen IS, *et al*. KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. *Science* 1998; 282: 1890–3.
- Biervert C, Schroeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ, *et al*. A potassium channel mutation in neonatal human epilepsy. *Science* 1998; 279: 403–6.

Table 1. Physiological roles and relating channelopathies of KCNQ subunits.

		KCNQ1	KCNQ2	Gene KCNQ3	KCNQ4	KCNQ5
Currents		I_{ks}	M current	OHC, I_{ks}	M current	M current
Expression location		Heart, cochlea	Brain, ganglia	Brain, ganglia	Cochlear	Brain, muscle
Sensory system	Olfactory		M current sensitive			
	Vision	√			√	√
	Hearing	√			√	
	Sensation		√	√		√
Neural circuits and disease	Pain		√	√	√	√
	BNFC		√	√		
	LQT1	√				
	DFNC2				√	
	Memory		√	√	√	
	Psychotic		√	?	√	

BNFC, benign familial neonatal convulsions; LQT, long QT-syndrome; DFNA2, dominant progressive hearing loss; OHC, outer hair cell.

- 7 Charlier C, Singh NA, Ryan SG, Lewis TB, Reus BE, Leach RJ, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet* 1998; 18: 53–5.
- 8 Kharkovets T, Hardelin JP, Safieddine S, Schweizer M, El-Amraoui A, Petit C, et al. KCNQ4, a K⁺ channel mutated in a form of dominant deafness, is expressed in the inner ear and the central auditory pathway. *Proc Natl Acad Sci U S A* 2000; 97: 4333–8.
- 9 Heidenreich M, Lechner SG, Vardanyan V, Wetzler C, Cremers CW, De Leenheer EM, et al. KCNQ4 K⁺ channels tune mechanoreceptors for normal touch sensation in mouse and man. *Nat Neurosci* 2012; 15: 138–45.
- 10 Smith JS, Iannotti CA, Dargis P, Christian EP, Aiyar J. Differential expression of *kcnq2* splice variants: implications to m current function during neuronal development. *J Neurosci* 2001; 21: 1096–103.
- 11 Huang H, Trussell LO. KCNQ5 channels control resting properties and release probability of a synapse. *Nat Neurosci* 2011; 14: 840–7.
- 12 Wang M, Gamo NJ, Yang Y, Jin LE, Wang XJ, Laubach M, et al. Neuronal basis of age-related working memory decline. *Nature* 2011; 476: 210–3.
- 13 Passmore GM, Selyanko AA, Mistry M, Al-Qatari M, Marsh SJ, Matthews EA, et al. KCNQ/M currents in sensory neurons: significance for pain therapy. *J Neurosci* 2003; 23: 7227–36.
- 14 Zhang H, Craciun LC, Mirshahi T, Rohacs T, Lopes CM, Jin T, et al. PIP(2) activates KCNQ channels, and its hydrolysis underlies receptor-mediated inhibition of M currents. *Neuron* 2003; 37: 963–75.
- 15 Li Y, Gamper N, Hilgemann DW, Shapiro MS. Regulation of Kv7 (KCNQ) K⁺ channel open probability by phosphatidylinositol 4,5-bisphosphate. *J Neurosci* 2005; 25: 9825–35.
- 16 Zaika O, Lara LS, Gamper N, Hilgemann DW, Jaffe DB, Shapiro MS. Angiotensin II regulates neuronal excitability via phosphatidylinositol 4,5-bisphosphate-dependent modulation of Kv7 (M-type) K⁺ channels. *J Physiol* 2006; 575: 49–67.
- 17 Bofill-Cardona E, Vartian N, Nanoff C, Freissmuth M, Boehm S. Two different signaling mechanisms involved in the excitation of rat sympathetic neurons by uridine nucleotides. *Mol Pharmacol* 2000; 57: 1165–72.
- 18 Delmas P, Wanaverbecq N, Abogadie FC, Mistry M, Brown DA. Signaling microdomains define the specificity of receptor-mediated InsP(3) pathways in neurons. *Neuron* 2002; 34: 209–20.
- 19 Zaika O, Tolstykh GP, Jaffe DB, Shapiro MS. Inositol triphosphate-mediated Ca²⁺ signals direct purinergic P2Y receptor regulation of neuronal ion channels. *J Neurosci* 2007; 27: 8914–26.
- 20 Gamper N, Shapiro MS. Calmodulin mediates Ca²⁺-dependent modulation of M-type K⁺ channels. *J Gen Physiol* 2003; 122: 17–31.
- 21 Gamper N, Li Y, Shapiro MS. Structural requirements for differential sensitivity of KCNQ K⁺ channels to modulation by Ca²⁺/calmodulin. *Mol Biol Cell* 2005; 16: 3538–51.
- 22 Gamper N, Shapiro MS. Regulation of ion transport proteins by membrane phosphoinositides. *Nat Rev Neurosci* 2007; 8: 921–34.
- 23 Gamper N, Shapiro MS. Target-specific PIP(2) signalling: how might it work? *J Physiol* 2007; 582: 967–75.
- 24 Lopes CM, Remon JJ, Matavel A, Sui JL, Keselman I, Medei E, et al. Protein kinase A modulates PLC-dependent regulation and PIP2-sensitivity of K⁺ channels. *Channels (Austin)* 2007; 1: 124–34.
- 25 Wen H, Jurkovicova D, Pickel VM, Gioio AE, Kaplan BB. Identification of a novel membrane-associated protein expressed in neurons of the squid and rodent nervous systems. *Neuroscience* 2002; 114: 995–1004.
- 26 Hernandez CC, Zaika O, Tolstykh GP, Shapiro MS. Regulation of neuronal KCNQ channels: signalling pathways, structural motifs and functional implications. *J Physiol* 2008; 586: 1811–21.
- 27 Hoshi N, Zhang JS, Omaki M, Takeuchi T, Yokoyama S, Wanaverbecq N, et al. AKAP150 signaling complex promotes suppression of the M-current by muscarinic agonists. *Nat Neurosci* 2003; 6: 564–71.
- 28 Li Y, Langlais P, Gamper N, Liu F, Shapiro MS. Dual phosphorylations underlie modulation of unitary KCNQ K⁺ channels by Src tyrosine kinase. *J Biol Chem* 2004; 279: 45399–407.
- 29 Li Y, Gamper N, Shapiro MS. Single-channel analysis of KCNQ K⁺ channels reveals the mechanism of augmentation by a cysteine-modifying reagent. *J Neurosci* 2004; 24: 5079–90.
- 30 Zhang Q, Zhou P, Chen Z, Li M, Jiang H, Gao Z, et al. Dynamic PIP2 interactions with voltage sensor elements contribute to KCNQ2 channel gating. *Proc Natl Acad Sci U S A* 2013; 110: 20093–8.
- 31 Chen L, Zhang Q, Qiu Y, Li Z, Chen Z, Jiang H, et al. Migration of PIP2 lipids on voltage-gated potassium channel surface influences channel deactivation. *Sci Rep* 2015; 5: 15079.
- 32 Zhang J, Shapiro MS. Activity-dependent transcriptional regulation of M-Type (Kv7) K⁺ channels by AKAP79/150-mediated NFAT actions. *Neuron* 2012; 76: 1133–46.
- 33 Storm JF. Action potential repolarization and a fast after-hyperpolarization in rat hippocampal pyramidal cells. *J Physiol* 1987; 385: 733–59.
- 34 Williams SR, Stuart GJ. Mechanisms and consequences of action potential burst firing in rat neocortical pyramidal neurons. *J Physiol* 1999; 521 Pt 2: 467–82.
- 35 Bean BP. The action potential in mammalian central neurons. *Nat Rev Neurosci* 2007; 8: 451–65.
- 36 Piccinin S, Randall AD, Brown JT. KCNQ/Kv7 channel regulation of hippocampal gamma-frequency firing in the absence of synaptic transmission. *J Neurophysiol* 2006; 95: 3105–12.
- 37 Brown DA, Passmore GM. Neuronal KCNQ (Kv7) channels. *Br J Pharmacol* 2009; 156: 1185–95.
- 38 Peters HC, Hu H, Pongs O, Storm JF, Isbrandt D. Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior. *Nat Neurosci* 2005; 8: 51–60.
- 39 Luebke JI, Chang YM. Effects of aging on the electrophysiological properties of layer 5 pyramidal cells in the monkey prefrontal cortex. *Neuroscience* 2007; 150: 556–62.
- 40 Goldman-Rakic PS. Cellular basis of working memory. *Neuron* 1995; 14: 477–85.
- 41 Dodson PD, Forsythe ID. Presynaptic K⁺ channels: electrifying regulators of synaptic terminal excitability. *Trends Neurosci* 2004; 27: 210–7.
- 42 Kim JH, Sizov I, Dobretsov M, von Gersdorff H. Presynaptic Ca²⁺ buffers control the strength of a fast post-tetanic hyperpolarization mediated by the alpha3 Na⁺/K⁺-ATPase. *Nat Neurosci* 2007; 10: 196–205.
- 43 Huang H, Trussell LO. Control of presynaptic function by a persistent Na⁺ current. *Neuron* 2008; 60: 975–9.
- 44 Gardiner M, Lehesjoki AE. Genetics of the epilepsies. *Curr Opin Neurol* 2000; 13: 157–64.
- 45 Ronen GM, Rosales TO, Connolly M, Anderson VE, Leppert M. Seizure characteristics in chromosome 20 benign familial neonatal convulsions. *Neurology* 1993; 43: 1355–60.
- 46 Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R, et al. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nat Genet* 1998; 18: 25–9.
- 47 Hirose S, Zenri F, Akiyoshi H, Fukuma G, Iwata H, Inoue T, et al. A novel mutation of KCNQ3 (c.925T->C) in a Japanese family with benign familial neonatal convulsions. *Ann Neurol* 2000; 47: 822–6.
- 48 Schroeder BC, Kubisch C, Stein V, Jentsch TJ. Moderate loss of func-

- tion of cyclic-AMP-modulated KCNQ2/KCNQ3 K⁺ channels causes epilepsy. *Nature* 1998; 396: 687–90.
- 49 Neyroud N, Tesson F, Denjoy I, Leibovici M, Donger C, Barhanin J, *et al.* A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome. *Nat Genet* 1997; 15: 186–9.
- 50 Schmitt N, Schwarz M, Peretz A, Abitbol I, Attali B, Pongs O. A recessive C-terminal Jervell and Lange-Nielsen mutation of the KCNQ1 channel impairs subunit assembly. *EMBO J* 2000; 19: 332–40.
- 51 Splawski I, Timothy KW, Vincent GM, Atkinson DL, Keating MT. Molecular basis of the long-QT syndrome associated with deafness. *N Engl J Med* 1997; 336: 1562–7.
- 52 Kubisch C, Schroeder BC, Friedrich T, Lutjohann B, El-Amraoui A, Marlin S, *et al.* KCNQ4, a novel potassium channel expressed in sensory outer hair cells, is mutated in dominant deafness. *Cell* 1999; 96: 437–46.
- 53 Kharkovets T, Dedek K, Maier H, Schweizer M, Khimich D, Nouvian R, *et al.* Mice with altered KCNQ4 K⁺ channels implicate sensory outer hair cells in human progressive deafness. *EMBO J* 2006; 25: 642–52.
- 54 Coucke PJ, Van Hauwe P, Kelley PM, Kunst H, Schatteman I, Van Velzen D, *et al.* Mutations in the KCNQ4 gene are responsible for autosomal dominant deafness in four DFNA2 families. *Hum Mol Genet* 1999; 8: 1321–8.
- 55 Kamada F, Kure S, Kudo T, Suzuki Y, Oshima T, Ichinohe A, *et al.* A novel KCNQ4 one-base deletion in a large pedigree with hearing loss: implication for the genotype-phenotype correlation. *J Hum Genet* 2006; 51: 455–60.
- 56 Jentsch TJ. Neuronal KCNQ potassium channels: physiology and role in disease. *Nat Rev Neurosci* 2000; 1: 21–30.
- 57 Talebizadeh Z, Kelley PM, Askew JW, Beisel KW, Smith SD. Novel mutation in the KCNQ4 gene in a large kindred with dominant progressive hearing loss. *Hum Mutat* 1999; 14: 493–501.
- 58 Akita J, Abe S, Shinkawa H, Kimberling WJ, Usami S. Clinical and genetic features of nonsyndromic autosomal dominant sensorineural hearing loss: KCNQ4 is a gene responsible in Japanese. *J Hum Genet* 2001; 46: 355–61.
- 59 Van Camp G, Coucke PJ, Akita J, Fransen E, Abe S, De Leenheer EM, *et al.* A mutational hot spot in the KCNQ4 gene responsible for autosomal dominant hearing impairment. *Hum Mutat* 2002; 20: 15–9.
- 60 Mencia A, Gonzalez-Nieto D, Modamio-Hoybjor S, Etxeberria A, Aranguex G, Salvador N, *et al.* A novel KCNQ4 pore-region mutation (p.G296S) causes deafness by impairing cell-surface channel expression. *Hum Genet* 2008; 123: 41–53.
- 61 Garcia-Pino E, Caminos E, Juiz JM. KCNQ5 reaches synaptic endings in the auditory brainstem at hearing onset and targeting maintenance is activity-dependent. *J Comp Neurol* 2010; 518: 1301–14.
- 62 Schroeder BC, Hechenberger M, Weinreich F, Kubisch C, Jentsch TJ. KCNQ5, a novel potassium channel broadly expressed in brain, mediates M-type currents. *J Biol Chem* 2000; 275: 24089–95.
- 63 Lerche C, Scherer CR, Seeböhm G, Derst C, Wei AD, Busch AE, *et al.* Molecular cloning and functional expression of KCNQ5, a potassium channel subunit that may contribute to neuronal M-current diversity. *J Biol Chem* 2000; 275: 22395–400.
- 64 Trussell LO. Synaptic mechanisms for coding timing in auditory neurons. *Annu Rev Physiol* 1999; 61: 477–96.
- 65 Strauss O. The retinal pigment epithelium in visual function. *Physiol Rev* 2005; 85: 845–81.
- 66 Quinn RH, Miller SS. Ion transport mechanisms in native human retinal pigment epithelium. *Invest Ophthalmol Vis Sci* 1992; 33: 3513–27.
- 67 Zhang X, Yang D, Hughes BA. KCNQ5/K(v)7.5 potassium channel expression and subcellular localization in primate retinal pigment epithelium and neural retina. *Am J Physiol Cell Physiol* 2011; 301: C1017–26.
- 68 Pattnaik BR, Hughes BA. Effects of KCNQ channel modulators on the M-type potassium current in primate retinal pigment epithelium. *Am J Physiol Cell Physiol* 2012; 302: C821–33.
- 69 Wickenden AD, McNaughton-Smith G. Kv7 channels as targets for the treatment of pain. *Curr Pharm Des* 2009; 15: 1773–98.
- 70 Rigdon RO. Protocols for the prevention of intravascular device-related infections. *Crit Care Nurs Q* 2001; 24: 39–47.
- 71 Devaux JJ, Kleopa KA, Cooper EC, Scherer SS. KCNQ2 is a nodal K channel. *J Neurosci* 2004; 24: 1236–44.
- 72 Zheng Y, Xu H, Zhan L, Zhou X, Chen X, Gao Z. Activation of peripheral KCNQ channels relieves gout pain. *Pain* 2015; 156: 1025–35.
- 73 Rivera-Arconada I, Martinez-Gomez J, Lopez-Garcia JA. M-current modulators alter rat spinal nociceptive transmission: an electrophysiological study *in vitro*. *Neuropharmacology* 2004; 46: 598–606.
- 74 Dost R, Rostock A, Rundfeldt C. The anti-hyperalgesic activity of retigabine is mediated by KCNQ potassium channel activation. *Naunyn Schmiedeberg Arch Pharmacol* 2004; 369: 382–90.
- 75 Szelenyi I, Nickel B, Borbe HO, Brune K. Mode of antinociceptive action of flupirtine in the rat. *Br J Pharmacol* 1989; 97: 835–42.
- 76 Swedberg MD. The mouse grid-shock analgesia test: pharmacological characterization of latency to vocalization threshold as an index of antinociception. *J Pharmacol Exp Ther* 1994; 269: 1021–8.
- 77 Diamantis W, Gordon R, Sofia RD. Analgesic activity following combined oral administration of flupirtine maleate and peripherally acting analgesics in mice and rats. *Postgrad Med J* 1987; 63 Suppl 3: 29–34.
- 78 Luo M, Fee MS, Katz LC. Encoding pheromonal signals in the accessory olfactory bulb of behaving mice. *Science* 2003; 299: 1196–201.
- 79 Xu F, Schaefer M, Kida I, Schafer J, Liu N, Rothman DL, *et al.* Simultaneous activation of mouse main and accessory olfactory bulbs by odors or pheromones. *J Comp Neurol* 2005; 489: 491–500.
- 80 Hendrickson RC, Krauthamer S, Essenberg JM, Holy TE. Inhibition shapes sex selectivity in the mouse accessory olfactory bulb. *J Neurosci* 2008; 28: 12523–34.
- 81 Kaba H, Hayashi Y, Higuchi T, Nakanishi S. Induction of an olfactory memory by the activation of a metabotropic glutamate receptor. *Science* 1994; 265: 262–4.
- 82 Castillo PE, Carleton A, Vincent JD, Lledo PM. Multiple and opposing roles of cholinergic transmission in the main olfactory bulb. *J Neurosci* 1999; 19: 9180–91.
- 83 Ghatpande AS, Sivaraaman K, Vijayaraghavan S. Store calcium mediates cholinergic effects on mIPSCs in the rat main olfactory bulb. *J Neurophysiol* 2006; 95: 1345–55.
- 84 Takahashi Y, Kaba H. Muscarinic receptor type 1 (M1) stimulation, probably through KCNQ/Kv7 channel closure, increases spontaneous GABA release at the dendrodendritic synapse in the mouse accessory olfactory bulb. *Brain Res* 2010; 1339: 26–40.
- 85 Martire M, Castaldo P, D'Amico M, Preziosi P, Annunziato L, Tagliatela M. M channels containing KCNQ2 subunits modulate nor-epinephrine, aspartate, and GABA release from hippocampal nerve terminals. *J Neurosci* 2004; 24: 592–7.
- 86 Shinoe T, Matsui M, Taketo MM, Manabe T. Modulation of synaptic plasticity by physiological activation of M1 muscarinic acetylcholine receptors in the mouse hippocampus. *J Neurosci* 2005; 25: 11194–200.
- 87 Anagnostaras SG, Murphy GG, Hamilton SE, Mitchell SL, Rahnama

- NP, Nathanson NM, et al. Selective cognitive dysfunction in acetylcholine M1 muscarinic receptor mutant mice. *Nat Neurosci* 2003; 6: 51–8.
- 88 Wess J. Muscarinic acetylcholine receptor knockout mice: novel phenotypes and clinical implications. *Annu Rev Pharmacol Toxicol* 2004; 44: 423–50.
- 89 Seol GH, Ziburkus J, Huang S, Song L, Kim IT, Takamiya K, et al. Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. *Neuron* 2007; 55: 919–29.
- 90 Boddeke EW, Enz A, Shapiro G. SDZ ENS 163, a selective muscarinic M1 receptor agonist, facilitates the induction of long-term potentiation in rat hippocampal slices. *Eur J Pharmacol* 1992; 222: 21–5.
- 91 Buchanan KA, Petrovic MM, Chamberlain SE, Marrion NV, Mellor JR. Facilitation of long-term potentiation by muscarinic M(1) receptors is mediated by inhibition of SK channels. *Neuron* 2010; 68: 948–63.
- 92 Dean B, Bymaster FP, Scarr E. Muscarinic receptors in schizophrenia. *Curr Mol Med* 2003; 3: 419–26.
- 93 Giessel AJ, Sabatini BL. M1 muscarinic receptors boost synaptic potentials and calcium influx in dendritic spines by inhibiting postsynaptic SK channels. *Neuron* 2010; 68: 936–47.
- 94 Madison DV, Lancaster B, Nicoll RA. Voltage clamp analysis of cholinergic action in the hippocampus. *J Neurosci* 1987; 7: 733–41.
- 95 Marrion NV, Smart TG, Marsh SJ, Brown DA. Muscarinic suppression of the M-current in the rat sympathetic ganglion is mediated by receptors of the M1-subtype. *Br J Pharmacol* 1989; 98: 557–73.
- 96 Ngo-Anh TJ, Bloodgood BL, Lin M, Sabatini BL, Maylie J, Adelman JP. SK channels and NMDA receptors form a Ca²⁺-mediated feedback loop in dendritic spines. *Nat Neurosci* 2005; 8: 642–9.
- 97 Fontan-Lozano A, Suarez-Pereira I, Delgado-Garcia JM, Carrion AM. The M-current inhibitor XE991 decreases the stimulation threshold for long-term synaptic plasticity in healthy mice and in models of cognitive disease. *Hippocampus* 2011; 21: 22–32.
- 98 Lampe BJ, Gaskill JL, Keim SC, Brown BS. Linopirdine reduces stimulus intensity threshold for induction of long-term potentiation in the Schaffer collateral/CA1 pathway in rat hippocampal slices. *Neurosci Lett* 1997; 222: 135–7.
- 99 Brown JT, Randall AD. Activity-dependent depression of the spike after-depolarization generates long-lasting intrinsic plasticity in hippocampal CA3 pyramidal neurons. *J Physiol* 2009; 587: 1265–81.
- 100 Grunnet M, Strobaek D, Hougaard C, Christophersen P. Kv7 channels as targets for anti-epileptic and psychiatric drug-development. *Eur J Pharmacol* 2014; 726: 133–7.