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# The Role of $K_v7$ Channels in Neural Plasticity and Behavior

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Activity-dependent persistent changes in neuronal intrinsic excitability and synaptic strength are widely thought to underlie learning and memory. Voltage-gated KCNQ/$K_v7$ potassium channels have been of great interest as the potential targets for memory disorders due to the beneficial effects of their antagonists in cognition. Importantly, *de novo* dominant mutations in their neuronal subunits *KCNQ2*/$K_v7.2$ and *KCNQ3*/$K_v7.3$ are associated with epilepsy and neurodevelopmental disorder characterized by developmental delay and intellectual disability. The role of $K_v7$ channels in neuronal excitability and epilepsy has been extensively studied. However, their functional significance in neural plasticity, learning, and memory remains largely unknown. Here, we review recent studies that support the emerging roles of $K_v7$ channels in intrinsic and synaptic plasticity, and their contributions to cognition and behavior.

**Keywords: KCNQ channel, $K_v7$, intrinsic excitability, synaptic transmission, neural plasticity, learning, memory, behavior**

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## INTRODUCTION

Voltage-gate channel potassium ($K^+$) subfamily Q member 1–5 (*KCNQ* 1–5) encodes $K_v7.1$–$K_v7.5$ channels (Gutman et al., 2005) that are critical regulators of excitability in neurons, muscles, and sensory cells (Soldovieri et al., 2011). All $K_v7$ subunits have six transmembrane segments (S1–S6; Robbins, 2001). The S1–S4 comprise a voltage-sensing domain with the S4 being the main voltage-sensor (Robbins, 2001). The pore domain consists of the S5-S6 flanking the pore loop important for $K^+$ ion selectivity (Sun and MacKinnon, 2017). The gate is formed by the intersection of four S6 segments (Cui, 2016; Sun and MacKinnon, 2017). Upon depolarization, the electric field on the basic residues of S4 promotes its translational rotation and outward displacement, which leads to the opening of the gate (Cui, 2016; Sun and MacKinnon, 2017). All $K_v7$ channels require phosphatidylinositol-4,5-bisphosphate ($PIP_2$) in the plasma membrane for channel opening (Zhang et al., 2003; Suh and Hille, 2008; Zaydman and Cui, 2014), and $PIP_2$ is proposed to couple the voltage-sensing domain to the pore domain in $K_v7.1$ (Zaydman et al., 2013; Sun and MacKinnon, 2020). Each $K_v7$ subunit also has a short intracellular N-terminal domain and a long intracellular C-terminal tail that harbors four helices (helices A–D; Haitin and Attali, 2008). Helices A and B bind to calmodulin (CaM; Strulovich et al., 2016; Sun and MacKinnon, 2017), whereas helices C–D mediate subunit assembly (Haitin and Attali, 2008).

In neurons, $K_v7$ channels open at subthreshold potentials around −60 mV and produce slowly-activating and non-inactivating outward $K^+$ currents that potently suppress repetitive and

burst firing of action potentials (APs; Brown and Passmore, 2009). Their functional significance in inhibiting neuronal excitability is underscored by the fact that mutations in their subunits cause epilepsy (Nappi et al., 2020), whereas $K_v7$ agonist retigabine inhibits seizures in rodents and humans (Miceli et al., 2008). Importantly, emerging new evidence suggests that $K_v7$ channels may contribute to activity-dependent persistent changes in neuronal intrinsic excitability and synaptic strength that are widely thought to underlie learning and memory. This review will summarize the function of $K_v7$ channels in the hippocampus and discuss recent studies that investigate their contributions to hippocampal plasticity, cognition, and behavior.

## BRAIN DISTRIBUTION OF $K_V7$ SUBUNITS AND THEIR CHANNELOPATHIES

$K_v7.2$, $K_v7.3$, and $K_v7.5$ are the major neuronal $K_v7$ subunits (**Table 1**). $K_v7.2$ and $K_v7.3$ show strong overlapping expression in the cerebral cortex, hippocampal formation, amygdala, basal ganglia, and hypothalamus (Wang et al., 1998; Cooper et al., 2001; Klinger et al., 2011). $K_v7.5$ is highly expressed in the brain stem and to less extent in the cerebral cortex, hippocampus, occipital, frontal, and temporal lobes (Lerche et al., 2000; Schroeder et al., 2000; Tzingounis et al., 2010; Fidzinski et al., 2015). While $K_v7.1$ and $K_v7.4$ are mainly found in the heart and cochlear hair cells, respectively (Wang et al., 1996; Kubisch et al., 1999), they are also detected at low level in multiple regions of the brain (Casimiro et al., 2001; Hansen et al., 2006; Goldman et al., 2009; Su et al., 2019; **Table 1**).

Importantly, >300 dominant mutations in *KCNQ2* and *KCNQ3* cause epilepsy including benign familial neonatal epilepsy (BFNE) and epileptic encephalopathy (EE; Rikee and ClinVar database). *KCNQ2* is the second most frequently mutated gene in neurodevelopmental disorder (Traynelis et al., 2017; Coe et al., 2019) characterized by cognitive and behavioral deficits (Mullin et al., 2013). A few mutations in *KCNQ1*, *KCNQ4*, and *KCNQ5* have been associated with epilepsy, autism, schizophrenia, and developmental disorder (**Table 1**). Haploinsufficiency in $K_v7$ function seems to underlie BFNE variants that cause the transient appearance of neonatal seizures (Soldovieri et al., 2011). EE patients display severe and often drug-resistant neonatal seizures and psychomotor retardation (Weckhuysen et al., 2012), and *de novo* EE mutations in *KCNQ2* and *KCNQ3* induce multiple defects in current and surface expression of $K_v7$ channels (Weckhuysen et al., 2012, 2013; Milh et al., 2013; Miceli et al., 2015; Kim et al., 2018; Zhang et al., 2020).

## GENERAL PROPERTIES AND REGULATION OF $K_V7$ CURRENTS

$K_v7.1$ assembles with auxiliary β subunit KCNE1 to produce the slow delayed rectifier $K^+$ current ($I_{Ks}$) important for the repolarization of cardiac APs (Barhanin et al., 1996). Importantly, coassembly with KCNE1 slows the activation

**TABLE 1** | Distribution of $K_v7$ subunit in the brain and the diseases associated with its pathogenic variants.

| Gene | Protein | Primary location | Distribution in the brain | | Pathogenic variants | |
|---|---|---|---|---|---|---|
| | | | Regions | Reference | Associated diseases | Reference |
| *KCNQ1* | $K_v7.1$ | Heart | CTX, HPF, MB, CB, BS | Casimiro et al., 2001; Goldman et al., 2009. AIBS, THPA | Long QT syndrome 1, JLNS, familial atrial fibrillation epilepsy, SUDEP, ASD, developmental disorder | ClinVar, LOVD, *denovo*-db |
| *KCNQ2* | $K_v7.2$ | Nervous system | CTX, HPF, A, HY, TH, OA, MD, SN, P, MY, CB | Wang et al., 1998; Cooper et al., 2001; Devaux et al., 2004; Klinger et al., 2011; D'Este et al., 2016; Galvin et al., 2020. AIBS, THPA | BFNE, EE, ASD, intellectual disability, developmental disorder, sporadic infantile spasm syndrome | ClinVar, RIKEE, *denovo*-db |
| *KCNQ3* | $K_v7.3$ | Nervous system | CTX, HPF, A, HY, TH, OA, MD, SN, P, MY, CB | Wang et al., 1998; Devaux et al., 2004; Klinger et al., 2011; Galvin et al., 2020. AIBS, THPA | BFNE, EE, ASD, intellectual disability, developmental disorder | ClinVar, RIKEE, *denovo*-db |
| *KCNQ4* | $K_v7.4$ | Inner ear | BS, OA, MD, RN, NA, MY, VTA, P | Hansen et al., 2006; Su et al., 2019. AIBS, THPA | DFNA2, ASD | ClinVar, *denovo*-db |
| *KCNQ5* | $K_v7.5$ | Nervous system | CTX, HPF, BS, CB | Lerche et al., 2000; Schroeder et al., 2000; Tzingounis et al., 2010; Fidzinski et al., 2015; Galvin et al., 2020. AIBS, THPA | EE, ASD, intellectual disability, schizophrenia | ClinVar, RIKEE, *denovo*-db |

*Brain regions: CTX, cortex; OA, olfactory areas; HPF, hippocampal formation; A, amygdala; NA, nucleus accumbens; BS, brain stem; TH, thalamus; HY, hypothalamus; MB, midbrain; RN, raphe nuclei; SN, substantia nigra; VTA, ventral tegmental area; PAL, pallidum; HB, hindbrain; CB, cerebellum; P, pons; MY, medulla. $K_v7$ channelopathies: JLNS, Jervell and Lange-Nielsen syndrome; SUDEP, sudden unexpected death in epilepsy; BFNE, benign familial neonatal epilepsy; EE, epileptic encephalopathy; ASD, autism spectrum disorder; DFNA2, nonsyndromic sensorineural deafness type 2. Database website: Allen Institute for Brain Science (AIBS, https://alleninstitute.org/what-we-do/brain-science/), The Human Protein Atlas (THPA, https://www.proteinatlas.org/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), Leiden Open Variation Database (LOVD, https://research.cchmc.org/LOVD2/home.php), denovo-db (http://denovo-db.gs.washington.edu/denovo-db/index.jsp), and Rational Intervention for KCNQ2/3 Epileptic Encephalopathy (RIKEE, https://www.rikee.org/).*

kinetics of $K_v7.1$ channel, potentiates its current amplitude, and eliminates its voltage-dependent inactivation (Barhanin et al., 1996; Sanguinetti et al., 1996; Tristani-Firouzi and Sanguinetti, 1998). Homomeric $K_v7.2$ channels activate at −60 mV and produce slow-activating and non-inactivating currents (Biervert et al., 1998). In comparison, currents through $K_v7.3$ channels are negligible due to an Ala residue in the pore domain (Wang et al., 1998; Gomez-Posada et al., 2010). $K_v7.5$ activates at −60 mV with slower kinetics than $K_v7.2$ and $K_v7.3$ (Schroeder et al., 2000; Gamper et al., 2003). $K_v7.4$ activates at −40 mV with slower activation kinetics than other $K_v7$ channels (Kubisch et al., 1999).

Neuronal $K_v7$ channels are mostly heterotetrameric channels composed of $K_v7.2$ and $K_v7.3$, and to a lesser extent $K_v7.3$ and $K_v7.5$ (Wang et al., 1998; Shah et al., 2002; **Table 1**). Compared to homomeric channels, significantly larger currents are generated by $K_v7.2/K_v7.3$ channels (Schroeder et al., 1998; Wang et al., 1998; Schwake et al., 2000) and $K_v7.3/K_v7.5$ channels (Schroeder et al., 2000; Gilling et al., 2013). $K_v7.2/K_v7.3$ channels produce M-current ($I_M$; Wang et al., 1998), which potently suppresses neuronal hyperexcitability (Wang et al., 1998; Yue and Yaari, 2004). $I_M$ is inhibited by muscarinic acetylcholine receptor activation (Selyanko et al., 2000) and the depletion of $PIP_2$ (Suh and Hille, 2002; Zhang et al., 2003). $K_v7$ channels are also inhibited by other G-protein coupled receptors, including substance P, bradykinin, serotonin, angiotensin, luteinizing hormone-releasing hormone, opioid, and metabotropic glutamate receptors (Marrion, 1997). General properties and diverse regulation of $K_v7$ channels are described in detail in a previous review (Soldovieri et al., 2011).

## ROLE OF $K_V7$ CHANNELS IN INTRINSIC EXCITABILITY AND PLASTICITY IN THE HIPPOCAMPUS

Brown and Adams have first reported in 1980 that inhibition of $I_M$ upon stimulation of muscarinic acetylcholine receptor results in repetitive firing of APs in bullfrog sympathetic ganglion neurons (Brown and Adams, 1980). In the hippocampus, strong expression of $K_v7.2$, $K_v7.3$, and $K_v7.5$ is detected in pyramidal neurons (Schroeder et al., 2000; Cooper et al., 2001; Devaux et al., 2004). $K_v7$ antagonists XE991 and linopirdine depolarize resting membrane potential (RMP) and reduce AP threshold of hippocampal CA1 pyramidal neurons, resulting in spontaneous AP firing (Aiken et al., 1995; Shah et al., 2008; **Figure 1A**). $K_v7$ antagonists also increase intrinsic excitability (Yue and Yaari, 2004, 2006; Shah et al., 2008), contribute to medium and slow afterhyperpolarization (AHP) currents (Gu et al., 2005), reduce spike frequency adaptation (Aiken et al., 1995), and ultimately lead to an increased AP firing rate (Lezmy et al., 2020; **Figure 1A**). Consistent with pharmacologic inhibition, suppression of $K_v7$ current by overexpressing $K_v7.2$ containing dominant-negative pore mutation G279S enhances intrinsic excitability and reduces spike frequency adaptation and mAHP in CA1 neurons (Peters et al., 2005). Similarly, conditional homozygous deletion of *KCNQ2* increases CA1 excitability due to longer-lasting spike afterdepolarization (ADP) and reduced medium AHP (Soh et al., 2014; **Figure 1A**). Thus, $K_v7$ channels serve as critical "brakes" on neuronal excitability (Soldovieri et al., 2011).

The inhibitory effects of $K_v7$ currents on neuronal excitability are largely attributed to axonal $K_v7$ channels. $K_v7.2/K_v7.3$ channels are preferentially enriched at the axonal plasma membrane compared to the somatodendritic plasma membrane in hippocampal neurons (Chung et al., 2006) with the highest concentration at the axonal initial segments (AIS; Chung et al., 2006; Pan et al., 2006) where AP initiates (Clark et al., 2009). CaM binding to $K_v7.2$ is critical for targeting $K_v7.2/K_v7.3$ channels to the axonal surface (Cavaretta et al., 2014), whereas disruption of this binding decreases $I_M$ and increases hippocampal neuronal excitability (Shahidullah et al., 2005). Furthermore, disrupting the enrichment of $K_v7$ channels at the AIS by blocking their interaction with ankyrin-G results in spontaneous firing of CA1 neurons by depolarizing RMP and reducing AP threshold (Shah et al., 2008).

In contrast to the well-documented function of axonal $K_v7$ channels discussed above, the existence and role of dendritic $K_v7$ channels are still in debate. Non-inactivating $K_v7$ current sensitive to muscarinic agonist is detected in the distal apical dendrites of CA1 neurons (Chen and Johnston, 2004). Dendritic $K_v7$ current can increase the threshold for initiating calcium ($Ca^{2+}$) spikes and induce spike bursts only in hyperexcitable conditions that promote $Ca^{2+}$ electrogenesis in these dendrites (Yue and Yaari, 2006). However, XE991 and linopirdine do not affect input resistance of CA1 dendrites (Shah et al., 2008), and focal inhibition of dendritic $I_M$ has no effect on the excitatory postsynaptic potential (EPSP) summation and excitability of CA1 neuron (Hu et al., 2007), indicating very low level of dendritic $K_v7$ current.

There is accumulating evidence for activity-dependent modulation of $K_v7$ channels and their contribution to persistent changes in intrinsic excitability termed "intrinsic plasticity." In the pilocarpine model of temporal lobe epilepsy, reduced $K_v7$ function and expression may contribute to muscarinic-dependent ictogenesis (Maslarova et al., 2013). However, acute induction of seizures increases *KCNQ2* and *KCNQ3* transcripts in the hippocampi as a homeostatic response to suppress neuronal hyperexcitability, and this regulation requires activation of L-type voltage-gated $Ca^{2+}$ channels (Zhang and Shapiro, 2012). Enhancing neuronal activity by $K_v7$ inhibition with XE991 also results in homeostatic suppression of firing rate over 48 h (Lezmy et al., 2020). In contrast, prolonged blockade of neuronal activity or N-methyl-D-aspartate (NMDA) receptors increases firing rate and reduces in *KCNQ3* transcript and $K_v7$ current in hippocampal neurons (Lee and Chung, 2014; Lee et al., 2015). In the avian cochlear neurons, depriving afferent inputs induces a switch from fast activating $K_v1$ to slow activating $K_v7.2$ channels at the AIS, resulting in enhanced excitability (Kuba et al., 2015). This activity-dependent regulation of $K_v7$ transcript and distribution offers a powerful means to control intrinsic excitability.

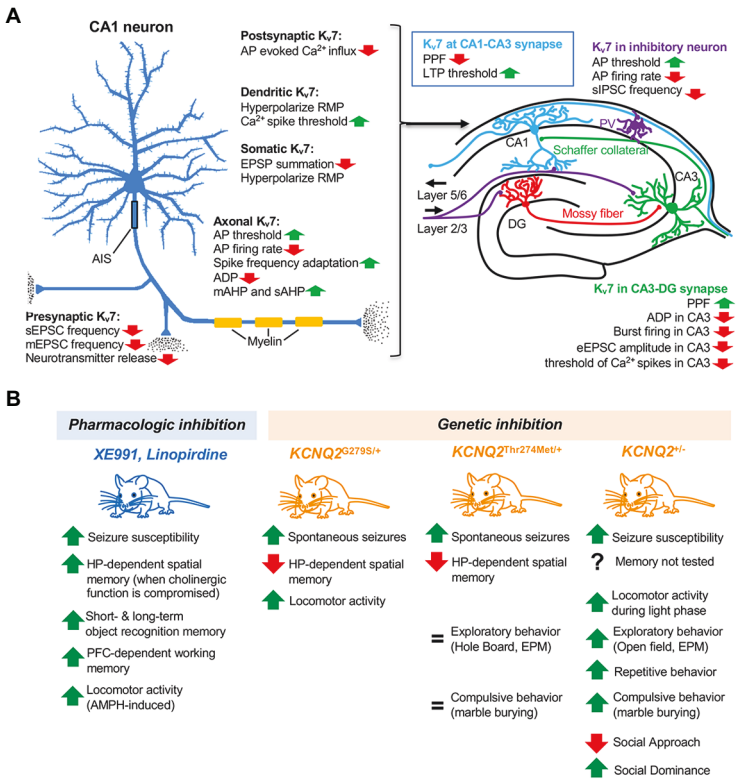


**FIGURE 1** | The role of $K_v7$ channels in hippocampal neurons, memory, and behavior. **(A)** Function of $K_v7$ channels in excitatory pyramidal neuron and GABAergic inhibitory neuron in the hippocampus. AP, action potential; RMP, resting membrane potential; EPSP, excitatory postsynaptic potential; ADP, afterdepolarization; mAHP, medium afterhyperpolarization; sAHP, slow afterhyperpolarization; sEPSC, spontaneous excitatory postsynaptic current; mEPSC, miniature excitatory postsynaptic current; PPF, paired-pulse facilitation; LTP, long-term potential; sIPSC, spontaneous inhibitory postsynaptic current; PV, parvalbumin; and eEPSC, evoked excitatory postsynaptic current. **(B)** Effects of pharmacological or genetic inhibition of $K_v7$ channels on memory and behavior. HP, hippocampus; PFC, pre-frontal cortex; AMPH, amphetamine; and EPM, elevated plus maze.

## ROLE OF $K_V7$ CHANNELS IN SYNAPTIC TRANSMISSION AND PLASTICITY IN THE HIPPOCAMPUS

Since the discovery of long-term potentiation (LTP) in the dentate gyrus of the hippocampus (Bliss and Lomo, 1973), persistent modification in synaptic strength termed "synaptic plasticity" has attracted significant attention as the cellular correlate of learning and memory (Nicoll, 2017). LTP at excitatory synapses can exert destabilizing influence on neural circuits by generating unconstrained synaptic strengthening (Turrigiano, 2012). Homeostatic plasticity counteracts such destabilizing condition by allowing neurons to adjust their synaptic strength (Turrigiano, 2012). While activity-dependent modulation of glutamate release and glutamate receptors serves as key mechanisms for LTP expression (Turrigiano, 2012; Humeau and Choquet, 2019), $K_v7$ channels and upstream muscarinic acetylcholine receptors have emerged as important regulators of excitatory synaptic transmission and plasticity.

Synaptic functions of $K_v7$ channels have been extensively studied at the excitatory synapses formed by hippocampal CA1 and CA3 pyramidal neurons (**Figure 1A**). These neurons show strong expression of $K_v7.2$ and $K_v7.3$ (Cooper et al., 2001; Pan et al., 2006). Conditional deletion of *KCNQ2* and *KCNQ3* increases the frequency of spontaneous excitatory postsynaptic currents (EPSC) in CA1 neurons (Soh et al., 2018), suggesting enhanced presynaptic release at CA1–CA3 synapses. Consistent with this notion, application of $K_v7$ antagonist XE991 increases whereas $K_v7$ agonist Flupirtine decreases miniature EPSC frequency in CA1 neurons (Sun and Kapur, 2012). Furthermore, $K_v7$ inhibition with linopirdine and XE991 treatment also increases neurotransmitter release (Nickolson et al., 1990; Martire et al., 2004; Peretz et al., 2007). While $K_v7$ current restrains AP-evoked $Ca^{2+}$ influx into the presynaptic terminal and decreases the paired pulse ratio of evoked EPSCs at the mossy fiber–CA3 synapses (Martinello et al., 2019), paired pulse facilitation of EPSP is higher at CA1–CA3 synapses in XE991-treated mice (Fontan-Lozano et al., 2011), suggesting differential roles of $K_v7$ channels in short-term plasticity at two different synapses.

$K_v7.2$ and $K_v7.3$ are expressed in GABAergic neurons including parvalbumin (PV)- and somatostatin (SST)-positive interneurons in the hippocampus (Cooper et al., 2001; Lawrence et al., 2006). Application of XE991 abolishes $I_M$, depolarizes RMP, and increases AP firing in SST+ interneurons (Lawrence et al., 2006) and enhances intrinsic excitability of PV+ interneurons

(Soh et al., 2018; **Figure 1A**). Furthermore, conditional deletion of *KCNQ2* and *KCNQ3* from PV+ interneurons increases their firing and spontaneous inhibitory postsynaptic current (sIPSC) frequency of CA1 neurons in the hippocampus (Soh et al., 2018).

These studies highlight the presynaptic influence of $K_v7$ channels at glutamatergic and GABAergic synapses. Given that increased firing rate and burst firing can enhance neurotransmitter release probabilities (Hansen et al., 2008), $K_v7$ inhibition may increase neurotransmitter release as a consequence of increased axonal excitability (Devaux et al., 2004; Shah et al., 2008; Klinger et al., 2011). Indeed, when CA3 neurons are depolarized upon elevating extracellular $K^+$ concentration, XE991 enhances EPSP amplitude in CA1 neurons as a consequence of increasing spike ADP and burst firing of CA3 neurons (Vervaeke et al., 2006). Alternatively, $K_v7$ channels at the presynaptic terminals (Cooper et al., 2001; Martire et al., 2004; Regev et al., 2009) may directly counteract the depolarization of the presynaptic membrane necessary for synaptic vesicle fusion and neurotransmitter release.

The postsynaptic role of $K_v7$ channels is unclear. A recent electron microscopy study shows that $K_v7.2$, $K_v7.3$, and $K_v7.5$ colocalize with muscarinic acetylcholine receptors at dendritic spines in layer III pyramidal neurons of the primate prefrontal cortex (Galvin et al., 2020), although the specificity of the immunolabeling needs to be further validated. In the CA1–CA3 synapses, the mEPSC amplitude is unaltered by agonist nor antagonists of $K_v7$ channels (Sun and Kapur, 2012), suggesting their negligible role in regulating postsynaptic glutamate receptor function at this synapse (**Figure 1A**).

Nonetheless, accumulating evidence suggests that $K_v7$ channels regulate hippocampal synaptic plasticity. At CA1–CA3 synapses, XE991 induces LTP by subthreshold theta-burst stimulation (Petrovic et al., 2012). Systemic administration of XE991 also decreases the threshold for LTP induction in the hippocampal CA1 area *in vivo* without affecting the field EPSP amplitude (Song et al., 2009; Fontan-Lozano et al., 2011). Lastly, homeostatic increase in excitatory synaptic transmission in CA1 neurons has been observed upon conditional deletion of *KCNQ2* and *KCNQ3* from GABAergic interneurons (Soh et al., 2018), suggesting the contribution of $K_v7$ channels in synaptic scaling.

## ROLE OF $K_V7$ CHANNELS IN HIPPOCAMPUS-DEPENDENT LEARNING AND MEMORY

Hippocampal LTP occurs during hippocampus-dependent learning and memory (Bliss et al., 2018) and its reduction is linked to memory loss in mouse models of Alzheimer's disease (Mango et al., 2019). Facilitation of LTP induction by XE991 (Song et al., 2009; Fontan-Lozano et al., 2011; Petrovic et al., 2012) suggests that pharmacologic $K_v7$ inhibition may enhance learning and memory. Indeed, linopirdine enhances the performance of rats in a hippocampus-dependent active avoidance test (Cook et al., 1990). XE991 improves memory in object recognition task in wild-type mice and mouse models of dementia induced by cholinergic depletion and neurodegeneration (Fontan-Lozano et al., 2011; Ballinger et al., 2016; Dennis et al., 2016) despite its ability to induce seizures at a higher dose (Fontan-Lozano et al., 2011; **Figure 1B**). In contrast, $K_v7$ agonists have yielded mixed results on affecting memory in rodents (Li et al., 2014; Frankel et al., 2016).

The cognition-enhancing effect of linopirdine is correlated with the increased release of acetylcholine in the hippocampus (Nickolson et al., 1990; Fontana et al., 1994), and stimulation of muscarinic acetylcholine receptor inhibits $I_M$ in hippocampal neurons (Shah et al., 2002). Consistently, muscarinic agonist improves whereas anticholinergic agent scopolamine impairs performance in hippocampus-dependent memory tasks (Fontana et al., 1994; Fontan-Lozano et al., 2011). Muscarinic acetylcholine receptors in the prefrontal cortex also modulate working memory in primates *via* $K_v7$ channels (Galvin et al., 2020). Since cholinergic depletion and dysfunction in the hippocampus and prefrontal cortex are implicated in age-related cognitive decline and Alzheimer's disease (Ballinger et al., 2016; Haam and Yakel, 2017), these studies support the therapeutic potential for $K_v7$ antagonists as cognitive enhancers.

Surprisingly, genetic inhibition or reduction of $K_v7$ currents induces an opposite effect on memory (**Figure 1B**). Deficits in hippocampal-dependent spatial memory and spontaneous seizures are observed in mice with conditional transgenic expression of dominant-negative mutant $K_v7.2$-G279S (Peters et al., 2005) and heterozygous knock-in mice for $K_v7.2$ containing epileptic encephalopathy loss-of-function variant T274M (Milh et al., 2020). Considering that $K_v7$ channels are critical for development and inhibition of neonatal brain (Peters et al., 2005; Soh et al., 2014), the memory impairment in these genetic models could be attributed to abnormal hippocampal morphology and/or hyperexcitability (Peters et al., 2005; Milh et al., 2020).

$K_v7$ channels also regulate multiple behaviors (**Figure 1B**). Behavioral phenotyping of the global or conditional homozygous *KCNQ2* knock-out mice has not been possible due to their early postnatal lethality or premature death, respectively (Watanabe et al., 2000; Soh et al., 2014). However, heterozygous *KCNQ2* knock-out mice are viable and display increased locomotor activity and exploratory behavior (Kim et al., 2020), consistent with behavioral hyperactivity induced by transgenic suppression of $K_v7$ currents (Peters et al., 2005) and amphetamine and XE991 (Sotty et al., 2009). These mice also show decreased sociability and increased repetitive and compulsive behavior (Kim et al., 2020), reminiscent of autism seen in some EE patients with dominant *KCNQ2* mutations (Weckhuysen et al., 2012, 2013; Milh et al., 2013). However, the precise circuitries responsible for these abnormal behaviors remain unknown.

## FUTURE PERSPECTIVES

The studies discussed in this review support the emerging concept that $K_v7$ channels contribute to neural plasticity, memory, and behavior. However, there is a significant knowledge gap in our understanding of the underlying molecular and cellular mechanisms. Future studies should continue to investigate structure-function and subcellular targeting of $K_v7$ channels, which will provide mechanistic insights for developing specific

modulators of their function and trafficking. Generation of mouse models in which deletion of a $K_v7$ subunit from specific neurons and subcellular localization with temporal control will be critical to delineate cell- and circuit-specific function of $K_v7$ channels in neural plasticity, cognition, and behavior.

## AUTHOR CONTRIBUTIONS

BCB and HC contributed to the conception and design of the manuscript. BCB, JZ, and HC also drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.