Published in final edited form as:
Brain Res Bull. 2014 April ; 103: 11–17. doi:10.1016/j.brainresbull.2014.01.002.

Channelopathies and Dendritic Dysfunction in Fragile X syndrome

Darrin H. Brager and **Daniel Johnston**
Center for Learning and Memory, University of Texas at Austin, Austin, TX 78712

Abstract

Dendritic spine abnormalities and the metabotropic glutamate receptor theory put the focus squarely on synapses and protein synthesis as the cellular locus of Fragile X syndrome. Synapses however, are only partly responsible for information processing in neuronal networks. Neurotransmitter triggered excitatory postsynaptic potentials (EPSPs) are shaped and integrated by dendritic voltage-gated ion channels. These EPSPs, and in some cases the resultant dendritic spikes, are further modified by dendritic voltage-gated ion channels as they propagate to the soma. If the resultant somatic depolarization is large enough, action potential(s) will be triggered and propagate both orthodromically down the axon, where it may trigger neurotransmitter release, and antidromically back into the dendritic tree, where it can activate and modify dendritic voltage-gated and receptor activated ion channels. Several channelopathies, both soma-dendritic (L-type calcium channels, Slack potassium channels, h-channels, A-type potassium channels) and axo-somatic (BK channels and delayed rectifier potassium channels) were identified in the *fmr1-/y* mouse model of Fragile X syndrome. Pathological function of these channels will strongly influence the excitability of individual neurons as well as overall network function. In this chapter we discuss the role of voltage-gated ion channels in neuronal processing and describe how identified channelopathies in models of Fragile X syndrome may play a role in dendritic pathophysiology.

Keywords

voltage-gated ion channels; dendrites; integration; *fmr1*; FMRP

INTRODUCTION

Fragile X syndrome (FXS) affects 1 in 4,000 males and 1 in 6,000 females in the general population. In addition to impairments of short-term memory, visuospatial skills, and

Correspondence to: Darrin H. Brager, Ph.D., Center for Learning and Memory, University of Texas at Austin, 1 University Station, C7000, Austin, TX 78712–0805, 512–475–7928 (voice), 512–475–8000 (fax), dbrager@mail.clm.utexas.edu.

CONFLICT OF INTEREST STATEMENT
The authors declare that there is no conflict of interest.

speech, the occurrence of epilepsy in patients with FXS is significantly higher than in the general population. Fragile X Mental Retardation Protein (FMRP) is highly expressed in neuronal cell bodies and dendrites (Steward and Levy, 1982; Feng et al., 1997; Weiler et al., 1997; Steward and Schuman, 2001) and binds to the mRNAs for many proteins critical for neuronal information processing including several voltage-gated channels (Brown et al., 2001; Darnell et al., 2001; Chen et al., 2003; Darnell et al., 2011) (Table 1). Voltage-gated ion channels play essential roles in the synaptic transmission, dendritic integration, dendritic spike generation, and action potential firing. Incorrect channel expression, function, and/or loss of channel plasticity can have substantial effects on the control of neuronal function (Beck and Yaari, 2008).

Functional Roles of Dendritic Voltage-Gated Ion Channels

The summation of synaptic inputs can, when of sufficient strength, lead to an action potential initiated in the axo-somatic region of the neuron. In addition to propagating orthodromically down the axon, the action potential can also back propagate into the dendrites of neurons (Stuart et al., 1997). The efficacy of back propagation is influenced by both the dendritic morphology and the complement of dendritic voltage-gated ion channels. The density, distribution and biophysical properties of voltage-gated Na^+ channels dictate whether action potentials will actively backpropagate into the dendrites (Stuart and Sakmann, 1994; Magee and Johnston, 1995; Spruston et al., 1995; Colbert and Johnston, 1996; Golding et al., 2001) or spread in a mostly passive manner (Stuart and Häusser, 1994).

While the presence of Na^+ channels aids action potential active back propagation, voltage-gated K^+ channels in the dendritic membrane can reduce the amplitude of back propagating action potentials (b-AP). In particular, voltage-gated A-type K^+ channels (I_{KA}) are critically important for normal dendritic function and play a prominent role in regulating bAP amplitude (Hoffman et al., 1997; Ramakers and Storm, 2002; Bernard and Johnston, 2003; Johnston et al., 2003). In hippocampal CA1 pyramidal neurons, A-type K^+ channels are composed primarily of $K_V4.2$ subunits (Chen et al., 2006) and the density of A-type K^+ channels increases linearly with increasing distance from the soma (Hoffman et al., 1997). Under normal conditions, the high dendritic density of A-type K^+ channels in CA1 pyramidal neurons limits the amplitude of b-APs. Dendritic EPSPs of sufficient amplitude can inactivate A-type K^+ channels and thereby boost b-AP amplitude, if the b-AP and EPSP occur closely in time and space (Magee and Johnston, 1997; Watanabe et al., 2002). By setting up this temporal restriction, A-type K^+ channels can control the timing requirements for some forms of long-term synaptic plasticity.

The depolarization from b-APs will open dendritic voltage-gated Ca^{2+} channels (Jaffe et al., 1992; Christie et al., 1995; Frick et al., 2003). In hippocampal pyramidal neurons, the overall distribution of voltage-gated Ca^{2+} channels is uniform along the apical dendrite, but the distribution of specific subtypes varies with location. The calcium signal from b-APs is important for several forms of synaptic plasticity and may provide feedback information to the dendrites, the site of synaptic input about axonal output (Frick and Johnston, 2005). In some neurons a burst of back propagating action potentials can lead to a local regenerative dendritic event mediated by voltage-gated Ca^{2+} channels (Larkum et al., 1999). The

frequency at which these dendritic events is triggered, called the critical frequency, is set by the membrane potential and influenced by the presence of h-channels (Berger et al., 2003). H-channels (I_h) are somewhat unique voltage-gated channels in that they are opened by hyperpolarization of the membrane potential (DiFrancesco, 1993; Pape, 1996). Although the h-channel has a relatively small single channel conductance (Kole et al., 2006), the high density in the dendrites enables h-channels to contribute significantly to the total membrane conductance and thereby exert strong influence over neuronal function in the voltage range near rest (Magee, 1998; Lörincz et al., 2002; Bittner et al., 2012).

In addition to a burst of b-APs, the synchronous activation of clustered synaptic inputs can trigger a local dendritic spike mediated by voltage-gated Na^+, Ca^{2+} or NMDA receptor activated channels (Stuart et al., 1997; Schiller et al., 2000; Wang et al., 2000; Gulledge et al., 2005; Larkum et al., 2007). These dendritic spikes play an important role in the supralinear integration of synaptic inputs (Polsky et al., 2004; Gasparini and Magee, 2006). The propagation efficacy of dendritic spikes is variable with some reliably invading the soma (Martina et al., 2000; Larkum and Zhu, 2002) and others isolated in the dendrites (Golding and Spruston, 1998; Losonczy and Magee, 2006; Losonczy et al., 2008). Dendritic spikes may play an important role in conveying sensory information to cortical neurons, because they occur in Layer 5 neurons in response to sensory input during whisker exploration (Xu et al., 2012). Interestingly, the enriched dendritic expression of voltage-gated K^+ channels compartmentalizes dendritic spikes, and the resultant Ca^{2+} signal, within individual branches of the elaborate dendritic tuft of layer 5 neurons (Harnett et al., 2013).

Plasticity of Dendritic Function

Although activity-dependent modifications of synaptic strength are believed to be the cellular substrates of learning and memory (Bliss and Collingridge, 1993), changes in intrinsic neuronal excitability can also occur in response to increased (or reduced) activity (Turrigiano et al., 1994; Aizenman and Linden, 2000; Wang et al., 2003; Frick et al., 2004; Fan et al., 2005; Magee and Johnston, 2005; Xu et al., 2005; Narayanan and Johnston, 2007; Losonczy et al., 2008). This plasticity of intrinsic excitability involves the modulation of voltage-gated ion channels (Desai et al., 1999; Golowasch et al., 1999; Frick et al., 2004; Kim et al., 2007). The activity-dependent modulation of ion channels may serve to not only counter changes in synaptic strength (Siegel et al., 1994; Turrigiano and Nelson, 2000; Zhang and Linden, 2003), but also changes in intrinsic excitability due to the modulation of ion channels elsewhere in the dendritic arbor.

Persistent changes in voltage-gated ion channels occur during and after periods of elevated neuronal activity. In CA1 pyramidal neurons, theta-burst pairing LTP induction is accompanied by a persistent increase in I_h throughout the dendrites of CA1 pyramidal neurons (Fan et al., 2005; Narayanan and Johnston, 2007; Campanac et al., 2008). Interestingly, the same LTP protocol produces a decrease in I_{KA}, due to a left shift in the voltage-dependence of inactivation and internalization of A-type K^+ channels, that is restricted to a specific dendritic region (Frick et al., 2004; Kim et al., 2007). The coordinated global increase in I_h and localized decrease in I_{KA}, in conjunction with input specific

synaptic potentiation, would result in the tuning of individual CA1 pyramidal neurons to a specific set of synaptic inputs.

Changes in voltage-gated ion channels are not limited to LTP induction paradigms *in vitro*. Experience-dependent plasticity of voltage-gated ion channels also occurs *in vivo*. Acoustic stimulation in rats increases the expression of the delayed rectifier K^+ channel $K_V3.1b$ in medial nucleus of the trapezoid body (Strumbos et al., 2010b). Rats reared in an enriched environment showed enhanced propagation of dendritic spikes mediated by a localized downregulation of A-type K^+ channels (Makara et al., 2009). Deficits in dendritic plasticity with or without associated changes in the function of voltage-gated channels will have profound impacts on the ability of neurons to modify their integrative properties in the face of changes in neuronal activity.

Pathology of voltage-gated ion channels in Fragile X syndrome

Fragile X Mental Retardation Protein (FMRP) can potentially regulate ion channel function and/or expression in multiple ways. FMRP is an mRNA binding protein that can regulate translation. Initially characterized as a translational repressor, binding of FMRP to target mRNAs prevents protein translation by interacting with the translation template and stalling of polyribosomes advancement (Li et al., 2001; Zalfa et al., 2003; Darnell et al., 2011). In this case, the absence of FMRP would lead to excessive translation of target mRNAs and the overexpression of ion channel proteins and/or their regulatory subunits (Strumbos et al., 2010a; Lee et al., 2011). More recently, evidence suggests that FMRP can also promote the translational of target mRNAs (Bechara et al., 2009; Fähling et al., 2009). While the mechanism for the FMRP-dependent promotion of mRNA translation is not entirely known, the absence of FMRP would reduce mRNA translation yielding lower expression of ion channel proteins (Gross et al., 2011). In addition to its translational control functions, FMRP plays a role in the activity-dependent transport of mRNA granules from the soma to axonal and dendritic locations (Antar et al., 2004; Kanai et al., 2004; Dictenberg et al., 2008). The absence of FMRP could possibly result in the trapping of ion channel mRNAs at the soma or the mislocalization of target mRNAs and subsequent proteins. Lastly, FMRP can also bind directly to target proteins. The absence of FMRP would alter the biophysical properties of ion channels by directly binding to pore-forming subunits or by regulating the interaction between pore-forming and auxiliary ion channel subunits (Brown et al., 2010; Deng et al., 2013).

Investigations into the cellular underpinnings of Fragile X syndrome have greatly benefited from the development of the Fragile X knockout mouse (The Dutch-Belgian Consortium, 1994). Previously, the focus of most investigations was on deficits in synaptic transmission and plasticity in the *fmr1-/y* mouse given the number of FMRP targets implicated in those processes (Comery et al., 1997; Nimchinsky et al., 2001; Huber et al., 2002; Hou et al., 2006; Pfeiffer et al., 2010). However, the mRNA for many voltage-gated ion channel proteins are also binding targets of FMRP (Table 1), and recently alterations in the expression and/or function of several voltage-gated ion channels were reported in the *fmr1-/y* mouse (Table 2).

One of the first identified channels mRNAs regulated by FMRP was the delayed rectifier potassium channel $K_V3.1$ (Darnell et al., 2001; Strumbos et al., 2010a). $K_V3.1$ channels play a prominent role in neurons that have a very fast spike rate where this channel allows for spike firing frequencies often in excess of 300 Hz with very little adaptation (Gan and Kaczmarek, 1998; Rudy and McBain, 2001). One group of neurons where these channels play important physiological roles is in the sound localization circuitry of the anterior ventricular cochlear nucleus (AVCN) and the medial nucleus of the trapezoid body (MNTB). In both the AVCN and MNTB, $K_V3.1$ channels permit extremely high and faithful rates (• 600 Hz) of synaptic transmission (Wang et al., 1998). In *fmr1-/y* mice, the normal gradient of $K_V3.1$ in the MNTB (highest at the medial aspect) is flattened (Strumbos et al., 2010a). Furthermore, the normal increase in $K_V3.1$ expression after acoustic stimulation observed in wildtype mice is absent in *fmr1-/y* neurons. The net effect of the loss of FMRP is the impaired encoding and processing of auditory information.

In cortical neurons, L-type calcium channels play an important role in the induction of certain forms of long-term synaptic plasticity (Grover and Teyler, 1990; Bi and Poo, 1998; Kapur et al., 1998). The threshold for spike timing-dependent plasticity in layer 2/3 pyramidal neurons of the prefrontal cortex is increased in *fmr1-/y* mice (Meredith et al., 2007). This elevated threshold is due to the increased failure rate of spine calcium transients during the spike timing protocol. In the frontal cortex of *fmr1-/y* mice, both the mRNA and protein for L-type calcium channels are reduced (Chen et al., 2003). Application of the L-type calcium channel blocker nimodipine reduced spine calcium transients in wildtype but not *fmr1-/y* neurons suggesting that there is a lack of functional L-type calcium channels in the dendritic spines of layer 2/3 pyramidal neurons in *fmr1-/y* mice (Meredith et al., 2007).

In apical dendrites of CA1 pyramidal neurons, the density of h-channels increases with distance from soma (Magee, 1998). There is an enhancement of this distal dendritic enrichment of I_h in CA1 neurons of the *fmr1-/y* mouse (Brager et al., 2012). This elevation in I_h appears to be due to increased distal dendritic expression of the HCN1 subunit of h-channels. The higher distal dendritic I_h significantly reduces temporal summation of dendritic EPSPs thereby significantly affecting the integrative properties of CA1 pyramidal neurons (Magee, 1999). Interestingly, the normal increase in I_h which occurs following theta-burst pairing LTP induction (Fan et al., 2005; Narayanan and Johnston, 2007) was absent in *fmr1-/y* neurons suggesting that although strong LTP of synaptic inputs is not significantly affected (Lauterborn et al., 2007; Brager et al., 2012), plasticity of intrinsic excitability may be altered in *fmr1-/y* mice.

Rapid stimulation of Schaffer collateral inputs to CA1 neurons results in several forms of short-term synaptic plasticity (for review see (Zucker and Regehr, 2002). *Fmr1-/y* mice have deficits in short-term synaptic plasticity associated with exaggerated presynaptic calcium influx (Deng et al., 2011). The higher calcium influx was due in part to significantly broader action potentials in CA3 neurons in *fmr1-/y* mice (Deng et al., 2013). The difference in action potential broadening between wildtype and *fmr1-/y* mice was absent in the presence of paxilline and iberiotoxin, blockers of large-conductance calcium-activated potassium channels (BK channels). In cortical neurons, BK channels are found in the soma, dendrite, and axon including the pre- and postsynaptic specializations (Misonou et al., 2006; Sailer et

al., 2006). Diversity of BK channel function is accomplished in part by the presence of two identified auxiliary β subunits: β2 and β4. Deng et al. demonstrated that FMRP can bind directly to the β4 subunit of BK channels (Deng et al., 2013). The absence of FMRP in *fmr1-/y* neurons presumably affects the co-assembly of β4 subunits with the pore-forming subunits of BK channels and lowers the calcium sensitivity (Brenner et al., 2000). The net effect of this would be reduced I_{BK} and more pronounced action potential broadening during repetitive firing. The physiological consequence of action potential broadening is altered neurotransmitter release and short-term synaptic plasticity at Schaeffer collateral synapses onto CA1 pyramidal neurons.

The Slack (for sequence like a Ca^{2+}-activated K^+ channel) gene encodes a potassium channel that shares similarity to BK channels including a large single channel conductance but are activated by rises in intracellular Na^+ instead of Ca^{2+} (Dryer, 1994). Because they are activated by rises in intracellular Na^+, Slack channels contribute to the afterhyperpolarization that occurs after both individual and bursts of action potentials. FMRP can activate Slack channels via direct protein-protein interaction with the C-terminus (Brown et al., 2010). Although there is a small but significant increase in Slack immunoreactivity and no difference in synaptosomal expression of Slack protein between wildtype and *fmr1-/y* MNTB neurons, $I_{K(Na)}$ is substantially reduced due to the lack of FMRP to bind to the Slack channel subunits (Brown et al., 2010). Given the identified role of Slack channels regulating the timing of high frequency action potential firing (Yang et al., 2007), the loss of Slack channel function in *fmr1-/y* mice may play a role in impaired signal processing in MNTB neurons.

Two studies demonstrated that FMRP can bind to and regulate the translation of $K_V4.2$ mRNA, the putative subunit of hippocampal A-type K^+ channels (Gross et al., 2011; Lee et al., 2011). However, these two studies came to opposite conclusions as whether there is more (Lee et al., 2011) or less (Gross et al., 2011) expression of $K_V4.2$ protein in *fmr1-/y* neurons. One possible reason for the discrepancy between these two conclusions is that the studies use different background strains of the knockout mice (Lee et al. used FVB129 mice while Gross et al. used C57BL/6). It is known that background strain can affect expression of the *fmr1-/y* phenotype (Paradee et al., 1999). A physiological investigation in CA1 pyramidal neurons found smaller maximum dendritic I_{KA} and a left shifted voltage-dependence of activation of A-type K^+ channels (Routh et al., 2013). The physiological consequences of the changes in I_{KA} were reduced attenuation of b-APs, greater b-AP-mediated calcium influx, and a reduced threshold for theta-burst pairing LTP induction. While the physiological results in Routh et al. agree with the findings in Gross et al., it is possible that hippocampal $K_V4.2$ protein expression is actually greater in *fmr1-/y* mice but that there are fewer functional channels. There are instances where immunohistochemistry and physiology of A-type K^+ channels do not always agree (Hoffman et al., 1997; Kerti et al., 2012). Furthermore, Brown et al. (2010) demonstrated that MNTB neurons from the *fmr1-/y* mouse have higher expression of Slack channel subunits but reduced maximal $I_{K(Na)}$.

SUMMARY

Voltage-gated ion channels play a critical role in regulating the excitability of all aspects of neuronal function. Depending upon their neuronal compartment location, voltage-gated ion channels can regulate synaptic transmission, local dendritic spikes, and back propagating action potentials. Additionally, modulation of ion channel function plays a critical role in allowing neurons to modify their input-output properties in response to varying patterns of neuronal activity and neuromodulation. The function and expression of several voltage-gated ion channels are altered in the *fmr1-/y* mouse model of Fragile X syndrome. In some cases these changes were identified as due to altered protein expression (Strumbos et al., 2010a; Gross et al., 2011; Lee et al., 2011) or protein-protein interactions (Brown et al., 2010; Deng et al., 2013). In others, the reason the loss of FMRP resulted in the identified channelopathy is not immediately clear (Meredith et al., 2007; Brager et al., 2012; Routh et al., 2013).

Channelopathies in Fragile X syndrome profoundly affect dendritic integration, signaling and neuronal output, thereby potentially causing deficits in information processing by neuronal networks and contributing to cognitive impairment. Spontaneously occurring UP states are prolonged in the *fmr1-/y* mouse suggesting that neocortical circuits are hyperexcitable (Gibson et al., 2008; Hays et al., 2011; Gonçalves et al., 2013). While changes in synaptic connectivity and strength play a role in producing hyperexcitable networks, channelopathies would undoubtedly alter the intrinsic excitability of individual neurons and have a strong influence on the neuronal network as a whole. It will be interesting to see which of the already identified, as well as any newly discovered, channelopathies in Fragile X syndrome are in response to changes in neuronal network excitability as opposed to directly regulated by FMRP (i.e. mRNA translation or protein-protein interactions). Given the large number of cellular substrates that control the expression and function of voltage-gated channels, these molecules, in addition to the ion channels themselves, represent potential new targets for the development of therapeutic agents for Fragile X syndrome.

LITERATURE CITED

Aizenman CD, Linden DJ. Rapid, synaptically driven increases in the intrinsic excitability of cerebellar deep nuclear neurons. Nat Neurosci. 2000; 3:109–111. [PubMed: 10649564]

The Dutch-Belgian Fragile X Consortium. Fmr1 knockout mice: a model to study fragile X mental retardation. Cell. 1994; 78:23–33. [PubMed: 8033209]

Antar LN, Afroz R, Dictenberg JB, Carroll RC, Bassell GJ. Metabotropic glutamate receptor activation regulates fragile x mental retardation protein and FMR1 mRNA localization differentially in dendrites and at synapses. Journal of Neuroscience. 2004; 24:2648–2655. [PubMed: 15028757]

Bechara EG, Didiot MC, Melko M, Davidovic L, Bensaid M, Martin P, Castets M, Pognonec P, Khandjian EW, Moine H, Bardoni B. A novel function for fragile X mental retardation protein in translational activation. PLoS Biol. 2009; 7:e16. [PubMed: 19166269]

Beck H, Yaari Y. Plasticity of intrinsic neuronal properties in CNS disorders. Nat Rev Neurosci. 2008; 9:357–369. [PubMed: 18425090]

Berger T, Senn W, Lüscher H-R. Hyperpolarization-activated current Ih disconnects somatic and dendritic spike initiation zones in layer V pyramidal neurons. J Neurophysiol. 2003; 90:2428–2437. [PubMed: 12801902]

Bernard C, Johnston D. Distance-dependent modifiable threshold for action potential back-propagation in hippocampal dendrites. J Neurophysiol. 2003; 90:1807–1816. [PubMed: 12966178]

Bi GQ, Poo MM. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. J Neurosci. 1998; 18:10464–10472. [PubMed: 9852584]

Bittner KC, Andrasfalvy BK, Magee JC. Ion channel gradients in the apical tuft region of CA1 pyramidal neurons. PLoS ONE. 2012; 7:e46652. [PubMed: 23056387]

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature. 1993; 361:31–39. [PubMed: 8421494]

Brager DH, Akhavan AR, Johnston D. Impaired dendritic expression and plasticity of h-channels in the fmr1(-/y) mouse model of fragile X syndrome. Cell Reports. 2012; 1:225–233. [PubMed: 22662315]

Brenner R, Jegla TJ, Wickenden A, Liu Y, Aldrich RW. Cloning and functional characterization of novel large conductance calcium-activated potassium channel beta subunits, hKCNMB3 and hKCNMB4. J Biol Chem. 2000; 275:6453–6461. [PubMed: 10692449]

Brown MR, Kronengold J, Gazula V-R, Chen Y, Strumbos JG, Sigworth FJ, Navaratnam D, Kaczmarek LK. Fragile X mental retardation protein controls gating of the sodium-activated potassium channel Slack. Nat Neurosci. 2010; 13:819–821. [PubMed: 20512134]

Brown V, et al. Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. Cell. 2001; 107:477–487. [PubMed: 11719188]

Campanac E, Daoudal G, Ankri N, Debanne D. Downregulation of dendritic I(h) in CA1 pyramidal neurons after LTP. Journal of Neuroscience. 2008; 28:8635–8643. [PubMed: 18716222]

Chen L, Yun SW, Seto J, Liu W, Toth M. The fragile X mental retardation protein binds and regulates a novel class of mRNAs containing U rich target sequences. Neuroscience. 2003; 120:1005–1017. [PubMed: 12927206]

Chen X, Yuan L-L, Zhao C, Birnbaum SG, Frick A, Jung WE, Schwarz TL, Sweatt JD, Johnston D. Deletion of Kv4.2 gene eliminates dendritic A-type K+ current and enhances induction of long-term potentiation in hippocampal CA1 pyramidal neurons. Journal of Neuroscience. 2006; 26:12143–12151. [PubMed: 17122039]

Christie BR, Eliot LS, Ito K, Miyakawa H, Johnston D. Different Ca2+ channels in soma and dendrites of hippocampal pyramidal neurons mediate spike-induced Ca2+ influx. J Neurophysiol. 1995; 73:2553–2557. [PubMed: 7666160]

Colbert CM, Johnston D. Axonal action-potential initiation and Na+ channel densities in the soma and axon initial segment of subicular pyramidal neurons. J Neurosci. 1996; 16:6676–6686. [PubMed: 8824308]

Comery TA, Harris JB, Willems PJ, Oostra BA, Irwin SA, Weiler IJ, Greenough WT. Abnormal dendritic spines in fragile X knockout mice: maturation and pruning deficits. Proc Natl Acad Sci USA. 1997; 94:5401–5404. [PubMed: 9144249]

Darnell JC, Jensen KB, Jin P, Brown V, Warren ST, Darnell RB. Fragile X mental retardation protein targets G quartet mRNAs important for neuronal function. Cell. 2001; 107:489–499. [PubMed: 11719189]

Darnell JC, Van Driesche SJ, Zhang C, Hung KYS, Mele A, Fraser CE, Stone EF, Chen C, Fak JJ, Chi SW, Licatalosi DD, Richter JD, Darnell RB. FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. Cell. 2011; 146:247–261. [PubMed: 21784246]

Deng P-Y, Rotman Z, Blundon JA, Cho Y, Cui J, Cavalli V, Zakharenko SS, Klyachko VA. FMRP Regulates Neurotransmitter Release and Synaptic Information Transmission by Modulating Action Potential Duration via BK Channels. Neuron. 2013; 77:696–711. [PubMed: 23439122]

Deng P-Y, Sojka D, Klyachko VA. Abnormal presynaptic short-term plasticity and information processing in a mouse model of fragile X syndrome. Journal of Neuroscience. 2011; 31:10971–10982. [PubMed: 21795546]

Desai NS, Rutherford LC, Turrigiano GG. Plasticity in the intrinsic excitability of cortical pyramidal neurons. Nat Neurosci. 1999; 2:515–520. [PubMed: 10448215]

Dictenberg JB, Swanger SA, Antar LN, Singer RH, Bassell GJ. A direct role for FMRP in activity-dependent dendritic mRNA transport links filopodial-spine morphogenesis to fragile X syndrome. Dev Cell. 2008; 14:926–939. [PubMed: 18539120]

DiFrancesco D. Pacemaker mechanisms in cardiac tissue. Annu Rev Physiol. 1993; 55:455–472. [PubMed: 7682045]

Dryer SE. Na(+)-activated K+ channels: a new family of large-conductance ion channels. Trends Neurosci. 1994; 17:155–160. [PubMed: 7517595]

Fan Y, Fricker D, Brager DH, Chen X, Lu H-C, Chitwood RA, Johnston D. Activity-dependent decrease of excitability in rat hippocampal neurons through increases in I(h). Nat Neurosci. 2005; 8:1542–1551. [PubMed: 16234810]

Fähling M, Mrowka R, Steege A, Kirschner KM, Benko E, Förstera B, Persson PB, Thiele BJ, Meier JC, Scholz H. Translational regulation of the human achaete-scute homologue-1 by fragile X mental retardation protein. J Biol Chem. 2009; 284:4255–4266. [PubMed: 19097999]

Feng Y, Absher D, Eberhart DE, Brown V, Malter HE, Warren ST. FMRP associates with polyribosomes as an mRNP, and the I304N mutation of severe fragile X syndrome abolishes this association. Mol Cell. 1997; 1:109–118. [PubMed: 9659908]

Frick A, Johnston D. Plasticity of dendritic excitability. J Neurobiol. 2005; 64:100–115. [PubMed: 15884001]

Frick A, Magee J, Johnston D. LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites. Nat Neurosci. 2004; 7:126–135. [PubMed: 14730307]

Frick A, Magee J, Koester HJ, Migliore M, Johnston D. Normalization of Ca2+ signals by small oblique dendrites of CA1 pyramidal neurons. Journal of Neuroscience. 2003; 23:3243–3250. [PubMed: 12716931]

Gan L, Kaczmarek LK. When, where, and how much? Expression of the Kv3.1 potassium channel in high-frequency firing neurons. J Neurobiol. 1998; 37:69–79. [PubMed: 9777733]

Gasparini S, Magee JC. State-dependent dendritic computation in hippocampal CA1 pyramidal neurons. Journal of Neuroscience. 2006; 26:2088–2100. [PubMed: 16481442]

Gibson JR, Bartley AF, Hays SA, Huber KM. Imbalance of neocortical excitation and inhibition and altered UP states reflect network hyperexcitability in the mouse model of fragile X syndrome. J Neurophysiol. 2008; 100:2615–2626. [PubMed: 18784272]

Golding NL, Kath WL, Spruston N. Dichotomy of action-potential backpropagation in CA1 pyramidal neuron dendrites. J Neurophysiol. 2001; 86:2998–3010. [PubMed: 11731556]

Golding NL, Spruston N. Dendritic sodium spikes are variable triggers of axonal action potentials in hippocampal CA1 pyramidal neurons. Neuron. 1998; 21:1189–1200. [PubMed: 9856473]

Golowasch J, Abbott LF, Marder E. Activity-dependent regulation of potassium currents in an identified neuron of the stomatogastric ganglion of the crab Cancer borealis. J Neurosci. 1999; 19:RC33. [PubMed: 10516335]

Gonçalves JT, Anstey JE, Golshani P, Portera-Cailliau C. Circuit level defects in the developing neocortex of Fragile X mice. Nat Neurosci. 2013

Gross C, Yao X, Pong DL, Jeromin A, Bassell GJ. Fragile X mental retardation protein regulates protein expression and mRNA translation of the potassium channel Kv4.2. Journal of Neuroscience. 2011; 31:5693–5698. [PubMed: 21490210]

Grover LM, Teyler TJ. Two components of long-term potentiation induced by different patterns of afferent activation. Nature. 1990; 347:477–479. [PubMed: 1977084]

Gulledge AT, Kampa BM, Stuart GJ. Synaptic integration in dendritic trees. J Neurobiol. 2005; 64:75–90. [PubMed: 15884003]

Harnett MT, Xu N-L, Magee JC, Williams SR. Potassium Channels Control the Interaction between Active Dendritic Integration Compartments in Layer 5 Cortical Pyramidal Neurons. Neuron. 2013; 79:516–529. [PubMed: 23931999]

Hays SA, Huber KM, Gibson JR. Altered neocortical rhythmic activity states in Fmr1 KO mice are due to enhanced mGluR5 signaling and involve changes in excitatory circuitry. Journal of Neuroscience. 2011; 31:14223–14234. [PubMed: 21976507]

Hoffman DA, Magee JC, Colbert CM, Johnston D. K+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. Nature. 1997; 387:869–875. [PubMed: 9202119]

Hou L, Antion MD, Hu D, Spencer CM, Paylor R, Klann E. Dynamic translational and proteasomal regulation of fragile X mental retardation protein controls mGluR-dependent long-term depression. Neuron. 2006; 51:441–454. [PubMed: 16908410]

Huber KM, Gallagher SM, Warren ST, Bear MF. Altered synaptic plasticity in a mouse model of fragile X mental retardation. Proc Natl Acad Sci USA. 2002; 99:7746–7750. [PubMed: 12032354]

Jaffe DB, Johnston D, Lasser-Ross N, Lisman JE, Miyakawa H, Ross WN. The spread of Na+ spikes determines the pattern of dendritic Ca2+ entry into hippocampal neurons. Nature. 1992; 357:244–246. [PubMed: 1350327]

Johnston D, Christie BR, Frick A, Gray R, Hoffman DA, Schexnayder LK, Watanabe S, Yuan L-L. Active dendrites, potassium channels and synaptic plasticity. Philos Trans R Soc Lond, B, Biol Sci. 2003; 358:667–674. [PubMed: 12740112]

Kanai Y, Dohmae N, Hirokawa N. Kinesin transports RNA: isolation and characterization of an RNA-transporting granule. Neuron. 2004; 43:513–525. [PubMed: 15312650]

Kapur A, Yeckel MF, Gray R, Johnston D. L-Type calcium channels are required for one form of hippocampal mossy fiber LTP. J Neurophysiol. 1998; 79:2181–2190. [PubMed: 9535977]

Kerti K, Lörincz A, Nusser Z. Unique somato-dendritic distribution pattern of Kv4.2 channels on hippocampal CA1 pyramidal cells. Eur J Neurosci. 2012; 35:66–75. [PubMed: 22098631]

Kim J, Jung S-C, Clemens AM, Petralia RS, Hoffman DA. Regulation of dendritic excitability by activity-dependent trafficking of the A-type K+ channel subunit Kv4.2 in hippocampal neurons. Neuron. 2007; 54:933–947. [PubMed: 17582333]

Kole MHP, Hallermann S, Stuart GJ. Single Ih channels in pyramidal neuron dendrites: properties, distribution, and impact on action potential output. J Neurosci. 2006; 26:1677–1687. [PubMed: 16467515]

Larkum ME, Kaiser KM, Sakmann B. Calcium electrogenesis in distal apical dendrites of layer 5 pyramidal cells at a critical frequency of back-propagating action potentials. Proc Natl Acad Sci USA. 1999; 96:14600–14604. [PubMed: 10588751]

Larkum ME, Waters J, Sakmann B, Helmchen F. Dendritic spikes in apical dendrites of neocortical layer 2/3 pyramidal neurons. J Neurosci. 2007; 27:8999–9008. [PubMed: 17715337]

Larkum ME, Zhu JJ. Signaling of layer 1 and whisker-evoked Ca2+ and Na+ action potentials in distal and terminal dendrites of rat neocortical pyramidal neurons in vitro and in vivo. Journal of Neuroscience. 2002; 22:6991–7005. [PubMed: 12177197]

Lauterborn JC, Rex CS, Kramár E, Chen LY, Pandyarajan V, Lynch G, Gall CM. Brain-derived neurotrophic factor rescues synaptic plasticity in a mouse model of fragile X syndrome. Journal of Neuroscience. 2007; 27:10685–10694. [PubMed: 17913902]

Lee HY, Ge W-P, Huang W, He Y, Wang GX, Rowson-Baldwin A, Smith SJ, Jan YN, Jan LY. Bidirectional Regulation of Dendritic Voltage-Gated Potassium Channels by the Fragile X Mental Retardation Protein. Neuron. 2011; 72:630–642. [PubMed: 22099464]

Li Z, Zhang Y, Ku L, Wilkinson KD, Warren ST, Feng Y. The fragile X mental retardation protein inhibits translation via interacting with mRNA. Nucleic Acids Res. 2001; 29:2276–2283. [PubMed: 11376146]

Losonczy A, Magee JC. Integrative properties of radial oblique dendrites in hippocampal CA1 pyramidal neurons. Neuron. 2006; 50:291–307. [PubMed: 16630839]

Losonczy A, Makara JK, Magee JC. Compartmentalized dendritic plasticity and input feature storage in neurons. Nature. 2008; 452:436–441. [PubMed: 18368112]

Lörincz A, Notomi T, Tamás G, Shigemoto R, Nusser Z. Polarized and compartment-dependent distribution of HCN1 in pyramidal cell dendrites. Nat Neurosci. 2002; 5:1185–1193. [PubMed: 12389030]

Magee JC. Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. J Neurosci. 1998; 18:7613–7624. [PubMed: 9742133]

Magee JC. Dendritic lh normalizes temporal summation in hippocampal CA1 neurons. Nat Neurosci. 1999; 2:508–514. [PubMed: 10448214]

Magee JC, Johnston D. Characterization of single voltage-gated Na+ and Ca2+ channels in apical dendrites of rat CA1 pyramidal neurons. J Physiol (Lond). 1995; 487(Pt 1):67–90. [PubMed: 7473260]

Magee JC, Johnston D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. Science. 1997; 275:209–213. [PubMed: 8985013]

Magee JC, Johnston D. Plasticity of dendritic function. Curr Opin Neurobiol. 2005; 15:334–342. [PubMed: 15922583]

Makara JK, Losonczy A, Wen Q, Magee JC. Experience-dependent compartmentalized dendritic plasticity in rat hippocampal CA1 pyramidal neurons. Nat Neurosci. 2009; 12:1485–1487. [PubMed: 19898470]

Martina M, Vida I, Jonas P. Distal initiation and active propagation of action potentials in interneuron dendrites. Science. 2000; 287:295–300. [PubMed: 10634782]

Meredith RM, Holmgren CD, Weidum M, Burnashev N, Mansvelder HD. Increased threshold for spike-timing-dependent plasticity is caused by unreliable calcium signaling in mice lacking fragile X gene FMR1. Neuron. 2007; 54:627–638. [PubMed: 17521574]

Misonou H, Menegola M, Buchwalder L, Park EW, Meredith A, Rhodes KJ, Aldrich RW, Trimmer JS. Immunolocalization of the Ca2+-activated K+ channel Slo1 in axons and nerve terminals of mammalian brain and cultured neurons. J Comp Neurol. 2006; 496:289–302. [PubMed: 16566008]

Narayanan R, Johnston D. Long-term potentiation in rat hippocampal neurons is accompanied by spatially widespread changes in intrinsic oscillatory dynamics and excitability. Neuron. 2007; 56:1061–1075. [PubMed: 18093527]

Nimchinsky EA, Oberlander AM, Svoboda K. Abnormal development of dendritic spines in FMR1 knock-out mice. Journal of Neuroscience. 2001; 21:5139–5146. [PubMed: 11438589]

Pape HC. Queer current and pacemaker: the hyperpolarization-activated cation current in neurons. Annu Rev Physiol. 1996; 58:299–327. [PubMed: 8815797]

Paradee W, Melikian HE, Rasmussen DL, Kenneson A, Conn PJ, Warren ST. Fragile X mouse: strain effects of knockout phenotype and evidence suggesting deficient amygdala function. Neuroscience. 1999; 94:185–192. [PubMed: 10613508]

Pfeiffer BE, Zang T, Wilkerson JR, Taniguchi M, Maksimova MA, Smith LN, Cowan CW, Huber KM. Fragile X mental retardation protein is required for synapse elimination by the activity-dependent transcription factor MEF2. Neuron. 2010; 66:191–197. [PubMed: 20434996]

Polsky A, Mel BW, Schiller J. Computational subunits in thin dendrites of pyramidal cells. Nat Neurosci. 2004; 7:621–627. [PubMed: 15156147]

Ramakers GMJ, Storm JF. A postsynaptic transient K(+) current modulated by arachidonic acid regulates synaptic integration and threshold for LTP induction in hippocampal pyramidal cells. Proc Natl Acad Sci USA. 2002; 99:10144–10149. [PubMed: 12114547]

Routh BN, Johnston D, Brager DH. Loss of Functional A-Type Potassium Channels in the Dendrites of CA1 Pyramidal Neurons from a Mouse Model of Fragile X Syndrome. Journal of Neuroscience. 2013; 33:19442–19450. [PubMed: 24336711]

Rudy B, McBain CJ. Kv3 channels: voltage-gated K+ channels designed for high-frequency repetitive firing. Trends Neurosci. 2001; 24:517–526. [PubMed: 11506885]

Sailer CA, Kaufmann WA, Kogler M, Chen L, Sausbier U, Ottersen OP, Ruth P, Shipston MJ, Knaus H-G. Immunolocalization of BK channels in hippocampal pyramidal neurons. Eur J Neurosci. 2006; 24:442–454. [PubMed: 16903852]

Schiller J, Major G, Koester HJ, Schiller Y. NMDA spikes in basal dendrites of cortical pyramidal neurons. Nature. 2000; 404:285–289. [PubMed: 10749211]

Siegel M, Marder E, Abbott LF. Activity-dependent current distributions in model neurons. Proc Natl Acad Sci USA. 1994; 91:11308–11312. [PubMed: 7526395]

Spruston N, Schiller Y, Stuart G, Sakmann B. Activity-Dependent Action Potential Invasion and Calcium Influx into Hippocampal CA1 Dendrites. Science. 1995:297–300. [PubMed: 7716524]

Steward O, Levy WB. Preferential localization of polyribosomes under the base of dendritic spines in granule cells of the dentate gyrus. J Neurosci. 1982; 2:284–291. [PubMed: 7062109]

Steward O, Schuman EM. Protein synthesis at synaptic sites on dendrites. Annu Rev Neurosci. 2001; 24:299–325. [PubMed: 11283313]

Strumbos JG, Brown MR, Kronengold J, Polley DB, Kaczmarek LK. Fragile X mental retardation protein is required for rapid experience-dependent regulation of the potassium channel Kv3.1b. Journal of Neuroscience. 2010a; 30:10263–10271. [PubMed: 20685971]

Strumbos JG, Polley DB, Kaczmarek LK. Specific and rapid effects of acoustic stimulation on the tonotopic distribution of Kv3.1b potassium channels in the adult rat. Neuroscience. 2010b; 167:567–572. [PubMed: 20219640]

Stuart G, Häusser M. Initiation and spread of sodium action potentials in cerebellar Purkinje cells. Neuron. 1994; 13:703–712. [PubMed: 7917300]

Stuart G, Spruston N, Sakmann B, Häusser M. Action potential initiation and backpropagation in neurons of the mammalian CNS. Trends Neurosci. 1997; 20:125–131. [PubMed: 9061867]

Stuart GJ, Sakmann B. Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. Nature. 1994; 367:69–72. [PubMed: 8107777]

Turrigiano G, Abbott LF, Marder E. Activity-dependent changes in the intrinsic properties of cultured neurons. Science. 1994; 264:974–977. [PubMed: 8178157]

Turrigiano GG, Nelson SB. Hebb and homeostasis in neuronal plasticity. Curr Opin Neurobiol. 2000; 10:358–364. [PubMed: 10851171]

Wang LY, Gan L, Forsythe ID, Kaczmarek LK. Contribution of the Kv3.1 potassium channel to high-frequency firing in mouse auditory neurones. J Physiol (Lond). 1998; 509(Pt 1):183–194. [PubMed: 9547392]

Wang SS, Denk W, Häusser M. Coincidence detection in single dendritic spines mediated by calcium release. Nat Neurosci. 2000; 3:1266–1273. [PubMed: 11100147]

Wang Z, Xu N-L, Wu C-P, Duan S, Poo M-M. Bidirectional changes in spatial dendritic integration accompanying long-term synaptic modifications. Neuron. 2003; 37:463–472. [PubMed: 12575953]

Watanabe S, Hoffman DA, Migliore M, Johnston D. Dendritic K+ channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons. Proc Natl Acad Sci USA. 2002; 99:8366–8371. [PubMed: 12048251]

Weiler IJ, Irwin SA, Klintsova AY, Spencer CM, Brazelton AD, Miyashiro K, Comery TA, Patel B, Eberwine J, Greenough WT. Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation. Proc Natl Acad Sci USA. 1997; 94:5395–5400. [PubMed: 9144248]

Xu J, Kang N, Jiang L, Nedergaard M, Kang J. Activity-dependent long-term potentiation of intrinsic excitability in hippocampal CA1 pyramidal neurons. J Neurosci. 2005; 25:1750–1760. [PubMed: 15716411]

Xu N-L, Harnett MT, Williams SR, Huber D, O'Connor DH, Svoboda K, Magee JC. Nonlinear dendritic integration of sensory and motor input during an active sensing task. Nature. 2012; 492:247–251. [PubMed: 23143335]

Yang B, Desai R, Kaczmarek LK. Slack and Slick K(Na) channels regulate the accuracy of timing of auditory neurons. Journal of Neuroscience. 2007; 27:2617–2627. [PubMed: 17344399]

Zalfa F, Giorgi M, Primerano B, Moro A, di Penta A, Reis S, Oostra B, Bagni C. The fragile X syndrome protein FMRP associates with BC1 RNA and regulates the translation of specific mRNAs at synapses. Cell. 2003; 112:317–327. [PubMed: 12581522]

Zhang W, Linden DJ. The other side of the engram: experience-driven changes in neuronal intrinsic excitability. Nat Rev Neurosci. 2003; 4:885–900. [PubMed: 14595400]

Zucker RS, Regehr WG. Short-term synaptic plasticity. Annu Rev Physiol. 2002; 64:355–405. [PubMed: 11826273]

Highlights

1. Channelopathies represent a novel area of investigation in the pathology of FXS
2. Voltage-gated ion channels are critical for normal and abnormal neuronal function
3. Alterations in several voltage-gated ion channels were identified in the *fmr1-/y* mouse
4. Voltage-gated ion channels represent a potential new set of therapeutic targets

Table 1

Ion channel mRNAs identified as FMRP targets

Voltage-gated potassium channels				
Name	**Gene**	**Type**	**Notes**	**Reference**
K_V1.2	*KCNA2*	delayed rectifier		d
K_V2.1	*KCNB1*	delayed rectifier		d
K_V3.1	*KCNC1*	delayed rectifier		a, confirmed in ref. e
K_V3.3	*KCNC3*	A-type		d
K_V4.2	*KCND2*	A-type		d, confirmed in ref. f and g
K_V10.1	*KCNH1*	delayed rectifier	EAG-related	d
K_V12.2	*KCNH3*	fast (partial) inactivation	EAG-related	d
K_V11.3	*KCNH7*	fast (partial) inactivation	EAG-related	d
K_V7.2	*KCNQ2*	delayed rectifier	M-current	d
K_V7.3	*KCNQ3*	delayed rectifier	M-current	d
Other potassium channels				
Name	**Gene**	**Type**	**Notes**	**Reference**
K_{Ca}1.1	*KNCMA1*	calcium-activated	BK, Maxi-K channel	d
K_{Ca}4.1	*KCNT1*	sodium-activated	Slack	d
K_{IR}3.3	*KCNJ9*	G-protein coupled inward rectifier	GIRK3	c
Voltage-gated sodium channels				
Name	**Gene**	**Type**	**Notes**	**Reference**
Na_V1.1	*SCN2A*	TTX-sensitive		d
Na_V1.6	*SCN8A*	TTX-sensitive		d
Voltage-gated calcium channels				
Name	**Gene**	**Type**	**Notes**	**Reference**
Ca_V2.1	*CACNA1A*	P/Q-type calcium channel	High voltage-activated	d
Ca_V2.2	*CACNA1B*	N-type calcium channel	High voltage-activated	d
Ca_V2.3	*CACNA1E*	R-type calcium channel	Intermediate voltage-activated	d
Ca_V3.1	*CACNA1G*	T-type calcium channel	Low voltage-activated	d
Ca_V3.3	*CACNA1I*	T-type calcium channel	Low voltage-activated	d
Ca_V1.3	CACNA1D	L-type calcium channel	High voltage-activated	c
	CANCB1	L-type calcium channel β1 subunit		d
	CACNB3	L-type calcium channel β3 subunit		b
Other channels				
Name	**Gene**	**Type**	**Notes**	**Reference**
HCN2	*HCN2*	h-channel	non-specific cation channel	b, d
CLCN3	*CLCN3*	chloride channel		d
TRPC4	*TRPC4*	Transient receptor potential channel, subclass C	non-specific cation channel	d
TRPM3	*TRPM3*	Transient receptor potential channel, subclass M	non-specific cation channel	d
VDAC	*VDAC1*	Voltage-dependent anion channel		c

ACCN	*ACCN1*	Amiloride-sensitive cation channel	d

References

a. Darnell et al., 2001

b. V. Brown et al., 2001

c. L. Chen et al., 2003

d. Darnell et al., 2011

e. Strumbos et al., 2010a

f. Gross et al., 2011

g. Lee et al., 2011

This table represents mRNAs for channel proteins that can bind to, and therefore be regulated by FMRP. The absence of an mRNA from this table does not however mean that the particular channel is not regulated by FMRP. It may reflect a low abundance of that particular mRNA and therefore not detected by the assay used in the indicated study.

Table 2

Ion channels dysfunctions identified in the *fmr1-/y* mouse model of Fragile X syndrome

Channel	Alteration	Technique Putative	Putative Mechanism of FMRP regulation	Brain Region	Reference
L-type	↑ threshold for STDP	WC CC	unknown	mPFC	Meredith et al., 2007
Ca^{2+} channel	↓ reliability of spine Ca^{2+} transients	2P-Ca^{2+} imaging			
	↓ functional L-type Ca^{2+} channels	2P-Ca^{2+} imaging			
Delayed rectifier	f tonotopic gradient	IHC / WC VC	mRNA translation	MNTB	Strumbos et al., 2010a
K^+ channel	lack of activity-dependent plasticity	IHC			
K_V3.1b					
Na^+-activated	↓ $I_{K(Na)}$	WC VC	protein-protein interaction	MNTB	Brown et al., 2010
K^+ channel, Slack	↑ Slack B expression	IHC			
A-type K^+ channel	↓ K_V4.2 expression	IHC/WB	mRNA translation	HPC	Gross et al., 2011
	↓ K_V4.2 surface expression	WB			
	↑ K_V4.2 expression	IHC/WB	mRNA translation	HPC	Lee et al., 2011
	↑ expression	WB			
	↑threshold for TBS LTP	EC			
	↓ dendritic I_{KA}	CA-VC	unknown	HPC	Routh et al, 2013
	↑distal dendritic bAP amplitude	WC CC			
	↓distance-dependence attenuation of dendriticCa^{2+} signaling	Ca^{2+} imaging			
	↓threshold for TBP LTP	WC CC			
h-channel	↑ dendritic I_h	WC CC	unknown	HPC	Brager et al., 2012
	↑ HCN1 expression	IHC / WB			
	Lack of activity-dependent plasticity	WC CC			
Ca^{2+}-activated					
K^+ channel (BK)	↑ activity-dependent AP broadening	WC CC	protein-protein interaction with beta subunit	HPC	Deng et al., 2013
	↓ Ca^{2+} sensitivity	WC VC			
	↑ short-term synaptic plasticity	WC VC			

Technique abbreviations: WC CC, whole-cell current clamp; 2P-Ca^{2+} imaging, two-photon calcium imaging; IHC, immunohistochemistry; WB, western blotting; WC VC, whole-cell voltage clamp; EC, extracellular recording; CA-VC, cell-attached voltage clamp.

Brain region abbreviations: mPFC, medial prefrontal cortex; MNTB, medial nucleus of trapezoid body; HPC, hippocampus