Chapter 24

Dendrites and disease

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Summary

While the functional properties of dendrites in the normal brain are the main focus of this book, there is a long history of research related to changes in dendrites that are associated with certain neurological, psychiatric, and developmental disorders. Much of this research has documented morphological changes in dendritic structure, but a significant increase in work has appeared since the second edition of this book in which changes in dendritic function have been described. In this chapter we briefly review some of the research relating structural changes in dendrites to disease, sufficient to provide a beginning reference source for readers interested in pursuing the subject further. The bulk of this chapter, however, will focus on the current state of knowledge related to dendritic "channelopathies." These are defined as genetic or acquired defects in the normal function or expression of ion channels (with a focus on voltage-gated ion channels) that are known to regulate how neuronal dendrites process and store information. The most specific and detailed information is available for epilepsy, which will be discussed at some length, but other data will be presented for certain neurodevelopmental disorders (e.g., autism, fragile X syndrome) and diseases of the adult and aging brain. Based on our knowledge of the normal properties of dendrites, we provide a framework for understanding how dendritic channelopathies can influence synaptic integration and plasticity and thus form the basis of abnormal brain function.

Introduction

Abnormalities in dendritic structure are a characteristic feature of many brain disorders. This is perhaps not surprising given the important role of dendrites as the principal site of synaptic contact for neurons. Changes in synaptic function or neuronal circuitry associated with disease might thus be expected to produce structural alterations resulting in, for example, loss of spines, changes in spine size and shape, reduced dendritic branching patterns, and shortened dendritic lengths. In fact, all of these structural changes have been described for different neurological disorders. What may be surprising, however, is how varied, extensive, and specific these structural changes are for each individually described disease state. In some cases the morphological changes in dendrites are actually used as a diagnostic fingerprint for the disorder. Unfortunately, much less is known about how these structural changes relate to the functional properties of neurons, such as synaptic integration, plasticity, excitability, and firing behaviors.

Neurodevelopmental disorders

Neurodevelopmental disorders (NDDs) are pathologies of the nervous system arising from defects in the way the nervous system grows and develops (Meredith, 2014). Such disorders may have

a plethora of consequences, including impairment in cognitive functions, speech, attention and concentration, social skills, and motor function as well as behavioral disturbances. NDDs often manifest in early childhood, leading to perturbations in developmental milestones or difficulties with socialization and integration into school. Well-known examples include autism spectrum disorders, intellectual disabilities, and attention-deficit/hyperactivity disorder (ADHD). Many NDDs have a strong genetic component, but environmental factors or trauma can also play a role (United States Environmental Protection Agency, 2013).

In 1974 Dominick Purpura published a highly influential paper in *Science* suggesting that dendritic spine abnormalities (dysgenesis) formed the basis of certain types of intellectual disability (Purpura, 1974). While this was certainly not the first time it had been suggested that changes in dendritic morphology were associated with neurological disease (cf. Marin-Padilla, 1972; Scheibel and Scheibel, 1973), it nevertheless stimulated significant further research in this area. It is now clear that there is a strong correlation between dendritic pathology and intellectual disability; in particular, this has been demonstrated for Down, Rett, fragile X (FXS), Williams, and Rubinstein–Taybi syndromes (Kaufmann and Moser, 2000), and autism spectrum disorders (Hutsler and Zhang, 2010; Tang et al., 2014).

In general, these and other developmental disorders (Nitkin, 2000) are characterized by changes in dendritic length, branching patterns, and spine number (Fiala et al., 2002). In the case of FXS and autism in particular spines are often long and thin. While it would be surprising if the dendrites were functioning normally under these conditions, it is unclear whether the altered morphology is the primary cause of the disease or rather a compensatory or secondary change to some other primary pathology. For example, many of these same changes can occur following deafferentation (Fiala et al., 2002). Nevertheless, it would be interesting and important to better understand the physiological consequences of these pronounced and striking changes in dendritic structure that are frequently associated with mental retardation.

In addition to the well-described changes in dendritic spine morphology, alterations in the function and/or expression levels of voltage-gated ion channels are also likely to play a profound role in the pathophysiology of a number of NDDs. Although this question has, to date, received scant attention, the important role of ion channels in many aspects of dendritic physiology mean that any polymorphism/mutation affecting the targeting, modulation, or biophysical properties of ion channels are likely to impact on dendritic function. The following sections illustrate the possible and known roles that ion channel defects play in disorders of this nature.

Autism spectrum disorders

Autism spectrum disorders (ASDs) comprise a heterogeneous group of disorders that fall under the category of pervasive developmental disorders. ASDs are diagnosed by the presence of a triad of core behavioral features including defects in social interaction, communication, and repetitive or stereotyped behavior. In addition to these endophenotypes, other comorbidities are often present, such as an increased risk of epilepsy, defects in sensory information processing, or motor defects and intellectual disability. Recent estimates from the Centers for Disease Control suggest that as many as one in seventy children may be affected by this spectrum of disorders. ASDs are suggested to have a strong genetic component; however, in most cases there is not one single genetic cause (reviewed in Schmunk and Gargus, 2013). Notable exceptions include well-characterized syndromes such as Angelman, Rett, and FXS. Indeed the wide heterogeneity of ASDs is probably caused by a unique combination of gene polymorphisms, mutations, and interactions with environmental factors that underlie the etiology of individual cases (Schmunk and Gargus, 2013).

According to the SFARIgene database (a curated list of genes associated with ASD; https://gene.sfari.org/autdb/HG_Home.do) more than 600 genes have been identified as playing a putative role in ASDs, including a substantial number of ion channels of the Ca^{2+}, K^{+}, and Na^{+} families as well as the HCN1 isoform of the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel family.

In particular, voltage-gated Ca^{2+} channels have been suggested to play an important role in ASDs (Krey and Dolmetsch, 2007). Evidence comes from genetic studies in human patients or behavioral analysis following deletion or pharmacological ablation of specific subunit types in mice (e.g., Jinnah et al., 1999). For example, loss of function of the genes encoding the alpha 1 subunit of L-type channels ($Ca_v1.2$) or an α_2-delta subunit 4 may arise from genomic deletion in ASDs (Smith et al., 2012). Rare missense mutations have been identified in the genes encoding the β_2-subunit in ASDs (Breitenkamp et al., 2014). Likewise, a missense mutation in the gene encoding the T-type Ca^{2+} channel subunit $Ca_v3.2$ (Splawski et al., 2006) or polymorphism in the gene encoding $Ca_v3.3$ (Lu et al., 2012) may also contribute to the etiology of ASDs.

T-type Ca^{2+} channels are expressed in the neocortex, hippocampus, thalamus, and cerebellum and exhibit a distinct somato-dendritic pattern of expression depending on the subunit in question (McKay et al., 2006). T-type calcium channels are expressed in both the shaft and the spines of dendrites in CA1 pyramidal neurons (Christie et al., 1995; Magee and Johnston, 1995; Sabatini and Svoboda, 2000), and in dendritic spines of neocortical pyramidal neurons (Koester and Sakmann, 2000). This pattern of expression suggests an important role in normal dendritic function. L-type Ca^{2+} channels are present in the dendritic shaft of CA1 pyramidal neurons (Christie et al., 1995; Magee and Johnston, 1995), and in both dendrites and spines in neocortical pyramidal neurons (Markram et al., 1995; Koester and Sakmann, 1998). Thus, the aforementioned mutations are likely to have important consequences, which so far have not been explicitly investigated.

Direct evidence for dendritic involvement in the pathophysiology of ASDs comes from analysis of the effects of a mutant type of L-type Ca^{2+} channel in rodent and human pluripotent stem cell-derived neurons. In both cases, the mutation present in Timothy's syndrome (TS; a rare monogenetic syndromic form of ASD) caused activity-dependent retraction of dendrites (Krey et al., 2013). Interestingly, this phenomenon was independent of Ca^{2+} signaling and instead involved ectopic activation of the RhoA signaling pathway through impaired interactions between the mutant channel and the RGK protein, Gem. This finding thus points to a novel role for L-type calcium channels in dendritic function. In addition, the TS mutation delays the voltage-dependent inactivation of the mutant channel, while at the same time accelerating the kinetics for Ca^{2+}-dependent inactivation (Barrett and Tsien, 2008). These alterations in gating properties could cause additional changes in excitability, which maybe contribute to the overall pathology of TS (reviewed in Szlapczynska et al., 2014).

Intellectual disability

Intellectual disability (ID; or intellectual development disorder) is a pathology encompassing a diverse group of disorders whose common feature is compromised mental abilities that impact on the individual's adaptive functioning (American Psychiatric Association, 2013). Diagnosis is based on mental function across three core domains (conceptive, social, and practical capacities) and may also incorporate a consideration of intelligence quotient (although this is no longer considered the sole criterion for diagnosis). IDs are considered to have a strong developmental component and may be classified as syndromic or non-syndromic based on the presence or absence (respectively) of accompanying comorbidities (van Bokhoven, 2011). Much of our understanding

of the mechanisms underlying ID comes from our ability to model these disorders in suitable animal models. Thus the majority of our understanding of ID comes from a somewhat limited subset of disorders (e.g., Rett syndrome, Angelman syndrome, FXS, Down syndrome). Nonetheless, in recent years, ID has been investigated in a growing number of novel animal models (e.g., SynGAP1; see Huang, 2009; Clement et al., 2012).

ID is often thought to arise from an underlying defect in synaptic function (e.g., Zoghbi and Bear, 2012) or from morphofunctional defects in dendrites or dendritic spines (e.g., as reviewed by Ramakers, 2002; Dierssen and Ramakers, 2006; Portera-Cailliau, 2012; Chang et al., 2013). Thus a large body of research has focused on these aspects as the causal mechanism, leading to a perhaps biased proliferation of models that assume an underlying synaptic cause. However, as mentioned above, these changes may be a consequence of altered signaling pathways rather than the causal feature of the disorder.

More than 450 genes have been associated with ID (reviewed in van Bokhoven, 2011), including a number of ion channel subunits (http://gfuncpathdb.ucdenver.edu/iddrc/iddrc/home.php). For example, two independent studies reported individual cases in which the deletion of *CACNAG1* (encoding the T-type calcium channel subunit, $Ca_v3.1$) was implicated in a novel form of syndromic ID disorder (Preiksaitiene et al., 2012; Harbuz et al., 2013). *KCNK9*, encoding the two-pore acid-sensitive K^+ channel, TASK3, is mutated in a rare syndromic form of ID, called Birk–Barel syndrome (Barel et al., 2008). The role of TASK3 in the brain is poorly understood, but the predominantly somato-dendritic expression of this channel (Marinc et al., 2014) suggests a role in dendritic function. In this case, the mutation resulted in a de novo inward current and an alteration in the sensitivity of the channel to a number of factors including Gαq-coupled muscarinic receptor activation. Mutations in genes (*KCNQ2, KCNQ3*, and *KCNT1*) encoding the K^+ channel subunits $K_v7.2$ and $K_v7.3$ have also been reported in more complex disorders involving both epilepsy and ID (Heron et al., 2012; Weckhuysen et al., 2012; Miceli et al., 2014). Both $K_v7.2$ and $K_v7.3$ are subunits underlying M-type current (for review see Judy and Zandi, 2013). Although mainly expressed at the somatic and axonal level (some dendritic expression has also been reported—reviewed in Szalpczynska et al., 2014), M-type channels not only control initiation of action potentials (APs) and neuronal excitability, but can also regulate excitatory postsynaptic potential (EPSP)–spike (E–S) coupling (Brown and Passmore, 2009; Shah et al., 2011). Their alterations could therefore also affect dendritic information processing. Finally, studies involving either genetic or pharmacological ablation of a number of ion channels involved in dendritic information processing support an important role for a number of these channels in cognitive function. Moreover, a recent study combining functional brain imaging with genetics suggests a strong association between voltage-gated cation channels and cognition (Heck et al., 2014).

Fetal alcohol syndrome (FAS)

Early (in utero) exposure to alcohol is known to have profound effects on the cognitive abilities of exposed individuals. These effects are caused in part by gross-scale circuit remodeling provoked by cell death; however, a cell-dependent mechanism may also partly explain the observed changes. Early postnatal exposure of mice to alcohol (modeling the effects of FAS in humans) leads to a reduced number and duration of dendritic spikes, consistent with a defect in dendritic electrogenesis in L5 neocortical pyramidal neurons (Granato et al., 2012). This effect is likely mediated through defects in the function of L-type Ca^{2+} channels, which have been shown to be important for dendritic spikes in these neurons (Almog and Korngreen, 2009).

Fragile X syndrome

In this sense FXS is perhaps the "prototypic" ID, being the most widely studied inherited ID disorder having a monogenic cause. It is also the most common inherited form of autism (Bassell and Warren, 2008). Symptoms include ADHD, anxiety and mood disorders, learning and intellectual disabilities, seizures, and autistic features. The syndrome is caused by the loss of expression of a protein called the fragile X mental retardation protein (FMRP) due to transcriptional silencing of the gene *FMR1,* which encodes FMRP. FMRP is an mRNA-binding protein that represses translation of the bound mRNA. The lack of FMRP can thus lead to enhanced translation of certain mRNAs. FMRP has multiple mRNA targets (Darnell et al., 2011), but it also can bind to other proteins and alter their function. A seminal paper by Huber et al. (2002) found an enhancement in the metabotropic glutamate receptor-mediated form of synaptic long-term depression in a mouse model of FXS in which *FMR1* was deleted. This and many subsequent studies led to the so-called mGluR theory for FXS (Bear et al., 2004), which suggested an enhancement of the mGluR signaling pathways in FXS. While very attractive, this view of FXS is probably too simplistic, and in fact several clinical trials of mGluR antagonists have failed to provide a statistically significant improvement over placebo in crossover clinical trials (reviewed in Scharf et al., 2015).

In recent years attention has focused on other FMRP-targeted mRNAs, including those associated with a number of voltage-gated ion channels that are heavily expressed in dendrites. Among the first voltage-gated ion channels identified as a target for FMRP were the L-type Ca^{2+} channel, a delayed-rectifier K^+ channel, $K_v3.1$, and Slack (sequence like a Ca^{2+} activated K^+) channel (Chen et al., 2003; Meredith et al., 2007; Brown et al., 2010; Strumbos et al., 2010). While $K_v3.1$ is a prominent channel in fast-spiking interneurons, Slack channels are heavily expressed in pyramidal neurons and dendrites in the hippocampus and parts of the cortex (Bhattacharjee and Kaczmarek, 2005). Interestingly, intracellular Na^+ (not Ca^{2+} as is the case for the many types of Ca^{2+}-dependent K^+ channels) activates Slack channels. Several recent studies have in fact explored the role of one type of Ca^{2+}-dependent K^+ channel, the BK channel, in FXS. Klyachko and colleagues found that FMRP binds directly to the β4 regulatory subunit of BK channels in a translation-independent manner to enhance the calcium sensitivity of the BK channels. The absence of FMRP therefore leads to a broadening of the AP and increases in presynaptic transmitter release (Deng et al., 2013). In a recent report Zhang et al. (2014) found a similar defect in L2/3 and L5 pyramidal neurons of the sensory cortex, both in vitro and in vivo. In addition, the authors described a dendritic hyperexcitability phenotype in L5 neurons due to BK (and HCN) channel dysfunction (Fig. 24.1). Several core features of this dendritic hyperexcitability and changes in AP firing were rescued with a BK channel opener (Fig. 24.1E), as was hypersensitivity to sensory (auditory) stimuli. These findings provide evidence for a link between an ion channel alteration and a core symptom of FXS (Zhang et al., 2014).

One of the first predominantly dendritic channels suggested to be abnormally expressed in FXS is the fast-inactivating K^+ channel $K_v4.2$ (Gross et al., 2011; Lee et al., 2011). This channel is known to be a prominent dendritic channel in a number of cell types including CA1 pyramidal neurons in the hippocampus (Hoffman et al., 1997; Johnston et al., 2000). The first two reports suggesting a $K_v4.2$ channelopathy in the mouse model of FXS, however, were somewhat contradictory. One suggested a reduction of dendritic $K_v4.2$ (Gross et al., 2011) and the other an increase (Lee et al., 2011). A recent third study used a more functional approach by making physiological recordings from hippocampal CA1 dendrites (Routh et al., 2013) and concluded that $K_v4.2$ channels were indeed downregulated in FXS, leading to hyperexcitability of the dendrites. The reasons for the discrepancies among the studies are not clear, but more recent experiments suggesting that channelopathies in FXS are specific to both cell types and brain regions may provide some clues.

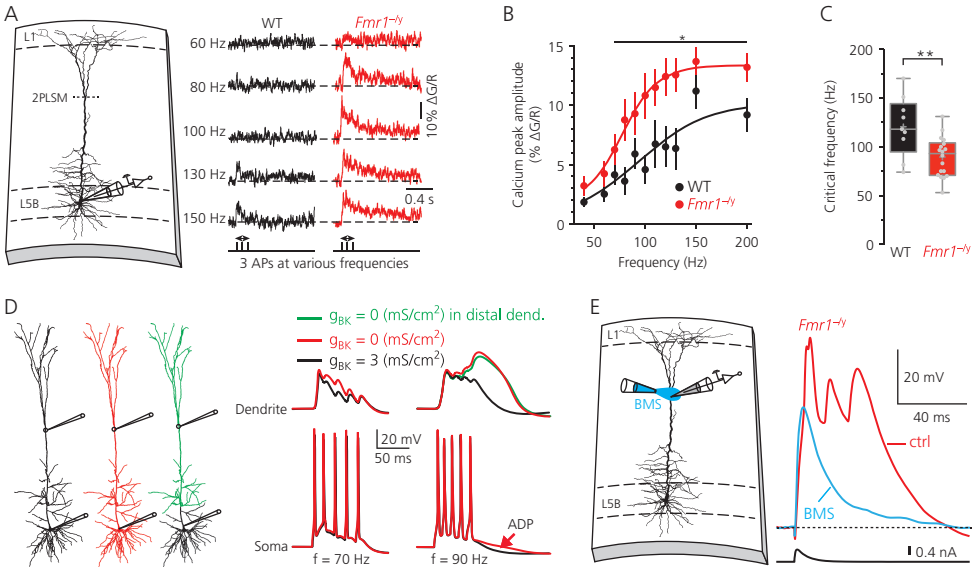

Fig. 24.1 Dysfunction of dendritic BK_{Ca} channels causes hyperexcitability of neocortical pyramidal neurons in a mouse model for fragile X syndrome. (A)–(C) Dendritic calcium measurements were performed near the major apical branch-points of L5B pyramidal neurons. (A) Dendritic Ca^{2+} traces accompanying trains of three backpropagating APs at various frequencies in a representative wild type (WT) and *Fmr1*$^{-/y}$ neuron. (B) Average Ca^{2+} peak amplitudes as a function of AP train frequency (*Fmr1*$^{-/y}$, $n = 18$; WT, $n = 9$; $P < 0.05$ for a range from 70 to 200 Hz). (C) Average critical frequency for the generation of dendritic Ca^{2+} spikes. (D) Computer simulation of the impact of BK_{Ca} channel reduction on dendritic excitability. Left: reconstruction of the morphology of a L5B pyramidal neuron used for the NEURON® simulations. Right: model responses at the major apical branch point (upper traces) and soma (lower traces) for AP trains evoked at the soma at a frequency below 70 Hz (left trace) and around the critical frequency (90 Hz; right traces). Red traces represent stimulation in a model without BK_{Ca} conductance, and the black traces stimulation in a model with a BK_{Ca} conductance of 3 mS/cm^2. Note that the generation of a dendritic spike was associated with an increased after-depolarization (ADP, red arrow) in the absence of a BK_{Ca} conductance. The green trace represents stimulation in a model with a BK_{Ca} conductance of 3 mS/cm^2 only in the soma and the proximal dendrites. This condition is similar to the one without BK_{Ca} conductance (red traces), indicating the role of more distal dendritic BK_{Ca} channels in the dendritic spike generation. (E) Dendritic whole-cell recordings were performed at the major branch point. Suppression of dendritic calcium spikes (evoked by current wave injections) following local puff application of the specific BK_{Ca} channel opener BMS-191,011 (100 μM) onto the dendrite of a *Fmr1*$^{-/y}$ neuron. Data are shown as the mean ± SEM $^{**}P < 0.01$, $^{*}P < 0.05$ (*Fmr1*$^{-/y}$ compared with WT). Statistical significance was calculated by repeated measure two-way ANOVA (B), or by an unpaired *t*-test.

As will be discussed more fully in the section on epilepsy, another prominent dendritic channel is the HCN channel, or so-called h-channel (Magee 1998, 1999), which in forebrain neurons is primarily encoded by HCN1 and HCN2 subunits. One of the first suggestions for a role of HCN1 channels in FXS came from a study by Brager et al. (2012) in which an upregulation of HCN1 channels was found to occur in the dendrites of hippocampal CA1 neurons. This was a surprising finding, because mGluR signaling has been shown to downregulate HCN channels in CA1 and other neurons. In fact, Zhang et al. (2014) and Kalmbach (in preparation) have shown downreguation of HCN channels in L5 neurons from both the sensory and prefrontal cortex. This leads to the interesting idea that FXS-related channelopathies, for the same ion channel, can have both neuron-type and brain-region specificity, and highlights the need to understand FXS and its treatment in a neuron-type/brain-region-specific manner.

Neuropsychiatric disorders

Neuropsychiatric disorders, for example schizophrenia, depression, and bipolar disorder, are complex pathologies, with etiologies that probably involve the convergence of multiple genetic and non-genetic factors (Sullivan et al., 2012). Several recent large-scale gene association studies have pointed to a role for polymorphisms in voltage-gated ion channels in the pathophysiology of these disorders (reviewed in Bhat et al., 2012; Berger and Bartsch, 2014). For example, polymorphisms within two genes encoding the L-type calcium channel subunit ($Ca_v1.2$) and the β_2 subunit of voltage-gated calcium channels have been linked with a cluster of psychiatric disorders including bipolar disorder, schizophrenia, and depression. Polymorphisms within the β_2 subunit were in addition associated with ADHD and ASD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). A functional cluster of voltage-gated cation channels has also been associated with working memory performance in individuals affected by schizophrenia.

Bipolar disorder has also been associated with mutations in the genes encoding $K_v7.2$ and $K_v7.3$, the major subunits responsible for the slow voltage-gated M-channel (for review see Judy and Zandi, 2013). As indicated above, although principally expressed in the soma and axons of neurons, M-channels not only control the initiation of APs and neuronal excitability but are also capable of regulating E–S coupling (Brown and Passmore, 2009; Shah et al., 2011). Thus any polymorphism/mutation that alters their function could conceivably play a role in dendritic information processing.

Lastly, BK channels might also be dysregulated in schizophrenia. Post-mortem analysis has demonstrated a reduction in BK channel mRNA in the prefrontal cortex of individuals affected by this pathology, compared with normal disease-free controls (Zhang et al., 2006). A reduction in the activity of BK channels has been associated with increased dendritic excitability (see the subsection Fragile X syndrome) thus suggesting a link between this finding and dendritic pathophysiology in schizophrenia (reviewed in Szlapczynska et al., 2014).

Neuropathic pain

While the pain neuroaxis consists of peripheral nociceptors, spinal cord, and supraspinal areas, forebrain structures are also receiving increased attention as possible sites for the central manifestations of chronic pain. In particular, the anterior cingulate cortex (ACC) appears to be consistently activated during nociception and chronic pain states (Wager et al., 2013). An interesting recent study used a sciatic nerve injury model in mice to test whether neuronal function in the ACC was altered and responsible for the development of neuropathic pain (Santello and Nevian,

2015). The results of this study were perhaps somewhat surprising, but not for the channelopathy theme of this chapter. The authors found that following neuropathic pain induced by nerve damage there was a specific decrease in dendritic HCN channel function in L5 pyramidal neurons in the ACC. The resulting decrease in I_h led to enhanced firing in response to synaptic input, or an increase in the overall excitability of these neurons. Because serotonergic inputs, and particularly 5-HT_7 receptors, are enriched in this region of the cortex, they further found that infusion of a 5-HT_7 receptor agonist into the ACC could reverse both the decrease in I_h as well as the pain-induced hypersensitivity to mechanical touch. They suggest that the chronic pain led to HCN channel plasticity in the dendrites of these neurons, a "pain memory," providing a potential new therapeutic target for neuropathic pain.

Neurodegenerative disorders

Neurodegenerative disorders are characterized by a progressive loss of the structure and function of neurons, and are typically associated with neuronal death. Neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). The most common neurodegenerative disorders, AD and PD, have both been linked with ion channel dysfunction, implicating changes in dendritic function in these disorders. In the following we will focus our discussion on PD and AD.

Parkinson's disease

PD is a common, debilitating, and progressive neurodegenerative condition, and is clinically characterized by motor symptoms including tremor, rigidity, postural instability, and bradykinesia (reviewed in Rivlin-Etzion et al., 2006; De Long and Wichmann, 2007; Hammond et al., 2007). In addition to these motor symptoms, PD encompasses non-motor symptoms such as cognitive and neuropsychiatric defects (Poewe and Luginger, 1999; Politis and Niccolini, 2015). The motor symptoms of PD are attributable to the degeneration of dopamine neurons of the substantia nigra pars compacta (SNc). In PD the amount of dopamine released in brain regions responsible for motor control (e.g., the striatum and globus pallidus) declines, leading to a progressive loss of movement. Other, non-dopaminergic systems such as the serotonergic (reviewed in Politis and Niccolini, 2015) and cholinergic (Hirsch et al., 1987; Rinne et al., 2008) system have also been implicated in PD.

In PD, dopaminergic neurons of the SNc display a decrease in dendritic length, a loss of dendritic spines, and several types of dendritic varicosities (Patt et al., 1991). A similar loss of dendritic spines has also been found in the medium spiny neurons of the striatum (Villalba and Smith, 2013). Several studies have provided evidence for a contribution of ion channels to the degeneration of SNc dopamine neurons and PD pathology. Among those ion channels are L-type Ca^{2+} channels ($Ca_v1.2$ and $Ca_v1.3$), T-type Ca^{2+} channels, metabolically regulated, ATP-sensitive K^+ channels, and Ca^{2+}-sensitive and voltage-gated A-type K^+ channels (reviewed in Dragicevic et al., 2015). These and other ion channels modulate dendritic function and firing properties, and therefore dopamine release by SNc dopamine neurons (reviewed in Dragicevic et al., 2015; see Dufour et al., 2014, for a description of the somato-dendritic ion channel landscape of these neurons). Surmeier and colleagues found that during pacemaking L-type Ca^{2+} channels contribute to the generation of dendritic Ca^{2+} oscillations and that the impact of these channels increases with distance from the soma (Guzman et al., 2010; Dryanovski et al., 2013). The dendritic Ca^{2+} waves, in turn, induce waves of mitochondrial oxidant stress in SNc dopamine neurons and defensive responses (Mosharov et al., 2009; Guzman et al., 2010; Surmeier et al., 2011a). Under normal conditions

these defensive mechanisms protect SNc neurons, but in vulnerable neurons the Ca^{2+} buffering capacity is insufficient for dealing with the oscillatory Ca^{2+} load (reviewed in Dragicevic et al., 2015). Pharmacological inhibition of L-type Ca^{2+} channel function in SNc dopamine neurons promises to be a suitable neuroprotective strategy (Surmeier et al., 2010; Parkinson Study, 2013).

Although the principal target of SNc dopamine neurons is the striatum, the most prominent pathophysiology in animal models of late-stage PD and in human patients occurs in the globus pallidus (GPe). In late-stage PD the firing patterns of GPe neurons change, resulting in suppression of their autonomous activity and the emergence of rhythmic bursting activity within the GPe–subthalamic nucleus network (reviewed in Rivlin-Etzion et al., 2006; DeLong and Wichmann, 2007; Hammond et al., 2007). HCN channels are crucial for the pacemaker activity of GPe neurons (Chan et al., 2004), and a recent study implicated a downregulation of all four pore-forming HCN channel subunits (HCN1–4) as well as of the HCN trafficking protein tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b) in the loss of this feature during PD (Chan et al., 2011). Autonomous pacemaking of GPe neurons was restored by upregulating HCN2 channel expression via viral expression (the channel subunit most affected in PD). This change in firing patterns, however, did not significantly improve motor deficits, suggesting that HCN channel downregulation is a homeostatic adaptation of the network pathology rather than a cause. Such changes in ion channel expression can act as a homeostatic mechanism (Turrigiano and Nelson, 2004; Frick and Johnston, 2005). Subsequently, the authors provided evidence that calcium influx through dendritic L-type Ca^{2+} channels during burst firing activity caused HCN channel downregulation (Chan et al., 2011).

Dopamine also has immediate influences on the intrinsic excitability of target neurons by modulating their ion channels, suggesting that a decline in dopamine levels during PD has additional consequences for neuronal/dendritic function. Most of the effects of dopamine on intrinsic excitability implicate protein kinase A (PKA)-dependent modulation of voltage-gated Ca^{2+}, Na^{+}, and K^{+} channels (reviewed in Surmeier et al., 2011b; Tritsch and Sabatini, 2012). The outcome will depend on which dopamine receptors are present in these neurons, namely D_1-like dopamine receptors (D_1 and D_5) or D_2-like dopamine receptors (D_2, D_3, and D_4) (Svenningsson et al., 2004; Hernandez-Lopez et al., 2000). For example, spiny projection neurons of the direct pathway express primarily D_1 receptors that increase their intrinsic excitability, while those of the indirect pathway express primarily D_2 receptors that decrease their intrinsic excitability. These changes have direct consequences for synaptic plasticity (reviewed in Surmeier et al., 2011).

Alzheimer's disease

AD is a progressive and fatal disease, and the most common neurodegenerative disorder. As such, AD accounts for the majority of patients experiencing memory loss. The accumulation of amyloid-β peptide (Aβ), leading to the formation of so-called amyloid plaques in the brain, is believed to be the core pathophysiological mechanism of AD (Hardy and Selkoe, 2002; Ross and Poirier, 2004). Several studies have demonstrated abnormal spine and dendritic morphology, as well as aberrant dendritic signaling, in AD. The role of dendrites in AD has been highlighted in recent reviews (Nestor and Hoffman, 2012; Cochran et al., 2014). The remainder of this section on AD is devoted to a discussion of alterations in dendritic excitability due to ion channel dysfunction.

Aβ causes aberrant dendritic signaling by selective binding to a variety of receptors as well as ion channels within the dendrites (reviewed in Cochran et al., 2014). In addition to this direct modulation, some of the putative Aβ receptors are linked to intracellular signaling cascades such

as mitogen-activated protein kinase (MAPK) that can alter ion channel function/expression. In the following we will focus on the direct consequences of the binding of Aβ to dendritic ion channels.

Abnormal levels of Aβ cause an imbalance of excitation to inhibition (Palop and Mucke, 2010). Dysfunction of dendritic ion channels may contribute to this imbalance, in particular via the effects of Aβ on $Ca^{2+,}$ K^+, and Na^+ channels that regulate dendritic excitability. Calcium dysregulation is a critical component of dysfunction in AD. In neuronal cultures, Aβ induces MAPK phosphorylation of Ca_v1 channels and increased calcium influx through these channels, thereby causing neurotoxicity. $Ca_v1.2$ channels are L-type Ca^{2+} channels that are located both extrasynaptically and in dendritic spines. In an AD mouse model, $Ca_v1.2$ is enriched in dendrites (Willis et al., 2010), and AD brain tissue shows increased Ca_v1 expression in the hippocampus (Coon et al., 1999).

More recently, a role for $Na_v1.1$ channels was also found in the pathophysiology of AD (Verret et al., 2012). In this study, the authors showed a decrease in $Na_v1.1$ subunit expression in parvalbumin-positive interneurons of the parietal cortex in both AD patients and a mouse model of AD. In the mouse model of AD, this decrease contributed to the reduced gamma oscillations and increased network synchrony seen in the mouse model (Verret et al., 2012). Together, their results suggest that a decreased expression of Na^+ channels in the cortex could contribute to the epileptiform activity and seizures observed in AD patients (Verret et al., 2012; Vossel et al., 2013). Although $Na_v1.1$ channels are predominantly expressed in the axon initial segment, thereby controlling the initiation and propagation of APs (Duflocoq et al., 2008), they are also expressed in the somato-dendritic compartment of neocortical and hippocampal pyramidal neurons (Gong et al., 1999), where changes in their expression would alter dendritic excitability.

Another Aβ-sensitive ion channel that strongly regulates dendritic excitability is the A-type K^+ channel (see Nestor and Hoffman, 2012). In hippocampal CA1 pyramidal neurons, these channels are highly expressed in oblique and distal apical dendrites, where they strongly regulate the efficacy of dendritic action potential backpropagation, synaptic summation, and the induction of synaptic and non-synaptic forms of plasticity (Hoffman et al., 1997; Frick et al., 2003, 2004; Chen et al., 2006; Kim et al., 2007; Losonczy et al., 2008; Makara et al., 2009). In cultured and acutely dissociated hippocampal neurons, as well as in acutely dissociated neurons from the diagonal band of Broca nucleus in the basal forebrain, Aβ blocks A-type K^+ channels (Good and Murphy, 1996; Xu et al., 1998; Jhamandas et al., 2001; Zhang and Yang, 2006). Other studies on cultured cerebellar neurons found either an increase in A-type K^+ currents or no effect depending on the aggregation state (Ramsden et al., 2001; Plant et al., 2006). A-type K^+ channels in cultured cortical neurons were either reduced or unaffected (Ramsden et al., 2001; Ye et al., 2003). From these studies, it has become clear that the brain region, culture condition, application time, and the aggregation state and peptide length of Aβ influence the modulation of K^+ channels.

The first direct evidence for an effect of Aβ on dendritic excitability was provided by a study by Chen (2005). Aβ treatment decreased A-type K^+ currents in dendritic membrane patches from CA1 pyramidal neurons in acute hippocampal slices. Dendritic currents were more significantly affected compared with somatic ones. The reduction in dendritic A-type K^+ currents caused an increase in the amplitude of backpropagating APs, consistent with their known role in regulating this phenomenon. A computational study found that the oblique dendrites would be most profoundly affected by changes in A-type K^+ currents (Morse et al., 2010), in agreement with experimental evidence (Frick et al., 2003). Moreover, a decrease in A-type K^+ current could contribute to the hyperexcitability phenotype found in hippocampal neurons in a mouse model of AD (Busche et al., 2012).

Epilepsy

Ion channelopathy in epilepsy: humans and animal models

Epilepsy, the disease state of spontaneously recurring seizures, is one of the most prevalent neurological conditions, affecting nearly 1% of the population. That ion channel dysfunction lies at the root of epilepsy has for decades seemed a self-evident truth. Ion channels, both voltage- and ligand-gated, mediate the excitable behavior of neurons, and since seizures result from neuronal hyperexcitability, altered biophysical properties or expression of ion channels must form the final common pathway of pathological hyperexcitability. This idea has been proven in human epilepsy by the discovery of a number of ion channel mutations underlying Mendelian genetic epilepsy, beginning with the finding that a mutation in nicotinic acetylcholine receptors causes autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (Steinlein et al., 1995). Since that first demonstration in 1995, a number of human genetic epilepsy syndromes have been conclusively linked to single gene mutations (Mantegazza et al., 2010). Notably, most of these genes code for voltage-gated or ligand-gated ion channel subunits or presumptive accessory subunits. The importance of these findings cannot be overstated: they prove that defects in the expression and function of individual ion channel subtypes can produce human genetic epilepsy syndromes.

However, most human epilepsy is of undetermined origin, and not clearly inherited. Are dysfunctional ion channels involved in the pathophysiology of these "idiopathic" epilepsies? A large-scale candidate gene sequencing study suggests that ion channel mutation is not responsible. Sequencing of 237 different ion channel genes found no increase in single nucleotide polymorphisms (SNPs) (i.e., putative mutations) when the genomes of people with sporadic epilepsy were compared with normal controls (Klassen et al., 2011). This still leaves the possibility that modification of the expression of those ion channel genes by any of a number of other mechanisms—transcriptional, translational, or post-translational—may affect neuronal excitability and produce epilepsy. Such ion channel modifications may be the final result of signaling cascades set into motion by any of the acquired insults to the brain that have a high probability of producing epilepsy, such as head injury, brain tumors, or cerebral hemorrhage. This "acquired channelopathy" hypothesis has attracted increasing amounts of experimental support in recent years. And interestingly, some of the ion channels most implicated are highly expressed in the dendrites of pyramidal neurons. In this section, we will discuss some of the evidence for dendritic channelopathy in epilepsy, in both animal models and humans.

One difficulty in proving that acquired channelopathy plays a causal role in human epilepsy is the relative inaccessibility of human brain tissue from patients with epilepsy. Unlike the case with genetic epilepsy where a tube of blood is all that is needed to survey a patient's genome, patients with acquired epilepsy do not give up brain tissue for analysis, with the exception of the most severely affected who present for brain surgery to resect the epileptogenic focus. Another equally significant problem is the lack of control tissue with which to make comparisons. For the most part, our understanding of acquired channelopathies has relied on animal modeling. Animal models provide the benefits of being able to study controls, as well as the ability to follow the time course of changes in ion channel expression after a neural insult, before spontaneous seizures have arisen.

The most widely used animal models of epilepsy are the post-status epilepticus (SE) models involving induction of SE by pilocarpine or kainic acid. With these protocols, pilocarpine or kainate are injected to produce a period of SE lasting about an hour, followed by termination with sedative drugs. This period of SE appears to produce foci of excitotoxic damage, particularly in the temporal lobe. The result is a very obvious epileptic phenotype in rodents, with spontaneously recurring convulsive seizures that originate in hippocampal and peri-hippocampal structures (Toyoda

et al., 2013). Because seizure onset is from the temporal lobe, the post-SE models appear to best replicate temporal lobe epilepsy (TLE), which is the most common epileptic syndrome in adult humans. And as in human TLE, the post-SE models show a "latent period" between the insult and the development of spontaneous seizures, as well as hippocampal pathology very similar to that seen in humans (known as "mesial temporal sclerosis"). A significant drawback to these models is the fact that they do not replicate a naturalistic insult: humans are rarely exposed to chemical convulsants. However, it has been argued that post-SE models are relevant because some human cases of adult TLE are associated with a history of febrile SE as a child. Additional models of epilepsy exist that attempt to reproduce human brain insults such as traumatic injury, stroke, or infection but vary in the robustness of their epileptic phenotypes (White, 2002).

There are multiple ways in which acquired alteration of ion channel function might contribute to epileptogenesis, either as a fundamental cause of hyperexcitability or as a mediator of the process in which spontaneous seizures progressively worsen the course of epilepsy (Ben-Ari et al., 2008). It is also possible that some ion channel alterations act to retard the development of epilepsy. When interpreting studies of changes in ion channel properties in epilepsy models, it is important to consider whether the changes seen reflect a seizure-dependent process or are set into motion by the initial insult and precede the onset of seizures. A further question is whether the changes seen are pro-convulsive or homeostatic: do they demonstrably increase the excitability of neurons, or do they diminish intrinsic excitability in response to recurrent seizures? With these thoughts in mind, we can consider recent evidence for both inherited and acquired ion channel changes in animal models of epilepsy, focusing on those species that are highly represented in the dendrites of pyramidal neurons found in the cortex and hippocampus. Whenever possible, we will seek correlation with findings in human epilepsy.

Specific dendritic ion channelopathies in epilepsy: HCN channels

HCN channels were originally identified in the sinoatrial node as a key regulator of heart rate, but have since been found widely in the brain, with the HCN1 subtype the predominant isoform in the neocortex and hippocampus, while the HCN2 subtype, although also found in the neocortex and hippocampus, is most highly expressed in subcortical regions such as the thalamus. The biophysical properties of these channels, and their contribution to neuronal excitability, are described elsewhere in this book. In brief, HCN channels are expressed predominantly in the dendrites of pyramidal neurons, including those of the CA1 hippocampus, entorhinal cortex, and neocortex. They principally act to diminish the excitability of pyramidal neurons by inhibiting the impact of excitatory postsynaptic potentials in distal dendrites. Thus, it would be predicted that epilepsy would be associated with loss of expression or function of HCN channels. Of the ion channels with predominantly dendritic expression, changes in HCN channels provide some of the most compelling evidence linking altered expression with epilepsy, particularly in animal models. In humans, the evidence linking HCN channelopathy with epilepsy is growing, but somewhat conflicting.

A recent study associated HCN1 channel mutations with a syndrome of catastrophic early childhood epilepsy characterized by unremitting seizures, intellectual disability, and autism (Nava et al., 2014). Six *HCN1* missense mutations were identified that were de novo mutations. When recombinant HCN1 channels with each of the mutations were exogenously expressed, diverse functional effects were seen: three of the mutations abolished I_h, the current mediated by HCN channels, whereas in the other three mutants I_h was upregulated via a depolarizing shift in its voltage-dependent activation. While interpretation of the functional consequences of these mutations must be cautious (since they were not studied in human brain tissue), this study appears to clearly link HCN1 channels and epilepsy. Another report linked a recessive mutation in the human

HCN2 gene with a phenotype of generalized epilepsy (DiFrancesco et al., 2011). Together, these results suggest that while HCN channels are not a well-recognized cause of Mendelian epilepsy, there are links between HCN channel dysfunction and genetic epilepsy in humans.

In acquired epilepsy in humans there is suggestive but inconclusive evidence that HCN channel expression is altered. HCN channel mRNA expression from temporal lobe resections overall showed no significant change in comparison with autopsy controls; however, a subgroup of patients with the greatest degree of mesial temporal sclerosis had an increase in HCN1 expression in the dentate gyrus (DG) (Bender et al., 2003). This finding was surprising, since DG neurons normally demonstrate very little I_h; thus this could be interpreted as "compensatory" upregulation of HCN1 expression in the most severely affected patients. Other investigators found that the magnitude of I_h measured in neocortical neurons from brain tissue acutely removed during epilepsy surgery inversely depended on the pre-surgical baseline frequency of seizures, suggesting that more severe epilepsy was associated with a loss of neocortical HCN channel function (Wierschke et al., 2010). As mentioned above, the lack of control comparisons makes these findings difficult to interpret. Also, whether the changes in HCN channel expression and the magnitude of I_h are a cause or a consequence of epilepsy is impossible to establish in these studies.

The above human studies provide suggestive evidence for genetic and acquired HCN channelopathies in epilepsy in humans. Studies in animal models with genetic deletions of HCN channels provide a more compelling case that this ion channel may be relevant to epilepsy. Constitutive knock-out of the mouse *hcn2* gene produces a phenotype of generalized epilepsy, consisting of spontaneous absence seizures and generalized 5-Hz spike-wave EEG discharges, most likely resulting from the loss of thalamic HCN2 expression (Ludwig et al., 2003).

Deletion of the *hcn1* gene in rodents does not produce epilepsy, as shown in two studies (Huang et al., 2009; Santoro et al., 2010). Neither of these studies detected spontaneous seizures in knock-out animals. However, both studies demonstrated that *hcn1* deletion increased the severity of SE acutely induced by kainic acid. In addition, the latency period from SE to the occurrence of the first spontaneous seizure was shortened to one-sixth of that in wild-type animals, thus demonstrating an effect of HCN1 channels on epileptogenesis after a brain insult. This study went one step further to examine pyramidal neuron excitability in *hcn1* knock-out mice. As expected, pyramidal neurons lacking the HCN1 subunit demonstrated both increased intrinsic excitability and prolonged excitatory responses to synaptic stimulation. This effect on synaptic transmission may reflect the loss of presynaptic HCN1 channels that normally constrain excitatory transmission (Huang et al., 2011). Thus, genetic deletion of HCN channels confirms that they exert an inhibitory and even anticonvulsant role on cortical and hippocampal excitability under control conditions. However, why HCN1 deletion produces cortical and hippocampal hyperexcitability while not producing epilepsy is not easily explained. One possible reason is that constitutive deletion of HCN1 channels leads to compensatory upregulation of a tonic $GABA_A$ receptor-mediated current that partially suppresses hyperexcitability (Chen et al., 2010).

HCN1 channel expression is also altered during epileptogenesis induced in animals by pilocarpine and KA or following hyperthermia-induced SE. One of the first studies to make this association found an increase in I_h at the soma of CA1 hippocampal pyramidal neurons after hyperthermia-provoked seizures (Chen et al., 2001). Subsequent studies that measured I_h in the dendrites, where its expression is greatest, found an acute loss of dendritic expression of HCN channels within the first week post-SE (Shah et al., 2004). This loss of expression was maintained in chronic epilepsy, and was associated with a hyperpolarizing shift in voltage-dependent gating that further downregulated I_h (Jung et al., 2007). Since HCN channels are activated by hyperpolarization, a hyperpolarizing shift in activation reduces the amount of I_h present at resting potential.

Interestingly, when recurrent seizures post-SE were blocked by administration of phenobarbital, the altered HCN channel gating reverted to normal while the loss of HCN channel expression persisted. This suggested that there are separate mechanisms of HCN channel downregulation in epilepsy, some clearly dependent on ongoing seizures and some independent of seizure activity. The altered gating of dendritic HCN channels nonetheless produces pyramidal neuron hyperexcitability. This gating change was dependent in part on a loss of p38 mitogen-activated protein kinase (p38 MAPK) activity in chronically epileptic animals, suggesting a role for phosphorylation-dependent mechanisms in maintaining the HCN channelopathy (Jung et al., 2010). Interestingly, lamotrigine, a commonly-used anti-epileptic drug, upregulates the gating of HCN channels in pyramidal neuron dendrites, an action that may contribute to its anti-epileptic action (Poolos et al., 2002).

The mechanisms underlying the loss of expression of HCN1 channels in epilepsy models have been studied in great detail, and the insights derived from these investigations may prove important for understanding how the expression of other ion channels is altered during the development of epilepsy following a brain insult. Dendritic HCN1 channelopathy in post-SE models appears to depend on several interwoven processes. Within the first hour post-SE, about half of the HCN1 channels undergo internalization from the dendritic plasma membrane, and are degraded within the first day post-SE (Jung et al., 2011). This effectively reduces the number of functional dendritic ion channels. Similar alterations in ion channel trafficking to the surface membrane post-SE have been described for A-type K^+ channels and $GABA_A$ receptor subunits, and thus may be a common theme in acquired channelopathy (Goodkin et al., 2008; Lugo et al., 2008; Terunuma et al., 2008). These latter examples are phosphorylation dependent; a similar mechanism may underlie altered trafficking of HCN1 channels in epilepsy, as it has been recently shown that surface expression of HCN1 channels under normal conditions is modulated by the activity of protein kinase C (Williams et al., 2015). Additional possible effectors of defective HCN1 channel trafficking include two accessory scaffolding proteins, Trip8b (Lewis et al., 2011; Piskorowski et al., 2011) and filamin A (Gravante et al., 2004). Trip8b expression is important for the establishment of the HCN1 channel gradient in CA1 pyramidal neuron dendrites, while filamin A appears to increase surface membrane expression of HCN1 channels, at least in heterologous expression systems.

Within the first days post-SE, and persisting into the chronic epilepsy phase, dendritic HCN1 expression remains diminished. This appears to be a result of reduced production of HCN1 mRNA (Brewster et al., 2002). This decrease in transcription appears to depend on the upregulation of a master transcriptional regulator, neuron restrictive silencing factor (NRSF) (McClelland et al., 2011). These results suggest that the development of HCN1 channelopathy is the result of several different mechanisms, each with a distinct temporal evolution. Whether these mechanisms proceed in a serial fashion, each dependent on signaling in the preceding mechanism, or exist as parallel processes, is as yet unknown. The identification of multiple signaling processes underlying dendritic HCN channelopathy points to the possibility of therapeutic interventions that might prevent or reverse altered HCN channel expression in epilepsy.

K^+ channels

In his classic textbook (Hille, 2001) Bertil Hille commented that K^+ channels were like the "stops on an organ," able to fine-tune neuronal excitability by their diverse biophysical properties. Perhaps not surprisingly, then, K^+ channel dysfunction has been demonstrated to underlie certain genetic epilepsy syndromes. The most well-understood is the Mendelian syndrome benign familial neonatal convulsions (or seizures, BFNC/BFNS), which results from mutation of the genes *KCNQ2* and

KCNQ3 (Biervert et al., 1998). More recently, cases of catastrophic early childhood epilepsy have also been associated with *KCNQ2* mutations (Weckhuysen et al., 2012). Other human genetic syndromes with an epileptic phenotype resulting from K^+ channel gene mutations include: episodic ataxia and epilepsy, due to *KCNA1* mutations that produce altered defective $K_v1.1$ channels; developmental delay, epilepsy, and neonatal diabetes (DEND), due to mutation in the inward-rectifier K^+ channel encoded by the gene *KCNJ11* (Gloyn et al., 2006); and epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST), due to mutation of another inward rectifier, *KCNJ10* (Reichold et al., 2010). In humans, there is a single report of a gene mutation leading to loss of functional $K_v4.2$ expression in an individual with epilepsy, a nonsense mutation in the *KCND2* gene leading to truncation of the $K_v4.2$ protein (Singh et al., 2006).

Of all the human epilepsy-associated K^+ channelopathies, only $K_v4.2$ has a clear association with dendritic physiology. KCNQ2 and KCNQ3 channels are localized primarily to axo-somatic compartments (Shah et al., 2008), and it is unclear whether the inward rectifiers implicated in human genetic epilepsy have a prominent dendritic localization in pyramidal neurons as they do in rodents (Chen and Johnston 2005). However, numerous studies in animal models of acquired epilepsy have identified downregulation of $K_v4.2$ and associated neuronal hyperexcitability. Interestingly, like HCN1, genetic deletion of this ion channel produces neuronal hyperexcitability but not epilepsy (Chen et al., 2006; Barnwell et al., 2009).

Like HCN1 channels, $K_v4.2$ channels mediating the A-type transient K^+ current (I_A) are also expressed at a higher density in distal dendrites of hippocampal pyramidal neurons, albeit with a somewhat less extreme gradient (about a seven-fold higher density in the apical dendrites than in the soma; Hoffman et al., 1997; Chen and Johnston 2004). The high dendritic density of rapidly activating $K_v4.2$ channels reduces the amplitude of EPSPs, activity-evoked intracellular calcium transients, and backpropagating dendritic APs. The discovery of its role in experimental epilepsy marked the first determination of a dendritic channelopathy (Bernard et al., 2004). This work found that $K_v4.2$ expression in chronically epileptic rats post-SE was diminished by about a third, as quantified by both protein and mRNA expression. The electrophysiological consequence of the loss of I_A was increased AP backpropagation in the dendrites, potentially allowing increased opening of other voltage-gated channels such as Ca^{2+} channels. An interesting additional finding was that the remaining $K_v4.2$ channels were more phosphorylated at a site recognized by the extracellular stimulus-related kinase (ERK), thus diminishing their activity (Hoffman and Johnston 1998; Yuan et al., 2002). $K_v4.2$ dysfunction seen in chronic epilepsy recapitulates the theme shown for HCN1 channels: multiple mechanisms of channelopathy that result in a loss of channel number, as well as functional downregulation of the remaining channels. Indeed, subsequent studies have shown that, like HCN1 channels, I_A is acutely downregulated in the first several hours post-SE due to internalization from the surface membrane (Lugo et al., 2008). This appears to be a phosphorylation-dependent mechanism, involving hyperactivity of the ERK pathway. How the acute loss of $K_v4.2$ expression in the first hour post-SE ultimately develops into a persistent state of downregulated $K_v4.2$ protein and mRNA expression during chronic epilepsy is thus far unknown.

Ca^{2+} channels

Ca^{2+} channels hold several associations with genetic epilepsy. Mutations in the *CACNA1* gene producing the $Ca_v2.1$ channel yield the Mendelian syndrome of episodic ataxia, familial hemiplegic migraine, and epilepsy. Several polymorphisms in the human *CACNA1H* gene underlying $Ca_v3.2$ channels have been described in patients with epilepsy (Heron et al., 2004). This latter channel

mediates the low-voltage-activated transient calcium current I_T. Numerous lines of experimental evidence implicate I_T in epilepsy and as a target of anti-epileptic drugs.

Transient T-type Ca^{2+} channels, along with high-voltage-activated R-type channels, are enriched in the dendrites of pyramidal neurons compared with their somatic densities (Magee and Johnston, 1995, 1997). T-type Ca^{2+} channels have a long association with experimental epilepsy, particularly due to their ability to promote neuronal burst firing by producing a depolarizing current that activates at voltages subthreshold to AP firing. Indeed, pharmacological blockers of I_T such as ethosuximide potently inhibit generalized absence seizures (Tringham et al., 2012). Dendritic T-type Ca^{2+} channels may also be relevant to TLE. CA1 pyramidal neurons develop bursting behavior post-SE in conjunction with an increase in dendritic I_T (Su et al., 2002; Yaari et al., 2007). This increase in I_T appears to be mediated solely by $Ca_v3.2$, and begins before the onset of spontaneous seizures, demonstrating that it is not a consequence of the seizures themselves (Becker et al., 2008). $Ca_v3.2$ upregulation appears to depend on a transcriptional mechanism. Interestingly, mice with genetic deletion of $Ca_v3.2$ channels become epileptic just as wild-type mice do post-induction with pilocarpine, but have a significantly reduced seizure frequency. This suggests that inhibition of Cav3.2 channels may exert an antiepileptic action. A similar result was seen in which transient pharmacological inhibition of $Ca_v3.2$ channels post-SE produced a long-lasting anti-epileptic effect (Doeser et al., 2015). Despite these intriguing studies linking T-type channels, particularly the $Ca_v3.2$ isoform, to seizure generation, no studies to date have looked in detail at the density or voltage-dependent properties of dendritic T-type channels to determine how these are altered in epilepsy.

Other ion channels

Na^+ channels have become an intense focus of channelopathy research owing to their involvement in two genetic epilepsy syndromes, generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). They would seem prime suspects in any investigation of the causes of acquired epilepsy. However, even in their associated genetic syndromes, the nature of Na^+ channel dysfunction remains unclear: initial evidence from heterologous expression systems suggested that mutations in $Na_v1.1$ causing GEFS+ produced a toxic gain of function (an incompletely inactivating Na^+ current, I_{Na}), yet neurons from transgenic mice containing $Na_v1.1$ mutations appear to show a loss of I_{Na} only in interneurons, the principal neuron I_{Na} being unchanged (Martin et al., 2010). Likewise, hippocampal pyramidal neurons from mice with a truncated $Na_v1.1$, mimicking mutations seen in SMEI, show no significant alteration in I_{Na}, while hippocampal interneurons have a substantial loss of I_{Na} and decreased repetitive firing in response to stimulation (Yu et al., 2006). Thus there does not appear to be a pathological alteration of dendritic Na^+ channels in hippocampal pyramidal neurons in these relatively more common genetic epilepsies. In models of acquired epilepsy, there is little specific evidence for altered biophysical properties of Na^+ channels, with AP threshold at the soma appearing unchanged in chronic epilepsy, although dendritic Na^+ channels were not specifically examined (Sanabria et al., 2001).

Likewise, ligand-gated GABAergic channels localized to pyramidal neuron dendrites have not been specifically implicated in epilepsy. While there is good evidence that GABAergic afferents from oriens lacunosum-moleculare interneurons to pyramidal neuron dendrites are diminished in chronic epilepsy (Cossart et al., 2001), there is so far no evidence to suggest that dendritic $GABA_A$ receptors themselves are altered in experimental or human epilepsy. However, given the studies that have shown selective up- and downregulation of $GABA_A$ receptor subunits following the induction of epilepsy in experimental models (reviewed in Houser et al., 2012), it is possible

that significant rearrangements of pyramidal neuron dendritic $GABA_A$ receptor subunits may occur during epileptogenesis.

Summary

The studies described here focus on one aspect of dendritic physiology implicated in epilepsy. Since dendrites comprise the majority of the surface membrane area of pyramidal neurons, it is likely that the majority of the cell's ion channel expression also occurs in dendrites. Perhaps it is no surprise then that significant alterations in dendritic ion channel expression and function occur during the development of epilepsy. Other aspects of dendritic biology, such as derangements to cytoskeletal integrity, may also contribute to neuronal hyperexcitability (Zeng et al., 2007; Casanova et al., 2012). As the signaling mechanisms underlying dendritic channelopathy become better understood, it is possible that novel treatments will emerge for reversing or preventing this common neurological disease.

Conclusions

As outlined in the early sections of this chapter, it is difficult to assess the functional significance of the changes in dendritic structure that are associated with certain disease states. Such changes could represent the primary mechanisms of the disease or merely be secondary to the loss of synaptic inputs or other brain pathology. This chapter has instead focused on the emerging field of ion channelopathies, and specifically, where known, on defects in ion channels known to be expressed in dendrites. Dendrites are highly plastic structures. Homeostatic changes in the functional properties of dendrites can occur (Turrigiano and Nelson, 2004; Frick and Johnston, 2005; Magee and Johnston, 2005) that might partially compensate for disease-related alterations in ion channels. It is critical to begin to study the physiology of dendrites directly, in both normal and animal models of disease, using dendritic recordings and imaging. As discussed above, this has been fruitful for epilepsy, FXS, and neuropathic pain, and we should expect significant advances in this area in the future for many of the other important and behaviorally relevant neurological and psychiatric disorders.

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