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Aberrant Dendritic Excitability: A Common Pathophysiology in CNS Disorders Affecting Memory?

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Abstract Discovering the etiology of pathophysiologies and aberrant behavior in many central nervous system (CNS) disorders has proven elusive because susceptibility to these diseases can be a product of multiple factors such as genetics, epigenetics, and environment. Advances in molecular biology and wide-scale genomics have shown that a large heterogeneity of genetic mutations are potentially responsible for the neuronal pathologies and dysfunctional behaviors seen in CNS disorders. Despite this seemingly complex array of genetic and physiological factors, many disorders of the CNS converge on common dysfunctions in memory. In this review, we propose that mechanisms underlying the development of many CNS disorders may share an underlying cause involving abnormal dendritic integration of synaptic signals. Through understanding the relationship between molecular genetics and dendritic computation, future research may uncover important links between neuronal physiology at the cellular level and higher-order circuit and network abnormalities observed in CNS disorders, and their subsequent affect on memory.

Keywords Dendritic excitability · Autism · Fragile-X · Alzheimer's disease · A-type K^+ channel · Hippocampus

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Introduction

Despite modern technological advances such as genome-wide association scans, the molecular mechanisms underlying sporadic cases of the most common and devastating central nervous system (CNS) disorders remain unknown, likely because multiple inherited and environmental factors combine to determine disease susceptibility. Disorders of the CNS display a broad array of behavioral symptoms but some, such as memory impairments resulting from changes in network excitability, are shared across disorders. While CNS disorders may have diverse molecular origins, the memory impairments common to these diseases represent impaired function at the synaptic, cellular, and network levels. Can some insight into the circuit mechanisms underlying CNS disorders be gained by focusing on aspects of synaptic and dendritic excitability?

In this review, we propose that memory conditions observed in CNS disorders of diverse etiology share the common pathophysiology of aberrant dendritic integration of synaptic signals. While much current research has focused on the synaptic basis of disease, we focus our discussion on how the integration of signals in dendrites may be commonly effected in CNS disorders. We propose that it is these abnormalities in dendritic function that may be responsible for dysfunction at the circuit level in CNS disorders affecting memory. Specifically, we argue that dendritic integration of synaptic signals, which serves as a link between synaptic molecular pathways and higher-order circuit functions, either through direct disease mechanisms acting on pathways affecting dendritic excitability, or through morphological changes, are potential sources of memory abnormalities in disorders of the CNS.

While synaptic dysfunction is an attractive and actively studied area of research into the molecular mechanisms behind CNS disorders, dendritic excitability and synaptic

integration have garnered relatively little attention. Dendrites are wide-ranging and complicated processes generally compromising the vast majority of the neuronal membrane. They receive most synaptic signals, which are then processed and transmitted to the cell body and axon initial segment, where action potentials (APs) are initiated. The receiving, integrating, and transforming of excitatory and inhibitory synaptic signals is a dynamic and active process. This process is driven in part by activity-dependent modulation of ion channel properties and expression, contributing to normal functioning synaptic integration [1].

The cellular mechanism of information storage (i.e., memory formation) is a thought to involve "synaptic plasticity" whereby the strength of the connections between neurons (synapses) is regulated by processes such as long-term potentiation (LTP) and long-term depression (LTD). Dendritic excitability in general has a role in synaptic plasticity [2] where action potentials back-propagating into dendrites are known to induce a specific from of plasticity called spike-timing dependent plasticity (STDP). In STDP, the timing of coincident synaptic input and postsynaptic activity (bAPs) in dendrites determines the magnitude and direction of changes in synaptic strength. During STDP, bAPs traveling down the dendrite increase dendritic Ca^{2+} and provide the depolarization necessary to relieve the Mg^{2+} block at *N*-methyl-D-aspartate receptors (NMDARs) at synapses [3]. The coincidental change in the membrane voltage at both the spine and dendrite and the subsequent influx of Ca^{2+} through NMDARs induce signal transduction cascades that result in LTP or LTD at active synapses. It has been shown that network activity resulting in LTP is optimized when the location-dependent variability of synapses is normalized by active dendrites [4].

Hippocampal-dependent memory requires both synaptic and dendritic protein synthesis and may play a role in driving both synaptic and dendritic plasticity like STDP [5]. Enhanced spatial learning observed in mutant mice may be due to changes in the expression level of proteins at synapses that facilitate LTP or LTD. Alterations in the expression of synaptic proteins that are involved in plasticity result in dysfunctional or unsynchronized activity between neurons [6]. This, in turn, may result in a loss of synaptic strength and network activity. Taken together, this suggests a central role for dendritic integration in CNS disorders involving memory impairments.

Many of the signaling pathways involved in synaptic plasticity also impact ion channel properties and trafficking [1]. Alterations in the expression or function of synaptic or dendritic proteins that are involved in plasticity may result in loss of function, hypo- or hyperactivity. Any of these would result in aberrant communication between neurons resulting in downstream dysfunction, altering other types of behavior dependent on network activity. Synaptic dysfunction propagating to network and behavioral effects may then come through any mechanism impacting the dendrite's integrative function including misregulation of synaptic proteins, altered ion channel function or expression, an imbalance of excitatory and inhibitory inputs, or through changes in dendritic morphology

Here, we highlight recent and established findings predicting altered dendritic excitability in CNS disorders affecting memory, including Alzheimer's disease, autism spectrum of disorders (ASD), and additional diseases with ASD components. Learning difficulties are often associated with ASD, but enhanced explicit memory is also commonly observed in autistic savants [7]. It is not our intention to provide an exhaustive review of all disease-related research potentially implicating changes in dendritic excitability and integration. Rather, after a brief introduction, for each disease, we highlight a vein of data implicating one or more molecular abnormalities that would be expected to alter the integrative function of dendrites. How might memory be affected in CNS disorders by changes in the morphology or integrative function in dendrites? Alterations in dendritic morphology can affect both the propagation of APs and bAPs resulting in impaired STDP and synaptic plasticity. In addition, gross anatomical changes in dendrites can affect how they integrate APs. Abnormal dendritic morphology, in turn, may play a role in dysfunctional population synchrony among pyramidal neurons, resulting in changes in the temporal patterns of excitation and inhibition across brain areas important for memory [8].

Alzheimer's disease

Alzheimer's disease (AD) is a progressive and fatal brain disease suffered by more than five million Americans [9]. AD is the seventh leading cause of death in the USA, with no current cure and very limited options for treating symptoms. As the most common form of dementia, AD accounts for the majority of patients experiencing memory loss. Although age is the most prominent risk factor for AD, early onset familial AD (inherited AD diagnosed before the age of 65) has revealed three genes now known to be sufficient to cause early onset AD. All three genes (*APP*, *PSEN1*, and *PSEN2*) increase the production of a toxic cleavage fragment of the amyloid precursor protein, which subsequently oligomerizes, namely, the amyloid beta peptide [10] (Aβ). There are also additional risk factor genes, the most important of which is APOε, which is associated with increased deposition of Aβ [11]. Discovery of these genes has produced the amyloid hypothesis of AD, which proposes that the accumulation of oligomerized Aβ peptides, as either plaques or microaggregates, in the brain underlies the neuron degeneration associated with the disease [12]. Outside of the general consideration that Aβ plaque buildup could interfere with communication between neurons and impacting their

survival, it is not clear what role plaques play in Alzheimer's disease. A central unanswered question, therefore, is how memory is targeted in this and other CNS disorders.

One clue as to the cause of memory loss in Alzheimer's comes from the observed shrinkage of the hippocampus in AD patients. The hippocampus is a region of the brain necessary for the formation of new memories and one of the first areas of the brain to display Aβ plaques (the hippocampus is also the focus of epileptic seizures, which have been observed in mouse models of AD [13]). Common findings of investigations into the cellular mechanisms of AD indicate impaired neurotransmission, including synaptic plasticity deficits, which may be specific to excitatory neurons [14, 15]. Aβ application to neurons of the hippocampus inhibits synaptic plasticity [16–18] as well as causing a loss of dendritic spines in the hippocampus [17, 19]. In fact, synaptic loss is one of the strongest correlates to the cognitive impairment in patients with AD [20]. Specific causes for spine loss have been proposed, including altered glutamate receptor trafficking [14, 15]. However, enhanced network excitability in mouse models of AD [13] may also result in pathophysiological levels of synaptic activation, which would predictably lead to the loss of spines [21]. In addition, it has been shown that increases in Aβ levels can lead to increases in glutamatergic tone, glutamate excitotoxicity, a decrease in glutamatergic neurons, and an increase in GABAergic neurotransmission in the hippocampus [22, 23]. These mechanisms of both synaptic and dendritic dysfunction are directly correlated with increases in synaptic depression and aberrant (excitatory/inhibitory (E/I) network synchronization) [24].

As key regulators of dendritic excitability in hippocampal CA1 neurons, A-type K^+ channel misregulation could contribute to aberrant excitability in CNS disorders like AD. An early demonstration of Aβ regulation of fast inactivating K^+ channels comes from Good and Murphy [25] where cultured (DIV 3–10) hippocampal neurons were exposed to synthetic Aβ peptides. Aβ(1–39), consisting of the first 39 aa of Aβ, acutely reduced the A-type K^+ currents with only minor effects on non-inactivating K^+ currents and no effects observed on Na^+ or Ca^{2+} currents. Aβ block of A-type currents was voltage-independent, suggesting an interaction at a site outside of the channel pore. The authors found that the Aβ effect was independent of aggregation state or Aβ peptide length as Aβ(1–28) was equally as effective as Aβ(1–39).

In acutely dissociated hippocampal neurons, Xu et al. [26] found Aβ(25–35) to dose-dependently block A-type currents with partial voltage dependence. This group did not, however, investigate different states of aggregation, which was critical for the Aβ effect on A-currents in a 2001 study by Ramsden et al. [27]. Working in primary cultured neurons from cerebellum, this study found that chronic (24 h) unaggregated Aβ(1–40) application *increased* A-current levels by 60 %. Aggregated peptide, however, had no effect on A-currents. Neither aggregated nor unaggregated peptide affected A-currents in cultured cortical neurons. In a later study, the same group showed that acute (2 h) and chronic (24 h) treatment with Aβ(1–40) and Aβ(1–42) increased A-type currents in cultured cerebellar granule cells [28]. No effect of Aβ(25–35) was found on A-currents nor did any peptide affect non-inactivating currents. Western blot analysis attributed the A-current changes to increased expression of the A-type K^+ channel primary subunit Kv4.2. Recombinant Kv4.2 was also enhanced by Aβ(1–40) when expressed in HEK293 cells.

It is clear from these studies that time of application, cell type, culture condition, and aggregation state of Aβ are important regulators of K^+ channels in cells. However, these studies also commonly show effects specific to A-type K^+ currents, which are expressed at high levels in the dendrites of hippocampal CA1 pyramidal neurons and impact synaptic signaling [29, 30]. Chen et al. [31] offered the first direct evidence of Aβ effects on dendritic excitability. Aβ(1–42) caused a decrease in A-type K^+ currents in patches of membrane extracted from CA1 pyramidal neuron dendrites taken from acute hippocampal slices. Interestingly, dendritic currents were more greatly affected than somatic currents, raising the possibility that distal channels may form a separate pool from somatic channels, perhaps due to different primary or auxiliary subunit makeup. Aβ(1–42) did not affect basic membrane properties such as input resistance or resting membrane potential. However, the amplitude of bAPs into dendrites increased by 34 % upon Aβ(1–42) application with only small effects on the amplitude of APs recorded in the soma. Aβ(25–35) had a smaller effect on dendritic APs, showing a 15 % increase, while the reverse peptide Aβ(42–1) caused only 5 % change. These findings are consistent with the critical role for A-type K^+ channels in regulating dendritic APs [29, 32].

In a computational study based on data from previous physiological studies on Aβ regulation of A-type K^+ channels, Morse et al. [33] found that distal oblique dendrites would be expected to be most sensitive to changes in A-type currents by Aβ. Simulations suggested that A-current loss would result in grossly hyperexcitable dendrites upon AP backpropagation leading to excessive, potentially exicitotoxic Ca^{2+} influx. The authors incorporate data from a number of physiological experiments using AD mouse models to test their prediction that smaller oblique dendrites are particularly vulnerable to Aβ-induced cytotoxicity. If, as suggested in the above modeling study, A-type current loss leads to pathogenically hyperexcitable dendrites, memory impairments would be expected. In fact, Kv4.2$^{-/-}$ mice, despite compensatory electrical remodeling in cortical areas [34], exhibit decreased A-current density and enhanced AP propagation into CA1 hippocampal dendrites [32]. Additionally, LTP induction is altered in these mice leading to spatial memory deficits [35].

Mouse models of AD show that, after Aβ plaque formation, there is a change in the morphological complexity of dendrites, suggesting that altered LTP and spatial memory deficits are correlated with dendritic excitability changes. In vivo imaging of Tg2576 APP mice revealed that normal dendritic complexity was significantly decreased after plaque formation [36]. This decrease in dendritic complexity is directly related to the loss of both synaptic integration and synchronous activity in cortical neurons, disrupting both convergent inputs and information propagation in these cells [37]. Dendritic diameter has also been shown to decrease in the neurons of AD mice. For instance, Tsai et al. [38] demonstrated a decrease in dendritic shaft diameter of 19 % in PS1/APP double mutant mice as compared with controls. This change in dendrite diameter may significantly alter normal signal integration in dendrites [39], resulting in a decrease in temporal integration of dendritic inputs and altered STDP [40].

Tau pathology observed in AD brains may also correlate with cognitive decline and reflect a separate biochemical phenotype of the disease. Pathological effects of Tau on dendritic excitability may be due in part to the trafficking of hyperphosphorylated Tau into dysfunctional aggregates in the soma and dendrites of neurons [41]. However, the mechanism by which Tau impairs dendritic and synaptic activity remains an open question. Some studies have shown that Tau aggregation in dendrites and dendritic spines has deleterious effects on both morphology and physiology [42–44], where others have shown no such correlation [45, 46].

Where data does suggest a pathological effect of Tau on neurons, more complex branching patterns in proximal apical dendrites in 12-week-old mice expressing human Tau have been reported [43]. Additionally, Tau-P301L mice showed an increase in the length of the terminal branch of apical dendrites in CA1 pyramidal neurons as compared to controls [42]. Pathological mislocalization of Tau into dendrites also affects dendritic spine morphology and function. Larger numbers of long-thin spines as compared to mushroom spines on both apical and basal dendrites have been observed in 12-week-old mice [43]. This correlates with the finding that hyperphosphorylated Tau is translocated to dendritic spines and suppresses normal AMPAR activity [47] and inhibits LTP [48].

These data suggest that there is a tight correlation between dendritic morphology, dendritic spine morphology, and pathophysiology related to AD disease. Specifically, changes in the morphology of spines and dendrites in AD may have a direct effect on E/I balance and overall network activation in the brain, resulting in the deficient encoding and processing of memory. Whether pathophysiological changes in dendrite morphology lead to changes in dendritic spine function or vice versa should be addressed by future research.

Autism Spectrum of Disorders

ASDs are a set of neurodevelopmental disorders that affect about 1 % of the population in the USA [49]. ASDs are typically diagnosed in male before 3 years of age and are marked by several clinically defined conditions that range from pervasive developmental disorder—not otherwise specified, to autistic disorder, to the milder Asperger syndrome. Enhanced spatial learning abilities in mice expressing genetic mutations commonly seen in ASDs is particularly interesting because this enhancement may share an analogue with enhanced hippocampus-dependent explicit memory [50] commonly observed in autistic savants [7].

Neuroligans and ASD

Dysfunctions in synaptic plasticity and dendritic excitation are commonly found in animal models of ASD. For instance, mice that contain genetic mutations that underlie ASDs show significant changes in synaptic excitation [51] and inhibition [52]. Neuroligans (NLs) are a family of postsynaptic proteins that are localized to excitatory and inhibitory synapses in the CNS [53, 54] and contain structural PDZ domains that interact with cytoskeletal proteins and PSD-95 [55]. Postsynaptic neuroligans bind to presynaptically localized β-neurexins, and this interaction is important for the development of functional synaptic contacts [56]. Mice that express a missence mutation in NL1, NL2, NL3, and NL4 have been identified in a subset of human patients with ASDs [57–59]. These mice show behavioral changes including impaired social interactions and enhanced spatial learning abilities.

Studies from knockout mice reveal that NL expression affects both inhibitory and excitatory synapses. NL1-KO mice show significant reductions in NMDA receptor mediated signaling, whereas NL2- and NL3-KO mice show decreased inhibitory neurotransmission. Specifically, recordings from CA1 pyramidal neurons taken from NL3-KO mice reveal an increase in spontaneous inhibitory synaptic transmission [52]. These data suggest that NL expression at synapses regulates *both* synaptic excitation and inhibition. Thus, the overall balance of synaptic activity in mice that express ASD-related gene mutations is either increased or decreased as compared to normal controls [60, 61]. This balance of excitatory and inhibitory inputs (E/I) is important for regulating dendritic integration in neurons and may play an important role in the development of ASDs [62, 63] For instance, in vivo recordings from the dentate gyrus of NL2-KO mice revealed that paired pulse inhibition is significantly reduced, whereas significantly higher amplitude population spikes were observed [64, 65]. E/I balance is perturbed in NL2-KO mice, driven by both an increased postsynaptic response at excitatory synapses and a lower threshold for AP generation in the dendrites of the dentate network [66, 67]. In addition NL2-KO mice have

significantly decreased GABAergic transmission via reduced GABAAR conductances [65]. These mice also demonstrate impairment of gephyrin clustering at inhibitory synapses, suggesting a decrease in GABAAR sequestering at synapses [65]. When NL2 was overexpressed in transgenic mice, enhanced maturation of inhibitory interneurons and an associated increase in vesicle reserve pools within inhibitory synapses was observed [68]

Further support for the hypothesis that cognitive deficits observed in ASDs may be associated with an overall shift in network E/I balance comes from dissociated cultures. Gutierrez et al. [69] found that overexpression of normal NL3 in dissociated rat hippocampal neurons enhanced the synchrony of spontaneous Ca^{2+} activity. When the autism-associated NL3 mutation (R471C-NL3) was expressed in these cells, synchronous Ca^{2+} activity was disrupted. Interestingly, when the authors stained the neurons for GAD-67, there was a significant decrease in both GAD-positive interneurons and inhibitory electrophysiological activity. These findings parallel what has been observed in NL2-KO mice.

It has been suggested that optimal information processing in memory storage areas of the CNS require less excitation and more inhibition to keep dendritic and synaptic "noise" under control-in order to enhance processing of salient stimuli and prevent seizure formation [62]. The concept of a lower threshold for AP formation in the dendrites of autistic neurons is supported both by evidence of high comorbidity of epilepsy and ASDs [70, 71] and changes in dendritic morphology that have been observed in the hippocampus following seizure induction [72].

A correlation between seizure threshold, dendritic excitability, and dendritic complexity in the etiology of ASD has also been observed in neuropilin-2 (NP2)-deficient mice. Single nucleotide polymorphisms in the autism susceptibility region of the gene encoding human NP2 are significantly associated with autism [73]. Gant et al. [71] observed that NP2-KO mice showed significant decreases in both dendritic branching and dendritic length with an 18 % decrease in dendritic length in CA1 pyramidal neurons. Additionally, Gant et al. [71] observed both a decrease in GABAergic interneurons and an increase in dendritic excitability, resulting in a decreased seizure threshold.

Together these findings suggest a link between dendritic morphology, dendritic excitability, epilepsy, and ASD. A combination loss of NMDARs as was observed in NL1-KO mice and gross changes in dendritic branching, as has been observed after knockout of normal NP2 signaling, could modulate both LTP and STDP in diseased networks. Recently, it has been demonstrated that L-LTP expression is dependent in part on both dendritic branching and the coincident timing of glutamatergic inputs at branch points [74]. Further studies will be needed to understand the relationship between changes in dendritic complexity, the number of associated branch points, and excitability in NL-KO mice. As with NP2, NL2-KO mice may also demonstrate a lower threshold for epileptogenesis. Many of the changes that have been reported in NL2-KO mice are in the dentate gyrus, the disinhibition of which may play a role in temporal lobe epilepsy [75].

Rett Syndrome and ASD

Another neurodevelopmental disorder that shares a partial etiology with ASD is Rett's syndrome, a disease that affects the gray matter of the brain and affects about 0.4% of the population, most of which are female [76]. Rett Syndrome patients show a high prevalence of ASDs and behaviors such as pervasive impairment in communication skills and in reciprocal social interaction skills that are most commonly associated with ASDs. In addition, Rett syndrome is accompanied by a high prevalence of mental retardation, microcephally, and seizures. Rett syndrome is caused by a de novo mutation in the gene that encodes for MeCP2 (methyl CpG binding protein 2), which is expressed at high levels in mature neurons and acts as a transcriptional repressor [77]. Analysis of miniature excitatory post-synaptic currents (mEPSCs) from mice lacking MeCP2 showed a 46 % reduction in the EPSC amplitude, a 41 % reduction in the readily releasable pool, and a 19 % reduction in the excitatory amino acid vesicular transporter VGLUT1. Thus, downregulation in MECP2 expression lead to altered synaptic protein synthesis and subsequent changes in synaptic activity [60]. In fact, Dani et al. [51] demonstrated that neurons from cortical slices of MeCP2-mutant mice showed a reduction in both spontaneous mIPSCs and mEPSCs. Furthermore, LTP was reduced in cortical [78] and hippocampal [79] neurons of MeCP2-mutant mice.

As with mutations in the NL system, mutations of MeCP2-mutant mice seem to have a negative effect on the E/I balance. Using MeCP2-mutants, Chao et al. [80] showed that these mice have MeCP2 deficiencies in GABAergic neurons as well, which results in significantly reduced theta burst LTP and impaired seizure formation in the hippocampus. Taken together, these data show that modulation of excitation and inhibition in ASDs is important in regulating AP initiation and therefore overall network activity. The authors of this study note that subtle changes in GABA control of excitability may have large effects on the E/I balance and overall network excitability. The important role GABAergic input plays in regulating dendritic excitability is underscored by morphological studies, which show that GABAergic interneurons specifically innervate defined dendritic compartments of pyramidal neurons [81]. These inhibitory inputs play a role in the spread of APs in dendrites and may modulate STDP [82].

Aberrant dendritic morphology is a clear phenotype in humans with Rett syndrome, particularly a decrease in

dendritic complexity in cortical pyramidal neurons [83, 84]. Recent reports have shown that cortical pyramidal neurons explanted from MeCP2-mutant mice into wild-type neonatal cortices exhibit decreased dendritic branching and complexity when compared to controls [85], and certain of MeCP2-KO mice exhibit decreased dendritic complexity [86]. The decreased dendritic complexity in MeCP2-mutant mice correlates with a reduction in both LTP and synaptic mEPSCs as well as the reduction observed in VGLUT expression in these mice. This correlation suggests that there may be a reciprocal relationship between dendritic surface area, functional synapses, and LTP induction [87].

Fragile-X and ASD

Transcriptional silencing of the FMR1 gene leads to the loss of expression of the Fragile-X mental retardation protein (FMRP) in neurons and Fragile-X syndrome [88]. Clinical studies show that 5 % of children with ASDs have Fragile-X syndrome, and 15–30 % of children with Fragile-X syndrome have ASDs, suggesting that FMRP plays an important role in the etiology of certain ASDs.

There are a number of ways in which FMRP loss may affect dendritic excitability. First, FMR1 KO mice exhibit significantly enhanced mGlurR-dependent LTD. This type of LTD is insensitive to translational inhibitors [89–91], suggesting that one aspect of ASDs is an overexpression of synaptic plasticity proteins in the hippocampus by changes in gene expression. It has been proposed that the overexpression of proteins involved in LTD in FMR1 KO mice leads to a net weakening of excitatory synapses relative to inhibitory ones, leading to the behavioral and cognitive deficits observed in ASDs [92].

Alterations in basal dendritic branching patterns may also have a significant impact on dendritic excitability and the integration of synaptic signals. Such changes have been observed in both visual and somatosensory cortex of adult FMR1-KO mice [93, 94]. Dendritic excitability may be affected via alterations in arborization patterns, with more spatially diffuse aborization seen during a restricted developmental period in superficial barrel cortex layers of the FMR1-KO mouse [95]. Alterations in basal dendritic branching may have a deleterious effect on dendritic excitability and plasticity because backpropagation into the dendritic tree is modulated by dendritic morphology [96]. Consistent with this, FMR1-KO mice showed a significant reduction in LTP at CA1 pyramidal neurons using a STDP protocol [97], which is dependent on the coupling of bAP-induced calcium spikes and the propagation of the bAP throughout the dendritic tree [98].

Like other disorders that result in ASDs, Fragile X syndrome may alter the overall E/I balance in the network. This may be due to changes in dendritic excitability induced by both dysfunctional protein expression and dendritic morphology. FMR1-KO mice exhibit decreases in messenger RNA (mRNA) expression and overall protein for GABAAR subunits [99, 100]. These changes in dendritic excitability and in normal E/I ratio may be related to mGluR activity. It has been shown that mGluRs are highly expressed at inhibitory interneurons [101]. FMR1-KO mice have demonstrated prolonged epileptiform activity that can be significantly reduced by the application of the mGluR antagonist MPEP [102]. Interestingly, using Ts65Dn mice, a Down's syndrome transgenic (not KO) mouse model, which shows impaired LTP, Kleschevnikov et al. [103] showed that application of picrotoxin restores LTP. STDP can also be induced by blocking GABAAR-mediated inhibition [104], and the attenuation of AP backpropagation is regulated in part by GABAergic inhibition [82] suggesting that E/I balance plays a direct role in modulating dendritic excitability in Fragile-X. Finally, FMR1-KO mice show altered K^+ channel distributions. Utilizing a wide-scale analysis of protein expression altered in FMR1-KO mice, Liao et al. [105] demonstrated a significant downregulation in the large conductance,

Table 1 Dendritic and synaptic pathophysiology observed in certain CNS disorders

Disease	Channels	Dendritic arborization	E/I balance	Synaptic plasticity
Alzheimer's	↓ Kv4.2 [A-type K^+ currents] [32]	↓ Dendrite diameter [38]	Enhanced network excitability Palop et al. [13]	↓ LPT [16–18]
		↓ Dendrite complexity [36]	Abberant E/I sync [24]	↑ LTD [16]
Autism Spectrum	↓ GABAR Jedlicka et al. [65]	↓Dendrite branching Gant et al. [71]	Altered E/I balance [60, 61]	↓ LTP [113]; Yun and Trommer [114]
		↓ Dendrite length [71]	Lower threshold for AP generation [70]	↑ LTD [115]
			Lower seizure threshold [67]	
Fragile X	↓ GABAR [99, 100]; ↓ BK [105]; ↓ Kv4.2 [106]	↓ Dendrite branching and complexity [95]	Prolonged epileptiform activity [102]	↓ LTP [97]
Rett Syndrome	↓ VGLUT1 [60]	↓ Dendrite branching and complexity [85, 86]	Impaired seizure formation [80]	↓ LTP [78, 79]

calcium-activated BK potassium channel subunit, Kcnma1α, which would be expected to result in hyperexcitable dendrites. Recently, Gross et al. [106] report that protein levels of Kv4.2 are reduced in the brain of FMR1-KO mice. They also found that FMRP is a positive regulator of Kv4.2 mRNA translation and protein expression and associates with Kv4.2 mRNA in vivo and in vitro [106].

Fragile-X shares in common with ASDs and Rett syndrome the phenotype that alterations in both dendritic morphology and excitability associated with the disesase result in altered E/I balance. Changes in this delicate balance have effects on the proper encoding of memory in the brain at excitatory synapses. In addition to a reduction in potassium channels in FMR1-KO mice-resulting in hyperexcitable dendrites, the threshold for action potentials is lowered by increased dendritic inhibitory conductances [107], which may be enhanced in ASDs. The concomitant changes observed in the morphology of dendrites combined with increases in excitability may facilitate the pathophysiological alteration of normal plasticity at excitatory synapses [108]. This has been reported as enhanced mGlurR-dependent LTD in FMR1-KO mice. Thus, abnormal dendritic morphology, excitability, and disturbances of the E/I balance may be a common cluster of phenotypes linking synaptic dysfunction and disorders that significantly impair cognition.

Conclusions

In summary, this review has shown that the pathophysiology observed in CNS disorders, through diverse mechanisms, can have a common endpoint in the alteration of normal synaptic integration and dendritic excitability (Table 1). Abnormal dendritic function as a result of genetic mutation or cytotoxicity has a palpable effect on network activity and synaptic plasticity in all four CNS disorders reported on in this review. In most cases, epileptiform activity has a high comorbidity with the disease, indicating dysfunctions in both the threshold of dendritic excitation and the amount of dendritic integration. Not surprisingly, certain types of hippocampal-dependent forms of epilepsy are modulated by the dendritic expression of A-type K^+ channels, which are responsible for b-AP amplitude and dendritic excitability [29, 109]. In conjunction, abnormalities in either LTP or LTD were observed as well as gross changes in normal behavior in both AD and ASDs. The balance of excitation and inhibition is impaired in ASDs, Rett, and Fragile-X. This E/I balance has important effects on the integration and processing of signals in dendrites. For instance, it has been demonstrated that the amplitude and propagation of bAPs can be modulated by GABAAR conductance shunts on primary apical dendrites of pyramidal neurons [110], suggesting that as E/I balance changes significantly, so too does dendritic processing. Changes in dendritic excitability are also expected in ASDs and schizophrenia where dysfunctional dendritic branching was caused by genetic mutations. STDP is sensitive to the coincident timing of synaptic EPSPs and bAPs, and it has been shown that coincidence detection in pyramidal neurons is tuned by their dendritic branching patterns [111]. When the timing of bAPs is suppressed, it can prevent LTP induction [112], impairing normal synaptic function. Future work toward understanding the role genetics plays in modulating both dendritic morphology and underlying excitability will be an important step in uncovering the etiology of complex CNS disorders.

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