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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. (Need to distinguish between pure genetic forms which are rare, and what most people get which is probable combination of genetic susceptibility and environmental insults). 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 diseases 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 diseases, and their subsequent affect on memory.

Keywords

Dendritic excitability; Autism; Fragile-X; Alzheimer’s Disease; A-type K+ channel; hippocampus

Introduction

Despite modern technological advances such as genome-wide association scans, the molecular mechanisms underlying sporadic cases of the most common and devastating 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 diseases 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

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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 diseases. We propose that it is these abnormalities in dendritic function that may be responsible for dysfunction at the circuit level in CNS diseases 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 diseases, 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 (Shah *et al.*, 2010).

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 (Spruston, 2008) 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 NMDARs at synapses (Yuste and Denk, 1995). 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 (Cook and Johnson, 1997).

Hippocampal-dependent memory requires both synaptic and dendritic protein synthesis and may play a role in driving both synaptic and forms of dendritic plasticity like STDP (Dan and Poo, 2006). 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 (Minerbi *et al.*, 2009). 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 (Shah *et al.*, 2010). 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

mis-regulation 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 (Heaton and Wallace, 2004). 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 disease 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 amongst pyramidal neurons, resulting in changes in the temporal patterns of excitation and inhibition across brain areas important for memory (Magee, 2000).

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive and fatal brain disease suffered by more than five million Americans (Querfurth & LaFerla, 2010). AD is the seventh-leading cause of death in the United States, 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, PSEN2*) increase the production of a toxic cleavage fragment of the amyloid precursor protein which subsequently oligomerizes, namely the amyloid beta peptide (Selkoe, 2004) (Aβ). There are also additional risk factor genes, the most important of which is APOε which is associated with increased deposition of Aβ (Corder *et al.*, 1993). 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 (Ross & Poirier, 2004). 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 (Palop *et al.*, 2007). Common findings of investigations into the cellular mechanisms of AD indicate impaired neurotransmission including synaptic plasticity deficits, which may be specific to excitatory neurons (Lacor *et al.*, 2007; Zhao *et al., 2010*). Aβ application to neurons of the hippocampus inhibits synaptic plasticity (Walsh *et al.*, 2002; Shankar *et al.*, 2008; Li *et al.*, 2009) as well as causing a loss of dendritic spines in the hippocampus (Shrestha *et al.*, 2006; Shankar *et al.*, 2008). In fact, synaptic loss is one of the strongest correlates to the cognitive impairment in patients with AD (Crews & Masliah, 2010). Specific causes for spine loss have been proposed, including altered glutamate receptor trafficking (Lacor *et al.*, 2007; Zhao *et al.., 2010*). However, enhanced

network excitability in mouse models of AD (Palop *et al.*, 2007) may also result in pathophysiological levels of synaptic activation, which would predictably lead to the loss of spines (Swann *et al.*, 2000). 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 (Minkeviciene et al. 2009; Palop and Mucke 2010). These mechanisms of both synaptic and dendritic dysfunction are directly correlated with increases in synaptic depression and aberrant (excitatory/inhibitory (E/I) network synchronization (Rissman & Mobley, 2011).

As key regulators of dendritic excitability in hippocampal CA1 neurons, A-type K^+ channel mis-regulation could contribute to aberrant excitability in CNS diseases like AD. An early demonstration of Aβ regulation of fast inactivating K^+ channels comes from Good and Murphy (1996) 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. (Xu *et al.*, 1998) 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., (Ramsden *et al.*, 2001). 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 (2h) and chronic (24 h) treatment with Aβ(1–40) and Aβ(1–42) increased A-type currents in cultured cerebellar granule cells (Plant *et al.*, 2006). 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's 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 (Hoffman *et al.*, 1997; Kim *et al.*, 2007). Chen (2005) offered the first direct evidence of Aβ effects on dendritic excitability. Aβ(1–42) caused a decrease of Atype 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 (Hoffman *et al.*, 1997; Chen *et al.*, 2006b).

In a computational study based on data from previous physiological studies on Aβ regulation of A-type K^+ channels, Morse *et al.* found that distal oblique dendrites would be

expected to be most sensitive to changes in A-type currents by Aβ (Morse *et al.*, 2010). Simulations suggested that A-current loss would result in grossly hyperexcitable dendrites upon AP back-propagation 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, Atype current loss leads to pathogenically hyperexcitable dendrites, memory impairments would be expected. In fact, $Kv4.2^{-/-}$ mice, despite compensatory electrical remodeling in cortical areas (Nerbonne *et al.*, 2008), exhibit decreased A-current density and enhanced AP propagation into CA1 hippocampal dendrites (Chen *et al.*, 2006a). Additionally, LTP induction is altered in these mice leading to spatial memory deficits (Lockridge & Yuan, 2010).

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 (Spires et al., 2005). 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 (Stern et al., 2004). Dendritic diameter has also been shown to decrease in the neurons of AD mice. For instance, Tsai *et al.* (2004) 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 (Sorra & Harris, 2000), resulting in a decrease of temporal integration of dendritic inputs and altered STDP (Knowles et al., 1999). Indeed, application of oligomeric Aβ leads directly to inhibition of STDP in an α7 nAChR mouse model. The alternation of STDP in these mice was shown to be glutamate dependent (Gu & Yakel, 2011).

Autism Spectrum of Disorders

ASDs are a set of neurodevelopmental disorders that affect about 1% of the population in the United States (Baird *et al.,* 2006). ASDs are typically diagnosed in males 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 (Pardo & Eberhart, 2007) commonly observed in autistic savants (Heaton and Wallace, 2004).

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 (Dani *et al.*, 2005) and inhibition (Tabuchi *et al.*, 2007). Neuroligans (NLs) are a family of postsynaptic proteins that are localized to excitatory and inhibitory synapses in the CNS (Sudhof, 2008; Song et al., 1999) and contain structural PDZ domains that interact with cytoskeletal proteins and PSD-95 (Irie *et al.*, 1997). Postsynaptic neuroligans bind to presynaptically localized β-neurexins and this interaction is important for the development of functional synaptic contacts (Scheiffele *et al.*, 2000). Mice that express a missence mutation in NL-1,2,3 and NL-4, have been identified in a subset of human patients with ASDs (Yan *et al.*, 2005; Laumonnier *et al.*, 2004;Varoqueaux *et al.*, 2006), and 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. NL-1-KO mice show significant reductions in NMDA-receptor mediated signaling whereas NL-2 and 3-KO mice show decreased inhibitory neurotransmission. Specifically, recordings from CA1 pyramidal neurons taken from NL-3-KO mice reveal an increase in spontaneous inhibitory synaptic transmission (Tabuchi et al., 2007). This data suggests 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 (Chao et al., 2007; Hanson and Madison, 2007). 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 (Rubenstein and Merzenich, 2003; Yizhar *et al.*, 2011) 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 (Blundell et al., 2009; Jedlicka et al., 2010). 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 (Jedlicka et al., 2009; Chauvet and Berger, 2002). In addition NL2-KO mice have significantly decreased GABAergic transmission via reduced GABAAR conductances (Jedlicka et al., 2010).

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 (Rubenstein and Merzenich, 2003). 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 (Gant et al, 2009; Clarke et al., 2005), and changes in dendritic morphology that have been observed in the hippocampus following seizure induction (Kato et al., 2001).

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 (Wu *et al.*, 2007). Gant *et al.* (2009) 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.* (2009) 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.

Rett Syndrome and ASD

Another neurodevelopmental disorder that shares a partial etiology with ASD is Rett’s Syndrome, a disease that affects the grey matter of the brain and affects about .4% of the population, most of which are female (Chahrour & Zogby, 2007). 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 (Chahrour *et al.*, 2008). 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, down-regulation in MECP2 expression lead to altered synaptic protein synthesis and subsequent changes in synaptic activity (Chao *et al*, 2007). In fact,

Dani *et al.*, (2005) 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 (Asaka et al., 2006) and hippocampal (Moretti et al., 2006) 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., (2010) 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, this data shows 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 (Klausberger and Somogyi, 2008). These inhibitory inputs play a role in the spread of APs in dendrites and may modulate STDP (Meredith and Groen, 2010).

Aberrant dendritic morphology is a clear phenotype in humans with Rett syndrome, particularly a decrease in dendritic complexity in cortical pyramidal neurons (Armstrong et al, 2005; Belichenko et al, 2009). 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 (Kishi & Macklis, 2010), and certain of MeCP2-KO mice exhibit decreased dendritic complexity (Jentarra *et al.*, 2010). 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 (Poirazi & Mel, 2001).

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 (Bagni & Greenough, 2005). 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 to LTD is insensitive to translational inhibitors (Huber *et al.*, 2002; Hou *et al.*, 2006; Nosyreva & Huber, 2006), 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 (Kelleher & Bear, 2008).

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 (Galvez et al., 2003; Restivo *et al.*, 2005). 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 (Bureau et al., 2008). Alterations in basal dendritic branching may have a deleterious effect on dendritic

excitability and plasticity because back-propagation into the dendritic tree is modulated by dendritic morphology (Vetter et al., 2001). Consistent with this, FMR1-KO mice showed a significant reduction in LTP at CA1 pyramidal neurons using a STDP protocol (Hu et al., 2008), which is dependent on the coupling of bAP-induced calcium spikes and the propagation of the bAP throughout the dendritic tree (Callaway and Ross, 1995).

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 mRNA expression and overall protein for GABAAR subunits (El Idrissi *et al.*, 2005; D'Hulst *et al.*, 2006). 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 (Lopez-Bendito et al., 2002). FMR1-KO mice have demonstrated prolonged epileptiform activity that can be significantly reduced by the application of the mGluR antagonist MPEP (Chuang *et al.*, 2005). Interestingly, using Ts65Dn mice, a Down's syndrome transgenic (not KO) mouse model which shows impaired LTP, Kleschevnikov *et al.*, 2004 showed that application of picrotoxin restores LTP. STDP can also be induced by blocking GABAAR-mediated inhibition (Campanac and Debanne, 2008), and the attenuation of AP back-propagation is regulated in part by GABAergic inhibition (Meredith and Groen, 2010) 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 (2008) demonstrated a significant downregulation in the large conductance, calcium-activated BK potassium channel subunit, Kcnma1a, which would be expected to result in hyperexcitable dendrites. Recently, Gross et al. (2011) 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* (Gross *et al.*, 2011). Add the Jan lab neuron paper showing opposite results or would that just be too confusing? If so, add in table too.

Conclusions

In summary, this review has shown that the pathophysiology observed in CNS diseases, 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 (Hoffman et al., 1997; Bernard et al., 2004). In conjunction, abnormalities in either LTP or LTD were observed and as well as gross changes in normal behavior in both CNS diseases. Interestingly, the balance of excitation and inhibition is impaired in all three diseases. 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 (Tsubokawa and Ross, 1996), 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 (Schaefer et al, 2003). When the

timing of bAPs is suppressed, it can prevent LTP induction (Sjostrom, and Hausser, 2006), 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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Table 1

Disease	Channels	Dendritic Arborization	E/I Balance	Synaptic Plasticity
Alzheimer's	↓Kv4.2 [A-type K+ currents] (Chen et al., 2006a)	↓ dendrite diameter (Tsai et al., 2004); ↓dendrite complexity (Spires et al., 2005)	* enhanced network excitability (Palop et al., 2007); * abberent E/I sync (Rissman & Mobley, 2011)	↓LTP (Walsh et al., 2002; Shankar al., 2008; Li et al., 2009) ↑LTD (Li et al., 2009)
Autism Spectrum	↓GABAR (Jedlicka et al., 2010)	↓dendrite branching (Gant et al, 2009); ↓ dendrite Length (Gant et al, 2009)	* altered E/I balance (Chao et al., 2007; Hanson and Madison, 2007); * lower threshold for AP generation (Clarke et al., 2005) * lower seizure threshold (Jedlicka et al., 2009)	↓LTP (Bangash et al, 2011; Yun & Trommer, 2011) ↑LTD (Bear et al, 2004)
Fragile-X	↓GABAR (El Idrissi et al., 2005; D'Hulst et al., 2006); ↓BK (Liao et al 2008); ↓Kv4.2 (Gross et al. 2011)	↓dendrite branching & complexity (Bureau et al., 2008)	*prolonged epileptiform activity (Chuang et al., 2005)	↓LTP (Hu et al., 2008)
Rett Syndrome	↓VGLUT1 (Chao et al, 2007)	↓dendrite branching & complexity (Kishi & Mack-lis, 2010; Jentarra et al., 2010)	*impaired seizure forma-tion (Chao et al., 2010)	↓LTP (Asaka et al., 2006; Moretti et al., 2006)