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Pathophysiology of Epilepsy in Autism Spectrum Disorders

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Epilepsy occurs frequently in individuals with autism spectrum disorders (ASD). However, the mechanisms responsible for increased seizure susceptibility in ASD are largely unknown. Clues to neural hyperexcitability in the autistic brain might be derived from disorders in which single gene mutations cause both epilepsy and an autistic phenotype, such as fragile X syndrome and tuberous sclerosis complex. This chapter summarizes current understanding of epilepsy in individuals with ASD and explores potential links between the genetic disruption of neural circuits and cellular signaling pathways that contribute to both epilepsy and ASD.

INTRODUCTION

Why are seizures so common in children with autism? This relatively straightforward question does not, unfortunately, have a straightforward answer. In this chapter, we explore this question from clinical, pathophysiological, and molecular perspectives, using as examples two genetic disorders that share a high prevalence of autism and epilepsy – fragile X syndrome (FXS) and tuberous sclerosis complex (TSC), with the hope that understanding the pathophysiology of these monogenic conditions will lead to broader understanding of neural hyperexcitability in other autism syndromes. We conclude by discussing cellular and network dysfunction that might be amenable to targeted treatments in these disorders, with potential wider applicability to idiopathic autism.

Autism spectrum disorders (ASD) are neurodevelopmental disorders that share abnormalities in 3 domains: language development, social interaction, and motor behavior with stereotypies and restricted interests. In this chapter, the term ASD encompasses classic childhood autism as originally described by Kanner,[1] Asperger syndrome, and pervasive developmental disorder not otherwise specified. The signs and symptoms of ASD can usually be recognized before age 3 years,[2] although recent evidence of an early, but slow, loss of skills in about

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three quarters of the infants who develop ASD is observed by 12 months.[3] Later, some individuals with ASD experience regression of language or behavior (autistic regression), a phenomenon that has been hypothesized to be related to epilepsy or epileptic discharges on the electroencephalogram (EEG).[4] The possibility that subclinical epileptiform discharges can contribute to the spectrum of disability in ASD or lead to regression of language or social skills, suggests that the brains of individuals with autism are hyperexcitable.

Clinical aspects of seizures and epilepsy within the autism spectrum have been reviewed in detail.[5–9] Up to 30% of individuals with ASD have epilepsy, and ASD is present in about 30% of patients with epilepsy, though these numbers are approximate due to historical differences in the definition of each condition and to different study methodologies.[10] Risk factors for epilepsy in ASD include mental retardation, motor impairment, symptomatic etiology, and seizure onset either early in life (before 5 years of age) or in adolescence.[9] However, the neurobiology of ASD as well as the mechanisms responsible for cellular hyperexcitability in ASD are not well understood and likely involve the interplay of genetic, epigenetic, and environmental contributions.[11–14]

There are several possible relationships between brain development, epilepsy and ASD (Figure 1).[15]; First, ASD and epilepsy might be distinct conditions with no causal relationship; however, this possibility is unlikely in view of the high co-occurrence rate (30%) between the two disorders. Second, a common neurobiological antecedent (e.g., structural or developmental lesions, genetic susceptibilities, and/or environmental insults) might lead to abnormal brain development that results in both epilepsy and ASD. Third, epilepsy could lead to autistic behavior or conversely, abnormal brain circuitry underlying ASD could predispose the brain to seizures. The second and third possibilities are not mutually exclusive, leading to the hypothesis that mechanisms of epilepsy and ASD are interdependent and that targeted therapies for one condition could ameliorate the impact or severity of the other, as will be discussed in more depth below. The possibility that common developmental mechanisms of epilepsy and ASD exist arises from observations that both disorders, though etiologically heterogeneous, involve abnormal brain plasticity, i.e., "dysplasticity" or the ability of neural circuits to function normally with regard to cognitive and social function.[13]

The etiologies of ASD are diverse and can be either idiopathic (non-syndromic) or secondary to an identifiable, underlying medical or genetic disorder (syndromic). The risk of epilepsy is increased in both idiopathic and syndromic forms of ASD, suggesting that there might be common pathophysiological alterations that decrease seizure threshold. Specific medical or genetic/genomic abnormalities have been identified in approximately 20% of ASD cases, though one study reports a 40% diagnostic yield.[16] In the future, the category of "idiopathic" autism might disappear as the molecular and genetic bases of ASD disorder become more fully defined. For now, the existence of known etiologies permits investigation into molecular and physiological aspects of brain function that lead to autistic behaviors.[17] Understanding the pathophysiological mechanisms of increased seizure susceptibility is facilitated by examination of genetic mutations leading to ASD. So far, the results of these studies are weighted toward defects in postsynaptic function and subcellular signaling.[18, 19]

While much of idiopathic ASD is likely to be multigenic with complex genetics, a small but increasing proportion of ASD has been identified with specific gene mutations; some single gene defects are associated with both ASD and seizures.[20] Examples include FXS, caused by mutation of the fragile X mental retardation 1 (*FMR1*) gene, and tuberous sclerosis complex (TSC), due to mutation of the *TSC1* or *TSC2* genes involved in the control of cell growth and differentiation. Other novel mutations with concurrent ASD and epilepsy are rapidly appearing in the literature and are reviewed in detail in elsewhere.[13] Several of these mutations involve genes regulating proteins critical for synapse development (e.g., neuroligins and neurexins)[21] or interneuron function (e.g., aristaless-related homeobox X-linked (*ARX*) gene mutations).[22] Likewise, patients with Rett syndrome, a neurodevelopmental disorder with progressive deterioration of motor skills, language, cognition, and behavior (autism), have a high risk of developing epilepsy.[23] Rett syndrome is due to mutation in the gene encoding methyl-CpG binding protein 2 (*MeCP2*), a transcriptional regulator of numerous genes. Whether genetic

mutations associated with syndromic ASD converge on common mechanisms that lead to neuronal hyperexcitability and epilepsy remains to be established.

FRAGILE X SYNDROME

Clinical and Genetic Aspects

FXS is the most common inherited form of cognitive impairment and the leading known monogenic disorder associated with ASD.[24] Using strict diagnostic criteria, 15%–30% of males with FXS have autism.[25] Approximately 20% of children with FXS have seizures, many of which are relatively benign and resolve beyond childhood. Autism in FXS ranges from mild to severe and tends to improve with age.[26, 27] Among children with FXS, those with comorbid autism have greater cognitive and verbal impairments than FXS children without autism.[27] Predominant impairments are in the communication domain.[28]

FXS arises when a CGG-repeat tract in the 5′ noncoding region of *FMR1* exceeds 200 repeats (i.e., the "full mutation" range), at which point the gene becomes hypermethylated and transcriptionally silent.[29] The absence of the *FMR1* fragile X mental retardation protein (FMRP), is responsible for the clinical phenotype and physical features, which include prominent ears, long face, high-arched palate, macroorchidism, and hyperextensible finger joints.[30] Approximately 85% of males and 25% of females experience cognitive impairment (IQ < 70); nearly all patients have behavioral problems, with males tending to present with attention deficit hyperactivity disorder (ADHD) and aggression, while females are more prone to shyness and social withdrawal.[31] Individuals with CGG expansions in the premutation range (55–200 CGG repeats) display a range of clinical features, including behavioral and cognitive involvement in children[31–33] and a late-adult-onset neurodegenerative disorder, fragile X-associated tremor/ataxia syndrome (FXTAS).[34] The prevalence of seizures in individuals with the premutation is reported to be in excess of 20%.[35]

FMRP is an RNA-binding protein that is believed to have multiple functions, including dendritic transport of various mRNA species[36] and the translational regulation of mRNAs whose protein products are involved in synaptic development, function, and plasticity.[37] Among the known targets of FMRP-coupled translational downregulation are the microtubule-associated protein 1B (MAP1B), which is important for modulating microtubule-coupled growth of dendritic spines and for dendritic arborization,[38] and Arc, which plays a role in the internalization of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits, a subtype of ionotropic glutamate receptors.[39]

Seizures occur in 10%-20% of FXS individuals with full mutations.[40–42] Interictal EEG patterns are similar to those seen in benign childhood epilepsy with centrotemporal spikes (rolandic epilepsy). In one study involving 16 children with FXS and epilepsy, 12 children had partial seizures, with 10 of the 12 having an EEG with centrotemporal spikes.[41] In addition, 23% of the children who did not have seizures displayed abnormal EEG patterns, typically centrotemporal spikes. In most children with FXS, seizures are readily controlled and tend to disappear in adolescence. Therefore, there are similarities between epilepsy in individuals with rolandic epilepsy and FXS, and any mechanism postulated to explain epileptogenesis in FXS must account not only for the relatively benign seizure manifestations, but also for their absence in the majority of FXS cases.[43]

Pathophysiology

The Metabotropic Glutamate Receptor Theory for Fragile X Syndrome

Numerous animal models and electrophysiological studies have examined the pathogenesis of FXS and the synaptic dysfunction that underlies the hyperexcitability and epileptiform features associated with the disorder. A key advance in the understanding of the molecular basis of FXS was that mice lacking FMRP displayed enhanced long-term depression (LTD) in hippocampal neurons and that this LTD was dependent on protein

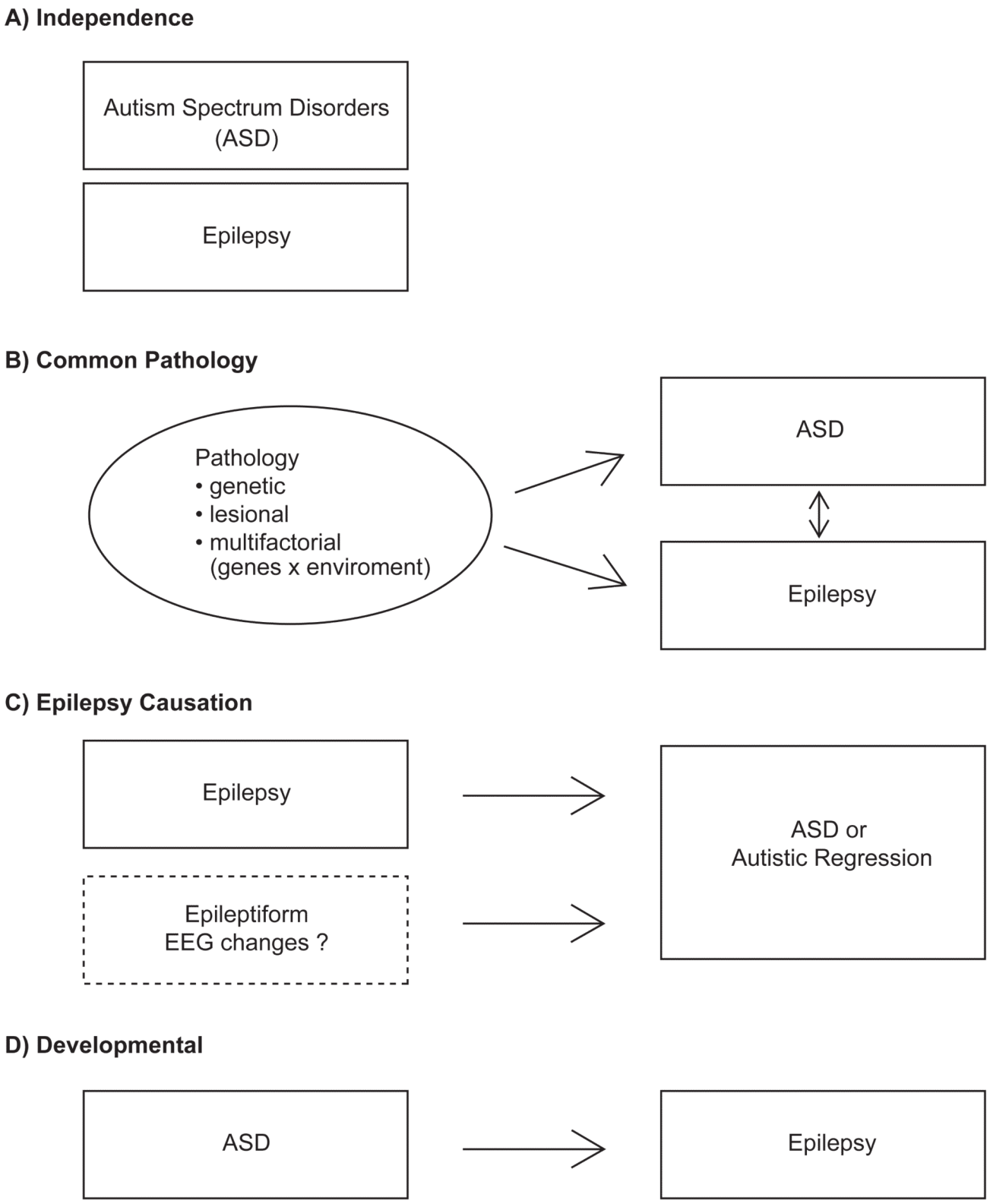

Figure 1. Possible relationships between brain development, epilepsy and autism spectrum disorders (ASD). (A) ASD and epilepsy might be distinct conditions with no causal relationship. This possibility is not likely due to the high comorbidity of these two disorders. (B) A common neurobiological antecedent (e.g., abnormal brain development, genetic defect) could lead to both epilepsy and ASD. Another possibility is that there is interaction between the pathophysiology of neural circuits underlying established ASD and epilepsy (i.e., at the level of the double-headed arrow). (C) Epilepsy or epileptogenic EEG changes (dashed box indicates uncertainty) could lead to ASD. (D) Conversely, abnormal brain circuitry underlying ASD could predispose the brain to seizures. These relationships are not mutually exclusive or unidirectional, such that mechanisms of epilepsy and ASD are interdependent and that targeted therapies for one disorder could benefit the other.

synthesis.[44, 45] LTD is a form of synaptic plasticity that underlies learning and memory, so dysfunctional LTD in FXS could reflect the cognitive deficiencies seen in patients.[46] In this model, LTD could be inhibited by blocking the metabotropic glutamate receptor 5 (mGluR5) with agents such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP). Further, FMRP normally functions to downregulate the translation of proteins, such as Arc, that are involved with the internalization of AMPA receptors from the postsynaptic surface. Thus, in the absence of postsynaptic FMRP, stimulation of mGluR5, either by receptor agonists or presynaptic glutamate release, results in increased postsynaptic protein translation, leading to excess internalization of AMPA receptors and eventual weakening of synaptic transmission (Figure 2). By contrast, premutation-associated disorders (FXTAS, fragile X-associated primary ovarian insufficiency, neurodevelopmental involvement)[47] are not a consequence of FMRP deficiency, *per se*; rather, mounting evidence from both human and animal studies indicates that these premutation-specific disorders are caused by a direct toxic gain-of-function of the CGG-repeat *FMR1* mRNA.[48, 49] Furthermore, reductions in hippocampal volume, activation, and associated memory deficit, as well as reduced amygdala activation[50] and psychopathology[51] appear much earlier in adulthood than do the symptoms of FXTAS, suggesting that the processes that ultimately will lead to FXTAS may be operating at a much earlier age. The reports of ADHD and ASD in young boys with the premutation also suggest a neurodevelopmental component to the premutation.[33] Recently, low-density hippocampal neuronal cultures from neonatal mice in the premutation range were shown to recapitulate neurodevelopmental and neurodegenerative aspects described *in vivo*.[52]

The mGluR model accounts for a number of the physical and behavioral features of FXS and predicts several aspects of the phenotype in various animal models, including enhanced seizure activity in an *Fmr1* knockout mouse model with audiogenic seizures.[53–55] One consequence of enhanced protein synthesis in the absence of postsynaptic FMRP in the knockout mouse is increased internalization of AMPA receptors at the postsynaptic surface. The augmented AMPA receptor internalization (a facet of the increased LTD observed in the knockout mouse) no longer requires protein synthesis, suggesting that the elevated protein levels present in the postsynaptic compartment are sufficient to establish the enhanced LTD.[56]

A potential caveat is that agents used in many animal studies, particularly those involving mGluR5 inhibitors (e.g., MPEP) or AMPA-receptor agonists, may have off-target effects that mimic the desired effect. To resolve this uncertainty, *Fmr1* knockout mice were crossed with animals heterozygous for deletion of the *Grm5* gene (50% reduction in mGluR5), thus mimicking drug-induced reductions in mGluR5 activity.[57] The resulting mice, *Fmr1*(−/Y)*Grm5*(+/−), displayed substantial correction of defects in experience and conditioning (i.e., ocular dominance plasticity and inhibitory avoidance extinction), normalization of dendritic spine density, a return to normal basal protein synthesis, attenuated susceptibility to audiogenic seizures, and rescue from early accelerated growth. These results clearly establish that the enhanced response to stimulation of the mGluR5 receptor plays a critical role in many of the phenotypic characteristics of FXS. Finally, it was shown that kindling promotes prolonged seizure activity and severe mossy fiber sprouting in the *Fmr1* knockout mouse and that this behavior could be at least partially blocked using either N-methyl-D-aspartate (NMDA)-receptor or mGluR5 inhibitors.[58]

Epileptogenic Mechanisms in Fragile X Syndrome

While the mGluR theory explains many of the phenotypic features of FXS, altered postsynaptic function arising from the absence of FMRP does not readily explain the central nervous system (CNS) hyperexcitability and seizure susceptibility associated with FXS. However, several recent studies have begun to reveal the connection. A recent investigation provides evidence that a voltage-gated inward current, $I_{\mathrm{mGluR(V)}}$, is the cellular basis for the epileptogenic behavior induced by activation of the mGluR5 receptor (Figure 2).[59, 60] Specifically, stimulation of mGluR5 by the agonist dihydroxyphenylglycine in mouse hippocampal slices led to prolonged epileptiform discharges that lasted more than 1 hour after washout of the agonist. Moreover, this inward current could be suppressed by inhibitors of downstream signaling pathways that mediate group I mGluR-coupled

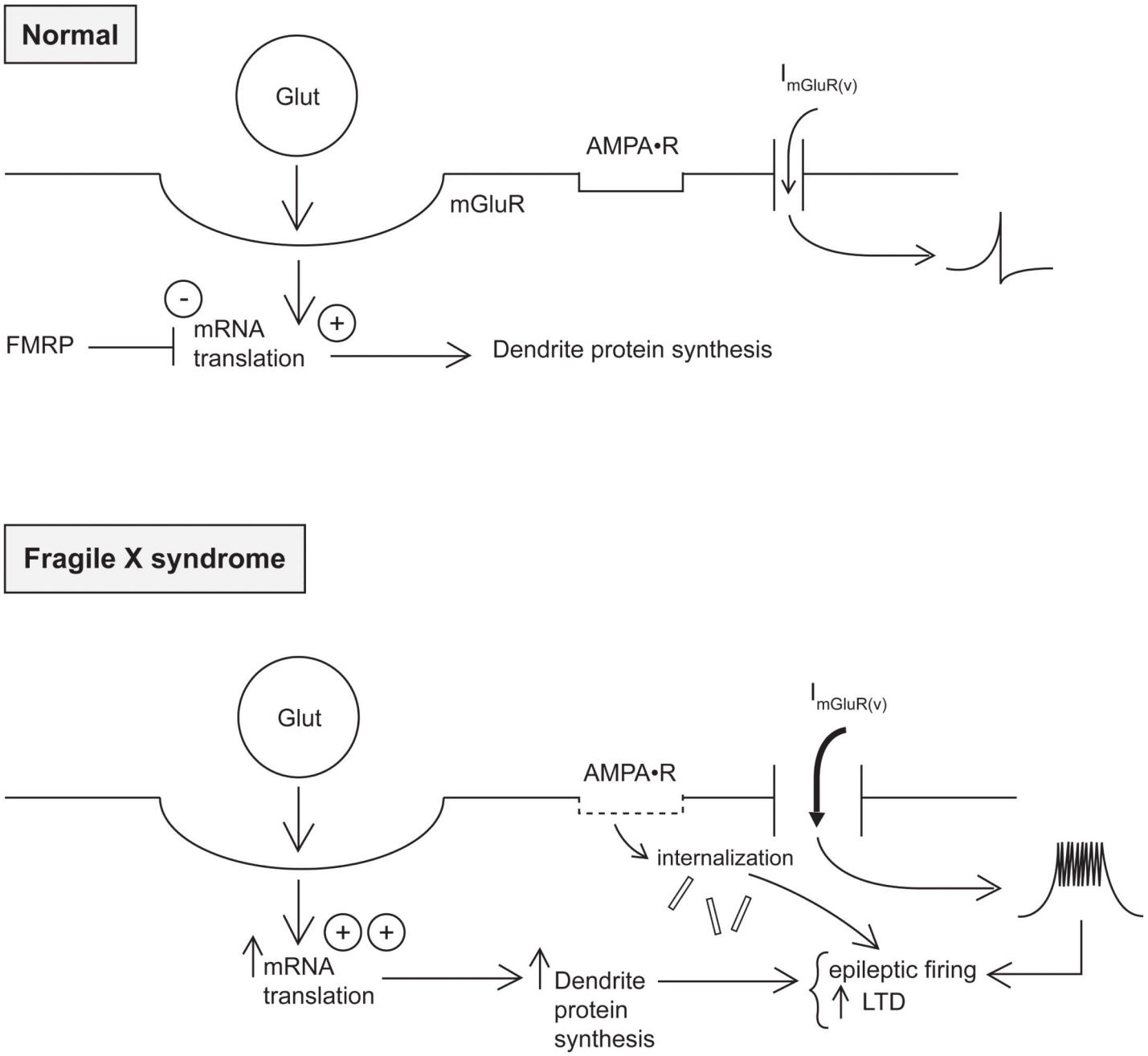

Figure 2. Possible mechanisms for seizures in fragile X syndrome (FXS). In the normal case (top), glutamate (Glut) activation of dendritic group I metabotropic receptors (especially mGluR5) enables intracellular gene transcription, leading to translation of dendritic proteins. This process is modulated by the fragile X mental retardation protein (FMRP), which keeps protein synthesis in check and prevents synaptic long-term depression. Activation of group 1 mGluR also activates a phospholipase C β1-dependent voltage-gated inward current ($I_{mGluR(V)}$), which, under normal conditions, allows hippocampal CA3 neurons to fire in brief bursts (thin curved arrow). In FXS (bottom), with absent FMRP, there is no inhibition of the downstream effects of mGluR activation, leading to excessive protein synthesis, increased LTD, and prolonged $I_{mGluR(V)}$ (thick curved arrow) which can lead to epileptic firing. Internalization of AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors as a consequence of mGluR activation enhances the tendency for epileptic firing. Concepts depicted here are derived from the work of several investigators (e.g., [39, 59, 60, 123]).

translation (e.g., tyrosine kinase, extracellular signal-regulated kinase [ERK]1/2).[61, 62] Remarkably, glutamate stimulation of glutaminergic synapses did not recapitulate this effect in wild-type mice, whereas $I_{mGluR(V)}$ was activated in hippocampal preparations from *Fmr1* knockout mice. The authors conclude that the induction of

$I_{mGluR(V)}$ serves as a form of synaptic plasticity to predispose to epileptogenesis. Thus, activation of mGluR5 at multiple synapses in the absence of FMRP translational control leads to heightened electrical excitability. The carrier of $I_{mGluR(V)}$ is not yet known, though evidence supports one or more of the transient receptor potential canonical (TRPC) channels that mediate Ca^{2+} entry in response to depletion of the endoplasmic reticulum Ca^{2+} stores.[63]

Evidence for a connection between the absence of *Fmr1* and epileptogenesis in the knockout mice was extended in a study of neocortical circuits.[64] In agreement with prior observations,[60] the authors documented increased intrinsic excitability in excitatory neurons from *Fmr1* knockout mice. However, there was an imbalance between this excitability and a relatively decreased excitatory drive present at fast-spiking inhibitory neurons. The net result was prolonged neocortical circuit activity (termed, UP state), induced by thalamic input. The heightened circuit activity, coupled with less synchronous network inhibition, was proposed as the underlying mechanism that leads to EEG abnormalities and epilepsy in FXS. Thus, the failure to properly modulate the mGluR5 response in the absence of FMRP results in neuronal hyperexcitability, mediated in part by the generation of a voltage-gated inward current, which in turn reduces excitatory input to inhibitory neurons and results in net increased excitability.[65]

Role of GABA Receptors

The increased excitability of hippocampal and neocortical circuits in FXS, due to dysregulation of glutaminergic neurons, can in turn disrupt the normal actions of inhibitory GABAergic neurons. Downregulation of $GABA_A$ receptor (GABR) subunits occurs at both the mRNA and protein levels - a situation that would further increase the excitatory character of limbic and cortical circuits.[66, 67] Recently, it was demonstrated that in addition to reductions in $GABA_A$ subunits, there is also lower expression of a number of genes involved in GABA metabolism, including *gad1*, *gat1* and *gat4,* in the brain of both mouse and *Drosophila* models of FXS.[68]

On a structural level, in the somatosensory cortex of the *Fmr1* knockout mouse, inhibitory circuits were found to be reorganized accompanied by a reduction in the density of GABAergic interneurons.[69] A separate investigation of the function of GABAergic neurons in the subiculum revealed that tonic, but not phasic, $GABA_A$ currents were downregulated in the *Fmr1* knockout mouse relative to wild-type controls.[70] These results were associated with reductions in tonic $GABA_A$ receptor subunits.

Several classes of pesticides of concern to human environmental health are known to interfere with GABA-mediated neurotransmission because they bind to GABA receptors and block their ability to mediate chloride fluxes. Organochlorine (OC) insecticides that possess polychloroalkane structures are known to bind to GABR in the mammalian brain and potently block their ability to conduct Cl-, with many having nanomolar affinity for their receptor binding site.[14] OC insecticides that are currently being used in the United States include endosulfan, dicofol and lindane. Because of their chemical stability, global distribution from countries that continue to use these compounds, and their propensity to bioaccumulate, exposures to OC insecticides continue to be a concern for human health. Yet relatively little is known about their developmental neurotoxicity and the long-term consequences of low-dose exposures.[71] An association between maternal residence near agricultural pesticide applications during key periods of gestation and the development of ASD has been documented.[72] Children of mothers living closest to agricultural fields with the highest endosulfan and dicofol use had a risk factor for autism that was 6.1 times higher than that of mothers not living near agricultural fields. The fact that OC and several newer widely used insecticides impair GABR function suggest that deficiencies in the function of the GABAergic system in the *Fmr1* knockout mouse would further upset the balance between excitatory and inhibitory function in the CNS, and may represent a valuable model for studying gene x environment interactions that cause hyper-excitation of the CNS.

Treatment Implications

The growth in knowledge of the pathogenesis of FXS, specifically regarding the linkage between abnormal neural function and epileptogenesis, presents numerous possibilities for targeted interventions.[30, 73] Perhaps the most attractive targeted treatment is blockade of the mGluR5 receptor, thus compensating for the absence of downstream control by FMRP. Clinical trials are presently underway with various mGluR5 inhibitors. An open-label, single-dose pilot trial in 12 individuals of the mGluR5 agonist, fenobam, demonstrated a reduction in anxiety and hyperactivity, with no significant adverse effects.[74] A second open-label treatment trial of 15 patients assessed the effects of lithium, which reduces mGluR5 activation of downstream processes.[75] There was significant improvement in behavior and verbal memory. Larger clinical trials are needed with both agents.

$GABA_A$ receptor subtypes comprise another potential therapeutic target.[76] *Fmr1* mutant *Drosophila* die during development if fed a high glutamate diet, consistent with the mGluR model of excess activation.[77] The authors exploited this lethal phenotype to screen for small molecules that would rescue the flies and found several, including GABA, that rescued the phenotype, providing additional evidence that GABR agonists might have a beneficial therapeutic effect. Finally, there is substantial evidence that GABR agonists, such as the neurosteroid allopregnanolone and a related analog, ganaxolone, possess significant antiseizure activity.[78]

Other approaches include an open label trial of minocycline, a metalloproteinase inhibitor that improves dendritic spine morphology in *Fmr1* knockout mice.[79] These and other pharmacologic agents will be used singly and in combination to target some of the most troubling behavioral manifestations in FXS.

In summary, epilepsy associated with FXS represents an opportunity to explore mechanisms of hyperexcitability in a disorder for which the molecular pathophysiology is unique and specific.[80] Seizures occurring in conjunction with FXS are generally mild, tend to disappear in childhood, typically respond to anticonvulsant treatment, and are associated with an EEG pattern of centrotemporal spikes. In several respects, the clinical and electrographic aspects of seizures in FXS resemble those of the benign focal epilepsies of childhood. Whether these similarities are coincidental or related mechanistically is an intriguing question for future investigation. The type of (and even need for) antiepileptic therapy for individuals with FXS must be weighed against potential adverse effects, which could be unique in this syndrome. Ideally, pathophysiological insights as reviewed here will lead to therapeutic interventions targeted to the specific molecular defects in FXS.

TUBEROUS SCLEROSIS COMPLEX

Clinical and Genetic Aspects

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder caused by a mutation in the *TSC1* or *TSC2* gene. *TSC1* (on chromosome 9q34) and *TSC2* (on chromosome 16p13) code for proteins (hamartin and tuberin, respectively) that form a dimeric complex that has guanosine triphosphatase (GTPase) activity and inhibits excessive cell growth and proliferation via the mammalian target of rapamycin (mTOR) signaling pathway.[81] Mutation of either gene causes dysregulation of mTOR, resulting in abnormal cellular proliferation, growth, and differentiation. This leads to the formation of tumors, usually benign, in many organs, including brain, kidney, and heart. Cellular regulation of the mTOR pathway and its dysfunction is discussed briefly below and is elaborated by Wong and Crino (mTOR and Epileptogenesis in Developmental Brain Malformations). Thus, TSC is a malformation of cortical development with a specific genetic basis that leads to a spectrum of neurological disability including multifocal epilepsy, mental retardation and ASD.[82, 83] Here, we focus on the relationship between epilepsy and ASD in TSC.

While any organ system can be affected in TSC, the brain is involved extensively. The neuropathological hallmark of TSC is cortical tubers.[84] Tubers are hamartomatous collections of dysplastic cells of both glial and neuronal origin with abnormal morphology, size, orientation, lamination and cellular connectivity. As such,

tubers or nearby extra-tuberal tissue are extremely epileptogenic and their extensive and varied cortical localization gives rise to multifocal sites of seizure generation.

In TSC, seizures are very common, affecting 60–90% of patients.[82, 85, 86] Seizures in TSC often begin in the first year of life, putting the developing brain at risk for seizure-induced neuroplastic changes.[87] Seizures of any type can be seen, particularly complex partial (related to the multifocal pathology), generalized tonic-clonic, and infantile spasms (IS). IS are very common in TSC and are frequently associated with subsequent autism.[88, 89] Seizures in TSC are often severe and intractable, with remissions occurring only rarely. In some cases, surgical resection of an offending tuber, especially if performed early in life, can result in seizure reduction and a more favorable developmental profile.[90, 91] However, there is a critical need to develop a nonsurgical treatment of TSC that not only reduces seizure occurrence but also prevents epileptogenesis, and by extension, its cognitive and behavioral/autistic sequelae.

About 25–50% of children with TSC have ASD, with girls and boys affected to a similar degree, in marked contrast to the male predominance in nonsyndromic ASD.[92] Tuber burden (number, extent) and location correlate with the degree of mental retardation, ASD, and seizure predisposition. Tubers located in the temporal lobes are highly correlated with ASD in TSC patients.[89, 93] Presumably, disruption of limbic circuitry, perhaps by the hypersynchronous neuronal activity comprising seizures or epileptiform EEG discharges, leads to abnormalities of language development and cognitive processing.[94, 95] There is also a high rate of ASD in TSC patients with tubers in the cerebellum.[96] Patients with *TSC2* mutations tend to have earlier onset of ASD and epilepsy but there is considerable overlap between those with *TSC1* and *TSC2* mutations.[86, 97] Although seizures, especially those with onset early in life, are a risk factor for ASD in TSC,[98, 99] ASD also occurs in patients with TSC who do not have epilepsy. Therefore, the relationship between seizures and ASD in TSC is complex with imprecise genotype/phenotype correlation and the potential for modification by epigenetic and environmental factors.[89, 100, 101] Since epilepsy precedes ASD in many cases of TSC, it is possible that abnormal neural firing alters the development of language and social function.

Pathophysiology

The mTOR protein is a central regulator of cell growth and proliferation.[102] Figure 3 depicts some of the molecules involved in this signal transduction pathway. Components of the mTOR pathway are present at synapses and play an important role in synaptic plasticity via regulation of local protein synthesis. Activation of either growth factor receptors of glutamate receptors sets into motion a subcellular signaling cascade that regulates cell growth and differentiation, mediated through the mTOR pathway that is in turn regulated by *TSC1* and *TSC2*. A mutation in *TSC1* or *TSC2* prevents mTOR activation, leading to unbridled protein transcription and translation and hence cell growth and proliferation. Upstream regulation of the *TSC1/2* complex and cellular signaling that can bypass *TSC1/2* function (such as the ERK pathway[103]) provides potential pathways for controlling this unchecked cell growth and epileptogenesis. Downstream from mTOR, a variety of kinases and translation factors serve as modulators of cell growth. Nevertheless, it is presently unclear how mTOR dysregulation leads directly to epilepsy or autism susceptibility.

Animal models of TSC afford the opportunity to study pathophysiological consequences of *TSC1* and *TSC2* mutations. The Eker rat is a spontaneous germline mutation in which one *TSC2* allele is inactivated. Eker rats demonstrate defective long-term potentiation (LTP), a form of synaptic plasticity involved in learning and memory; LTP is even more abnormal after seizures in Eker rats.[104, 105] Other models have been created by knocking out of *TSC1* or *TSC2* in neurons or glia, allowing investigation of the structural, epileptic and cognitive effects. *TSC2* knock outs have upregulation of the mTOR pathway and abnormal learning and memory.[106] Conditional *TSC1* knock outs have abnormal hippocampal-dependent learning and memory as well as social behaviors, mimicking key autistic features; they demonstrate abnormal cellular architecture and progressive epilepsy as well.[107] Using such models, a variety of pathophysiological findings have been found including altered glutamate transporter, potassium channels, and gap junctions, all of which are consistent with enhanced

excitability (and seizure activity).[108, 109] Other factors that alter the excitation/inhibition balance in the TSC brain have also been documented in favor of excessive excitation, including specific abnormalities of glutamate receptors.[110]

Treatment Implications

Targets for therapeutic intervention in TSC include several components of the mTOR signaling cascade (Figure 3). There is considerable excitement about rapamycin, an inhibitor of mTOR that is already in clinical use as an immunosuppressant, which ameliorates the epileptic and cognitive consequences of TSC.[111] In *TSC1* knockout mice, rapamycin prevents neuronal hypertrophy.[112] Early treatment of *TSC1* knockout mice with rapamycin prevents epileptogenesis, and seizures return if rapamycin is discontinued. [106, 113] A case report of a clinical trial with rapamycin in a 10-year-old girl with TSC claims marked seizure reduction without adverse side effects.[114] Obviously this finding must be expanded in case series. Rapamycin may have utility in acquired epilepsy as well. In a model of temporal lobe epilepsy in mice induced by kainic acid, rapamycin blocked both acute and chronic phases of seizure-induced mTOR activation. It also prevented seizure-induced cell death and reduced subsequent epileptogenesis.[115]

Another strategy in TSC is to suppress seizures with an anticonvulsant drug. Vigabatrin inhibits GABA reuptake into the presynaptic terminal, thus prolonging the availability of GABA to mediate inhibition at its postsynaptic receptors. This agent is particularly useful for treatment of IS in TSC patients, lessening the subsequent risk for epilepsy and autistic/cognitive deficiencies.[116, 117] In fact, vigabatrin appears to be uniquely effective for IS in TSC, suggesting that there is some specificity of the drug for the pathophysiological mechanism.

CONCLUSION - IS THERE A CONVERGENT PATHWAY BETWEEN AUTISM AND EPILEPSY?

Returning to the question that opens this chapter, why is epilepsy so common in children with autism spectrum disorders? The heterogeneous etiologies of ASD and epilepsy make it unlikely that a single common mechanism explains seizure predisposition in both disorders, and recent genetic studies point to numerous, diverse gene mutations that have autism and epilepsy as joint sequelae.[20] Yet, hints about the pathogenesis of at least some forms of ASD are emerging. First, the majority of mutations focus on the synapse.[17, 19] This association is not surprising, as neuronal excitability is governed by the function and dysfunction of synaptic elements such as receptors and their subtypes; neurotransmitters and their synthesis, metabolism and vesicular release; developmental regulation of cell adhesion; and the ratio of excitation to inhibition as a result of the above factors. Alterations in synaptic plasticity could underlie autistic and cognitive symptoms, especially if selected circuits are involved.

Second, as discussed here, dysfunction in subcellular signaling pathways of diverse conditions (e.g., FXS, TSC) may in fact have common convergence points contributing to pathophysiology as exemplified by mTOR dysregulation. In dendrites, mTOR is activated by stimulation of mGluR. The reported involvement of the mTOR pathway in FXS emphasizes a potential commonality between FXS and TSC, with a pathophysiological link to abnormal cellular signaling that could lead to ASD. In *Fmr1* knockout mice, the mTOR pathway is upregulated, providing a functional link between mGluR overactivation and abnormal synaptic plasticity.[118] Additional evidence for the mTOR pathway in autism and epilepsy comes from mutations in the tumor suppressor gene *PTEN* (phosphatase and tensin homolog on chromosome ten), which is involved in upstream regulation of mTOR by inhibiting the interaction of phosphatidylinositol 3-kinase (PI3K) and phosphoinositol 3,4,5-triphosphate (PIP3) (Figure 3). Conditional knockout of *Pten* in mice results in an increase in mTOR activation and clinical manifestations that include spontaneous seizures and ASD-like symptoms of anxiety and deficiencies in social interaction.[119] Rapamycin treatment rescues all of these neurologic deficits.[120]

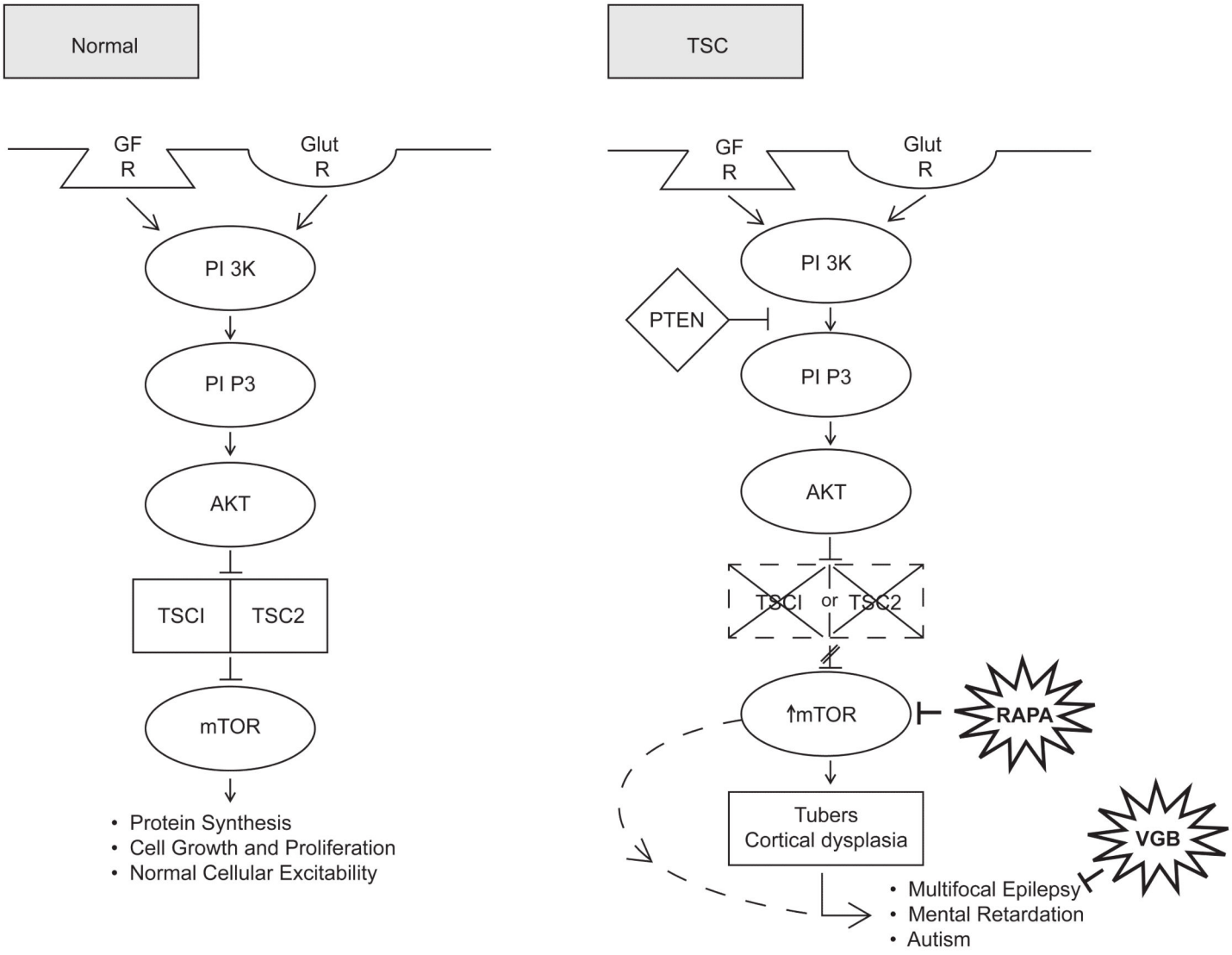

Figure 3. Simpified signaling pathway in tuberous sclerosis complex (TSC) with possible functional consequences that could lead to increased seizure susceptibility. In the normal situation (left), activation of receptors (R) for growth factors or glutamate leads to an intracellular signaling cascade that limits mTOR activation via the TSC1 and TSC2 gene heterodimer. Therefore, protein synthesis is modulated and aberrant cell growth is prevented; likewise, cellular excitability is normal. If TSC1 or TSC2 is mutated (right), mTOR is hyperactivated, leading to cellular dysplasia and tuber formation, along with neuronal hyperexcitability, epilepsy and cognitive/behavioral deficits and autistic symptomatology. It is also possible that epilepsy and ASD can occur independently of dysplasia tubers (dashed arrow). This pathological signaling pathway can be modulated at several points by agents that inhibit mTOR (RAPA) or suppress seizures (VGB).

Abbreviations: GF, growth factors; GLUT, glutamate; R, receptor; PI3K, class I phosphatidylinositol 3-kinase; PIP3, phosphoinositol 3,4,5-triphosphate; AKT, activated tyrosine kinase; TSC, tuberous sclerosis complex; mTOR, mammalian target of rapamycin; PTEN, phosphatase and tensin homolog on chromosome ten; RAP, rapamycin; VGB, vigabatrin.

Third, thinking beyond the synapse to neuronal function on a network scale, both epilepsy and autism involve abnormal synchrony of widespread systems of the brain.[121] Alterations in functional connectivity between brain structures critical for language and social development are also pivotal in the synchronization that occurs in many epilepsy syndromes.[122] Information about the functional pathology of such systems is just emerging. Unexpected mechanisms may evolve from genetic studies, involving proteins not expected to participate in the control of cognition or cellular excitability. Such molecules are already being linked to ASD and represent additional sites of intervention that give hope for the future.

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