Introduction

Autism spectrum disorders (ASD) and epilepsy are among the most devastating and common neurological disorders of childhood, affecting about 0.5-1% of the population. ASD and epilepsy are often associated, suggesting that common neurodevelopmental bases may exist for these two disorders. The neurodevelopmental bases of both ASD and epilepsy have been clearly showed by a number of genetic, neuroimaging and neuropathological studies. In recent years, dysfunction of inhibitory GABAergic circuits has been proposed as a cause for both disorders. Several studies performed on both animal models and postmortem human samples indicate that GABAergic neurons and circuits are altered in both ASD and epilepsy, suggesting that the excitation/inhibition imbalance resulting from neurodevelopmental defects in GABAergic circuitry might represent a common pathogenetic mechanism for these disorders. Here, we will review the most significant studies supporting this hypothesis.

Keywords: Seizure, mental retardation, neurological disorder, neurotransmission

Review Article

The role of GABAergic system in neurodevelopmental disorders: a focus on autism and epilepsy

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Abstract: Autism spectrum disorders (ASD) and epilepsy are very common neurological disorders of childhood, with an estimated incidence of about 0.5 – 1 % in worldwide population. ASD and epilepsy are often associated, suggesting that common neurodevelopmental bases may exist for these two disorders. The neurodevelopmental bases of both ASD and epilepsy have been clearly showed by a number of genetic, neuroimaging and neuropathological studies. In recent years, dysfunction of inhibitory GABAergic circuits has been proposed as a cause for both disorders. Several studies performed on both animal models and postmortem human samples indicate that GABAergic neurons and circuits are altered in both ASD and epilepsy, suggesting that the excitation/inhibition imbalance resulting from neurodevelopmental defects in GABAergic circuitry might represent a common pathogenetic mechanism for these disorders. Here, we will review the most significant studies supporting this hypothesis.

Keywords: Seizure, mental retardation, neurological disorder, neurotransmission

y-amino butyric acid (GABA) is the major inhibitory neurotransmitter in the brain. A number of studies have implicated the GABAergic system dysfunction in epilepsy and ASD. An increasing body of evidence suggests that a downregulation of GABAergic function is critical in ASD-associated epilepsy. Quantitative autoradiographic studies examining the density and distri-
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Distribution of GABAergic receptor subunits indicated a downregulation of GABAergic function in the hippocampus of ASD patients with seizures [11]. Furthermore, altered packing of GABAergic interneurons in the CA1 and CA3 hippocampal subfields where malformations are associated with the generation of seizures have been described [12]. Several studies have demonstrated a loss of inhibitory interneurons in the epileptic brain [13,14]. Human genetics studies clearly indicate an association between ASD and genes for GABA receptor subunits as well as genes controlling GABAergic neuron development or GABAergic synapse structure. Moreover, recent studies, performed on both animal models and postmortem human samples, suggest that GABAergic neurons and circuits may be altered in ASD patients. Here we examine the link between ASD and epilepsy with particular focus on the role of GABAergic dysfunction in the pathogenesis of these diseases. In particular, we will describe some of the key human and animal studies further outlining the link between epilepsy and ASD and the potential mechanistic role of GABA dysfunction.

Genetics of ASD

ASD represent a very heterogeneous group of neurodevelopmental disabilities of proven genetic origin, with an incidence of about 60-70/10,000 [15]. A gender distortion is observed in ASD (4:1 males to females ratio) [16], reflecting a possible involvement of the X chromosome or imprinting mechanisms. The genetic factors play an important role in the pathogenesis of these diseases [17], as documented by the recurrence risk in families and twin studies. These studies show a concordance rate of 82–92% in monozygotic versus 1–10% in dizygotic twins. Heritability is estimated above 90% and sibling recurrence risk is above 6–20% [16,18]. About 10%–20% of individuals with an ASD have an identified genetic etiology. Chromosomal alterations have been reported in ~5% of cases. Genetic forms of ASD include monogenic and complex disorders. The most common single gene mutation in ASD is FMR1 associated with FXS, present in ~2% of cases. Other monogenic disorders include neurofibromatosis (NF1), tuberous sclerosis (TSC1, TSC2), Angelman syndrome (UBE3A) and Rett syndrome (MECP2), covering only the 2–5% of the ASD cases [19].

Cytogenetic investigations and genome-wide scans have been performed to identify chromosomal regions containing ASD susceptibility genes [20,21]. The most common chromosomal rearrangement is the maternal duplication of 15q11-q13, which accounts for approximately 1-2% of ASD cases [22]. Recent genome-wide association (GWA) studies have identified novel candidate loci between the cadherin genes CDH9 and CDH10 (5p14.1) [23] and between the SEMA5A and TAS2R1 genes (5p15.2) [24]. In addition, the Autism Genome Project (AGP) Consortium has genotyped 1,558 ASD families for one million single nucleotide polymorphisms (SNPs), identifying a novel locus near the gene MACROD2 (20p12.1) [25]. Syndromic forms of ASD have been associated with both copy number variations (CNVs) and rare mutations in several genes, including SHANK3, NLGN3, NLGN4, NRXN1 and HOXA1 [26]. A recent extensive meta-analysis of the literature [27] allowed identification of 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behaviour. The vast majority of these genes and loci have been also causally implicated in epilepsy [27]. For example, chromosome 15q, which contains genes coding for GABA receptor subunits, has been reported to be a common site for mutations in ASD and syndromic epilepsy [28].

GABAergic dysfunction in ASD and epilepsy

Abnormalities in GABAergic interneuron function and/or connectivity might represent the anatomical substrate of an unbalanced ratio of excitation/inhibition in sensory, mnemonic, social and emotional systems, that has been postulated to occur in the autistic brain [29]. Indeed, several studies showed that impaired maturation of the GABAergic circuitry results in an immature structure and function of the cerebral cortex, that remains more plastic and sensitive to alterations in sensory inputs [30-32]. An immature structure and function of the cerebral cortex is considered a major feature of neurodevelopmental disorders [29].

Several studies have described alterations in the GABAergic system in post-mortem brains of autistic patients. A 50% reduction in GAD65/67 protein levels was reported in the cerebellum and parietal cortex of ASD patients [33]. Reduced levels of GAD67 and GAD65 mRNAs were also detected in Purkinje cells and dentate nuclei neurons in the cerebellum from ASD cases [34]. Interestingly, the same authors also re-
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reported an increase of GAD67 mRNA levels in GABAergic basket cells that was interpreted as a compensatory up-regulation to supply the loss of Purkinje cells in ASD brains [35]. Several studies showed a significant decrease in GABA<sub>a</sub> receptor α4, α5, β1 and β3 subunits [11,36,37], as well as a significant reduction of benzodiazepine binding sites in ASD brains [38]. GABAA receptors were also reduced in restricted regions of the cerebral cortex in ASD patients [39]. Recently, a transcranial magnetic stimulation study detected a reduced cortical inhibition (interpreted as a possible disruption of GABA<sub>a</sub> receptor activity) in the brain of a subset of ASD patients [40]. Taken together, these data support the hypothesis of a GABAergic signalling deficit in ASD.

As for ASD, several evidence link the pathophysiology of epilepsy with GABA neurotransmission and imbalanced excitation/inhibition. Abnormalities of GABAergic function have been observed in several genetic and experimental animal models of epilepsy [41]. In addition, reductions of GABA-mediated inhibition, activity of glutamate decarboxylase, binding to GABA<sub>a</sub> and benzodiazepine sites, GABA in cerebrospinal fluid and brain tissue have all been reported in studies of human epileptic brain tissue [42]. Furthermore, GABA agonists suppress seizures, and GABA antagonists produce seizures [43]. There are two main aspects to the role of GABA dysfunction in the pathogenesis of epilepsy in ASD. First, absence of GABA signaling results in loss of inhibitory neuronal firing that normally prevents the spread of paroxysmal discharge. Furthermore, normal GABAergic function is crucial in brain development, and alteration in this function may significantly affect neuronal migration, differentiation, synaptogenesis and circuit formation. In addition to the direct effect of altered GABA system on the ability of interneurons to inhibit the generation of synchronized discharges, there is a vast array of ASD candidate genes involved in secondary regulation of the GABAergic system during development that may play a role in the pathogenesis of epilepsy-autism disorders.

Taken together, these data provide a sound rationale for proposing GABA dysfunction, (primarily through loss of GABA transmission, and secondarily through altered circuit formation in development) as a potential link between epilepsy and ASD, possibly even a common pathology. The range of genes involved may reflect the spectrum of pathologies associated with ASD and epilepsy and warrant more detailed investigation. Overall, these data indicate that the ASD-epilepsy condition is a spectrum disorder within itself. The severity of the ASD condition (e.g., presence or absence of mental retardation) is closely associated with the severity of the epilepsy phenotype (e.g., seizure frequency, severity and intractability). Early diagnosis and suitable treatment protocols are vital for successful outcomes [44,45]. Properly constructed prospective clinical studies, aimed at profiling the progression of the disease in a growing cohort of cases, could provide vital insights required to develop successful therapeutic approaches for epilepsy in ASD.

**ASD and epilepsy: common neurodevelopmental bases**

The co-occurrence of ASD and epilepsy has been well studied in genetic conditions that result in abnormal excitability and disrupted synaptic plasticity in the developing brain such as fragile X syndrome (FXS), Rett syndrome (RTT), tuberous sclerosis complex (TSC), all of which include ASD and epilepsy, and in several animal models lacking genes involved in brain development such as DLX, NRP2, ARX and EN2.

**Fragile X syndrome**

Fragile X syndrome (FXS) is the most frequent form of inherited mental retardation and often presents with ASD and epilepsy. FXS results from the expansion of triplet repeats in the untranslated region of the FMR1 gene, preventing synthesis of the FMR1 gene product FMRP. FMRP regulates mRNA transport and local protein synthesis in neuronal dendrites and spines. Patients with FXS show increased spine density in the neocortex and the abundance of long, thin dendritic spines with an immature morphology [46,47]. Fmr1 knockout mice show a phenotype resembling the human disease: altered learning and behaviour, greater susceptibility to seizures, altered synaptic plasticity [48] and an excess of long, thin dendritic spines [49]. Recently, an increased intrinsic excitability of the excitatory neurons was described in Fmr1 knockout mice supporting a connection to epileptogenesis [50]. Alterations in the glutamatergic system in FXS could disrupt the normal actions of inhibitory GABAergic neurons, resulting...
in downregulation of GABA receptor subunits [51-53] and altered expression of a number of enzymes involved in the metabolism of GABA [54]. Several studies show a strong reduction in the expression of GABA_α receptor subunit mRNAs and proteins in adult Fmr1 knockout mice [54,55], that is accompanied by abnormal GABAergic transmission [56,57], deficits of parvalbumin (PV) but not calbindin (CB) or calretinin (CR) cortical interneurons and increased audiogenic seizure susceptibility [58].

Rett Syndrome. Rett syndrome (RTT) is a postnatal neurodevelopmental disorder typically emerging between 6 – 18 months of age consisting of progressive loss of cognitive and motor function and the emergence of epilepsy [59]. Seizures have been reported in 50 – 90% of RTT patients [60,61]. RTT is caused by mutations in the gene encoding for the methyl-CpG binding protein 2 (MeCP2), a transcriptional regulator involved in chromatin remodeling and splicing. MeCP2 regulates gene expression by binding to methylated CpG dinucleotides leading to chromatin compaction and transcriptional repression [62]. Recent evidence suggests that in same cases MeCP2 can also act as a transcriptional activator [63]. Reduced brain size and increased neuronal density have been observed in several brain regions of RTT patients, including the cerebral cortex, hypothalamus and the hippocampus [64]. Studies of RTT autopsy material revealed a reduction of the size and complexity of pyramidal neurons dendritic trees in the cortex and in the hippocampus [65]. In addition, autoradiography studies in the frontal cortex and basal ganglia of autopsy RTT brains revealed abnormalities in the density of neurotransmitter receptors, such as excitatory NMDA, AMPA, kainate and metabotropic glutamate receptors as well as inhibitory GABA receptors [66]. Mice with truncated MeCP2 recapitulate many RTT features [67]. Mecp2-null mice are behaviourally normal until 5 weeks of age, when they begin to show behavioural deficits resembling RTT patients’ symptoms. Initially body tremors, motor abnormalities and spontaneous seizures appear. Later on the mutant mice show pronounced stereotypic forelimb motions and clamping when suspended by the tail, resembling the typical hand-wringing seen in RTT patients [67]. Despite the evident behavioural abnormalities, Mecp2-mutant mice show no major neuropathological phenotype. They show only a reduction in brain weight and a simplified dendritic tree of pyramidal neurons, neuronal anatomical features observed also in many RTT patients [68]. Electrophysiological studies showed a reduction in excitatory synaptic strength and glutamatergic synapse numbers [69] and alteration inhibitory strength in the cortex, hippocampus and brainstem of MeCP2 null mice [70]. More recently, the observation that cortical wild-type GABAergic neurons express 50% more MeCP2 than non-GABAergic neurons suggested a specific role of MeCP2 in GABAergic function [71]. Loss of Mecp2 in inhibitory neurons expressing the vesicular GABA transporter (VIAAT/VGAT) resulted in ASD-like repetitive and stereotyped behaviours, EEG abnormalities and seizures. Interneurons immunolabelling in VGAT-Mecp2 mutants also showed a reduction of GAD65 and GAD67 mRNA in the cerebral cortex. Moreover, electrophysiological recordings indicated that Mecp2 deficiency in GABAergic neurons determines a reduction the neurotransmitter release due to a reduction of the enzyme GAD in presynaptic terminals [71]. Interestingly, loss of MeCP2 in GABAergic neurons, both globally and in a subset, reveals a multitude of neuropsychiatric phenotypes encompassing social behaviour, learning/memory, motor function, stereotyped behaviours and sensorimotor gating [71].

Tuberous Sclerosis. Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome characterized by benign tumors, early onset epilepsy, intellectual disability, and autism. TSC results from mutations of TSC1 (hamartin) or TSC2 (tuberin) genes that lead to the formation of hamartomatous growths in one or more body systems (skin, central nervous system, kidneys, heart, lungs, and retina). Hamartin and tuberin form a protein complex that inhibits the phosphatidylinositol 3-kinase (PI3) and the mTOR signaling pathways. Mutations of hamartin or tuberin in TSC lead to hyperactivation of the mTOR, and other downstream signaling pathways resulting in increased cell growth, proliferation, and abnormal gene expression. Mice with a heterozygous inactivating mutation in the TSC genes show deficits in learning and memory and abnormal social behaviour [72]. Furthermore Tsc1 or Tsc2 loss increases spine length and decreases dendritic spines density in hippocampal slice cultures [73]. In addition to structural changes in dendrites, the mTOR pathway is reported to play a role in post-synaptic AMPA receptor expression [74]. Alterations in expression of specific glutamate and GABA receptor subunits have been also described in
cortical tubers from human TSC patients indicating that imbalances of excitation and inhibition may contribute to the TSC phenotype [75,76].

**Neurexins and neuroligins**

Neurexins (NRXNs) are presynaptic proteins, binding postsynaptic neuroligins. This interaction is thought to trigger postsynaptic differentiation and control the balance of inhibitory GABAergic and excitatory glutamatergic inputs [77,78]. There are three NRXN genes (NRXN 1–3) in mammals; among these, mutations and chromosomal rearrangements in NRXN1 has been associated with ASD [79-81]. Recently it has been shown that NRXNs can bind not only neuroligins but also GABAA receptors [82]. The effect of this ligand-receptor interaction decreases GABAergic transmission. Neuroligins (NLGNs) are neural cell adhesion molecules, which act as ligands for neurexins [77,78]. NLGNs play a key role in the formation, organization, and remodeling of synapses and different isoforms are associated with different synaptic types. NLGN1, NLGN4X and NLGN4Y are localized at glutamatergic synapses [17,83]. NLGN3 is present in both excitatory and inhibitory synapses [84,85], whereas NLGN2 is located in GABAergic synapses [17,83,86]. Mutations in NLGN1, 3 and 4X genes have been identified in patients with familial ASD [87-89]. Mice carrying the R451C mutation in the Nlgn3 gene show behavioural phenotypes related to ASD (lack of social behaviours, reduced ultrasound vocalization; [90,91]). In addition, Nlgn3 R451C knock-in mice present an increase in the number of GABAergic synapses (as evaluated by vesicular GABA transporter and gephyrin immunostaining) and in the amplitude of inhibitory currents, suggesting that the R451C mutation switches Nlgn3 synaptic specificity from glutamatergic to GABAergic [91]. Further characterization of these mutants demonstrated that loss of PV-positive basket cells is detectable across the two hemispheres in these mice [92]. As neurorexins and neuroligins control the formation of both excitatory and inhibitory synapses they may contribute to alter the balance between excitatory synapses and inhibitory synapses that in turn could affect cognition and social behaviour as well as contribute to epilepsy.

**Genes regulating brain development**

Evidence is accumulating that several genes associated with both ASD and epilepsy play roles in the development of cortical inhibitory interneurons including the members of the distal-less homeobox (DLX) family, neurexin 2 (NPN2), reelin (RELN), aristaless-related homeobox (ARX) and engrailed 2 (EN2) [93-97]. The human DLX genes are located head-to-head on chromosomes 2q31 (DLX1 and DLX2) and 7q21.3 (DLX5 and DLX6), two regions previously associated to ASD susceptibility in several genome-wide linkage studies [98]. Two studies examining SNPs in the DLX1 and DLX2 genes have found an association with ASD, suggesting that common genetic variations in these genes play a critical role in the disease [99,100]. DLX genes encode homeodomain transcription factors key regulators in forebrain and basal ganglia development. The DLX genes are mainly expressed in the basal ganglia, the amygdala, the hypothalamus and in local circuit neurons of the cerebral cortex [29]. The Dlx transcription factors regulate the development of basal ganglia GABAergic projection neurons and of the cortical inhibitory interneurons [101]. Mice lacking Dlx1 display a selective loss of somatostatin (SST), neuropeptide Y (NPY), CR and RELN expressing interneurons accompanied by reduced GABAergic inhibitory transmission and late-onset epilepsy [102]. More recently, additional behavioural abnormalities (such as conditioned fear response) linked to impairment of GABAergic systems were described in Dlx1-null mice [103]. While the role of Dlx1/2 in brain development is well established, little information is available on the function of Dlx5/6. Dlx5 is known to promote differentiation of olfactory bulb interneurons [104,105]. Because Dlx1/2 are required to induce expression of Dlx5/6 in the lateral and medial ganglionic eminence [106,107], the contribution of Dlx5/6 to the Dlx1/2 phenotype has not been established. Recently a role of Dlx5/6 in the development of PV interneurons has been described [108].

Deficits in inhibitory interneurons and reduced seizure threshold were observed in NPN2 deficient mice [109]. The gene for NPN2 (also known as NRP2) is coded for at 2q34, a region known to be strongly associated with ASD [94]. NPN2 functions as a chemorepulsive receptor for the axon guidance molecule Semaphorin 3F, regulate neuronal migration and differentiation, contributing to brain development and network formation. NPN2 deficient mice had shorter seizure latencies, increased vulnerability to seizure-induced neuronal death and developed chemically-induced spontaneous recurrent sei-
zures [109]. Importantly, NPN2 null mice had a reduced number of GABA, PV and NPY interneurons [109].

GABAergic neuron development dysfunction may also occur in conjunction with abnormalities in the RELN gene, coding for the extracellular matrix glycoprotein Reelin which is involved in neuronal migration and lamination of the cerebral cortex during embryogenesis [110]. Reelin binding to membrane receptors enhances signal transduction pathways leading to synaptic plasticity and axonal growth (Beffert, 2005). RELN maps to 7q22 human chromosome [111]. Linkage in this region is among the most robust genetic findings in ASD. In family-based and case–control studies the 5′-untranslated region (5′-UTR) GGC repeat alleles was associated with ASD [112]. Mice lacking the Reelin gene (reeler mice) show a disorganization of laminated brain regions such as cerebral cortices and cerebellum, resulting in a dramatic impairment of neuronal migration in the cerebral cortex [113]. Reeler mice also show a decrease of dendritic spine density and a decreased GABA turnover [114]. Recently, ASD-like behaviours and loss of PV interneurons was reported in Reeler mice [115].

The aristaless-related homeobox gene (ARX), in chromosome Xp22, is a transcription factor that belongs to a family of paired-class homeobox genes, and plays a pivotal role in the development of the central nervous system. ARX large deletions, protein truncating mutations and missense mutations in the homeobox region lead to X-linked lissencephaly with abnormal genitalia, while other ARX mutations cause intellectual disability, ASD and epilepsy without cortical malformations. Arx expression has been detected in the developing lateral and medial ganglionic eminence (LGE and MGE) and later in cortical progenitors and migrating interneurons [116-119]. Arx expression is controlled by the Dlx genes in cells derived from basal ganglia progenitor domains [120]. Studies in animal models showed that ARX is critical for radial migration of cortical progenitors and is crucially involved in the development and migration of GABAergic interneurons [96]. In Arx-null embryos, migration from the LGE and the MGE are nearly absent, whereas migration through the cortical layers is only partially impaired. As a consequence, CB- and CR-expressing cells are severely reduced and NPY interneurons are nearly absent throughout the brain [118,121]. Defective tangential migration is similarly observed after electroporation into the MGE of rat brain slices [122]. Studies on Arx knock-out mice described abnormal expression of several transcription factors, potentially important for migration and differentiation of certain population of neurons [118,121].

Among the numerous ASD associated genes EN2 (coding for the homeobox-containing transcription factor Engrailed-2) was originally shown to be involved in posterior brain (midbrain/hindbrain) embryonic development [123]. EN2 maps to a region of chromosome 7 implicated in ASD susceptibility, and GWA studies indicated EN2 as a candidate gene for ASD [124]. Namely, two SNPs in the human En2 gene have been associated to ASD, one of which (rs1861973, A-C haplotype) is functional: when tested in a luciferase reporter assay in rat, mouse and human cell lines, this SNP markedly affected En2 promoter activity [124]. En2 null mice display cerebellar hypoplasia and a reduced number of Purkinje cells [123]. Importantly, ASD-like behaviours such as decreased play, reduced sociality, and impaired spatial learning and memory were described in these mutants [125]. Recently we showed that En2 is also expressed in telencephalic structures involved in epileptogenesis. Accordingly, an increased susceptibility to seizures was detected in En2 null mice, that was accompanied by reduced PV immunostaining on cell bodies of CA3 pyramidal neurons and reduced SST immunostaining in the stratum lacunosum moleculare of the hippocampal formation [126]. These findings suggest that the En2 gene may be involved in GABAergic system development and maintenance, and altered En2 function may be a common cause of ASD and seizures.

Conclusions

Several studies suggest that an impairment of inhibitory neurotransmission and the subsequent imbalance in excitation/inhibition in the developing brain may constitute a fundamental event in the development of both ASD and epilepsy. ASD and epilepsy are often associated, and defects in the development, maintenance and function of GABAergic interneurons have been postulated as a pathogenic mechanism of ASD-epilepsy syndromes. However, a direct, causal demonstration of a GABAergic dysfunction...
in the brain of ASD patients is still lacking. Conversely, data from mouse models of ASD strongly support the hypothesis of GABAergic dysfunction in ASD-epilepsy; further analyses on these and novel models will contribute to unravel the common neurodevelopmental basis of ASD and epilepsy.

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