



Neuropathological Mechanisms of Seizures in Autism Spectrum Disorder

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OPEN ACCESS

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Specialty section:

This article was submitted to
Child and Adolescent Psychiatry,
a section of the journal
Frontiers in Neuroscience

Received: 18 March 2016

Accepted: 18 April 2016

Published: 10 May 2016

Citation:

Frye RE, Casanova MF, Fatemi SH,
Folsom TD, Reutiman TJ, Brown GL,
Edelson SM, Slattery JC and
Adams JB (2016) Neuropathological
Mechanisms of Seizures in Autism
Spectrum Disorder.
Front. Neurosci. 10:192.
doi: 10.3389/fnins.2016.00192

This manuscript reviews biological abnormalities shared by autism spectrum disorder (ASD) and epilepsy. Two neuropathological findings are shared by ASD and epilepsy: abnormalities in minicolumn architecture and γ -aminobutyric acid (GABA) neurotransmission. The peripheral neuropil, which is the region that contains the inhibition circuits of the minicolumns, has been found to be decreased in the post-mortem ASD brain. ASD and epilepsy are associated with inhibitory GABA neurotransmission abnormalities including reduced GABA_A and GABA_B subunit expression. These abnormalities can elevate the excitation-to-inhibition balance, resulting in hyperexcitability of the cortex and, in turn, increase the risk of seizures. Medical abnormalities associated with both epilepsy and ASD are discussed. These include specific genetic syndromes, specific metabolic disorders including disorders of energy metabolism and GABA and glutamate neurotransmission, mineral and vitamin deficiencies, heavy metal exposures and immune dysfunction. Many of these medical abnormalities can result in an elevation of the excitatory-to-inhibitory balance. Fragile X is linked to dysfunction of the mGluR5 receptor and Fragile X, Angelman and Rett syndromes are linked to a reduction in GABA_A receptor expression. Defects in energy metabolism can reduce GABA interneuron function. Both pyridoxine dependent seizures and succinic semialdehyde dehydrogenase deficiency cause GABA deficiencies while urea cycle defects and phenylketonuria cause abnormalities in glutamate neurotransmission. Mineral deficiencies can cause glutamate and GABA neurotransmission abnormalities and heavy metals can cause mitochondrial dysfunction which disrupts GABA metabolism. Thus, both ASD and epilepsy are associated with similar abnormalities that may alter the excitatory-to-inhibitory balance of the cortex. These parallels may explain the high prevalence of epilepsy in ASD and the elevated prevalence of ASD features in individuals with epilepsy.

Keywords: autism spectrum disorder, seizures, epilepsy, genetic syndrome, metabolic disorders, excitatory-to-inhibitory cortical balance, gamma-aminobutyric acid

INTRODUCTION

Autism spectrum disorders (ASD) is a behaviorally defined disorder that has recently been estimated to affect as many as 1 out of 45 individuals (Zablotsky et al., 2015). Although, ASD is defined by behavioral features, it is associated with co-occurring medical conditions. For example, epilepsy is more prevalent in ASD than in the typically developing children with a prevalence ranging from 5 to 38% (Deykin and Macmahon, 1979; Volkmar and Nelson, 1990; Tuchman and Rapin, 2002; Danielsson et al., 2005; Hara, 2007). Data from surveys performed by the Autism Research Institute on over 1200 participants suggests that the prevalence is between 15 and 19%. Epilepsy is one of the most disabling ASD co-morbidities as children with ASD and epilepsy are more likely to have intellectual disability (Tuchman, 2013) and increased mortality (Shavelle et al., 2001; Pickett et al., 2011) as compared to children with ASD without epilepsy. In addition, epilepsy in ASD tends to be more treatment-resistant as compared to epilepsy in typically developing children (Sansa et al., 2011).

One of the major questions in ASD research is its etiology. Much ASD research concentrates on genetic causes (Rossignol and Frye, 2012b) even though inherited single gene and chromosomal defects only account for a minority of ASD cases (Schaefer et al., 2013). However, genetic etiologies may be overrepresented in children with ASD and epilepsy as many genetic syndromes and gene mutations associated with ASD include epilepsy as a common feature (Murdoch and State, 2013; Tuchman et al., 2013).

Although some have suggested that clinical seizures do not have any special causative significance in ASD (Tuchman and Rapin, 1997), ASD coexists with epilepsy in several disorders (see Section Specific Medical Disorders Associated with Both ASD and Epilepsy) suggesting that the same neuropathology may result in both ASD and epilepsy. Thus, this manuscript reviews the shared biological abnormalities in ASD and epilepsy in two sections. The section called Basic Neuropathological Mechanisms of Seizures in ASD discusses two neuropathological mechanisms that have been described in ASD that can also cause epilepsy. Both mechanisms involve an abnormal reduction in inhibitory mechanisms of the brain, thereby resulting in an increase in the excitatory-to-inhibitory balance. The section called Specific Medical Disorders Associated with Both ASD and Epilepsy will review specific clinical disorders that have been described in both ASD and epilepsy with special reference to underlying neuropathological mechanisms that can cause seizures.

Overall, our review finds that many disorders associated with ASD increase the excitatory-to-inhibitory balance by either (1) reducing inhibitory circuits in the brain through a decrease in the inhibitory neurotransmitter γ -aminobutyric acid (GABA), or (2) increasing excitatory circuits in the brain through an increase in glutamate neurotransmission. Elevation in the excitatory-to-inhibitory balance in the brain can lead to seizures.

Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; ASD, autism spectrum disorder; ATP, adenosine-5'-triphosphate; CNS, central nervous system; GABA, γ -aminobutyric acid.

By carefully outlining these disorders, insight into the etiologies that underlie ASD may be better understood.

BASIC NEUROPATHOLOGICAL MECHANISMS OF SEIZURES IN ASD

Several neuropathological processes associated with ASD are also associated with epilepsy. Here we review two such neuropathological processes: (1) minicolumn architecture and (2) GABA neurotransmission.

Minicolumn Architecture

The minicolumn is a radially-oriented assembly of neurons and cellular elements considered to be an elemental modular microcircuit of the neocortex (Buxhoeveden and Casanova, 2002; Casanova et al., 2006). The minicolumn core contains pyramidal cell arrays surrounded by a peripheral neuropil space that contains GABAergic inhibitory interneurons and other cells such as the double-bouquet cell (Mountcastle, 1997; Buxhoeveden and Casanova, 2002; Defelipe, 2005). Double-bouquet cells feature axonal bundles which provide a vertical stream of inhibition (Mountcastle, 1997). This inhibitory stream insulates the minicolumn core from the excitation from other surrounding minicolumns (Defelipe et al., 1990; Favorov and Kelly, 1994; Defelipe, 1999).

The peripheral neuropil space has been shown to be reduced in post-mortem brain tissue from ASD individuals (Buxhoeveden and Casanova, 2002), with this reduction most prominent over the prefrontal cortex (Casanova et al., 2006). The neuropil space is reduced within the region that contains the inhibition circuits of minicolumns (Defelipe et al., 1990; Favorov and Kelly, 1994; Defelipe, 1999). These architectural changes should, theoretically, disrupt the normal balance between excitation and inhibition influences within the columnar organization of the cortex (Casanova et al., 2003). A reduction of GABAergic inhibitory activity has been proposed to result in hyperexcitability of minicolumn circuits and can explain some of the symptomatology observed in ASD, including the high incidence of seizures and auditory-tactile hypersensitivity (Rubenstein and Merzenich, 2003). Networks of inhibitory interneurons acting as GABA gated pacemakers are also critically involved in gamma oscillations (Grothe and Klump, 2000). Abnormalities in gamma oscillations are associated with problems with binding and the coactivation of neural assemblies. A deficit in binding and gamma oscillations has been proposed to explain many of the symptoms related to ASD (e.g., visuoperceptual defects, understanding and using context; Grice et al., 2001; Brock et al., 2002; Brown et al., 2005; Rippon et al., 2007; Tommerdahl et al., 2007).

GABA Transmission

GABA is the major inhibitory neurotransmitter of the central nervous system (CNS). Abnormalities in GABA neurotransmission have been associated with epilepsy. GABBR1A, GABBR1B, and GABBR2 receptor subunits are reduced in the hippocampi of patients with temporal lobe epilepsy (Princivalle et al., 2003), and animal models have also

shown a link between GABA receptor expression and epilepsy (Schuler et al., 2001; Han et al., 2006). Individuals with ASD have been shown to have abnormalities in GABAergic brain systems (Blatt et al., 2001; Dhossche et al., 2002; Fatemi, 2008), as well as a reduction in GABA_A (Fatemi et al., 2009) and GABA_B (Fatemi et al., 2009) receptor subunits in both the frontal and parietal cortices, as compared to controls, with the ASD group also demonstrating a markedly higher rate of epilepsy than the controls. In addition, the GABA subunits found to be reduced in individuals with ASD (i.e., GABR α 1 and GABBR1) have been associated with childhood absence epilepsy, juvenile myoclonic epilepsy, and atypical absence seizures (Delgado-Escueta, 2007; Kang et al., 2009).

SPECIFIC MEDICAL DISORDERS ASSOCIATED WITH BOTH ASD AND EPILEPSY

Genetic Disorders

The neurobiological mechanisms leading to seizures in genetic syndromes that are associated with ASD are diverse and complex. Imbalances in GABA and glutamate have been suggested to underlie CNS dysfunction in several of these genetic syndromes. Defects in GABA_A function has been implicated in Fragile X (D'hulst and Kooy, 2007) and recent studies on Fragile X suggest that mGluR5 dysfunction results in heightened excitability and secondary alterations in GABA function (Frye, 2014). Dysfunction in GABA_A receptor function has also been implicated in Angelman syndrome (Pelc et al., 2008). Indeed, a cluster of genes coding for three GABA_A receptor subunits lie adjacent to the critical Angelman region (i.e., UBE3A). Mutations within the Rett syndrome gene (i.e., MECP2) decreases expression of GABRB3, a gene responsible for encoding the β_3 subunit of the GABA_A receptor, and DLX5, a gene which regulates the production of enzymes responsible for GABA production.

Some genetic syndromes associated with epilepsy and ASD are associated with metabolic abnormalities. For example, mouse models of both Angelman and Rett syndromes demonstrate mitochondrial dysfunction (Kriaucionis et al., 2006; Su et al., 2011) and mitochondrial dysfunction is reported in a Rett syndrome case (Condie et al., 2010). Phelan-McDermid Syndrome (PMS) and duplication of the 22q13 region are both associated with ASD and mitochondrial dysfunction (Frye, 2012b; Frye et al., 2016a). As mentioned below, disruption of mitochondrial metabolism can result in changes to the excitatory-to-inhibitory balance.

Single gene disorders associated with both ASD and epilepsy have been associated with abnormalities in the excitatory- to-inhibitory balance (Srivastava and Schwartz, 2014). Mutations in CNTNAP2 (Peñagarikano et al., 2011) or CNTNAP4 (Karayannis et al., 2014) result in reduced GABAergic neurotransmission. The SYNGAP1 haploinsufficiency animal model shows an increase in neuronal excitability and an increase in seizure susceptibility (Clement et al., 2012). Other genes are associated with a relative decrease in the excitatory-to-inhibitory

balance. Animal model with NLGN3 mutations demonstrates increased inhibitory neurotransmission (Tabuchi et al., 2007). Cellular (Shcheglovitov et al., 2013) and animal models (Bangash et al., 2011; Wang et al., 2011b) demonstrate a reduction in excitatory neurotransmission when SHANK3 is disrupted. Animal models with decreased synapsin I (SYN1) demonstrate reduced glutamate release (Li et al., 1995).

Metabolic Disorders

Disorders of Energy Metabolism

Disorders of energy metabolism have been associated with ASD (Giulivi et al., 2010; Frye and Naviaux, 2011; Frye, 2012c; Rose et al., 2014a,b) and epilepsy (Frye, 2015). Some children with ASD have mitochondrial dysfunction that is different than classic mitochondrial disease (Frye and Rossignol, 2011; Rossignol and Frye, 2012a; Frye, 2012a). Of children with mitochondrial disease and ASD, 41% have seizures (Rossignol and Frye, 2012a).

Other disorders of energy metabolism are associated with ASD and epilepsy, including disorders of creatine metabolism (Póo-Argüelles et al., 2006; Longo et al., 2011) and adenylosuccinate lyase deficiency (Spiegel et al., 2006; Jurecka et al., 2008). Creatine and phosphocreatine play important roles in energy storage and transmission of high-energy phosphates. Adenylosuccinate lyase deficiency is a rare autosomal disorder of *de novo* purine synthesis (Spiegel et al., 2006; Jurecka et al., 2008). The purine nucleotide cycle regulates cellular metabolism by controlling levels of fumarate, a citric acid cycle intermediate, and adenosine, the precursor to adenosine-5'-triphosphate (ATP) (Spiegel et al., 2006).

An energy deficiency can result in seizures. Neurons with high firing rates, such as inhibitory GABA interneurons (Anderson et al., 2008), are disproportionately affected by an energy deficit. In addition, processes critically involved in the release and reuptake of neurotransmitters and maintenance of the neuronal resting potential, such as calcium homeostasis, are critically dependent on mitochondrial function (Li et al., 2004; Quiroz et al., 2008; Chen and Chan, 2009).

Disorders of GABA Neurotransmission

Several metabolic disorders directly lead to GABA metabolism abnormalities. Pyridoxine and its primary biologically active form, pyridoxal-5-phosphate, are essential cofactors for over 110 enzymes, including glutamic acid decarboxylase (GAD), the enzyme that produces GABA from glutamate. Pyridoxal-5-phosphate depletion reduces GAD activity which, in turn, increases glutamate, decreases GABA synthesis and decreases cortical inhibition (Gospe et al., 1994; Gospe, 2002; Mills et al., 2006). This occurs in pyridoxine dependent seizures.

Succinic semialdehyde dehydrogenase deficiency is an autosomal recessive disorder of GABA metabolism. It results from a defect in the aldehyde dehydrogenase gene (ALDH5A1; Jakobs et al., 1981). Aldehyde dehydrogenase is partially responsible for the degradation of GABA and when this enzyme is deficient GABA is degraded through an alternative pathway, resulting in the formation of gamma-hydroxybutyric acid and GABA elevations in the brain. Positron emission tomography studies suggest that chronic elevation in GABA down-regulates

GABA_A receptors, leading to a deficit in cortical inhibition and an elevation in the excitatory-to-inhibitory balance (Pearl et al., 2009a,b).

Disorders of Glutamate Neurotransmission

Two types of metabolic disorders (urea cycle defects and phenylketonuria) may result in dysfunction of glutamate neurotransmission. Glutamate is the major excitatory cortical neurotransmitter and excess glutamate results in an elevation in the excitatory-to-inhibitory balance, leading to seizures.

Urea cycle defects result in ammonia elevations. Astrocytes exposed to ammonia do not express glutamate reuptake transporters that normally reduce extracellular glutamate (Rose, 2006). Thus, increased ammonia levels in the brain can result in elevated extracellular glutamate.

Neurological consequences of phenylketonuria are usually avoided by dietary treatment starting at birth (Williams et al., 2008). However, epilepsy and ASD may develop in untreated children and in those noncompliant to the prescribed diet (Baieli et al., 2003). Such children demonstrate high levels of phenylalanine in the brain. Phenylalanine antagonizes both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors (i.e., α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; Glushakov et al., 2003). Chronic elevation in phenylalanine leads to an upregulation of several NMDA and AMPA receptor subunits (Glushakov et al., 2005), increased glutamate receptor density and increased glutamate release (Martynyuk et al., 2005). Such changes in glutamate neurotransmission predispose the brain to heightened excitability and seizures, especially if the phenylalanine level is transiently lowered (Martynyuk et al., 2005).

Mineral Deficiencies

Magnesium is essential in neurotransmitter metabolism and in modulating neurotransmitter receptor function. Ionized magnesium is important in seizure control. Ionized magnesium is a NMDA antagonist (Ault et al., 1980; Hallak, 1998) and may be a factor in some epilepsies (Hallak et al., 1992; Mathern et al., 1998; Mikuni et al., 1999). NMDA receptor activation by glutamate results in calcium influx (Macdermott et al., 1986; Delorenzo and Limbrick, 1996), which is pro-epileptogenic (Delorenzo, 1986; Heinemann and Hamon, 1986). Low ionized magnesium or altered balance between ionized magnesium and ionized calcium may precipitate seizures (Chaistitwanich et al., 1987). Patients with epilepsy have been shown to have significantly lower mean ionized magnesium levels and an increase in the ionized calcium to ionized magnesium ratio in spite of normal total serum magnesium levels (Sinert et al., 2007).

The role of zinc in epilepsy is not clear. Low zinc levels has been associated with seizures in children (Ganesh and Janakiraman, 2008; Mollah et al., 2008) and in the EL epileptic mouse (Fukahori and Itoh, 1990). Zinc acts as an anticonvulsant (Williamson and Spencer, 1995; Cole et al., 2000) and decreases seizure susceptibility (Fukahori and Itoh, 1990). However, zinc has been shown to be proconvulsant in a mouse model (Pei et al., 1983). Zinc co-localizes with glutamate where it inhibits

the reuptake of synaptic GABA, thereby increasing the cortical inhibitory tone (Cohen-Kfir et al., 2005). Thus, a zinc deficiency could increase the relative excitatory-to-inhibitory balance.

Vitamin Deficiencies

Children with ASD have been shown to have abnormalities in cobalamin dependent pathways (Frye and James, 2014), and cobalamin supplementation improves metabolites in these pathways (James et al., 2009a; Adams et al., 2011; Frye et al., 2013a; Hendren et al., 2016) and behavior (Adams et al., 2011; Frye et al., 2013a,b; Hendren et al., 2016). The exact mechanism in which cobalamin deficiency causes seizures is unclear but infants with cobalamin deficiency manifest seizures (Benbir et al., 2007; Erol et al., 2007). Cobalamin is essential for myelin synthesis and methylation (Kumar, 2004). Neurons with damaged myelin sheaths are more susceptible to the excitatory effects of glutamate (Akaike et al., 1993).

Cerebral folate deficiency (CFD) is characterized by low 5-methyltetrahydrofolate in the CNS and is associated with ASD and seizures (Ramaekers et al., 2002; Ramaekers and Blau, 2004). Children with idiopathic ASD have a high prevalence of folate receptor alpha autoantibodies that causes CFD (Frye et al., 2013c, 2016b). Folate is essential in a wide range of metabolic processes, including redox and homocysteine metabolism and gene methylation (Obeid et al., 2007). Disruption in these processes could disrupted redox metabolism, thereby depleting glutathione which, in turn, can decreased glutamate degradation, leading to increased cortical excitability (Deepmala et al., 2015).

Heavy Metals

Several epidemiologic studies support a relationship between ASD and exposure to mercury or other heavy metals (Rossignol et al., 2014). Epilepsy has been associated with exposure to toxic levels of heavy metals including lead (Silbergeld et al., 1979; Swartzwelder, 1985; Lockitch et al., 1991; Arrieta et al., 2005) and mercury (Torres et al., 2000). Heavy metals may have toxic effects on the brain by reducing mitochondrial function (James et al., 2009b; Belyaeva et al., 2011; Wang et al., 2011a; Rose et al., 2015), causing apoptosis (Wang et al., 2011a; Pal et al., 2012), and increasing levels of reactive oxygen species (James et al., 2009b; Furieri et al., 2011; Wang et al., 2011a). Although the mechanism(s) by which heavy metals cause epilepsy are not clear, both mitochondrial dysfunction (Rossignol and Frye, 2012a) and high levels of reactive oxygen species (Riazi et al., 2010; Specchio et al., 2010; Waldbaum and Patel, 2010), have been linked to epilepsy.

Immune Dysregulation

Multiple studies have demonstrated evidence of abnormal immune system activation in individuals with ASD. Unusually high levels of proinflammatory cytokines have been found in the cerebrospinal fluid of individuals with ASD (Vargas et al., 2005). Abnormal activation of the intrinsic immune system in the cerebral cortex, white matter, and cerebellum has been demonstrated in individuals with ASD at autopsy (Vargas et al., 2005).

Children with ASD manifest autoantibodies implicated in childhood epilepsy syndromes associated with language regression (Connolly et al., 2006) and cognitive and behavioral changes (Ganor et al., 2004; Vincent et al., 2004) and drug-resistant epilepsy (Majoie et al., 2006) as well as autoantibodies to critical brain elements, such as myelin basic protein, brain derived neurotrophic factor and endothelial cells (Connolly et al., 1999). GAD65 autoantibodies are associated with several neurological disorders including drug-resistant epilepsy (Blanc et al., 2009). One study found GAD65 autoantibodies in 15% of children with ASD (Rout et al., 2012) but other studies have failed to find these autoantibodies in ASD children (Kalra et al., 2015).

Certain autoantibodies, such as the folate receptor alpha autoantibody, could result in specific syndromes like CFD and a recent study suggests that the folate receptor alpha autoantibody may also interfere with cobalamin metabolism (Frye et al., 2016b). Autoantibodies associated with specific seizure syndromes could also result in the dysfunction of specific neural elements. Autoantibodies can also be an epiphenomenon of underlying immune dysregulation.

SUMMARY

Many of these disorders associated with both seizures and ASD increase the excitatory-to-inhibitory balance. Some disorders reduce brain inhibition by reducing the inhibitory neurotransmitter GABA by a reduction in GABA production, metabolic failure of inhibitory GABA neurons or dysfunction of GABA receptors. Other disorders increase brain excitation by increasing the excitatory neurotransmitter glutamate through increased production, alterations in degradation, or altering glutamate receptors. Independent of these disorders, neuropathological research on ASD points to abnormalities in inhibitory GABA pathways.

A few studies suggest that some gene mutations are associated with a reduction in the excitatory-to-inhibitory balance. This appears to contradict the classic association

of seizures with cortical excitability. It may be that these changes cause instability in neuronal networks or compensatory changes at the neuronal level that may create abnormalities in neural excitability. For example, although brain GABA is increased in patients with succinic semialdehyde dehydrogenase deficiency, GABA receptors are down regulated, leading to an elevation in the excitatory-to-inhibitory balance (Pearl et al., 2009a,b).

Clearly further research examining these pathways in more detail could help guide the development of targeted treatments and improve our understanding of the clinical implication of these changes. This review suggests that neurological dysfunction in at least a subset of children with ASD is based on alterations in the excitatory-to-inhibitory balance in the brain.

AUTHOR CONTRIBUTIONS

This manuscript was developed as part of the Elias Tembenis Seizure Think Tanks at the Autism One Meeting in Chicago in May of 2009 and 2010 and at the Autism Canada Meeting in Toronto, Canada in October of 2009. These Think Tanks included scientists and clinicians with expertise in seizures related to ASD. The participants represented a wide variety of researchers and practitioners who treat ASD. Individual participants who provided written text for the supplement or contributed in the editing of the document are recognized as authors. Dr. Fatemi's research fellows assisted with the writing despite not attending the Think Tank so they are recognized as authors.

ACKNOWLEDGMENTS

This research has been supported by a National Institute of Child Health and Development grant to SF. This manuscript was supported by the Elias Tembenis Seizure Think Tanks conducted at the Autism One Meetings, the Autism International Association and the Autism Research Foundation.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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