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GABAergic Dysfunction in Autism and Epilepsy

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1. Introduction

Autism spectrum disorders (ASD) and epilepsy are among the most devastating and common neurological disorders of childhood, with an estimated incidence of about 0.5 – 1% in worldwide population. Autism and epilepsy are often associated: about 30% of autistic patients develop epilepsy, and a relevant percentage of epileptic patients in paediatric age shows ASD symptoms. This suggests that – at least in certain cases – common neurodevelopmental bases may exist for these two diseases (Brooks-Kayal, 2010).

The neurodevelopmental bases of both autism and epilepsy have been clearly showed by a number of clinical, neuroimaging and neuropathological studies. A large series of evidence also indicates that both autism and epilepsy have a primarily genetic origin. A wide variety of genes have been associated to these diseases, including genes regulating brain development, gene transcription, synaptic scaffolding, neurotransmission and signal transduction. Indeed, genetic heterogeneity is recognised as a typical feature of both autism and epilepsy, meaning that different mutations may result in similar disease phenotypes. Since autism and epilepsy are neurological disorders involving multiple genes and resulting in complex pathological traits, understanding the underlying mechanisms is a very difficult task. Moreover, even though the two diseases may have a common neurodevelopmental origin, a precise link between these two pathologies still remains to be determined.

In recent years, inhibitory circuit dysfunction gained increasing attention in ASD research. γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain, and 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. It is likely that the imbalance between excitation and inhibition resulting from neurodevelopmental defects in GABAergic circuitry might represent a common cause for ASD and epilepsy. Here, we will review the genetic, cellular, anatomical and neurophysiological studies that support this hypothesis.

2. Genetic determinants of ASD

ASD represent a group of very heterogeneous group of neurodevelopmental disabilities of proven genetic origin, with an incidence of about 60-70/10,000 (Fombonne, 2009). A gender distortion is observed in ASD (4:1 males to females ratio; Abrahams & Geschwind, 2008), reflecting a possible involvement of the X chromosome or imprinting mechanisms. The genetic factors play an important role in the pathogenesis of these diseases (Persico et al., 2006), 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% (Abrahams & Geschwind, 2008; Toro et al., 2010). The genetic architecture of ASDs is complex; only 10–20% of ASD patients have an identified genetic etiology, whereas in the majority of patients the origin of the disorder remains unknown. Genetic forms of ASD include monogenic and complex disorders, as well as chromosomal abnormalities. Monogenic disorders include neurofibromatosis (NF1), fragile X syndrome (FMR1), tuberous sclerosis (TSC1, TSC2), Angelman syndrome (UBEA3A) and Rett syndrome (MECP2), covering only the 2–5% of the ASD cases (Hatton et al., 2006). Cytogenetic investigations and genome-wide scans have been performed to identify chromosomal regions containing ASD susceptibility genes. Results from these genome-wide linkage scans indicate potential susceptibility regions that spread across the entire genome, but only a few loci (Freitag, 2007; Yang & Gill, 2007). The most common chromosomal rearrangement is the maternal duplication of 15q11-q13, which accounts for approximately 1-2% of ASD cases (Vorstman et al. 2006). Recent genome-wide association (GWA) studies have identified novel candidate loci between the cadherin genes CDH9 and CDH10 (5p14.1; Wang et al., 2009) and between the SEMA5A and TAS2R1 genes (5p15.2 ; Weiss et al., 2009). 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; Anney et al., 2010). 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 (Lintas & Persico, 2009). A recent extensive metanalysis of the literature (Betancur, 2011) allowed identification of 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behaviour. It is interesting to note that the vast majority of these genes and loci have been also causally implicated in epilepsy (including genes regulating brain development, gene transcription, synaptic scaffolding, neurotransmission and signal transduction), suggesting that these two neurodevelopmental disorders share common genetic bases (Betancur, 2011). Specifically, several evidences suggest that an impairment of inhibitory neurotransmission may constitute a fundamental event in the development of both ASD and epilepsy (Rubenstein & Merzenich, 2003). Since GABA is the major inhibitory neurotransmitter in the brain, here we briefly summarize the genes involved in GABAergic dysfunction and their relation with susceptibility to ASD and epilepsy.

2.1 Genes regulating GABAergic neuron development
Several genes control the process of development of GABAergic neurons, including DLX1, DLX2, MASH1 and RELN (Wonders & Anderson, 2006). The DLX1 and DLX2 genes encode homeodomain-containing transcription factors and are located head-to-head on chromosome 2q31, a region previously associated to autism susceptibility in several

genome-wide linkage studies. 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 (Liu et al., 2009; Chang et al., 2010). 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 (Forster et al., 2002). RELN maps to 7q22 human chromosome (De Silva et al., 1997). 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 (Persico et al., 2001). Importantly, Reelin (the product of RELN gene) is expressed in GABAergic neurons the adult brain (van Kooten et al., 2005).

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 (mesencephalon/hidbrain) embryonic development (Joyner et al., 1991). Recent studies on En2 null mice suggest that En2 deletion may alter GABAergic circuitry in the adult brain (Tripathi et al., 2009; see section 3.3.2). EN2 maps to a region of chromosome 7 implicated in ASD susceptibility, and GWA studies indicated EN2 as a candidate gene for ASD (Benayed et al., 2009). 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 (Benayed et al., 2009).

2.2 Genes coding for GABA$_A$ receptor subunits

Genes coding for GABA receptors has been extensively studied to evaluate their role in the pathogenesis of ASD. Three classes of GABA receptors exist in the mature mammalian brain, named as GABA$_A$, GABA$_B$ and GABA$_A$-rho (GABA$_C$). GABA$_A$ receptor is a ionotropic receptor that allows chloride ion fluxes through the neuronal membrane. Nearly 20 GABA$_A$ subunits have been reported in humans (Olsen & Sieghart, 2009). Mutations in GABA$_A$ receptor subunits genes have been associated to ASD. The chromosome 15q11, containing the genes coding the three GABA$_A$ receptor subunits α5, β3 and γ3 (GABRA5, GABRB3 and GABRG3, respectively) has been linked to ASD, and SNPs in the above mentioned genes have been associated to ASD (Buxbaum et al., 2002; Hogart et al., 2007, 2009). It is interesting to note that, among these genes, GABRB3 has also been indicated as susceptibility gene for childhood absence epilepsy (Urak et al., 2006).

2.3 Genes involved in GABAergic synapse structure and function

Different genes involved in the development and function of inhibitory GABAergic synapses have been associated to ASD. 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 (Graf et al., 2004; Scheiffele et al., 2000). There are three NRXN genes (NRXN 1–3) in mammals; among these, mutations and chromosomal rearrangements in NRXN1 has been associated with ASD (Feng et al., 2006; Kim et al., 2008; Wisniowiecka-Kowalnik et al., 2010). Recently it has been shown that NRXNs can bind not only Neuroligins (NLGNs) but also GABA$_A$ receptors (Zhang et al., 2010). The effect of this

ligand-receptor interaction decreases GABAergic transmission. NLGNs are neural cell adhesion molecules, which act as ligands for neurexins (Graf et al., 2004; Scheiffele et al., 2000). 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 (Persico et al., 2006; Craig & Kang, 2007). NLGN3 is present in both excitatory and inhibitory synapses (Chih et al., 2005; Budreck & Scheiffele, 2007), whereas NLGN2 is located in GABAergic synapses (Craig & Kang, 2007; Persico et al., 2006; Varoqueaux et al., 2006). Mutations in NLGN1, 3 and 4X genes have been identified in patients with familial ASD (Jamain et al., 2003; Laumonnier et al., 2004; Lawson-Yuen et al., 2008).

The MECP2 gene, coding for the epigenetic regulator methyl-CpG-binding protein 2, is the causative gene for Rett syndrome, which belong to the family of ASD. Rett syndrome is characterized by loss of language capability, motor stereotyped behaviors, severe mental retardation and seizures (Chahrour & Zoghby, 2007). Recent studies indicate that Mecp2 dysfunction in GABAergic interneurons severely impacts GABA signaling and results in ASD-like phenotypes in the mouse (Chao et al., 2010; see section 3.3.6).

Fragile X syndrome (FXS) is one of the disorders included in ASD. FXS is caused by an expansion of the trinucleotide repeat in the promoter region of the fragile X mental retardation 1 (FMR1) gene (Verkerk et al., 1991). FMR1 gene encodes the fragile X mental retardation protein (FMRP), a mRNA binding protein with a key role in the intracellular transport and translation of 4–8% of synaptic proteins (Bassell & Warren, 2008). Recent evidence also indicates the involvement of the GABAergic system in the pathogenesis of FXS (D'Hulst & Kooy, 2007, 2009; Olmos-Serrano et al., 2010; see also 3.3.7).

3. Deficits of GABAergic neurons and circuits in ASD

From the literature data reported in the previous chapter, it is evident that genetic defects in genes regulating GABAergic neuron development as well as GABAergic synapse structure and function are crucially involved in ASD pathogenesis. Alterations of GABAergic neurons and circuits have been reported in postmortem brain tissue samples from ASD patients, as well as in mouse models of the disease. Here we will review the more significant findings from these studies.

3.1 GABAergic neuron defects in the brain of ASD patients

The analysis of postmortem tissues revealed that many brain regions are affected in ASD patients, including the cerebral cortex, limbic system and cerebellum. Minicolumns represent the cellular and functional organization of glutamatergic and GABAergic neurons in the cerebral cortex (De Felipe et al., 1990; Mountcastle, 1997; Polleux & Lauder, 2004). Minicolumns are anatomically characterized by vertical arrays of pyramidal neurons with their dentrides and axon projections. Pyramidal cells arrays are accompanied by their GABAergic interneurons that establish synapses with pyramidal cells bodies, their axons emergences and dentrites. A narrowing of cortical minicolumns (namely, a reduced distance between columns) has been shown in ASD patients (Casanova et al., 2002). This reduced intercolumnar distance was proposed to depend on structural/anatomical defects in GABAergic interneurons surrounding principal pyramidal cortical neurons (Casanova 2003; Casanova & Trippe 2009, Raghanti et al., 2010). An increased cell density and a reduced cell

size have long been reported in the limbic system of ASD patients (Kemper & Bauman, 1993). More recently, a significant increase in the number of parvalbumin-, calbindin- and calretinin-positive interneurons has been reported in the hippocampus of ASD patients (Lawrence et al., 2010). In the cerebellum, a clear reduction in the number of inhibitory Purkinje neurons has long been reported in ASD postmortem tissues (Kemper & Bauman, 1993). More recent studies confirmed the selective loss of calbindin-positive Purkinje cells but not parvalbumin-positive stellate and basket interneurons in the ASD cerebellum (Whitney et al., 2008, 2009).

3.2 GABAergic signaling deficits in the brain of ASD patients

Several studies suggest a GABAergic signaling dysfunction in ASD, mainly due to altered levels of the GABA synthetic enzyme (glutamic acid decarboxylase, GAD) and GABA receptors. Two GAD isoforms exist, named GAD65 (GAD2) and GAD67 (GAD1), respectively localized on chromosome 10 and 2 in humans (Karlsen et al., 1991; Kaufman et al., 1991; Martin & Rimvall, 1993). Several studies were conducted in post-mortem brains of autistic patients focusing on parietal cortices and cerebellar alterations in terms of GAD proteins amount and Purkinje cells quantification. A 50% reduction in GAD65/67 proteins levels was reported in the cerebellum and parietal cortex from ASD patients (Fatemi et al., 2002). Accordingly, reduced levels of GAD67 and GAD65 mRNAs were also detected in Purkinje cells and dentate nuclei neurons in the cerebellum from ASD cases (Yip et al., 2007, 2008). Interestingly, the same author also reported an increase of GAD67 mRNA levels in GABAergic basket cells in the cerebellar molecular layer that was interpreted as a compensatory up-regulation to supply the loss of Purkinje cells in ASD brains (Yip et al., 2008). Several studies showed a significant decrease in GABA$_A$ receptor α4, α5, β1 and β3 subunits (Blatt et al. 2001; Fatemi et al., 2010, Samaco et al. 2005), as well as a significat reduction of benzodiazepine (the GABA$_A$ receptor ligand) binding sites (Oblak et al., 2011) in ASD brains. GABA$_B$ receptors were also reduced in restricted regions of the cerebral cortex from ASD patients (Oblak et al., 2010). Importantly, a recent preliminary study performed by transcranial magnetic stimulation allowed to detect a reduced cortical inhibition (interpreted as a possible disruption of GABA$_A$ receptor activity) in the brain of a subset of ASD patients (Enticott et al., 2010). Taken together, these data support the hypothesis of a GABAergic signaling deficit in ASD.

3.3 Evidence from animal studies

Impaired function of inhibitory circuits has been proposed as a major pathogenic cause of ASD (Rubenstein & Merzenich, 2003). Evidence is essentially limited to human genetic association studies as well as expression analyses performed on postmortem samples from ASD and control patients (see above). Conversely, this hypothesis is strongly supported by a vast number of studies performed on animal models recapitulating different aspects of the ASD pathology. So far, several transgenic and pharmacological mouse models have been developed to mimic different features of ASD-like syndromes. These include mutant mice for DLX1/2, EN2, GABRB3, RELN, NLGN3, MECP2 and FMR1.

Different anatomical and functional deficits of the GABAergic system were discovered in all these mouse models, and loss of parvalbumin (PV) expressing interneurons seems to be a hallmark of ASD-like dysfunctions in all models analyzed. The physiological formation of synaptic connections between PV-positive interneurons and principal pyramidal neurons

has been implicated in functional maturation of the postnatal cerebral cortex, and deficits in this process have been proposed as a pathogenic mechanism of ASD (Di Cristo, 2007). PV-positive interneurons approximately represent the 40% of GABAergic interneurons of the cerebral cortex, and comprise basket and chandelier fast spiking cells (Rudy et al., 2010). The other two principal groups of cortical interneurons are somatostatin (SST) positive neurons (about 30%) and neurons expressing the 5HT3a serotonin receptor (about 30%); other less-represented cortical interneuron subtypes are those expressing the calcium binding proteins calretinin (CR) and calbindin (CB) and neuropeptide Y (NPY) (Rudy et al., 2010). Defects in different interneuron subtypes, and more generally in the anatomical organization and physiological function of the GABAergic system, have been reported in several mouse models of ASD. The principal findings are described in the following paragraphs.

3.3.1 Dlx1/2 knockout mice

The family of Dlx homeobox transcription factors regulates the development of inhibitory interneurons; members of this family, namely Dlx1, Dlx2, Dlx5, and Dlx6, control the differentiation of GABAergic neurons in basal ganglia and cerebral cortex (Pleasure, 2000). The principal finding reported in Dlx1/2 mutant mice is a migration defect of GABAergic interneurons into the cerebral cortex (Anderson et al., 1997a, 1997b). Dlx1 null mice displayed a selective loss of SST-, NPY-, CR- and reelin-expressing interneurons accompanied by reduced GABAergic inhibitory transmission and late-onset epilepsy (Cobos et al., 2005). More recently, additional behavioural abnormalities (such as conditioned fear response) linked to impairment of GABAergic systems were described in Dlx1-null mice (Mao et al., 2009).

3.3.2 Engrailed2 knockout mice

En2 null mice have been proposed as a model for ASD, due to their complex anatomical and behavioural phenotype. En2 null mice display cerebellar hypoplasia and a reduced number of Purkinje cells (Joyner et al., 1991; Kuemerle et al., 1997). These abnormalities resemble some of those reported in ASD (see section 3.1). Importantly, ASD-like behaviours such as decreased play, reduced sociality and impaired spatial learning and memory were described in these mutants (Cheh et al., 2006). Recently we showed an increased susceptibility to seizures in En2 null mice, that was accompanied by reduced PV immunostaining on cell bodies of CA3 pyramidal neurons, and reduced SST immunostaining in the the stratum lacunosum moleculare of the hippocampal formation (Tripathi et al., 2009). 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.

3.3.3 GABRB3 knockout mice

Mice lacking the GABA$_A$ receptor subunit β3 (GABRB3) display high mortality rate and symptoms consistent to Angelman's syndrome, including learning and memory deficits, poor motor skills, stereotyped behaviours and seizures suscetibility (Homanics et al., 1997; DeLorey et al., 1998). More recently, GABRB3 gene deficient mice have been shown to exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules, thus resembling a wide renge of ASD phenotypes (DeLorey et al., 2008).

3.3.4 Reeler mice

Reelin is an extracellular glycoprotein belonging to the family of serine proteases (Fatemi et al., 2005). Reelin binding to membrane receptors enhances signal transduction pathways leading to synaptic plasticity and axonal growth (Beffert, 2005). Reeler mice are lacking the Reelin gene. In these mice, neuronal migration in the cerebral cortex is dramatically impaired. This results a disorganization of laminated brain regions as cerebral cortices and cerebellum (Curran & D'Arcangelo, 1998). Reeler also mice show a decrease of dentritic spine density and a decreased GABA metabolism turnover (Carboni, 2004). ASD-like behaviours and loss of PV interneurons was recently reported in Reeler mice (Macrì et al., 2010).

3.3.5 NLGN3 knock-in mice

Mice carrying the R451C mutation in the NLGN3 gene show behavioural phenotypes related to ASD (lack of social behaviours, reduced ultrasound vocalization; Radyushkin et al., 2009; Tabuchi et al., 2007). 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 (Tabuchi et al., 2007). Further characterization of these mutants demonstrated that loss of parvalbumin-positive basket cells is detectable across the two hemispheres in these mice (Gogolla et al., 2009).

3.3.6 Mecp2 knockout mice

Several conditional MeCp2 mutants mice were generated in order to remove Mecp2 from distinct neuronal populations. With respect to ASD, the most interesting data were recently obtained in conditional mutants lacking Mecp2 in inhibitory neurons expressing Viiat (Vesicular inhibitory aminoacid transporter, required to load GABA and glycine into synaptic vesicles) (Chao et al., 2010). Viaat-Mecp2 conditional mutants started to exhibit ASD-like repetitive and stereotyped behaviours, developing also self-injury behaviours. Interneurons immunolabelling in Viaat-Mecp2 mutants also showed a reduction of GAD65 and GAD67 mRNA in the cerebral cortex. Mecp2 loss in inhibitory neurons also resulted in EEG abnormalities and seizures. Moreover, electrophysiological recordings showed decreased miniature inhibitory post-synaptic currents (mIPSC) in cortical slices of Viaat-Mecp2 mutants, demonstrating that Mecp2 deficiency in GABAergic neurons determines a reduction of GABA neurotransmitter release due to a reduction of GAD amount in presynaptic terminals. Thus, loss of Mecp2 in inhibitory neurons might be a crucial determinant of severe forms of ASD.

3.3.7 Fmr1 knockout mice

Several studies show a strong reduction in the expression of $GABA_A$ receptor subunit mRNAs and proteins in adult Fmr1 knockout mice (Adusei et al., 2010; D'Hulst et al., 2009), that is accompanied by abnormal GABAergic transmission (Centonze et al., 2008; Curia et al., 2009), deficits of PV (but not CB- or CR-) cortical interneurons (Selby et al., 2007) and increased audiogenic seizure susceptibility (Musumeci et al., 2007). Table 1 summarizes the major GABAergic deficits described in ASD mouse models.

Mouse	Genetics	Signaling	Anatomy	Behaviour	Seizures	Sections in text
Dlx1/2 null	SNPs in Dlx1/2 genes found in ASD patients	-	Interneuron migration defects Loss of SST, NPY, CR and reeling interneurons	Impaired conditioned fear response	Late-onset epilepsy	2.1 3.3.1
En2 null	SNP found in ASD patients	-	Cerebellar hypoplasia Reduced PV and SST staining in hippocampus	Learning and memory deficit Reduced social behaviours	Increased susceptibility to kainic acid	2.1 3.3.2
Gabrb3 null	Mutation in Gabrb3 linked to ASD	-	Cerebellar hypoplasia	Learning and memory deficit Stereotypies Attention deficits	Yes	2.2 3.3.3 4.2.1
Reeler	GGC repeat in 5'UTR associated with ASD	Decreased GABA metabolism turnover	Neuronal migration defects Abnormal lamination of cerebral cortex and cerebellum Loss of PV interneurons	ASD-like behaviours	Yes	2.1 3.3.4
Nlgn3 R451C knock-in	R451C mutation is causative of ASD	Increased IPSCs	Increased mumber of GABAergic synapses Loss of PV interneurons	Lack of social behaviours Reduced ultrasound vocalization	-	2.3 3.3.5
Mecp2 knockout in GABA neurons	Mecp2 mutation is causative of Rett syndrome	Decreased GAD mRNA Decreased IPSCs	Loss of GABA interneurons (cerebral cortex)	ASD-like behaviours	Yes	2.3 3.3.6
Fmr1 null	Fmr1 mutation is causative of Fragile X syndrome	Reduced GABA$_A$ receptor subunit mRNAs and GABA transmission	Loss of PV interneurons (cerebral cortex)	-	Audiogenic seizures	2.3 3.3.7

Table 1. GABAergic defects in genetic mouse models of ASD.

4. GABAergic dysfunction in autism and epilepsy

Epilepsy is a neurological disorder characterised by spontaneous recurrent seizures. Epilepsy, similar to ASD, is increasingly being considered as a spectrum disorder due to the range of pathologies, seizures and behavioural and cognitive deficits associated with it (Jensen, 2011). As with ASD, epileptic seizures are considered to be as a result of imbalance between excitation and inhibition in the brain (Bradford, 1995; Olsen & Avoli, 1997). It is of particular relevance to developmental disorders, since seizures are the most common neurological emergency in children and occur most frequently in the first two years of life (Hauser, 1990; Chin et al., 2006), a critical period in brain development.

A strong association has been shown between epilepsy and ASD. The incidence of epilepsy in ASD has been reported to be between 5 – 40% (Canitano, 2007). Factors such as referral criteria, age and severity of cognitive impairments all contribute to the variability in report rate (Canitano, 2007; Tuchman et al., 2009). Children that co-express autism and epilepsy show a poorer outcome in cognitive and adaptive behaviour than those without epilepsy (Danielsson et al., 2005; Hara, 2007). The severity of the epilepsy phenotype seems to be closely related to the severity of ASD and is not associated with one particular type of seizure; simple and complex partial seizures, atypical absence, tonic-clonic and myoclonic seizures have all been reported. In particular, coexpression of mental retardation with autism is a risk factor for epilepsy (Volkmar & Nelson, 1990). Early onset of seizure is also an indicator of poor outcome in children with ASDs with more developmental disorders and greater seizure intractability reported (Wong, 1993; Bombardieri et al., 2010). "Seizures beget seizures" was a phrase coined by Sir William Gowers in 1881 and it may go some way to explaining this poorer outcome associated with early onset of ASD and seizures. Where seizures are initially a manifestation of the underlying imbalance in excitation/inhibition they may ultimately contribute to progressive increase in seizure severity and secondarily, behavioural and cognitive deficits. This is particularly evident in the developing brain where susceptibility to seizure-induced neuropathology leads to epilepsy and further cognitive deficits in later life (Ben-Ari, 2006; Ben-Ari & Holmes, 2006). Here we examine the link between ASD and epilepsy with particular focus on the role of GABAergic dysfunction of 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 (e.g., the presence of mental retardation) and the potential mechanistic role of GABA dysfunction.

4.1 Clinical evidence of a role for GABAergic involvement in epilepsy-autism disorders

An increasing number of studies have implicated the GABAergic system dysfunction in epilepsy and ASD. Chromosome 15q, which contains genes coding for GABA receptor subunits, has been reported to be a common site for mutations in ASDs (Schroer et al., 1998). This data is further supported by association studies linking GABA receptor subunit genes and SNPs associated with autism and seizures (Collins et al., 2006). An increasing body of evidence suggests a downregulation of GABAergic function is critical in ASD-associated epilepsy. Quantitative receptor autoradiographic studies examining the density and distribution of GABAergic subunits indicated a downregulation of GABAergic function in the hippocampus of ASD patients with seizures (Blatt et al., 2001). Furthermore, altered packing of GABAergic interneurons in the CA1 and CA3 hippocampal subfields where malformations are associated with the generation of seizures (Bauman & Kemper, 2005).

Supporting this human studies have demonstrated that there is a loss of inhibitory interneurons in the epileptic brain (Zhu et al., 1997; Wittner et al., 2001).

As outlined above, FXS is one such autism-related disorder that is a leading cause of mental retardation (Bardoni et al., 2006). It is also strongly associated with abnormal EEG activity with a mean epilepsy prevalence of between 22 – 25% (Wisniewski et al., 1991; El Idrissi et al., 2005). Fragile X appears to have a wide profile with some reporting a benign condition with generalised seizures responding well to antiepileptic drugs (AEDs) treatment (Wisniewski et al., 1991) that disappear after childhood. Other groups report long lasting generalised and partial epilepsy and EEG abnormalities in adults with fragile X (Sabaratnam, 2000). Furthermore, Gauthey et al describe a more severe phenotype with children with fragile X presenting with status epilepticus (seizures lasting > 30 min) at their initial seizure with recurrent prolonged seizures on follow-up (Gauthey et al., 2010). Status epilepticus in the developing brain is known to significantly increase the risk of epilepsy, hippocampal sclerosis and further behavioural and cognitive deficits in later life in human and animals studies (Raspall-Chaure et al., 2006; Dunleavy et al., 2010). There is a large amount of data from animal studies (described above) to support a role for disruption of normal GABAergic function in seizure generation in FXS.

Rett syndrome 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 (Chahrour and Zoghbi, 2007). Seizures have been reported to be present in between 50 – 90% of patients (Witt Engerstrom, 1992; Steffenburg et al., 2001). As with FXS, epilepsy is most severe through childhood and young adulthood while the phenotype ranges from mild seizures that are well controlled with AEDs to refractory epilepsy, most common types being partial complex and tonic-clonic seizures (Steffenburg et al., 2001; Jian et al., 2006).

4.2 Experimental evidence of a role for GABAergic involvement in epilepsy-autism disorders

There are two main aspects to the role of GABA dysfunction in the pathogenesis of epilepsy in autism. Firstly, absence of GABA signaling results in loss of inhibitory neuronal firing that normally prevents the spread of paroxysmal discharge. Furthermore, normal GABAergic function is integral in the brain development alteration in this function can have significant effects on neuronal migration, differentiation, synaptogenesis and circuit formation. Presently, we will outline the current data from animal studies and examine the mechanisms involved in these processes.

4.2.1 Reduced GABA transmission

GABAergic inhibition can be affected in two ways, presynaptically by a reduction in GABA release into the synapse or postsynaptically by an alteration in GABA receptor function. There is some evidence that both of these situations may contribute in epilepsy-autism disorders. GAD65 is one of two glutamate decarboxylase isoforms that synthesis GABA in the brain. Previously linked to animal models of ASD, GAD65 knockout mice have also been shown to display an epileptic phenotype, with animals undergoing spontaneous seizures involving the limbic system (Kash et al., 1997). The presence of the seizures and altered behaviour was attributed to the loss of tonic inhibition to prevent hyperexcitability in the developing nervous system (Stork et al., 2000). $GABA_A$ receptor dysfunction has been well

documented the hippocampus and neocortex in human epilepsy (Loup et al., 2000, 2006). Animal models of temporal lobe epilepsy (Pirker et al., 2003) and absence seizures (Li et al., 2006) suggest alterations in receptor subunit expression and receptor localization as potential mechanisms. Data is limited for epilepsy-autism disorders, however mice lacking the GABA$_A$ receptor subunit β3 (see above) displays altered EEG along with a reduced threshold to chemoconvulsant seizures (DeLorey et al., 1998; Liljelund et al., 2005).

4.2.2 Altered brain development as a result of GABAergic dysfunction

In addition to the direct effect of altered GABA system on the ability of interneurons to inhibit the generation of synchronized discharges, there are 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.

The effects of Mecp2 and En2 mutations on interneuron and seizure susceptibility has been described in the previous sections. Similarly, deficits in inhibitory interneurons and reduced seizure threshold were observed in neuropilin 2 (NPN2) deficient mice (Gant et al., 2009). The gene for NPN2 (also known as NRP2) is coded for at 2q34, a region known to be strongly associated with autism (Wu et al., 2007). NPN2 functions as a chemorepulsive receptor for the axon guidance molecule Semaphorin 3F, and together 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 seizures (Gant et al., 2009). Importantly, NPN2 null mice had a reduced number of GABA, PV and NPY interneurons (Gant et al., 2009).

As described in the table above, Fmr1 mutant mice also showed increased susceptibility to audiogenic seizures (Musumeci et al., 2000) but not chemoconvulsants (Chen & Toth, 2001). An imbalance in the inhibition–excitation system (mainly due to reduced GABA$_A$ receptor expression; El Idrissi et al., 2005) is thought to be the major cause of increased susceptibility to seizures in these mutants. Importantly, hyperexcitibility of Fmr1 mutant mice was shown to be reduced by pharmacological intervention with a GABAergic agonist, augmenting tonic inhibitory tone (Olmos-Serrano et al., 2010).

Taken together, all 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 autism, possibly even a common pathology. The range of genes involved may reflect the spectrum of pathologies associated with autism and epilepsy and warrant more detailed investigation. Overall, these data indicate that the ASD-epilepsy condition is a spectrum disorder within itself. It appears that the severity of the autism condition, presence or absence of mental retardation, is closely associated with the epilepsy phenotype, in seizure frequency, severity and intractability. Early diagnosis and suitable treatment protocols are vital for successful outcomes (Tuchman, 2000; Bombardieri et al., 2010). The Australian Rett Syndrome Database (Laurvick et al., 2006) is an ongoing longitudinal study profiling the progression of the disease in a growing cohort of cases. Similar properly constructed prospective clinical studies throughout ASD could provide vital insights required to develop successful therapeutic approaches for epilepsy in ASD. Key to advancing the experimental models will be temporal and spatial conditional deletions of various levels of the signaling system will allow greater insight into the contributions of the various genes in migration, differentiation and circuit formation.

4.3 Antiepileptic drugs in epilepsy-autism disorders

Due to the clinical heterogeneity of epilepsy and ASD significant issues exist regarding the treatment of epilepsy in children with ASD. Current treatment of epilepsy in ASD patients is based on the existing strategies for treating childhood epilepsy. Treatment with traditional AEDs such as phenobarbital, valproic acid and lamotrigine have all been shown to reduce abnormal EEG discharge (Depositario-Cabacar & Zelleke, 2010). Although, despite some studies reporting improved cognitive performance following treatment, the results from other studies are equivocal. It is clear, however, that there is an increased risk of the patient being refractory to treatment where developmental disabilities coexist (Alvarez et al., 1998; Airaksinen et al., 2000).

Studies of treatment on non autism-related epilepsies in children also raise a number of concerns about effects of AED treatment which are relevant to the current discussion. GABA is the principal inhibitory neurotransmitter in the adult brain. However, during embryonic development and up until early postnatal development in both humans and rodents, high expression of the $Na^+/K^+/2Cl^-$ (NKCC1) cotransporter and weak expression of the K^+/Cl^- cotransporter (KCC2) are present. As a result, opening of the GABAergic channels leads to depolarization and excitation of the neuron (Ben-Ari, 2002). There is an increasing body of evidence that this property of GABAergic neurons in the developing brain plays a crucial role in the development of normal neuronal circuitry, facilitating the development of both inhibitory and excitatory synapses (Akerman & Cline, 2007). In this respect, the use of GABAergic agonists to treat seizures in ASD children during developmental age might increase excitation and could result detrimental. In addition, approximately 30% of children are refractory to AED treatment (Treiman et al., 1998; Lowenstein, 2006). Furthermore, when epileptic seizures are successfully suppressed, AED treatment is associated with decreased cognitive and behavioural developmental outcomes (Loring et al., 2007), which may play a role in exacerbating the autistic condition, or at least moderate the positive outcome from absence of seizures (Tuchman, 2000). Careful monitoring for behavioural and cognitive side-effects is required since they still have the potential to exacerbate the existing ASD-related deficits. Elucidating the role of GABA dysfunction in autism-epilepsy disorders will provide greater insight into the pathogenesis of these diseases and hopefully facilitate more targeted approach producing improved outcomes in both disorders.

5. Conclusion

ASD and epilepsy both have a clear neurodevelopmental origin, and are characterized by a high degree of genetic heterogeneity. Genes regulating brain development, gene transcription, synaptic scaffolding, neurotransmission and signal transduction have been implicated in their pathogenesis, indicating that these two neurodevelopmental disorders may share common genetic bases. Indeed, epilepsy and ASD are often associated. Typically, severe forms of ASD and ASD-related pathologies always present seizures. Defects in the development, maintenance and function of GABAergic interneurons in the cerebral cortex and other brain areas have been postulated as a pathogenic mechanism of ASD-epilepsy syndromes. However, a direct, causal demonstration of a defect of GABAergic neurotransmission in restricted brain areas of ASD patients is still lacking. Conversely, evidence from several genetic mouse models of ASD strongly supports the hypothesis of GABAergic dysfunction in ASD-epilepsy. In the near future, it will be crucial to use these models to test the efficacy of GABAergic drugs to rescue ASD-like anatomical, physiological

and behavioural deficits in preclinical studies. If successful, these studies might contribute to developing novel therapies against human ASD.

6. Acknowledgment

7. References

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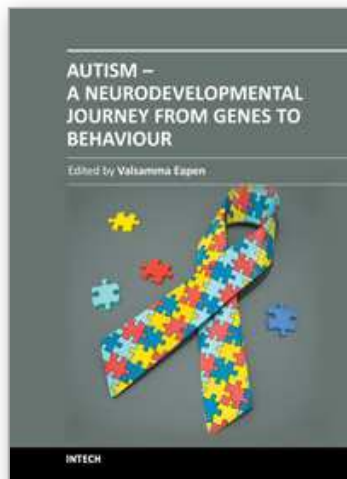
Autism - A Neurodevelopmental Journey from Genes to Behaviour

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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