Convergence of Genetic and Environmental Factors in the Pathogenesis of Autism and Epilepsy.

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Abstract

Autism spectrum disorders (ASD) and epilepsy are common neurological diseases of childhood, with an estimated incidence of approximately 0.5–1% of the worldwide population. Several genetic, neuroimaging and neuropathological studies clearly showed that both ASD and epilepsy have developmental origins and a substantial degree of heritability. Most importantly, ASD and epilepsy frequently coexist in the same individual, suggesting a common neurodevelopmental basis for these disorders. Genomewide association studies recently allowed for the identification of a substantial number of genes involved in ASD and epilepsy, some of which are mutated in syndromes presenting both ASD and epilepsy clinical features. At the cellular level, both preclinical and clinical studies indicate that the different genetic causes of ASD and epilepsy may converge to perturb the excitation/inhibition (E/I) balance, due to the dysfunction of excitatory and inhibitory circuits in various brain regions. Metabolic and immune dysfunctions, as well as environmental causes also contribute to ASD pathogenesis. Thus, an E/I imbalance resulting from neurodevelopmental deficits of multiple origins might represent a common pathogenic mechanism for both diseases. Here, we will review the most significant studies supporting these hypotheses. A deeper understanding of the molecular and cellular determinants of autism–epilepsy comorbidity will pave the way to the development of novel therapeutic strategies.

Introduction

Autism spectrum disorders (ASD) and epilepsy are common neurological diseases of childhood, with an estimated incidence range from 0.5 to 1%. Several clinical studies indicate that ASD and epilepsy frequently co-occur; epilepsy occurs in 6–27% of ASD patients, while the rate of ASD diagnosis in epileptic children is estimated from 5 to 37% (Jeste & Tuchman, 2015; and references therein). Several studies reported that epilepsy could both precede and follow the occurrence of ASD symptoms, and a diagnosis of ASD–epilepsy comorbidity is usually reached in early childhood or adolescence (Jeste & Tuchman, 2015; and references therein). These observations led to the hypothesis that both disorders may have, at least in certain cases, common neurobiological basis. Indications in support of this hypothesis result from genetic conditions such as Fragile X (FXS), tuberous sclerosis, Rett, maternal duplications on chromosome 15q11.2-q13.1 (Dup15q) and Phelan-McDermid syndromes, which are characterized by both early-onset epilepsy and ASD symptomatology (Jacob, 2016). These genetic conditions are all characterized by intellectual disability (ID) comorbidity (Jeste & Tuchman, 2015). Moreover, it is widely accepted that both ASD and early-onset epilepsy (even when not co-occurring) may have genetic causes that impact synaptic function and brain development (reviewed by de la Torre-Ubieta et al., 2016; and Bozzi et al., 2012). One of the most consistent hypotheses to explain ASD–epilepsy comorbidity postulates that neurodevelopmental defects of multiple origins (e.g. genetic, metabolic, immune and environmental) lead to an altered structure and function of excitatory and inhibitory circuits, ultimately resulting in a persistent excitation/inhibition (E/I) imbalance and hyperexcitability. Neurodevelopmental deficits of inhibitory circuits and subsequent E/I imbalance seem to be disturbances may also compromise the E/I balance, leading to ASDepilepsy comorbidity (Frye, 2015; Frye & Rossignol, 2016; Frye et al., 2016).

All these deficits, when occurring during embryonic and early postnatal brain development, may impact synaptic plasticity and connectivity, and predispose the developing brain to hyperexcitability, cognitive delay, ID and behavioral impairments. Here, we review the most significant studies supporting these hypotheses, mainly focusing on developmental defects of GABAergic and glutamatergic systems. Metabolic, immune and environmental causes of ASD–epilepsy comorbidity have been extensively reviewed by other authors (Frye, 2015; Frye & Rossignol, 2016; Frye et al., 2016) and will be only briefly addressed here.

GABAergic dysfunction in ASD and epilepsy: studies on human subjects

A defect in GABAergic interneuron signaling has long been established as a key mechanism of epileptogenesis, and will not be reviewed here. For an extensive discussion on GABAergic dysfunction in epilepsy, the reader is referred to previous studies (Treiman, 2001; Bernard, 2012; Jiang et al., 2016). However, it is worth mentioning that GABA-mediated inhibition, the activity of glutamate decarboxylase (GAD), the number of GABAergic interneurons, ligand binding to $GABA_A$ receptors and GABA levels have all been reported to be decreased in human epileptic brain tissues. A causal role of GABAergic dysfunction in ASD was first hypothesized in early 2000s by Hussman, Rubenstein and Merzenich (Hussman, 2001; Rubenstein & Merzenich, 2003). Since then, several genetic, neuropathological, and neuroimaging studies showed that GABAergic dysfunctions occur in ASD and might contribute to ASD– epilepsy comorbidity.

Genetic data

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Many of the genes associated with ASD have also been implicated in epilepsy. These genes are mainly involved in regulating synaptic transmission and DNA methylation/chromatin remodeling. Recently, exome sequencing of ASD cohorts revealed a large number of ASD gene candidates with de novo loss-of-function mutations or de novo missense variants (Iossifov et al., 2014). When mutated in mice, some of these genes result in epilepsy and ASD-like behaviors (Noebels, 2015). Direct genetic evidence of GABAergic gene defects associated with ASD–epilepsy comorbidity comes from the study of a particular form of 'syndromic autism', the Dup15q syndrome. This disorder (as FXS, tuberous sclerosis, Rett and PhelanMcDermid syndromes) is characterized by the co-occurrence of ASD and epilepsy symptomatology. Dup15q syndrome arises from maternal duplications on chromosome 15q11.2-q13.1, which lead to the overexpression of several genes, including UBE3A (ubiquitin ligase E3A) and a cluster of $GABA_A$ receptor subunits (Schroer et al., 1998). Association studies linking single-nucleotide polymorphisms in GABA receptor subunit genes to ASD and epilepsy further support this interpretation (Buxbaum et al., 2002; Collins et al., 2006).

Neuropathological findings

The reduction in minicolumns observed in post-mortem samples of ASD patients (Casanova et al., 2002) led to the hypothesis that inhibitory circuits were disrupted in the autistic brain (Casanova et al., 2003); minicolumns are elemental modular microcircuits of the neocortex, composed of excitatory pyramidal neurons surrounded by GABAergic inhibitory neurons. Indeed, post-mortem studies indicate that GABAergic neurotransmission is altered in ASD. Significantly reduced levels of $GABA_A$ receptor subunits, $GABA_B$ receptors and GAD67/65, and reduced binding to $GABA_A$ receptors were detected in ASD brains (Blatt et al., 2001; Fatemi et al., 2002, 2010; Samaco et al., 2005; Oblak et al., 2010, 2011). Another study performed on post-mortem tissues showed an increased density of calbindin (CB), calretinin (CR) and parvalbumin (PV) positive interneurons within ASD hippocampi, as compared to control samples (Lawrence et al., 2010).

Several histopathological studies revealed malformations of cortical development (focal cortical dysplasia and heterotopias) in both ASD and epilepsy brain tissues (Blackmon, 2015). However, only one study on post-mortem tissues identified an increased number of proliferating neuronal precursors in the subventricular zone of ASD patients with epilepsy, as compared to healthy controls or ASD cases alone (Kotagiri et al., 2014). Experiments performed on human neural progenitors derived from induced pluripotent stem cells (iPSCs) carrying a 15q11.2 microdeletion might help to shed light on the role of neuronal precursor proliferation in the pathogenesis of ASD, epilepsy and other neuropsychiatric disorders. Copy number variants (CNVs) of 15q11.2 have been linked to ASD, epilepsy and schizophrenia (SCZ; Yoon et al., 2014; and references therein). The 15q11.2 chromosomal region contains CYFIP1, a gene controlling neuronal precursor polarity. The CYFIP1 protein interacts with gene products involved in several neuropsychiatric disorders including ASD, SCZ and ID (De Rubeis et al., 2013), and CYFIP1 deficiency in mice results in ectopic localization of neuronal progenitors outside of the ventricular zone (Yoon et al., 2014). Accordingly, human iPSC-derived neural progenitors carrying a 15q11.2 microdeletion exhibit localization deficits in vitro (Yoon et al., 2014). Similarly, CYFIP1 knockdown in human neural progenitors results in compromised cytoskeletal remodeling and overrepresentation of SCZ and epilepsy genes (Nebel et al., 2016). Thus, deficiency of CYFIP1 during the early stages of brain development might result in severe neuronal migration deficits that would predispose to ASD and epilepsy; however, it remains to be determined which neuronal subtypes would be mostly affected by the deficiency of CYFIP1.

EEG and brain imaging studies

People with ASD present a marked increased incidence of epileptiform activity (interictal spikes) in electroencephalogram (EEG) recordings (Jeste & Tuchman, 2015; Buckley & Holmes, 2016). Also, altered c-band oscillations have been described in resting state EEGs from autistic patients (van Diessen et al., 2015), suggesting a dysfunction of parvalbumin (PV)-positive interneurons (which are responsible for c-band oscillations; Buzsaki & Wang, 2012). Conversely, a detailed analysis of the EEG profiles of patients suffering from ASD and epilepsy vs. ASD alone is still lacking.

Brain imaging studies provided some evidence in support of a shared pathogenesis for ASD and epilepsy. Magnetic resonance imaging (MRI) studies identified abnormal gray/white matter volumes and aberrant brain growth trajectories in both ASD and pediatric epilepsies (Blackmon, 2015). GABAergic signaling defects in ASD patients were detected by single-photon emission computed tomography (SPECT) and positron emission tomography (PET) brain imaging studies. ^{123}I-iomazenil binding showed decreased quantities of $GABA_A$ receptors in the frontal cortex (Mori et al., 2012b), while in vivo binding experiments using a radioactive ligand specific for $GABA_A$ a5 subtype receptors revealed a significant reduction in binding in two limbic brain regions, the amygdala and nucleus accumbens (Mendez et al., 2013). More recently, Robertson et al. (2016) used magnetic resonance spectroscopy to show that reduced GABA levels were associated with deficits of visual perception in the visual cortex of ASD patients. A systematic literature review and meta-analysis of proton magnetic resonance spectroscopy (^{1}H-MRS) studies recently confirmed that GABA levels are indeed reduced in ASD brains (Sch€ur et al., 2016), thus providing a direct evidence for the presence of disrupted inhibitory signaling in the autistic brain. Few imaging studies instead investigated GABAergic system alterations specifically in ASD–epilepsy patients. ^{123}I-iomazenil SPECT and ^{1}H-MRS revealed a significant decrease in $GABA_A$ receptor binding and increased GABA levels in cortical tubers from tuberous sclerosis complex (TSC) patients (Mori et al., 2012a). TSC presents a high degree of ASD–epilepsy comorbidity (Sahin & Sur, 2015; Buckley & Holmes, 2016; Sahin et al., 2016). The authors hypothesized that seizures in TSC might be caused by decreased inhibition that was secondary to the reduced levels of GABA receptors in the cortical tubers, increased GABA levels being a compensatory mechanism for reduced inhibition (Mori et al., 2012a).

Taken together, these data indicate that GABAergic neurotransmission is compromised in ASD, and support the hypothesis that a disruption in inhibitory signaling might be related to ASD–epilepsy comorbidity. It remains to be determined whether and how these anatomical malformations may impact GABAergic function and contribute to the co-occurrence of autistic behavior and brain hyperexcitability. Genetic, histopathological, EEG and imaging studies comparing ASD and ASD–epilepsy patients will be needed to identify specific pathogenic mechanisms of ASD–epilepsy comorbidity.

The data collected from human subjects have two limitations. First, post-mortem neuroanatomical studies do not allow us to establish a causal relationship between the clinical phenotype and the observed

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anatomical defect. Second, it is important to point out that few studies have been performed to identify neuroanatomical and functional biomarkers of ASD–epilepsy comorbidity (Buckley & Holmes, 2016). More compelling evidence supporting the hypothesis of GABAergic defects in ASD–epilepsy comorbidity comes from animal studies. In mice, mutations in many ASD-associated genes result in neurodevelopmental defects of the inhibitory system, subsequently leading to ASD-like behaviors and epilepsy at early postnatal age or adulthood. In the following paragraphs, we will present recent advances in understanding the genetic determinants of ASDepilepsy comorbidity, as they emerge from the study of ASD mouse models, and discuss the importance of these studies for the development of novel therapeutic strategies.

GABAergic dysfunction in ASD and epilepsy: mouse model data

In recent years, the increasing number of available mouse models provided a powerful tool to investigate the molecular, neuroanatomical and behavioral consequences of gene dysfunction in ASD. These studies also allowed us to identify comorbidities associated with ASD-like behaviors. We, therefore, took advantage of the Simons Foundation Autism Research Initiative (SFARI) database (the largest database of ASD-related genes and animal models; https://gene.sfari.org/) to compile a list of all known genetic mouse models displaying the co-occurrence of ASD-like behaviors and seizures. Table 1 shows a total number of 26 genes and 36 mouse models associated with ASD–epilepsy comorbidity. As reported in previous review studies (de la Torre-Ubieta et al., 2016), most of these genes code for proteins relevant to transcriptional regulation, protein synthesis and synaptic function. From the analysis of mouse models, it emerges that genetic lesions responsible for ASD–epilepsy comorbidity often result in decreased inhibition in selected brain regions. Here, we summarize the most relevant gene expression, neuroanatomical and electrophysiological data supporting this hypothesis (Fig. 1).

Transcriptome data

So far, transcriptome profiling has been performed in five mouse models showing ASD-seizure comorbidity (ARX, En2, Fmr1, Rbfox1 and Pten mutant mice). These studies analyzed mRNA expression in different brain structures (hippocampus, cerebellum and cerebral cortex) at various embryonic and postnatal ages. A first study using the differential display technique showed reduced expression of the $GABA_A$ receptor d subunit in the hippocampus of Fmr1 knockout mice (Gantois et al., 2006). More recent RNA sequencing experiments performed on Fmr1, Rbfox1 and Pten mutant brains showed that deregulated mRNAs were enriched in genes involved in brain development and autism but not epilepsy or GABAergic function (Prilutsky et al., 2015; Lee et al., 2016; Tilot et al., 2016). More interestingly, transcriptome analysis of embryonic (E12.5) telencephalon from ARX mutant mice revealed, among deregulated genes, a significant enrichment (12%) of genes implicated in ASD and epilepsy (Mattiske et al., 2016). Similarly, we recently showed significant enrichment of ASD and epilepsy genes among differentially expressed genes in the adult hippocampus of En2 knockout ($En2^{/}$) mice (Sgado et al., 2013b; Provenzano et al., 2016). Moreover, genes involved in pre- and postsynaptic GABAergic transmission were significantly enriched among downregulated genes in the $En2^{/}$ adult hippocampus (Provenzano et al., 2016). Thus, mutations of transcriptional regulators of brain development (both ARX and En2 are homeobox-containing transcription factors) seem to affect developmental programs of forebrain structures involved in epileptogenesis.

Histopathological data: loss of GABAergic interneurons

The majority of GABAergic interneurons are generated in the ganglionic eminences of the basal forebrain, from where they migrate along the subventricular zone into the neocortex (Marın, 2012). Interneuron subtypes are identified by their morphological, neurochemical and electrophysiological properties (Ascoli et al., 2008). PV and somatostatin (SST) containing interneurons, which derive from the medial ganglionic eminence, account for about 70 and 90% of all interneurons in the cerebral cortex and hippocampus respectively (Rudy et al., 2011; Tricoire et al., 2011). Other interneuron subtypes, deriving from the caudal ganglionic eminence, include those expressing CR, neuropeptide Y (NPY), vasointestinal peptide (VIP) or reelin (Fishell & Rudy, 2011). All these different interneuron subtypes develop and mature at different embryonic and early postnatal ages (Fishell & Rudy, 2011).

Several studies performed in mouse models of ASD–epilepsy, summarized in Table 1, show profound alterations in GABAergic interneuron number and positioning. These studies revealed a consistent defect of PV-positive interneurons in most of the analyzed models (Cntnap2, En2, Fmr1, Nrp2 and Plaur), except for ARX and Tsc1 mutants (in some models, such as reeler and Viaat-conditional MeCP2 mutants, interneuron subtypes were not specifically investigated). Defects in PV neurons have also been described in ASD mouse models lacking an epileptic phenotype (Gogolla et al., 2009).

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TABLE 1. E/I imbalance in genetic mouse models of ASD showing an increased seizure phenotype

Gene symbol	Function	Model genotype	Seizure paradigm	GABAergic/inhibitory defects	Glutamatergic/ excitatory defects	Age at testing	Main references
ALDH5A1	Succinate semialdehyde dehydrogenase	KO (*hom*)	General observations, survival analysis	Increased brain GABA levels	Not reported	P20–P50	Hogema *et al.* (2001)
ARHGAP32	Rho GTPase activating protein 32	KO (*hom*)	KA-induced seizures	Reduced mIPSC amplitude in hippocampal CA1	Not reported	6–10 weeks	Nakamura *et al.* (2016)
ARX	Homeobox transcription factor	GCG triplet expansion (*hom*)	EEG	Reduction in CB, NPY but not PV or CR interneurons	Not reported	3–10 weeks	Price *et al.* (2009)
BCKDK	Branched chain ketoacid dehydrogenase kinase	KO (*hom*)	Handling-provoked seizures	Not reported	Not reported	6–7 months	Novarino *et al.* (2012)
CELF4	CUGBP, Elav-like family member 4 (RNA-binding protein)	cKO (*hom*) (embryonic)	General observations, EEG	No change in synaptic inhibitory transmission	Increased mEPSCs in neocortical neurons	1–6 months	Wagnon *et al.* (2011)
		cKO (*hom*) (*emx1*$^{+}$ *excitatory neurons*)	EEG	No change in interneuron number	Not reported	Not reported	Wagnon *et al.* (2011)
		cKO (*hom*) (CaMK2α^{+} *forebrain neurons*)	EEG	Not reported	Not reported	Not reported	Wagnon *et al.* (2011)
CNTNAP2	Contactin-associated protein-like 2 (cell adhesion molecule)	KO (*hom*)	General observations, EEG	Loss of CB, NPY, GAD67 and PV interneurons	Not reported	6 months	Peñagarikano *et al.* (2011)
EN2	Homeobox transcription factor	KO (*hom*)	KA-induced seizures	Loss of NPY, PV and SST interneurons	Not reported	3–5 months	Tripathi *et al.* (2009), Sgadò *et al.* (2013a), Provenzano *et al.* (2014)
				Reduced expression of $GABA_A$ receptor β3 subunit	Not reported	3–5 months	Provenzano *et al.* (2015)
FMR1	RNA-binding protein	KO (*hom*)	Audiogenic seizures	Not reported	Increased mGlu5 signaling	Adult	Michalon *et al.* (2012)
				Loss of PV interneurons	Not reported	Adult	Selby *et al.* (2007)
				Reduced $GABA_A$ receptors	Not reported	Adult	D'Hulst *et al.* (2009), Sabanov *et al.* (2017)
				Altered GABAergic transmission	Not reported	1–6 months	Centonze *et al.* (2008), Curia *et al.* (2009), Sabanov *et al.* (2017)
				Increased excitatory GABA reversed by bumetanide and oxytocin-dependent signaling	Increased mEPSCs	P0–P15	Tyzio *et al.* (2014)
				Impaired phasic and tonic inhibition, reduced GAD65/67 immunoreactivity, reduced GABA release in the amygdala	Not reported	P20–30	Olmos-Serrano *et al.* (2010)
				GABAergic synaptic transmission unaffected	Decreased excitatory drive on PV neurons in the somatosensory cortex	P14–16	Gibson *et al.* (2008)
				Reduced expression of $GABA_A$ receptor δ subunit	Not reported	9–13 weeks	Gantois *et al.* (2006)

(continued)

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Table 1. (continued)

Gene symbol	Function	Model genotype	Seizure paradigm	GABAergic/inhibitory defects	Glutamatergic/ excitatory defects	Age at testing	Main references
GABRB3	$GABA_A$ receptor β3 subunit	KO (*hom/het*)	EEG	Not reported	Not reported	2–10 months	DeLorey *et al.* (1998), Liljelund *et al.* (2005)
		KO (*hom*)	Not reported	Reduced $GABA_A$ and benzodiazepine binding	Not reported	2 months	Sinkkonen *et al.* (2003)
		KO (*het*)	PTZ-induced seizures	Not reported	Not reported	Not reported	DeLorey *et al.* (2011)
MECP2	Transcriptional regulator	KO (*hom*)	EEG, spontaneous seizures	Not reported	Not reported	3–10 months	Shahbazian *et al.* (2002)
				Unaltered IPSCs in neocortex	Reduced mEPSCs in neocortex	P30–35	Dani *et al.* (2005)
				Reduced GABAergic synaptic transmission, presynaptic GABA release, and levels of Viaat and $GABA_A$ receptor subunits α2-α4 in brainstem neurons	Increased mEPSCs in brainstem neurons	P7	Medrihan *et al.* (2008)
				Reduced inhibitory rhythmic activity in hippocampus	Decreased spontaneous glutamate receptor-mediated synaptic currents in CA3 neurons	2–3 months	Zhang *et al.* (2008)
				Reduced GABA currents and impaired allopregnanolone-dependent potentiation of GABA currents in locus coeruleus	Not reported	3 weeks	Jin *et al.* (2013a,b)
		cKO (*Viaat$^+$ neurons*)	EEG, spontaneous seizures	Reduced inhibitory quantal size, GAD6 and GABA-IR	Unaltered mEPSCs	3–10 months	Chao *et al.* (2010)
NRP2	Neuropilin 2	KO (*hom*)	General observations	Decreased interneuron number	Not reported	2–4 months	Gant *et al.* (2009)
OXTR	oxytocin receptor	KO (*hom*)	EEG	Reduced GABAergic synapses	Not reported	3–4 months	Sala *et al.* (2011)
				Delayed GABA switch	Increased mEPSCs	P0–P60	Leonzino *et al.* (2016)
PLAUR	Plasminogen activator, urokinase receptor	KO (*hom*)	General observations, ECoG	Decreased PV expression	Not reported	Not reported	Powell *et al.* (2003)
PRICKLE1	Prickle homolog 1	KO (*het*)	MES	Not reported	Not reported	Not reported	Tao *et al.* (2011)
PRICKLE2	Prickle homolog 2	KO (*hom/het*)	MES, PTZ-induced seizures	Not reported	Not reported	Not reported	Tao *et al.* (2011)
PTEN	Phosphatase and tensin homolog	cKO (*hom*) (*NSE$^+$ hippocampal and cortical neurons*)	Spontaneous seizures, EEG	Not reported	Dendritic hypertrophy and increased spine density in dentate granule neurons	3–9 months	Kwon *et al.* (2006)
PV	Parvalbumin (Ca^{2+}-binding protein)	KO (*hom*)	PTZ-induced seizures	Loss of PV gene	Reduced evoked EPSCs	Adult	Wöhr *et al.* (2015)
RELN	Reelin (secreted extracellular matrix protein)	*Reeler* (*hom*)	Electroshock-induced seizures	Not reported	Not reported	Adult	Patrylo *et al.* (2006)
				Reduced GAD67 levels	Not reported	Adult	Liu *et al.* (2001)
				Abnormal interneuron positioning	Not reported	Adult	Hammond *et al.* (2006)
RBFOX1	RNA binding protein, fox-1 homolog	cKO (*hom/het*) (*nestin$^+$ neuron precursors*)	General observations	Not reported	Not reported	Not reported	Gehman *et al.* (2011)

(continued)

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Table 1. (continued)

Gene symbol	Function	Model genotype	Seizure paradigm	GABAergic/inhibitory defects	Glutamatergic/ excitatory defects	Age at testing	Main references
SCN1A	Sodium channel 1A	KO (*hom*)	General observations	Not reported	Not reported	P9–P15	Yu *et al.* (2007)
		KO (*het*)	Spontaneous seizures	Reduced miniature inhibitory post synaptic currents	Not reported	4 months	Han *et al.* (2012)
		cKO (*het*) *(PV neurons)*	Spontaneous and thermally induced seizures, EEG	Deletion of SCN1A/Nav1.1 in PV neurons	Increased spontaneous EPSCs in neocortical neurons, reduced evoked EPSPs in CA1 neurons	3–5 weeks	Rubinstein *et al.* (2015)
		R1407X KI (*hom*)	General observations, ECoG	Decreased spike amplitude in PV neurons	Not reported	P12–P16	Ogiwara *et al.* (2007)
		R1648H KI (*het*)	Spontaneous and fluorotyl-induced seizures	Not reported	Not reported	Adult	Hawkins *et al.* (2011)
Syn*	Synapsin	SynI KO (*hom*)	Spontaneous and handling-provoked seizures	Reduced releasable pool of synaptic vesicles at inhibitory synapses	Not reported	4–5 months	Rosahl *et al.* (1995), Baldelli *et al.* (2007), Etholm *et al.* (2012)
		SynII KO (*hom*)	Spontaneous and handling-provoked seizures	Reduced basal transmission at inhibitory synapses	Decreased post-tetanic potentiation	4–5 months	Rosahl *et al.* (1995), Etholm *et al.* (2012)
SYNGAP1	Synaptic Ras GTPase activating protein 1	Syngap1 KO (*het*) Syngap1 cKO ($emx1^{+}$ *excitatory neurons*)	Fluorothyl-induced seizures	Unaltered synaptic properties of inhibitory neurons	Increased mEPSCs	2 weeks–4 months	Ozkan *et al.* (2014)
TERT	Telomerase reverse transcriptase	Transgenic (*hom*)	Electrically induced seizures	Not reported	Increased NMDA receptor expression	4 weeks	Kim *et al.* (2016)
TSC1	Tuberous sclerosis 1	cKO (*Dlx5/6 interneuron precursors*)	General observations, EEG	Reduced numbers of GABAergic interneuron subtypes	Not reported	1–6 months	Fu *et al.* (2012)
TSC2	Tuberous sclerosis 2	KO (*hom*)	EEG	Not reported	Not reported	2–8 weeks	Zeng *et al.* (2011)
UBE3A	Ubiquitin protein ligase E3A	KO *(het)*	No seizure abnormalities	Reduced tonic inhibition and degradation of GAT1 in cerebellar granule neurons	Not reported	P25–P75	Egawa *et al.* (2012)
		cKO (*het*) *(glutamatergic neurons)*	No seizure abnormalities	Unaltered $GABA_A$ receptor binding sites	Not reported	2 months	Sinkkonen *et al.* (2003)
		cKO (*het*) *(GABAergic neurons)*	No seizure abnormalities	Reduced cortical inhibition	Not reported	2–3 months	Judson *et al.* (2016)
			Fluorotyl/audiogenic seizures, EEG	No change in cortical inhibition	Not reported	2–3 months	Judson *et al.* (2016)

Table shows all mouse models carrying targeted inactivation of ASD-associated genes listed in SFARI database (https://gene.sfari.org), which present a seizure susceptibility phenotype. This list was generated by filtering all ASD genetic mouse models annotated in the Animal Model Module of SFARI database by applying the filter 'seizure' to 'phenotype category'. The list is updated at December 20, 2016 and may be incomplete due to partial or absent annotation of seizure phenotypes for all available mouse models. As an example, a seizure phenotype is not reported in the SFARI database for SynI and SynII knockout mice (*), which are also known to show ASD-like deficits (Greco *et al.*, 2013). Table also summarizes GABAergic and glutamatergic defects reported in these models, with relevant references. Abbreviations: cKO, conditional knockout; ECoG, electrocorticogram; EPSPs, excitatory postsynaptic potentials; GAT1, GABA transporter 1; IR, immunoreactivity; het, heterozygous; hom, homozygous; KA, kainic acid; KI, knockin; KO, knockout; MES, maximal electroconvulsive seizure threshold test; mEPSCs, miniature excitatory postsynaptic currents; mIPSCs, miniature inhibitory postsynaptic currents; NMDA, N-methyl-D-aspartate; P, postnatal day; PTZ, pentylenetetrazol; Viaat, vescicular inhibitory amino acid transporter. Other abbreviations as in the text. For more references see https://gene.sfari.org.

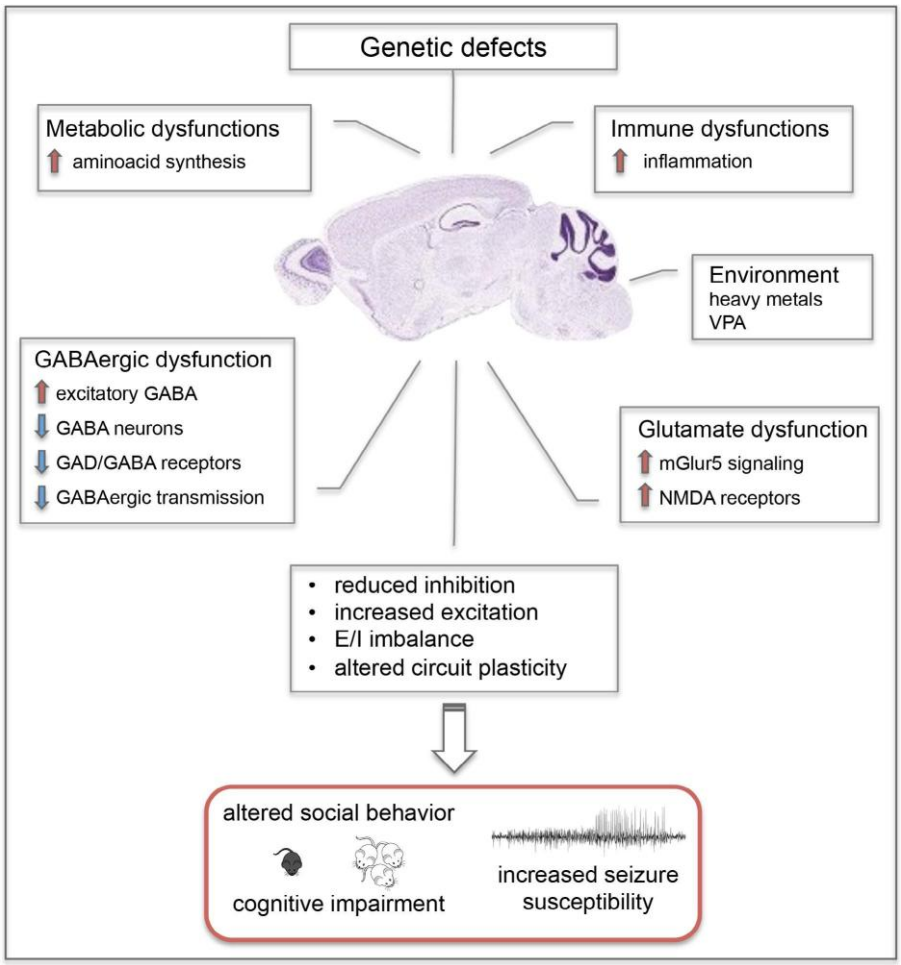

Fig. 1. Neural substrates of ASD/epilepsy comorbidity in rodent models. The figure schematically shows a multi-factorial model for the expression of ASD-like and epileptic behaviors in rodents. Studies performed in mouse models of ASD with epilepsy (see Table 1) indicate that GABAergic and glutamatergic signaling deficits of neurodevelopmental origin contribute to ASD/epilepsy comorbidity. Many ASD genes code for proteins involved in synaptic signaling, transcriptional/post-transcriptional regulation and cell adhesion. Loss of function of these genes may result in decreased inhibition by impairing GABA signaling at multiple levels (e.g. altered positioning or loss of PV, SST and other GABAergic interneuron subtypes, reduced expression of GABA receptors; blue arrows) or increased excitation (due to impaired NKCC1/KCC2 switch and subsequent persistent excitatory action of GABA during postnatal development, or enhanced mGlur5/NMDA receptor signaling; red arrows). Metabolic and immune dysfunctions, as well as environmental causes, may also contribute to ASD/epilepsy pathogenesis. As a consequence, E/I imbalance and resulting altered circuit plasticity may ultimately lead to altered social behavior, epilepsy and cognitive impairment. Experimental evidence suggests that similar mechanisms may also occur in the human brain (see text for details). The sagittal brain section is a Nissl stain taken from the Allen Mouse Brain Atlas (http://www.brain-map.org/). Abbreviations as in the text.

More interestingly, PV knockout mice (W€ohr et al., 2015) and mice conditionally lacking Nav1.1 sodium channels in PV- but not SSTpositive interneurons (Rubinstein et al., 2015) both display ASD-like deficits and increased seizure susceptibility. These studies suggest that defects of PV interneurons exert a causal role in the pathogenesis of ASD–epilepsy comorbidity.

In all these studies, PV-positive neurons were detected by immunohistochemistry. It is important to understand whether the observed reduction in PV immunostaining is the result of a decrease in PV expression or a loss of the PV-expressing GABAergic interneuron subtype; these two alternatives would likely lead to opposing effects on the E/I balance. In fact, decreased PV expression would likely result in enhanced inhibition due to increased presynaptic GABA release and postsynaptic GABA-mediated currents (Vreugdenhil et al., 2003). Conversely, loss of PV neurons would reduce inhibitory input to principal excitatory neurons (Marın, 2012). A recent study addressed this point using quantitative RT-PCR and immunoblotting analyses for PV expression, combined with double staining immunohistochemistry for PV and Vicia Villosa Agglutinin (VVA, a lectin recognizing the extracellular matrix enwrapping PV interneurons). The results showed that, in $PV^{+/}$, $Shank1^{/}$ and $Shank3B^{/}$ 'autistic' mice, the observed reduction in PV-positive interneurons was due to lower PV mRNA/protein levels without loss of PV cells (Filice et al., 2016). Dysregulation of GABAergic marker expression has been linked to hyperexcitability, as seizures modify GAD, NPY and SST mRNA levels (Takahashi et al., 2000). However, PV mRNA/protein downregulation does not seem to be related to hyperexcitability, since $Shank1^{/}$ and $Shank3B^{/}$mutant mice (contrary to $PV^{/}$ mice; Table 1) do not show seizures (see data on https://gene.sfari.org). Conversely, Shank3 overexpressing mutant mice do not display ASD-like behaviors but do exhibit seizures and an epileptic EEG, consistent with synaptic E/I imbalance (Han et al., 2013). Indeed, inhibitory postsynaptic currents (IPSCs) and inhibitory (gephyrin/VGAT-positive) synaptic puncta were reduced in cultured hippocampal pyramidal neurons from Shank3 transgenic mice (Han et al., 2013).

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However, no data are available about the interneuron subtypes affected in these mutants.

The recent findings by Filice et al. (2016) suggest that the loss of PV expression, which shifts E/I balance toward enhanced inhibition, might represent a common feature of some mouse models of ASD that are not necessarily associated with epilepsy comorbidity. It remains to be determined whether loss of PV expression but not PV-expressing cells also occurs in the above-mentioned ASD–epilepsy models (Cntnap2, En2, Fmr1, Nrp2 and Plaur mutants). Moreover, opto- and pharmacogenetic modulation of PV cell activity could be used to unravel the causal role of PV interneurons in the pathogenesis of ASD–epilepsy comorbidity. For example, optogenetics or 'designer receptors exclusively activated by designer drugs' (DREADDs; Wess et al., 2013) might be used to inactivate PV interneurons in the brain of wild-type mice to see whether this leads to an ASD–epilepsy phenotype. Optogenetics could also be used to reactivate PV cell function in specific brain areas of ASD mouse models, aiming to rescue ASD-like and epileptic behaviors.

Electrophysiological and gene expression data: GABAergic transmission

Studies performed in mouse models of ASD–epilepsy also showed profound alterations in GABAergic transmission. In general, these studies revealed a lower tone of basal inhibitory transmission. The releasable pool of synaptic vesicles, quantal size and miniature postsynaptic currents were reduced at inhibitory synapses in synapsin I/ II (SynI/II), MeCP2 and Scn1A mutant mice respectively. A reduced number of GABAergic synapses was also detected in adult oxytocin receptor knockout (Oxtr$^{-/-}$) mice (Table 1). Gene expression studies also suggest that $GABA_A$ receptor-mediated neurotransmission is compromised in some mouse models. Reduced mRNA and protein levels of GAD65/67 and/or $GABA_A$ receptor subunits were detected in Fmr1 (D'Hulst et al., 2009; Olmos-Serrano et al., 2010; Sabanov et al., 2017), Gabrb3 (Sinkkonen et al., 2003), En2 (Provenzano et al., 2015; our unpublished data) but not Ube3A mutants (Sinkkonen et al., 2003; see also Table 1). Thus, it appears that at least certain models of ASD and epilepsy comorbidity (En2, Fmr1, Gabrb3, conditional MeCP2, Scn1A and Syn mutants) are characterized by a markedly reduced (and not enhanced) inhibitory transmission.

The role of excitatory GABA

In the immature brain, GABA exerts an excitatory action, promoting depolarization of postsynaptic neurons. Brain maturation is associated with a depolarizing-to-hyperpolarizing GABA shift, which is due to a progressive reduction in intracellular Cl concentration in GABA-sensitive neurons. This excitatory-to-inhibitory GABA shift occurs during early postnatal brain development and depends on the decreased expression of the sodium-potassium-chloride cotransporter 1 (NKCC1, which imports Cl) and concurrent increased expression of potassium-chloride cotransporter 2 (KCC2, which extrudes Cl) in GABA-responding neurons (Ben-Ari, 2014). Recent studies performed in animal models of ASD and epilepsy showed a persistent excitatory action of GABA (Fmr1 knockout mice; Tyzio et al., 2014) and an upregulation of NKCC1 and downregulation of KCC2 (Oxtr$^{-/-}$ mice; Leonzino et al., 2016) in specific brain areas, such as the hippocampus. Thus, ASD–epilepsy comorbidity appears to be characterized by immature properties of GABA signaling, such as persistently high NKCC1/KCC2 ratio, high intracellular Cl concentrations in GABA-responding neurons and excitatory action of GABA. Oxytocin appears to regulate the excitatory-to-inhibitory GABA switch. Recent results show that, in rodents, oxytocin determines a short-lasting reduction in intracellular Cl concentration in hippocampal neurons at birth, and this action of oxytocin is abolished in the Fmr1 ASD–epilepsy model during delivery. In Fmr1 mutant mice, maternal pretreatment with the NKCC1-blocker bumetanide restored a physiological phenotype in offspring, whereas the offspring of na€ıve mothers treated with an oxytocin receptor antagonist showed ASD-like behaviors and hyperexcitability (Tyzio et al., 2014; Ben-Ari, 2015). A study performed on hippocampal neurons from Oxtr$^{-/-}$ mice recently confirmed the importance of oxytocin signaling in regulating the GABA switch during early postnatal development. In this study, the authors showed that Oxtr signaling controls the timing of the GABA switch by upregulating KCC2 activity via phosphorylation. Accordingly, Oxtr$^{-/-}$ mature hippocampal neurons show electrophysiological alterations consistent with lower levels of KCC2 and epileptic phenotype observed in adult Oxtr$^{-/-}$ mice (Leonzino et al., 2016). Taken together, these results stress the importance of oxytocinmediated GABAergic inhibition in the pathogenesis of ASD–epilepsy comorbidity, indicating that NKCC1 antagonists, KCC2 agonists and oxytocin might exert potential therapeutic benefits.

Glutamate dysfunction in ASD and epilepsy: human subjects and mouse model data

Evidence for excessive glutamate in ASD with epilepsy comes from human genetics and mouse model studies. Increased levels of glutamate have been detected in both blood and platelets of ASD subjects (Aldred et al., 2003; Shinohe et al., 2006), but no data are available for patients with ASD and epilepsy. Most importantly, single-gene disorders characterized by ASD–epilepsy comorbidity (such as FXS, TSC and Phelan-McDermid syndromes) are caused by mutations in genes regulating glutamate receptor signaling (Fmr1, Tsc and Shank3 respectively). Mouse studies showed an increased excitatory neurotransmission in some models of ASD–epilepsy comorbidity. Miniature excitatory postsynaptic currents (mEPSCs) have been detected in neocortical/hippocampal neurons of Fmr1$^{-/-}$ (Tyzio et al., 2014), Oxtr$^{-/-}$ (Leonzino et al., 2016) and Scn1A$^{+/-}$ (Rubinstein et al., 2015) mice. Contrasting results have been instead obtained in MeCP2 mutants (see Table 1). It is likely that increased excitation in these mutant strains is a consequence of reduced inhibition (see Table 1), but a direct impairment of glutamatergic transmission cannot be excluded. Glutamatergic transmission alterations have been poorly investigated in mouse models of ASD–epilepsy, except for Fmr1$^{-/-}$ mice (see Table 1). The Fmr1 gene codes for Fragile X mental retardation protein (FMRP), and its mutation causes FXS, a severe condition characterized by mental retardation and ASD. FMRP is an RNA-binding protein that regulates the intracellular transport and translation of 4–8% of synaptic proteins (Bassell & Warren, 2008). FMRP negatively regulates metabotropic glutamate receptor 5 (mGluR5) signaling: in FXS, the absence of FMRP leads to increased synthesis of synaptic proteins downstream of mGluR5 (Bear et al., 2004). mGluR5 upregulation has been detected in post-mortem brain samples from ASD patients, along with reduced FMRP expression (Fatemi & Folsom, 2011; Fatemi et al., 2011). Interestingly, upregulation of mGlur5 and downregulation of FMRP has been reported in En2$^{-/-}$ mice (Provenzano et al., 2015), which

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display an increased seizure susceptibility (Tripathi et al., 2009) and share brain anatomical abnormalities with Fmr1$^{/}$ mice (Ellegood et al., 2015).

Other mechanisms: metabolic, immune and environmental factors

Metabolic and immune dysfunctions, as well as environmental factors, have been implicated in ASD pathogenesis and E/I imbalance associated with ASD. These mechanisms have been recently reviewed by other authors (Estes & McAllister, 2015, 2016; Frye, 2015; Frye & Rossignol, 2016; Frye et al., 2016) and will be only briefly discussed here.

Alterations of GABAergic and glutamatergic transmission directly occur as a consequence of several metabolic disorders. For example, depletion of pyridoxal-5-phosphate (a cofactor of the GAD enzyme) results in decreased GAD activity, GABA synthesis and cortical inhibition, while untreated children suffering phenylketonuria may develop ASD and epilepsy due to persistently elevated levels of phenylalanine. Chronically high levels of phenylalanine lead to upregulation of glutamate receptors, thus compromising E/I balance (Frye et al., 2016; and references therein). Amino acid metabolism dysfunctions also lead to autism, epilepsy and ID. Inactivating mutations in branched chain ketoacid dehydrogenase kinase (BCKDK; Novarino et al., 2012) or amino acid transporter (Slc7a5; Tarlungeanu et al., 2016) result in altered brain amino acid profiles and neurobehavioral deficits in both humans and mice. Interestingly, Bckdk knockout mice positively responded to dietary supplementation of branched-chain amino acids, thus indicating a novel therapeutic strategy for ASD presenting with ID and epilepsy caused by BCKDK mutations (Novarino et al., 2012).

Other metabolic disorders associated with ASD and epilepsy include vitamin deficiencies (such as cobalamin and cerebral folate deficiency), mitochondrial diseases and other disorders of energy metabolism; all these conditions may be characterized by seizures and ASD (Frye & Rossignol, 2016). Immune dysfunctions have been widely associated with ASD, including increased levels of autoantibodies against brain-specific proteins (both in ASD children and mothers who have had children with ASD) and abnormal levels of immunoglobulins in the blood. Microglia activation in post-mortem brain samples and altered levels of cytokines in the blood, brain and cerebrospinal fluid have been detected in ASD patients (Estes & McAllister, 2015, 2016; Frye & Rossignol, 2016). Neuroinflammation is known to markedly contribute to epileptogenesis (Aronica et al., 2017), so it is likely that the above-mentioned immune dysfunctions may be involved in seizure occurrence in ASD; however, a systematic analysis of the role of immune dysregulation in ASD, epilepsy and ID is still lacking. Finally, environmental factors may contribute to ASD and associated comorbidities. Exposure to heavy metals such as mercury is associated with ASD and the occurrence of epilepsy. Although the mechanisms by which heavy metals may cause neurodevelopmental disorders have not been elucidated, the toxic effects of heavy metals on mitochondrial function, energy metabolism and cell survival are known (Frye et al., 2016). Several clinical studies have shown that exposure to the anti-convulsant and a mood stabilizer valproic acid (VPA) in utero is associated with birth defects, cognitive deficits and increased risk of ASD (Roullet et al., 2013). Molecular, anatomical, electrophysiological and behavioral studies in rats and mice confirmed that in utero exposure leads to VPA to ASD-like behaviors in the offspring, accompanied by GABAergic interneuron defects (Gogolla et al., 2009) and E/I imbalance (Banerjee et al., 2013). Therefore, environmental factors also seem to contribute to increased excitability in ASD.

Therapeutic perspectives

Based on the data reported above, several strategies have been followed to develop novel therapeutic agents against ASD–epilepsy comorbidity (reviewed in Oberman, 2012; Loth et al., 2014; Jeste & Tuchman, 2015; Frye & Rossignol, 2016). Here, we discuss the most relevant, as they emerged from recent clinical and animal studies.

Reversal of delayed GABA switch

Treatment with the NKCC1 blocker bumetanide already gave promising results in ASD and FXS patients (Lemonnier et al., 2012, 2013). A pilot study recently showed that chronic bumetanide treatment improved the recognition of different facial expressions in ASD adolescents, resulting in increased activation of brain areas involved in face, emotional and social processing (e.g. the inferior occipital cortex, amygdala and superior temporal cortex respectively; Hadjikhani et al., 2015). Interestingly, a better behavioral improvement was observed when ASD patients were exposed to a combined educative and bumetanide treatment (Du et al., 2015). It is important to point out that the effect of bumetanide on seizures occurring in ASD children was not investigated since children with epilepsies were not included in these trials (Ben-Ari et al., 2016). Some promising results were obtained by treating temporal lobe epilepsy patients with bumetanide (Eftekhari et al., 2013), but the phase I/II NEMO trial designed to test the efficacy of bumetanide against newborn seizures gave negative results (Pressler et al., 2015). Thus, further studies are needed to understand whether bumetanide may be useful to ASD patients with epilepsy. Another possibility to restore the proper NKCC1/KCC2 balance would be to test drugs enhancing KCC2 action in ASDepileptic patients. As an example, Cl extrusion enhancers activating KCC2 have been identified as novel therapeutic agents against neuropathic pain (Gagnon et al., 2013), and might be tested with ASD-epileptic patients.

Currently, there are 34 ongoing clinical trials testing the efficacy of oxytocin in ASD (www.ClinicalTrials.gov), but none of them are specifically designed to study ASD–epilepsy patients. In light of the recent findings showing the role of oxytocin signaling in regulating GABA switch through KCC2 in Fmr1 and Oxtr mutant mice (Tyzio et al., 2014; Leonzino et al., 2016), it would be interesting to further test oxytocin efficacy in other mouse models of ASD–epilepsy comorbidity. If successful, these studies might create opportunities for novel pilot studies and clinical trials.

GABA agonists

Data from both animal models and clinical studies suggest that GABAergic transmission is reduced in subjects with ASD and epilepsy (see above). Thus, it would be reasonable to assume that there are beneficial effects of GABA agonists in cases of ASD–epilepsy comorbidity. Indeed, Scn1a mutant mice showed behavioral improvements after treatment with the $GABA_A$ agonist clonazepam (Han et al., 2012). However, the effect of benzodiazepines in other ASD–epilepsy models has not been tested yet. It should also be kept in mind that drugs acting on $GABA_A$ receptors may have paradoxical

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reactions in ASD patients that are likely due to persistent excitatory GABA action. As an example, diazepam has been shown to increase anxiety in some ASD patients (Marrosu et al., 1987). Recent studies revealed that agonists specific to $GABA_A$ receptors containing a2/a3 subunits could rescue ASD-like deficits in mice (Han et al., 2014), thus suggesting that drugs acting at selective $GABA_A$ receptor subtypes might represent a valid alternative to classical benzodiazepines. Further studies are, however, needed to test such drugs in ASD–epilepsy models. Finally, the $GABA_B$ agonist R-baclofen (arbaclofen, STX209) reversed disease-related phenotypes in Fmr1 mutant mice (Henderson et al., 2012) and other models of ASD (Silverman et al., 2015). Clinical trials on FXS patients revealed that STX209 might improve some symptoms in children with ASD (Berry-Kravis et al., 2012; Veenstra-VanderWeele et al., 2016).

Finally, other GABAergic drugs such as riluzole, gaboxadol, tiagabine and vigabatrin, have been proposed as potential therapeutics in ASD–epilepsy syndromes (Lozano et al., 2014). However, evidence supporting the beneficial effect of GABAergic drugs in ASD is still limited and controversial (Brondino et al., 2016). GABA agonists (benzodiazepines) may be less effective in certain forms of ASD–epilepsy, such as 15q11.2 duplication (Jeste & Tuchman, 2015), and a paradoxical response to treatment with conventional GABAergic agonists has been reported in ASD (Bruining et al., 2015). Further studies will be needed to replicate these findings and extend them to cases of ASD–epilepsy comorbidity.

Neurosteroids

Neurosteroids act as positive allosteric modulators of $GABA_A$ receptors (Lozano et al., 2015). Among these, ganaxolone (also known as CCD-1042) is a synthetic analog of the progesterone metabolite allopregnanolone. Ganaxolone treatment reduced seizures in a rat model of infantile spasms (Yum et al., 2014) and neurobehavioral deficits in two mouse models of ASD, namely Fmr1$^{/}$ (Braat et al., 2015) and BTBR mice (Kazdoba et al., 2016). Phase II clinical trials showed ganaxolone′s efficacy and safety in the treatment of both children and adults affected by refractory epilepsy. A phase II proof-of-concept clinical trial is currently ongoing to investigate the effectiveness and safety of ganaxolone in children and adolescents with FXS (www.ClinicalTrials.gov, NCT01725152; Lozano et al., 2015).

Glutamate receptor antagonists

Enhanced glutamatergic transmission has been linked to ASD in both humans and animal models (see above and Table 1). Accordingly, several glutamatergic anatgonists have been tested in syndromic ASD and patients with FXS (reviewed in Oberman, 2012). In agreement with the ‘mGluR theory′ of FXS pathogenesis mentioned above (Bear et al., 2004), mGluR antagonists were able to rescue learning and behavioral deficits associated with FXS in both young and adult mice (D€olen et al., 2007; Michalon et al., 2012). However, several clinical trials with mGluR antagonists failed in patients with FXS or other syndromic forms of ASD (reviewed in Oberman, 2012; Lozano et al., 2015; Scharf et al., 2015). The NMDA receptor antagonist memantine has been shown to restore normal levels of glutamatergic synapses in Fmr1$^{/}$ mice (Wei et al., 2012) and to rescue ASD-like behaviors in transgenic mice overexpressing the telomerase reverse transcriptase (TERT; Kim et al., 2016). Interestingly, positive effects of memantine have been recently reported as the result of clinical trials in ASD patients (see, e.g. Joshi et al., 2016; www.ClinicalTrials.gov). Thus, NMDA glutamate receptor antagonism might be effective to reduce hyperexcitability associated with ASD, but its specificity in cases of ASDepilepsy comorbidity needs to be specifically investigated.

Insulin-like growth factor 1

Insulin-like growth factor 1 (IGF-1) is a polypeptide hormone primarily released by hepatocytes in response to growth hormone but is also produced in the brain, where it plays a crucial role in development, growth and synapse maturation (Vahdatpour et al., 2016; and references therein). Animal studies showed that IGF-1 could rescue anatomical, physiological and behavioral deficits of MeCP2 mutant mice, leading to a series of clinical studies and a phase 2 trial in Rett syndrome patients; phase 2 trials with recombinant human IGF-1 have also been performed in FXS and PhelanMcDermid patients. Based on the positive outcomes of these studies, other trials are ongoing to test IGF-1 efficacy in Rett syndrome and ASD (reviewed in Vahdatpour et al., 2016).

mTOR inhibitors

The mammalian target of rapamycin (mTOR) pathway is crucially involved in the regulation of different cellular processes, including growth, proliferation, survival and protein translation. In the brain, components of the mTOR pathway are localized to synapses, in which they control dendritic spine morphology and synaptogenesis. Dysregulation of the mTOR pathway is detected in several human diseases, including cancer and ASD. As an example, mutations in TSC and phosphatase and tensin homolog (PTEN) lead to overactivation of the mTOR pathway and are associated with syndromic forms of ASD (Huber et al., 2015; Sahin & Sur, 2015). Several lines of evidence indicate that the mTOR inhibitor rapamycin can rescue neurobehavioral defects in mouse models of ASD (Huber et al., 2015). Of interest, a phase 3 clinical trial showed efficacy in reducing seizure frequency in refractory epilepsy associated with TSC (French et al., 2016). Clinical trials are currently ongoing with mTOR inhibitors in patients suffering TSC, ASD and PTEN-related disorders (Roach, 2016; www.ClinicalTrials.org).

Concluding remarks

Studies performed in ASD patients and mouse models indicate that the E/I imbalance toward hyperexcitability may contribute to ASDepilepsy comorbidity. Current research suggests that different pharmacological treatments leading to delayed GABA switch, potentiation of GABA signaling or inhibition of glutamate transmission might represent effective therapeutic strategies against ASD–epilepsy comorbidity. A deeper understanding of neural development, receptor signaling pathways and synaptic transmission in appropriate mouse models might help in the design of novel therapeutic strategies to restore physiological inhibition. Moreover, the comparative analysis of mouse models of ASD with or without epilepsy might help to identify the underlying mechanisms of ASD–epilepsy comorbidity. In this respect, the recent anatomical clustering analysis of 26 different mouse models of ASD performed by Ellegood et al. (2015) might provide some clues for further investigations. Based on brain anatomy similarities, these authors classified these models into three groups. Group 1 contains models showing ASD-like

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symptoms with (MecP2 and CNTNAP2 mutants) or without (Gtf2i mutants) epilepsy. Group 2 is prevalently composed of models not presenting with epilepsy (such as BTBR and neuroligin-3 mutants), while Group 3 mostly contains models with increased seizure susceptibility (such as Shank3, Fmr1 and En2 mutants). Thus, further comparative analyses of Group 2 vs. Group 3 models might help identify molecular, anatomical, physiological or behavioral features specific to ASD–epilepsy comorbidity. It is interesting to observe that neuroligin-3 mutants display increased GABAergic transmission and no seizures (Tabuchi et al., 2007; F€oldy et al., 2013), whereas Group 3 mice mainly show reduced GABAergic transmission and increased seizure susceptibility (Table 1). Finally, in patients, a precision medicine approach (Loth et al., 2016) to compare clinical cases of ASD with or without epilepsy might help to identify novel biomarkers and drug targets of ASD–epilepsy comorbidity.

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Data accessibility

Original data cited in Table 1 can be accessed at https://gene.sfari.org.

Abbreviations

[1] H-MRS, proton magnetic resonance spectroscopy; ASD, autism spectrum disorder; BCKDK, branched chain ketoacid dehydrogenase kinase; CB, calbindin; cKO, conditional knockout; CR, calretinin; DREADDs, designer receptors exclusively activated by designer drugs; Dup15q, maternal duplications on chromosome 15q11.2-q13.1; E, embryonic day; E/I, excitation/inhibition; ECoG, electrocorticogram; EEG, electroencephalogram; EPSPs, excitatory postsynaptic potentials; FMRP, Fragile X mental retardation protein; FXS, Fragile X syndrome; GABA, c-aminobutyric acid; GAD65/67, glutamic acid decarboxylase (65/67 kDa isoform); GAT1, GABA transporter 1; het, heterozygous; hom, homozygous; ID, intellectual disability; IGF-1, insulin-like growth factor 1; IR, immunoreactivity; KA, kainic acid; KI, knockin; KO, knockout; mEPSCs, miniature excitatory postsynaptic currents; MES, maximal electroconvulsive seizure threshold test; mGluR5, metabotropic glutamate receptor 5; mIPSCs, miniature inhibitory postsynaptic currents; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; P, postnatal day; PET, positron emission tomography; PTEN, phosphatase and tensin homolog; PTZ, pentylenetetrazol; PV, parvalbumin; SPECT, single-photon emission computed tomography; SST, somatostatin; Syn, synapsin; TERT, telomerase reverse transcriptase; TSC, tuberous sclerosis complex; UBE3A, ubiquitin-protein ligase E3A; Viaat vescicular inhibitory amino acid transporter; VIP, vasointestinal peptide; VPA, valproic acid; VVA, Vicia Villosa agglutinin; WT, wild-type.

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