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CRITICAL REVIEW

Interneuronopathies and their role in early life epilepsies and neurodevelopmental disorders

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Summary

GABAergic interneurons control the neural circuitry and network activity in the brain. The advances in genetics have identified genes that control the development, maturation, and integration of GABAergic interneurons and implicate them in the pathogenesis of epileptic encephalopathies and neurodevelopmental disorders. For example, mutations of the aristaless-related homeobox X-linked gene (ARX) may result in defective GABAergic interneuronal migration in infants with epileptic encephalopathies like West syndrome (WS), Ohtahara syndrome, or X-linked lissencephaly with abnormal genitalia (XLAG). The concept of "interneuronopathy," that is, impaired development, migration, or function of interneurons, has emerged as a possible etiopathogenic mechanism for epileptic encephalopathies. Treatments that enhance γ-aminobutyric acid (GABA) levels may help seizure control but do not necessarily show disease modifying effect. On the other hand, interneuronopathies can be seen in other conditions in which epilepsy may not be the primary manifestation, such as autism. In this review, we plan to outline briefly the current state of knowledge on the origin, development, and migration and integration of GABAergic interneurons, present neurodevelopmental conditions, with or without epilepsy, that have been associated with interneuronopathies, and discuss the evidence linking certain types of interneuronal dysfunction with epilepsy and/or cognitive or behavioral deficits.

KEY WORDS: GABA, Interneuronopathy, Dravet syndrome, West syndrome, Autism, Lissencephaly, Schizophrenia.

Interneuronopathies refer to a group of disorders that are associated with impaired development, migration, or function of interneurons. Kato and Dobyns proposed this term in 2005 in reference to the pathology observed in X-linked lissencephaly with abnormal genitalia, which showed a defect in the tangential migration of interneurons and caused intractable epilepsy.[1] Currently, interneuronopathies have been associated with early-life epilepsies and neurodevelopmental disorders. Interneuronopathies have been implicated in the pathogenesis of epileptic encephalopathies such as West syndrome (WS), Ohtahara syndrome (OS), Dravet syndrome (DS) and in the pathology of lissencephaly as well. They are also involved in disorders that are not necessarily characterized by epilepsy, such as autism spectrum disorders (ASD) and schizophrenia. The purpose of this review is to summarize our current state of knowledge about interneurons, focus on developmental conditions that are linked to interneuronopathies, and try to answer the following questions. Can interneuronopathies be causative factors for early-life epilepsies? If so, is there a spectrum of manifestations characteristic of interneuronopathy-related epilepsies? Can interneuronopathies contribute to neurodevelopmental abnormalities in the absence of epilepsy? Are interneuronopathies strictly an age-specific etiology limited

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Key Points

- Interneuronopathy is a key feature of several early-life epilepsies and neurodevelopmental disorders
- Both genetic and nongenetic etiologies as well as disease processes may contribute to the interneuronal loss or dysfunction
- Interneuronal loss or dysfunction may also be a feature of late-onset neurological or neuropsychiatric diseases
- Studies on the causes, consequences, and classification of primary and secondary interneuronopathies may rationalize therapy strategies

to early-life epilepsies and neurodevelopmental disorders? Do seizures or other etiologies of seizures trigger or deteriorate interneuronopathies, leading to progression of epilepsies and/or associated comorbidities?

Interneurons

The mammalian cerebral six-layered neocortex includes two major classes of neurons: the excitatory pyramidal cells that project to cortical and subcortical targets, and the inhibitory nonpyramidal cells, the cortical interneurons.[2] Although GABAergic interneurons compose only 10–25% of the total cortical neuronal population, they play a vital role in controlling the neural circuitry and network activity of the central nervous system (CNS) because they form numerous connections with other neuronal types. They are the only source of γ-aminobutyric acid (GABA) and the main source of inhibition in the mammalian CNS. Once generated and specified in their respective areas of origin, GABAergic interneurons migrate to their ultimate destinations within the cerebral cortex.[3,4] Migration is very important for the establishment and integration of interneurons during embryonic and early postnatal life in both humans and rodents. There are several migration routes for interneurons.[5,6] Failure or disruption of interneuronal migration leads to abnormal distribution of interneurons and alterations of the inhibitory control of the postnatal brain but also deprivation of the neurotrophic role of GABA in early development, resulting in epilepsies or other neurological disorders.[4,7–11]

In humans, the subcortical ganglionic eminences are thought to participate in cortical interneuronogenesis.[12] Early interneuronal progenitors have been detected in human cortical progenitor zones, particularly at the anterior brain regions, between gestational weeks 10 and 25.[13] Intracortical interneuronogenesis may start earlier than the time when tangential migration of interneurons from the medial ganglionic eminence (MGE) occurs.[13]

In rodents, the majority of cortical interneurons are generated within the ventral telencephalon: in the MGE (produces 50–60% of cortical interneurons) and caudal ganglionic eminence (CGE; 30–40%) with a smaller contribution by the preoptic area (POA; ~10%) of the hypothalamus.[2,3,14–16] In addition, evidence suggests a lesser contribution of the lateral ganglionic eminence (LGE), rostral migratory stream (RMS), septal region in the generation of cortical interneurons in rodents. Unlike humans, intracortical interneuronogenesis is less likely.[17] In rodents, GABAergic interneurons start migrating at embryonic day 12.5 (E12.5) tangentially, through the intermediate zone and to a lesser extent through the preplate.[3] At E14–15, interneurons migrate through the *tangential migratory streams*, directed toward the marginal zone (MZ), the cortical plate (CP), and the lower intermediate zone (IZ)/subventricular zone (SVZ).[3] A variety of mitogens (secreted factors that influence migration), chemotactic or transcription factors, as well as neurotransmitters are involved in the complicated process of interneuronal migration.[3,16,18–21]

In the rodent cerebral cortex, there are many, perhaps more than 20, GABAergic interneuronal subtypes. The expression of calcium-binding proteins (such as calretinin [CR], calbindin [CB], and parvalbumin [PRV]) or other markers (e.g., somatostatin [SST], neuropeptide Y [NPY], cholecystokinin [CCK], serotonin receptor 3A [5HT3aR], vasoactive intestinal peptide [VIP], reelin, and neuronal nitric oxide synthase [NOS]), their morphology, connectivity pattern, synaptic properties, and intrinsic firing properties are features that help to differentiate the various interneuronal subtypes (Table 1).[3,22] Neocortical GABAergic neurons in rodents belong to one of three groups defined by the expression of PRV (40% of interneurons; neocortical layers II–VI), SST (30% of interneurons; neocortical layers I–V), and the ionotropic 5HT3AR (30% of interneurons; neocortical layers I–III).[3] The latter (5HT3AR-positive) are further distinguished into VIP-positive (neocortical layers II/III) and VIP-negative/reelin-positive interneurons (neocortical layers I–VI). Each of these classes shows heterogeneity and few identifiable subtypes, although more research needs to be done to fully characterize all these subtypes of cortical interneurons.[23] Specific interneurons are generated from discrete regions: MGE generates precursors to PRV, SST, NOS, and a subpopulation of the CB and NPY interneurons. In contrast, the CGE generates CR, 5HT3aR, reelin, VIP, CCK, and a lesser subpopulation of CB and NPY (reviewed in 6).

There are species differences in interneuronal subtypes, e.g., CB-positive double bouquet cells are present in primates, but not in rodents.[24] In humans, at the early stages of neocortical development (12th postconceptional week), CR-positive interneurons are more abundant in the anterior than at the caudal pole of the cortex, raising the possibility that the origin of these early CR interneurons is not necessarily the CGE.[13] Therefore, in regard to neurodevelopmental disorders and the role of interneuronal deficits in their pathogenesis, the available studies provide evidence that many developmental rules may run across species but

Table 1. Neocortical GABAergic interneurons

Cell type	Cell marker	Cortical layers	Firing properties	Connectivity	Functional relevance	References
Basket cells						
Large basket cells	PRV, CB, NPY, SST, CCK	II/III, IV, V, VI	FS	Proximal dendrites/soma of pyramidal cells Basket cells Interneurons	Feed-forward inhibition Lateral inhibition across cortical columns Gamma oscillations	3,14,23,114,162–164
Nest basket cells	PRV, CCK, SST, CB, NPY (CB1R)	II/III, IV (V, VI)	Irregular spiking	Proximal dendrites/soma of pyramidal cells	Tonic inhibition Theta oscillations	
Small basket cells	PRV, VIP, CCK, CB	IV, II/III (V, VI)		Axonal contacts on cell bodies and proximal dendrites of other cells		
Chandelier cells	PRV, CB	II/III, V (IV, VI)	FS	Axonal initial segment of pyramidal cells	Synchronization within 1 column	23,114,163,164
Martinotti cells	SST, CCK, NPY, CR, CB	VI, V, IV, II/III	Regular spiking Burst spiking Frequency adapting	Dendrites, axonal plexus in layer I Horizontal connections in distal dendrites of pyramidal cells	Feedback inhibition in the setting of high network firing	3,14,23,114,162–164
Double-bouquet cells	5-HT3AR, VIP, CCK (CR, CB)	II/III, V (IV)	Non-FS	Descending axons targeting dendritic spines and shafts across layers	Interlayer and intracolumnar inhibition	3,23,114,163,164
Neurogliaform cells (spiderweb cells)	NPY, 5-HT3AR, Reelin, NOS + or −	I, II/III (IV–VI)	Late spiking Fast adapting	Densely branched axons Electrical synapses with other inhibitory neurons GABA neurons	Volume transmission inhibition in local circuits and networks Functional hyperemia	3,14,23,114,162–164
Small bipolar cells	5-HT3AR VIP, CR	II/III, IV, V, VI	Irregular spiking	Proximal dendrites	Inhibition of vertically oriented pyramidal neurons	3,14,23,165
Multipolar cells	NPY, Reelin		Fast adapting	Dendritic shafts Blood vessels		14
Arcade cells	VIP	III	Burst spiking	Short ascending main axons with collaterals forming axonal arcades		166
Layer I Interneurons (Cajal Retzius cells, large and small multipolar cells)	Reelin, NPY, VIP, CR, SST	I	Late spiking Burst spiking		Role in neuronal migration, cortical lamination Synchronized network activity in neocortex	163,167–169

CB, calbindin; CB1R, cannabinoid receptor; CCK, cholecystokinin; CR, calretinin; FS, fast spiking; GABA, γ-aminobutyric acid; 5-HT3AR, serotonin receptor 3A; NOS, nitric oxide synthase; NPY, neuropeptide Y; PRV, parvalbumin; SST, somatostatin; VIP, vasoactive intestinal peptide.

also raise the caution that species differences may complicate the extrapolation of observations across species.

Developmental Equivalency Between Humans and Rodents and Relevance to the Maturation of the GABAergic System

To validate an animal model and translate the observations stemming from animal models to humans, especially for disorders that occur during brain development, it is important to recognize how maturational processes proceed in various species and determine whether these are relevant to the developmental stages when the human disorder occurs. There are several differences between humans and rodents in anatomy, genetics, biology, brain development, maturation patterns, lifestyle, and life span, which complicate the translation of findings across species.[25–27] The current staging of developmental periods between humans and rodents has been based on the species-specific maturation of the reproductive system and hypothalamus-pituitary-gonadal axis or on crude measures of brain growth, as will be discussed below.

According to the development of the hypothalamus-pituitary-gonadal axis, in the majority of studies, a rodent is considered as neonatal between postnatal (PN) days 0 and 6, infantile between PN7 and PN21, juvenile between PN21 and PN32 in females and PN21 and PN35 in males, early pubertal between PN32 and PN36 in females and PN35 and PN45 in males, and young adult on PN60.[28] However, it was suggested that PN8–10 rats can be compared to full-term human newborns, after across-species comparisons of brain growth, DNA, cholesterol, and water content were done.[25] The brain growth spurt occurring at birth in humans takes place about 1 week postnatally in rats, suggesting that the last trimester of human gestation corresponds to PN1–10 in rats.[29,30] Different developmental processes, however, mature asynchronously and at different rates in humans and rodents, making generalizations difficult (reviewed in 25,28,31). An example that underlines that such assumptions on developmental equivalence of milestones are very crude is the observation that eye opening in rodents does not happen until PN13–15, whereas human newborns already have their eyes open. Rodent pups are only able to fully ambulate during the third week of life, a milestone that occurs after the first year of human life.[32] Therefore, studies of age-specific disorders that affect the motor system, such as early-onset infantile spasms (IS), which usually start during the first year of life, need to consider the motor milestones in rodents.[27] Overall, when extrapolating results from developing rodent brains to the human condition, it is necessary to take into account the evidence on the maturation rate and correspondence of the specific developmental processes studied in both rodents and humans.[26]

In the case of the GABAergic system, in both humans and rodents many changes normally occur early in life and involve the migration of GABAergic interneurons to their final destinations such as the cerebral cortex, the neuronal differentiation and development of GABAergic dendritic arbor and synapses, the expression and subunit composition of $GABA_A$ receptors ($GABA_ARs$) (e.g., decrease in $\alpha 3$ and increase in $\alpha 1$ subunits), or the switch from depolarizing to hyperpolarizing $GABA_AR$ signaling. These are reviewed extensively in other publications.[7,9,25,33,34]

In humans, only 20% of GABAergic interneurons migrate prenatally and the rest during the first 6 postnatal months.[35] The density of GABAergic interneurons (GAD65/67 positive cells/mm^2) in the human frontal association cortex peaks around the 40th postconceptual week (full-term birth equivalent) and declines thereafter during the first 6 postnatal months, even when densities are adjusted to the growing cortical width during this period.[35] Tracking the various types of interneurons, by staining them with calcium-binding protein markers (e.g., calretinin [CR], calbindin [CB], parvalbumin [PRV]), shows that they appear at different developmental periods. In humans, whereas CR and CB interneurons are expressed within the first 2 weeks from birth, PRV interneurons first appear between the 3rd and 6th month after birth.[36] A delayed appearance of PRV interneurons also occurs in rodents, that is, these first appear on PN5 (our unpublished observations) in Sprague Dawley rats and PN8 in Wistar rats.[37]

Possible explanations for the postnatal decline in GABAergic interneuronal densities may include postnatal apoptosis or expanding dendritic or axonal arborization that presents as an apparent decrease in density of interneurons.[35] There was no evidence for apoptosis in the human early postnatal neocortex to justify this decline in the density of GABAergic interneurons.[35] The increasing expression of GAD65 protein immunoreactivity in the cortex during this 6-month period and of GAD67 during the first 5 years of life suggests that the developing dendritic or axonal arborization may underlie the declining density of GABAergic interneurons.[35] In mice, GAD67 interneurons increase in number in the developing neocortex between PN0 and PN5, and subsequently decline till PN20. The reduction in the interneuronal densities in the cortex in mice is likely also due to programmed cell death, which peaks around PN7–11 in the visual neocortex.[38,39]

The activity of the synthesizing enzyme for GABA, glutamate decarboxylase (GAD), in rodent cortical neurons reaches levels equivalent to those of a full-term human neonate in PN7–9 rats.[28] In contrast, in a study comparing the protein expression of KCC2 and NKCC1 using Western blots, the expression of the chloride cotransporters NKCC1 and KCC2 that control whether $GABA_AR$ responses will be depolarizing or hyperpolarizing, reach protein expression levels in the rat cerebral cortex equivalent to full-term human newborns after PN20 or around PN16,

respectively.[40] However, isoform-specific differences in the developmental expression of KCC2 and NKCC1 have been described and the reader is referred to the relevant reviews on this subject. Further differences exist in the maturational trajectory of various cell types, regions, or the connectivity patterns according to which such brain circuits are formed as a function of sex.[9] For example, we have demonstrated in rats that the timing of the switch from depolarizing to hyperpolarizing $GABA_AR$ signaling occurs at different times in subcortical brain regions, like the substantia nigra (SN), compared to hippocampal CA1 pyramidal neurons and may occur earlier in females than in males, in certain sexually dimorphic brain regions.[7,8,33,41–43] Such differences have not been well studied in humans. Activation or inhibition of $GABA_ARs$ in specific brain regions, like the SN pars reticulata, may have age- and sex-specific effects on seizure control.[9]

Neurological Disorders Associated with Interneuronopathies: Early-Life Epilepsies and Neurodevelopmental and Psychiatric Disorders

Research during the past decades has identified a wide range of neurodevelopmental conditions linked to interneuronopathies. This is not surprising given that the infantile period is a transitional stage in the maturation of the GABAergic system (discussed above), including the migration of interneurons in the cortical cortex, development of GABAergic synapses and dendritic arbor, as well as the changing expression, composition, and function of $GABA_A$ receptors, resulting from the depolarizing to hyperpolarizing switch in their responses. These neurodevelopmental conditions may be associated with epilepsy, such as in West syndrome and Dravet syndrome, or may not necessarily present with epilepsy, such as in autism spectrum disorders. We include schizophrenia as a disorder that may manifest later in life because of its relevance to interneuronal abnormalities. We will discuss the evidence from animal models of these neurological disorders on their association with interneuronopathies (here broadly defined as disturbance in migration, survival, differentiation, or function of interneurons). We will attempt to address whether interneuronopathies are syndrome-, phenotype-, or age-specific pathologies and whether they are cause or consequence of these epilepsies of other neurological disorders.

West syndrome: Infantile epileptic encephalopathy with infantile spasms (IS)

The International League Against Epilepsy (ILAE) has defined epileptic encephalopathies as syndromes in which *"the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time."*[44] The ILAE commission report considers this a conceptual clinical definition and discloses that in certain situations the origin of the cognitive decline may be less discrete, and the underlying etiology may contribute to a significant extent to the cognitive dysfunction.[44] These impairments may either be general or more specific, and their range of severity may be wide. The term "epileptic encephalopathies" is mainly used for particular syndromes. However, the effects of seizures and epilepsy on the brain could appear in any form of epilepsy.[1,27] Neonatal and infantile epileptic encephalopathies are of special concern because of their possible dire consequences on the neurodevelopmental growth of these infants as well as their distinct—and not always satisfactory—treatment approaches.[44]

West syndrome (WS) was described by W. J. West in 1841 in a report of the symptoms manifested in his own son.[45] WS is a severe infantile epileptic encephalopathy, which manifests with characteristic seizures consisting of IS, that is, flexion or extensor spasms, a chaotic, high-amplitude, and multifocally epileptic interictal background (hypsarrhythmia) in the electroencephalography (EEG) studies, as well as poor neurodevelopmental and epilepsy outcomes.[46–48] Two of these three features are sufficient for the diagnosis. It is an age-specific disorder, typically starting in infants during the first year of life, although late-onset WS has been described, too.[45] Mortality is significant ranging between 9% and 49%, depending on the cohort and duration of long-term follow-up of the study.[48–51] The main differentiating features of IS from other types of epileptic seizures are the electroclinical manifestations described above. Their distinct pathogenesis is also suggested by the fact that IS have different pharmacosensitivity profile than other epileptic seizures.[48,52] respond to different pharmacological treatments than most epileptic seizures, such as adrenocorticotropic hormone (ACTH). Although both cortical and subcortical pathologies and networks have been implicated in the pathogenesis of IS, the exact pathogenic processes involved are unclear because numerous etiologies, such as structural, metabolic, and genetic, have been associated with WS. Still, in a third of the infants with IS the etiology cannot be identified with the current methods.

Several animal models of IS have been generated.[27,53] Table 2 summarizes some of the chronic models of IS, which demonstrate an evolving phenotype of IS, other seizures, and possibly cognitive deficits. In this review, we also refer to IS as "spasms" for brevity, one reason being that in certain animal models, spasms do not necessarily manifest during the infantile age.

Table 2. Comparative description of features of rodent models of IS and associated etiologies

Mouse model	Genetic defect/ induction method	Viability	Spasms	Other seizures	Cognitive/ neurodevelopmental deficits	Pathology	References
Arx^{KO}	Stop codon, exon 2	Perinatal death	No data	N/A	N/A (lethal)		54
Arx$^{-/Y}$		Perinatal death			N/A (lethal)(In humans: hypothalamic dysregulation, early death)	Gene-specific expression changes in ZI and TRN; loss of dopaminergic neurons in ZI; reduced expression of GAD67 in ZI/TRN	88
Arx$^{-/Y}$ Emx1^{Cre}	cKO in pallial progenitor cells of cortical projection neurons		Not reported (vEEG in adulthood)	No (96 h vEEG)	Less anxiety/sociability HyperactiveNormal spatial learning/ memory/fear memory	No interneuronopathy Reduced cortical thickness, CC/AC hypoplasia, smaller amygdala	63
Arx$^{-/Y\ CKO}$	Dlx5/6^{CIG} cKO in ganglionic eminence interneuronal progenitors	≥120 days, but significant perinatal mortality	Spasms in adulthood	Racine stage 5 seizures ≥PN14	NR	Interneuronopathy P14: reduced ARX+ cells in upper cortical layers and hippocampus; reduced CB+ cells in hippocampus; reduced vNPY+ cells in the neocortex (males only); no change in SST+ neurons; decrease in PRV+ cells in the hippocampus and increase in the neocortex (males only). Adult: reduced CB+ cells in neocortex and hippocampus; reduced CR+ cells in the neocortex; no change in SST+ neurons	54,57
Arx$^{333ins(GCG)7/Y}$	pA1, 7GCG triplet insertion	Most die ≤3 months	No	70% have GTC (1 month old); no interictal spikes	Impaired learning, motor coordination, increased locomotor activity and anxiety Yes in humans; hypothalamic dysfunction	Interneuronopathy more severe in striatum (reduced SST, NPY, NOS, and lack of cholinergic interneurons) than cortex; ectopic NPY expression in mossy fibers in mice with seizures	61
Arx$^{333ins(GCG)7/Y}$	pA1, 7GCG triplet insertion		No	PN15–17: No clinical seizures; spontaneous ictal/interictal discharges (CA1, *in vitro*)	NR	No interneuronopathy in cortex and hippocampus (PN14-15); glutamate network remodeling	62
Arx$^{(GCG)10+7}$	pA1, 8GCG triplet insertion		Spasms PN7–11	Seizures with arrest; limbic, GTC; interictal spikes	Yes Low anxiety, impaired associative learning and social interactions	Interneuronopathy: reduced CB interneurons in the cortex, hippocampus, and striatum; reduced cholinergic and NPY interneurons in striatum; no deficits in PRV or CR interneurons	58

Continued

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Table 2. Continued.

Mouse model	Genetic defect/ induction method	Viability	Spasms	Other seizures	Cognitive/ neurodevelopmental deficits	Pathology	References
Arx $^{PL/Y}$	P355L	≥6 months	No	Rare (1/10 mice had tonic seizure) Low threshold to bicuculline seizures	Slightly impaired learning; impaired learning, motor coordination, increased locomotor activity and anxiety	Interneuronopathy more severe in striatum than cortex [less GABAergic (SST, NPY, NOS) and cholinergic neurons in striatum, medial septum, ventral forebrain]; normal size neonatal brains	61
Arx $^{PR/Y}$	P355L	Perinatal death (by PN1)	No data	N/A	N/A (lethal)	Interneuronopathy severe at both cerebral cortex and striatum (severe impairment of tangential and radial migration); microcephaly	61
Apc CKO in CamKII neurons	CKO deletion of *Apc* gene in excitatory cortical and striatal inhibitory neurons (negative regulator of β-catenin)	Through adulthood	Flexion-extension spasms (PN5–14)	Adults: spontaneous electroclinical seizures	Adults: learning, memory deficits, impaired sociability, stereotypies	APC/β-catenin pathway malformation; interneuronal deficits are not reported in these mice.	170,171
Apc CKO in Dlx5/6 or 112b interneurons	CKO deletion of *Apc* gene in Dlx5/6 (embryonic) or 112b (late postnatal) interneurons	*Dlx5/6:* Early death (up to PN7) *112b:* Improved survival	No data	No data	No data	Impaired tangential migration of interneurons	172
Apc CKO in Nex projection neurons	CKO deletion of *Apc* gene in Nex projection neurons	No data	No data	No data	No data	No impairment of the migration of interneuron or projection neurons	172
Multiple-hit rat model	R. intracerebral doxorubicin/ lipopolysaccharide (PN3), PCPA (PN5)	Through adulthood	Spasms (PN4–13)	Other seizures after PN9; spontaneous motor seizures in adulthood	Impaired motor milestones; impaired spatial learning/ memory/sociability	Right cortical/ hemispheric/periventricular lesion; interneuronopathy: reduced PRV interneurons contralateral to infusion	32,173–176
Tetrodotoxin (TTX) rat model	TTX chronic infusion in the cortex or hippocampus (PN10–38)	Through adulthood	Spasms ~PN21 till adulthood	Yes	NR	Effect on interneurons not reported; focal neocortical lesion at site of infusion	69,177

AC, anterior commissure; *Apc*, adenomatous polyposis coli; *Arx*, aristaless related homeobox gene; CA1, cornu ammonis field 1; CamKII, calcium calmodulin protein kinase II; CB, calbindin; CC, corpus callosum; CKO, conditional knockout; CR, calretinin; Dlx, distal-less homeobox; GTC, generalized tonic-clonic seizures; KO, knockout; N/A, not applicable; Nex, neuronal helix-loop-helix protein; NOS, nitric oxide synthase; NPY, neuropeptide Y; NR, not reported; pA1, 1st polyalanine repeat; PCPA, p-chlorophenylalanine; PN, postnatal; PRV, parvalbumin; SST, somatostatin; TRN, thalamic reticular nucleus; TTX, tetrodotoxin; vEEG, video-EEG; ZI, zona incerta.

Interneuronopathies in genetic models of IS: X-linked aristaless-related homeobox (Arx) models

The discovery that *ARX* mutations are related to WS suggested that defects in GABAergic interneuronal migration could be a potential etiopathogenic mechanism.[1] *ARX* is a homeobox gene encoding a transcriptional factor that is involved in ventral telencephalon morphogenesis, migration of GABAergic interneurons, and early commitment of cholinergic neurons.[54] According to clinical studies, *ARX* gene variants have been found in patients with IS or other early-life epileptic encephalopathies and may present with pronounced abnormalities (i.e., X-linked lissencephaly with abnormal genitalia [XLAG]), although certain cases have no detectable structural lesions.[55,56] Loss, mistargeting, and/or abnormal expression of the ARX protein has been implicated in the pathogenesis of the observed pathology and phenotype. It was recently proposed that the loss of function of ARX impairs the migration of interneurons and favors their placement in more ventral locations.[57]

Among the reported ARX models, only two have demonstrated epileptic spasms, although at different developmental periods: the conditional *Arx* knockout (*Arx* CKO mouse) and the knockin *Arx* mouse model (*Arx* KI mouse).

The *Arx* CKO mouse model involves targeted knockdown of the *Arx* gene in ganglionic eminences, where interneurons are generated, using the Dlx5/6 enhancer element I56i that is preferentially expressed in CB neurons.[54] Initial studies had shown a significant loss of CB and to a lesser extent CR-positive interneurons from the cerebral cortex and hippocampus, although PRV interneurons remained uninfluenced.[54] More detailed subsequent analysis of the interneurons in this model demonstrated a ventral shift of interneuronal precursors and reduced numbers of interneurons at PN14 and adulthood in the neocortex, affecting CB, CR, NPY, and PRV interneurons.[57] *Arx* CKO mice are characterized by early-life limbic seizures in PN14–17, whereas epileptic spasms were observed in adulthood.

The *Arx* KI mouse model was generated to reproduce the human triplet repeat expansion of the first polyalanine (pA1) tract of *Arx* from 16 to 23 alanine codons.[58] This genetic defect was shown in vitro to cause partial loss of ARX function, causing abnormal aggregation of ARX in the nucleus[59] and misregulation of a subset of the normal target genes of Arx, in subpallial-derived neurons, but not in the dorsal brain.[60] In *Arx* KI mice, there is a reduction in the number of cortical, hippocampal, and striatal interneurons, mainly of the CB, NPY, and cholinergic neurons, whereas the CR and PRV neurons are spared.[58]

In general, most studies on mice with *Arx* mutations that are expected to occur in interneuronal progenitors result in interneuronopathy (in striatum, neocortex, and hippocampus but with genotype-specific differences in the distribution) and may result in epilepsy and cognitive and behavioral deficits but with variable severity, hypothesized to be due to the functional severity of the mutation. Epilepsy was more consistently evaluated in older age groups because long-term EEGs are technically difficult in very young mice. Therefore, the presence of seizures, not necessarily spasms, was more consistently linked with some of these *Arx* mutations, although its incidence may depend on the specific genotype. For example, only 10% of the $Arx^{PL/Y}$ mice manifested spontaneous seizure.[61] An exception is the report by Beguin et al.,[62] which did not document clinical epilepsy or interneuronopathy in PN15–17 mice but attributed the cause of in vitro seizure-like discharges in PN14–15 hippocampal slices to enhanced excitatory drive.[52] Interestingly, selective deletion of *Arx* in neocortical projection neurons did not result in epilepsy, although recordings were only done for 96 hours. Instead, very mild behavioral deficits were seen,[63] proposing that *Arx* knockout in interneurons is more relevant to the pathogenesis of *Arx*-associated epilepsy and cognitive/developmental disorders, whereas *Arx* knockout in cortical pyramidal neurons contributes to a small degree in the behavioral deficits. The type of genetic defects and the type of cells affected by such genetic variations seem to provide an explanation for some of these differences in phenotype. The studies with CKOs suggest that the pathogenic effects of *Arx* are due to the effects on interneurons rather than the excitatory cells. Methodological differences, age or sex effects, and variability in the efficacy of the genetic manipulations (e.g., X inactivation, mosaicism) may also contribute to some of the reported differences, as suggested by Marsh et al.[57]

Interneuronopathies in acquired models of IS

IS caused by structural lesions have a worse prognosis and response to treatment.[64] The majority of these infants suffer from neurodevelopmental deficits and drug-resistant epilepsies. Prior studies have shown that functional or structural impairment of cortical and/or subcortical structures or their connections may be involved (reviewed in 65).

To model this more severe form of IS, we have developed a nongenetic animal model, the multiple-hit rat model of IS, by intentionally inducing a structural injury.[66] In this animal model, doxorubicin is injected stereotactically into the right cerebral ventricle, and lipopolysaccharide is administered on the right intracortical side on PN3. These compounds create a combination of cytotoxic injury with disruption of focal neuronal and white matter connections, along with inflammation. Then, on PN5, p-chlorophenylalanine (PCPA; inhibitor of serotonin synthesis) is delivered intraperitoneally,[67] on the basis of reports of disrupted serotonin metabolism in infants with IS.[32] Rats develop spasms with decremental responses in the EEG appearing between PN4 and PN13. These ages have been considered so far as neonatal rat ages, but they do correspond to the infantile stage of motor milestones, equivalent to the first year of life when IS usually first appear in humans, because they are the period when pups learn to ambulate.[64,67] The underlying pathology involves the right cortical region, right

hippocampus, and periventricular area.[53] In addition, there is also a remarkable layer-specific reduction in PRV interneurons in cortical regions contralateral to the lesion, and many of the remaining interneurons show abnormalities and malformations in morphology, which indicate an acquired interneuronopathy.[68]

The tetrodotoxin (TTX) rat model is induced by chronically infused TTX in the right cortex or hippocampus of the rats, starting at PN10–12. Rats start manifesting epileptic spasms around PN21, and these continue through adulthood. The EEG, starting around PN40, shows hypsarrhythmic background and decremental responses with the spasms.[69] This is also a model of epileptic spasms due to structural lesions, according to the term proposed by the recent ILAE classifications.[44,70,71] There is no report yet of interneuronopathy or cognitive and/or neurodevelopmental deficits in this model.

These studies overall provide evidence that early-life interneuronopathies can manifest in certain genetic or acquired causes of IS and could be associated with the development of epilepsy and cognitive/behavioral abnormalities. Etiology, however, can affect the type and severity of interneuronopathy but also its phenotypic correlates. The documented epilepsy can be of variable severity and may not necessarily encompass IS, although we should note that the technical difficulty of recording video EEG for long periods of time in very young pups is a limiting factor in documenting the presence of IS or hypsarrhythmia. In the *Arx* KI mouse model, 17β-estradiol was investigated as a potential treatment because of its known effects in influencing neuronal survival, migration, gene expression, dendritic spine formation, and synapse formation.[72] A prior study also showed that neonatal administration of 17β-estradiol in PN5 male reeler mice rescued them from the interneuronopathy and behavioral deficits.[73] The investigators reported that only early (PN3–10), and not late, postnatal treatment with estradiol, prior to the onset of spasms in this model, was effective in restoring the interneuronal deficits and preventing epilepsy.[72] The effects on the behavioral deficits were not reported. Although vigabatrin may be effective against IS, especially when associated with the tuberous sclerosis complex, there is currently no evidence (clinical or experimental) in the general population of patients with IS due to either structural or unknown etiologies that it may improve the neurodevelopmental or long-term epilepsy outcomes. It is therefore possible that interneuronopathy may act in concert with concomitant pathologies and remodeling of the brain in these epileptic encephalopathies. In certain situations, as suggested by the *Arx* KI mouse model estradiol study,[72] early interventions that prevent the interneuronal impairment might be therapeutic in providing disease modification, when given in specified developmental stages. However, the big challenge is to identify these critical periods for intervention and the likelihood to benefit humans. Although interneuronopathies affecting different interneuronal types are seen in epilepsies, with or without IS, and may contribute to the expression of IS, it is still not clear which specific factors determine whether an animal will develop IS versus other types of epileptic seizures and at what age. More research is needed to clarify the age-specific factors that ultimately determine which specific epilepsy syndrome will ensue.

Dravet syndrome and genetic epilepsy with febrile seizures plus syndrome (GEFS+)

Dravet syndrome is an infantile-onset drug-refractory epilepsy, with impairment of cognitive and motor development and increased mortality risk.[74] It usually presents at around 6 months of age and is characterized by prolonged febrile seizures, clonic or hemiclonic, as well as afebrile seizures, including myoclonic, typical absences, focal onset, or generalized seizures, usually not responsive to antiseizure treatment. Sudden death in epilepsy (SUDEP) may occur.[75] It has been shown that 70–80% of infants suffering from this syndrome have loss-of-function mutations of the sodium channel 1A (*SCN1A*) gene; although other genes have been implicated, too. Missense mutations of the *SCN1A* gene, altering channel activity, are also associated with genetic epilepsy with febrile seizure plus syndrome (GEFS+), which manifests with increased incidence of febrile and afebrile seizures, focal or generalized in the same families without necessarily cognitive or motor impairments.[76]

A great variety of animal models has been generated with either deletion or KI mutations of the *Scn1a* gene, reproducing various phenotypic features of either Dravet or GEFS+ syndrome, and some have offered evidence for interneuronal dysfunction (Table 3). These studies indicate the vital role of interneurons, especially PRV interneurons, in the pathogenesis of the epilepsy in Dravet and GEFS$^+$ syndromes, suggesting that loss of function of *Scn1a* could disturb the balance between excitation and inhibition by impairing the function of inhibitory interneurons, possibly promoting excitation of excitatory neurons, leading to severe epilepsy, motor and cognitive impairments, and, in some cases, even death.[77,78] The animal models of Dravet and GEFS+ syndromes provide a link between the interneuronal dysfunction and seizures and epilepsy. Behavioral and autistic features have been described only in one model of Dravet,[79] and these were reversed by pretreatment with low doses of clonazepam, suggesting a potential value in enhancing the effects of GABAergic interneurons in treating these deficits. However, it is unclear whether the preexisting epilepsy may have contributed to these behavioral deficits and to which extent the clonazepam effect might have also been due to effects on the ongoing epileptic activity. Further studies corroborating these observations in other models of Dravet syndrome and clarifying the pathogenic interactions of seizures,

Table 3. Animal models of Dravet syndrome or GEFS+

Animal models	Genetic defect	Pathology in interneurons/GABA	Epilepsy	Cognitive/behavioral/other neurological deficits	Human syndrome	References
Scn1a CKO	Exon 25 deletion, in forebrain GABAergic neurons	Selective loss of Nav1.1 in forebrain cortical and hippocampal GABAergic neurons	Spontaneous seizures (stage 3–5, Racine) Premature death after seizures (PN18–22) Thermal-induced seizures (PN22)	NR	Dravet	178
Scn1a CKO	Conditional deletion of exon 7	Deletion in global inhibitory neurons	*Heterozygous* develop spontaneous seizures (PN16) with occasional subsequent death	*Homozygous*: PN10–15: hypoactivity, jerks; death by PN15	Dravet	179
		Deletion in forebrain excitatory neurons	No spontaneous seizures			
		Deletion in forebrain excitatory neurons and haploinsufficiency in inhibitory neurons	Ameliorates seizure-related sudden death			
		Deletion in PRV interneurons	*Homozygotes:* Spontaneous seizures (PN14); death by PN30 *Heterozygotes:* Spontaneous seizures, and death after PN16	Ataxia (PN10)		
Scn1a KI, R1407X	Human R1407X nonsense mutation	*Heterozygous:* Reduced number of $Na_v1.1$ expressing GABAergic interneurons in cerebral cortex and hippocampus Intact number of GABAergic interneurons	*Heterozygous:* Low threshold in PTZ seizures *Heterozygous and homozygous*: Spontaneous seizures (1 month old)	*Heterozygous:* Hyperactivity, stereotypies, social interaction deficits, impaired context-dependent spatial memory, aversion to novel odors Deficits in sociability and fear memory rescued by low-dose clonazepam	Dravet	79,130,180
Scn1a KI, R1648H	Human R1648H mutation	Cortical interneurons with reduced firing, slower recovery from inactivation and increased use-dependent inactivation of sodium channels	*Homozygous*: Spontaneous generalized seizures (jump, jerks, head nodding, clonus, hindlimb extension) Lower thresholds to hyperthermic or flurothyl seizures Premature death PN16-26 *Heterozygous*: less severe phenotype than homozygous	NR	GEFS+	181

Continued

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Table 3. Continued.

Animal models	Genetic defect	Pathology in interneurons/GABA	Epilepsy	Cognitive/behavioral/other neurological deficits	Human syndrome	References
BAC transgene with R1648H mutation	R1648H mutation	Cortical interneurons with slower recovery from inactivation and increased use-dependent inactivation of sodium channels	More severe kainic acid seizures	NR	GEFS+	182, 183
Scn1a KI, S1231R (Drosophila)	S1231R mutation	Loss of function mutation: Reduced sodium current activity and repetitive firing in cortical interneurons	Spontaneous and thermal seizures	NR	Dravet	80

BAC, bacterial artificial chromosome; CKO, conditional knockout; GABA, γ-aminobutyric acid; GEFS+, generalized epilepsy with febrile seizures plus; KI, knockin; KO, knockout; NR, not reported; PN, postnatal; SCN1A, sodium channel, voltage-gated, type I, alpha subunit.
Modified from Galanopoulou and Moshé (2015)[184] with permission from Elsevier.

interneuronal dysfunction, and associated cognitive and behavioral comorbidities are important.

Classical Lissencephaly

Classical lissencephaly or "smooth brain" is a severe malformation in which the brain loses the characteristic gyri and sulci as a result of incomplete neuronal migration during the 9th to 13th embryonic week and defective neurogenesis.[80,81] Affected children manifest with severe mental retardation, epilepsy, and often facial abnormalities.[82,83] Classical lissencephaly may present as isolated lissencephaly sequence (ILS) or Miller-Dieker syndrome (MDS). ILS has no other major abnormalities than lissencephaly.[82] ILS is most commonly associated with defects in the *PAFAH1B1* (platelet-activating factor acetyl hydrolase 1B; which helps direct neuronal migration) gene, also known as *LIS1* gene; less commonly with Doublecortin (*DCX*) gene variants; and infrequently with *TUBA1A* (α-tubulin) gene defects. *PAFAH1B1* is located at the 17p13.3 locus. In MDS, lissencephaly is associated with distinct facial abnormalities and is linked to deletions within chromosome band 17p13.3 in almost all patients.[83] This region includes the *LIS1* gene (*PAFAH1B1*), which has been implicated in lissencephaly, as well as other genes contributing to the complex phenotype (e.g., *YWHAE* gene; encodes 14-3-3 protein epsilon). Lissencephaly may be associated with significant early mortality, depending on the severity of underlying abnormalities.[84]

Several genetic variants associated with classical lissencephaly have been identified, most commonly involving the *LIS1* or *DCX* genes.[85] *LIS1* gene is required for interneuronal migration, coupling the nucleus to the centrosome, nuclear movements, cell proliferation, interneuronal survival, neural stem cell division, chromosomal behavior, neurogenesis, and spindle orientation. DCX, a microtubule-associated protein, is used as a marker for neurogenesis and is essential for both radial and nonradial interneuronal migration into the cerebral cortex. Overexpression of DCX results in changes in microtubule skeleton, because of alterations in microtubule organization and stabilization during neuronal migration.[86] *TUBA1A* gene (its protein helps formulate microtubules) is infrequently encountered in ILS and more commonly in lissencephaly with cerebellar hypoplasia.[11] TUBA1A protein helps formulate the microtubules. More genes have been associated with other types of lissencephaly, such as the *ARX* gene that may cause XLAG syndrome.[87–90]

In MDS, there is impaired migration to the neocortex, the cerebellum, and through the corpus pontobulbare.[91] Although CR-expressing interneurons are remarkably reduced in the fetuses with MDS, only minimal reductions are present in children diagnosed with MDS.[92] Heterotopic CR and CB interneurons, suggesting impaired migration to the neocortex, hippocampus basal ganglia, and cerebellum,

were also reported in MDS.[93] Such abnormalities contribute to the development of epilepsy and intellectual diabiilties.[92] In lissencephaly due to DCX defects, deficits in CR and CB neurons are also observed, although with regional differences.[93] In contrast, in XLAG due to ARX defects there is hypocellularity in the lateral geniculate eminence, suggesting a deficit at the generation of interneurons, along with deficit in Cajal-Retzius neurons in layer I.[93] CB-positive interneurons are reduced in the telencephalon in ARX deficiency.[93] When MDS-, DCX-, and XLAG-deficient brains are compared with a control brain, there are no differences in the number of PRV interneurons in infratentorial structures, although the age of the fetuses was too young (34–35 conceptional weeks) to fully assess PRV expression.[93] However, the ARX-deficient XLAG brain had paucity of PRV from the telencephalon, whereas sparse PRV staining is seen in the basal pallidum of MDS- and DCX-deficient brains.[93]

So far, no animal models of MDS have been created, although models of *Lis1* genetic defects exist (see Table 4). Table 4 shows animal models with defects in genes that have been linked with lissencephaly. The existing *Arx* models have been discussed in West syndrome: infantile epileptic encephalopathy with infantile spasms (IS) and are not included herein or in Table 4. Although experimental evidence has been obtained for *Lis1*, *Dcx*, and ARX involvement in neuronal (interneuronal and excitatory neurons) migration, detailed characterization of specific interneuronal deficits has best been studied in *Arx*-deficient mice, where CB interneurons are the most affected, although impaired CR and NPY interneurons may also be seen (see West syndrome: infantile epileptic encephalopathy with infantile spasms (IS) and Table 2).[54,58,94] In the *Lis1* heterozygous knockout mice, GABAergic neurons, including the CR-positive, show both autonomous and nonautonomous migrational deficits in speed and distance traveled.[95] In $Dcx^{-/+}$ mice, no deficits in PRV interneurons were observed in the hippocampus, although the neocortex was not studied.[96] As discussed earlier, PRV interneurons are not the main interneuronal type affected in DCX-deficient syndromes. In summary, human and experimental model data support that the interneuronal dysfunction in these conditions predominantly affects CB and/or CR interneurons and probably not as much PRV interneurons, although PRV deficits have been reported in Marsh et al.[57] However, non-cell-autonomous effects are seen with some of these genetic defects as well as occasional overt structural brain abnormalities that could affect the connectivity and

Table 4. Animal models of classical lissencephaly

Genes	Genetic defect/ induction method	Pathology	Epilepsy	Cognitive/behavioral/ other deficits	Human syndrome	References
Lis1	*Lis1*^{ko}:		NR	Peri-implantation lethality	Classical lissencephaly: ILS MDS	117,119–121,123,125–129,185,186
	Lis1$^{+/ko}$ mutants	Disorganized hippocampus, defects in neuronal migration and neurogenesis	Seizure susceptibility	Mental retardation, (impaired rotarod test and spatial learning)		
	Lis1^{cko}	Neuronal migration defects in hippocampus, cerebellum, olfactory bulb				
	Lis1$^{cko/ko}$	Cortical disorganization, neuronal heterotopias, enlarged ventricles, microcephaly	Seizure susceptibility	Motor and cognitive impairments		
Dcx	*Hemizygous males*	Gross neocortical disorganization Malformed hippocampus	NR	Postnatal lethality, variable fertility for survivors Defects in context and cued conditioned fear	X-linked forms of lissencephaly, ILS	116,118,122
	Heterozygous females, (Dcx$^{-/+}$*)*	Double cortex syndrome Disruptions of hippocampus	NR	Defects in context and cued conditioned fear		
	Dcx mutants:			Learning and memory deficits		

CA3, cornu ammonis field 3; CKO, conditional knockout; DCX, Doublecortin; ILS, isolated lissencephaly sequence; KO, knockout; LIS1, lissencephaly-1; MDS, Miller-Dieker syndrome; NR, not reported; XLAG, X-linked lissencephaly with abnormal genitalia.

neuronal network function contributing to the observed neurodevelopmental or epilepsy-related deficits.

Autism Spectrum Disorders

Autism is considered a heterogeneous neurodevelopmental disorder in regard to etiologies and phenotype.[97–99] There are four core characteristics of ASDs: impairments in reciprocal social interactions, impairments in language, repetitive and ritualized behaviors, and a narrow range of interests.[100,101] Certain patients may have mental retardation or epilepsy of variable severity,[102] anxiety, and mood disorders.[103]

Both genetic and environmental factors can contribute to the complex pathogenesis of ASD. In this review, we emphasize models that help understand the role of GABAergic interneurons and defects in ASD (Table 5). Although some of these genetic models may not necessarily bear relevance to etiologies known in humans with ASD, they help clarify the role of various interneuronal dysfunctions in the pathogenesis of certain ASD traits. The observed GABAergic interneuronal dysfunction in these models includes reduced numbers of GABAergic interneurons in the neocortex and/or hippocampus and/or striatum, or reduced GABAergic neuropil, or reduced expression of calcium-binding proteins that characterize subclasses of interneurons (e.g., PRV) or impaired $GABA_AR$ signaling, and less frequently increased density of PRV interneurons in the sensory cortex or hippocampus (Table 5). The subtypes of interneurons affected vary across models with ASD features and may include PRV, SST, or NPY or may be less specific (Table 5). Epilepsy has been less consistently studied in these models of ASD because video-EEG studies have either not been done or have been done briefly. Therefore, concurrent epilepsy cannot be entirely excluded so as to attribute these deficits to a pure ASD phenotype rather than an epilepsy-related comorbidity. When spontaneous seizures were reported in all the EEG-recorded Nse-PTEN CKO mice,[104] the seizure frequency was considered too low to acutely affect the observed cognitive and behavioral deficits. However, the possibility that the observed deficits could be secondary to delayed or lingering effects of ongoing epileptogenesis on cognition and behavior cannot be entirely excluded. Given the dual and intertwined effects of interneurons on both epileptogenesis and cognitive processes, a more detailed characterization of the natural history of epilepsy and cognitive/comorbidity phenotypes would be needed to firmly conclude which interneuronal deficit is more strongly implicated in these phenotypes. Furthermore, alterations to GABAergic circuits during the development of syndromic autism may be caused or may contribute to a wide variety of neurobiological dysfunctions beyond interneurons and GABA signaling, which, as a whole, may underlie the pathogenesis of ASD.[105]

Schizophrenia

According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-V*),[106] developed by the American Psychiatric Association, schizophrenia is a condition that combines neurocognitive dysfunctions, negative symptoms, and social or occupational deterioration. It affects approximately 1% of the world population.[107] Diagnostic criteria include positive symptoms (e.g., hallucinations, thought disorder), negative symptoms (e.g., anhedonia, social withdrawal), and cognitive deficits.[108] Genetic, developmental, and environmental factors may be implicated in the pathogenesis of schizophrenia. Table 6 lists the animal models of schizophrenia that are related to interneuronopathies.

Deficits of interneurons, mainly PRV, are one of the most undeviating findings in postmortem studies of patients diagnosed with schizophrenia. Altered GABA neurotransmission seems to play an important role in the impaired cognitive control associated with the disease. Lower levels of the mRNA for the principal synthesizing enzyme for GABA, GAD67, are prominent in PRV interneurons in subjects with schizophrenia, leading to diminished cortical GABA synthesis and prefrontal cortical dysfunction in patients, which has been considered a pathophysiological substrate and not a consequence of the disorder.[109] Developmental changes in the axon terminals of basket and chandelier interneuronal cells, affecting the following developmental pathways as well, occur during the perinatal period and peak prior to the onset of puberty.[110] Although GABA-related alterations in schizophrenia are hardly related to arrested development,[109] it has been suggested that dorsolateral prefrontal cortex (pFc) circuitry dysfunction impairs levels of working memory load in patients suffering from schizophrenia.[110,111] In addition, altered local circuit function in schizophrenia is not restricted in the dorsolateral pFc but is conserved across multiple cortical areas.[112] Delays in GABAergic maturation, in some cases after puberty onset, result in cognitive impairments during adolescence.[113] Moreover, *DISC-1* gene linked to schizophrenia, which encodes a scaffolding protein widely expressed in the brain,[114] is highly involved in neurodevelopment, including that of interneurons. Mutations in *DISC-1* may disrupt the tangential migration of interneurons, causing spatial and temporal disruption in different interneuron subtypes and resulting in defects implicated in schizophrenia.[115]

Discussion

The animal studies reviewed here reveal a spectrum of early-life epilepsies and neurodevelopmental or other neurological disorders that may manifest with interneuronopathies. Although the existing evidence implies an important role for GABAergic interneurons in the

Table 5. Genetic animal models of autism spectrum disorders

Gene	Genetic defect	Pathology	Seizures/epilepsy phenotype, EEG	Cognitive/behavioral deficits	Human syndrome	References
Reelin	ΔC-KI: deletion of C-terminal region of reelin	Ectopic Purkinje cells	NR	Hyperactivity, reduced anxiety, impaired sociability and working memory	Features of ASD, schizophrenia, bipolar disorder	187,188
Reelin	Haploinsufficiency of Reelin gene (reeler mouse) in males	Reduced Purkinje cells (adult) Reduced amygdala PRV interneurons (adult)	*Reeler homozygotes only*: low threshold and more behavioral seizures after minimal electroshock; higher susceptibility to isoflurane-induced behavioral seizures	Altered ultrasonic vocalizations, motor development delay Impaired sociability (infants); reduced cognitive flexibility (adult male) Neonatal estradiol (PN5) rescues ASD and interneuronal deficits, but not the cerebellar deficits	Features of ASD	73,189–191
En2	*En2* KO	Increased PRV, SST, and NPY interneurons in visual cortex (PN30) Reduced GABA interneurons in hippocampus and cerebral cortex (PRV, SST, and NPY: layers II/III, NPY: layers V/VI) (adulthood)	Increased susceptibility to kainic acid seizures	Impaired sociability, learning, fear conditioning, reduced PPI, motor coordination, grip strength	ASD	192–196
Pten	*Pten* deletion from excitatory neurons (Nse-PTEN CKO)	Macrocephaly, neuronal hypertrophy	Sporadic seizures (11.5% of mice observed behaviorally; 100% of mice observed via 3-day-long EEG)	Abnormal social interaction, exaggerated response to sensory stimuli	Macrocephaly, ASD	104,197
	Pten deletion from MGE and POA progenitors (Nkx2.1-PTEN CKO)	Preferential loss of SST interneurons (PN30 neocortex, hippocampus, striatum) and reduced SST neuropil Ectopic increase in PRV neuropil in the cortex	NR (seizures) EEG with reduced gamma oscillations at baseline, increased during social behavior testing	Impaired sociability 2-fold increase in sIPSCs in layers II/III	ASD	198
Brinp1	*Brinp1* KO	Increased density of PRV interneurons in sensory cortex and hippocampus (adults)	NR	Reduced sociability, hyperactivity, impaired short-term memory, altered vocalization	ASD	199
Prv	Loss of *Prv* gene	*PRV*$^{+/-}$: Reduced PRV expression (medial pFc,	*PRV*$^{-/-}$: Increased PTZ seizure susceptibility reported in PRV$^{-/-}$ mice but no	*PRV*$^{+/-}$: Abnormal sociability and communication, stereotypies Reduced pain sensitivity and startle	ASD	200–202

Continued

Table 5. Continued.

Gene	Genetic defect	Pathology	Seizures/epilepsy phenotype, EEG	Cognitive/behavioral deficits	Human syndrome	References
		somatosensory cortex, striatum)	spontaneous seizures are observed	responses No evidence for anxiety, depression, or schizophrenia		
Shank1	*Shank1* KO	Reduced PRV expression (medial pFc, somatosensory cortex, striatum)	NR	Motor deficits No definite genotype-associated sociability deficit or stereotypies	Linked with ASD in humans	200,203
Shank3B	*Shank3B* KO	Reduced PRV expression (medial pFc, somatosensory cortex, striatum)	NR	Sociability deficits, hyperactivity, anxiety, stereotypies	ASD	200,204
Gabra5	*Gabra5* KO	Absent GABRA5	NR (seizures) Altered sleep EEG patterns	Reduced sociability, impaired executive function, reduced vocalizations, impaired maternal retrieval	ASD	205
Btbr	*Btbr* inbred mice	Increased tonic and phasic $GABA_AR$ responses in the hippocampus (neonatal BTBR) Reduced frequency of GABAergic sIPSCs (adults)	No epilepsy Lower threshold to 6-Hz seizures Shorter latency to SKF83822-induced seizures Normal susceptibility to flurothyl or PTZ seizures	Impaired sociability, grooming Ganaxolone increases exploration, social approaches and interactions R-baclofen rescues social approaches, reduces stereotypies	ASD	206–210
Gad67	*Gad67* deficiency in Gpr88 expressing striatal projection neurons (striatum, SN)	Reduced GAD67 in striatum and SN but not in the cerebral cortex or cerebellum.	NR	Impaired socialization/social preference, spatial learning, olfactory preferences Clonazepam or bumetanide improve social behaviors	ASD	211
Px-rics	*Px-rics* deficiency	Impaired $GABA_A$ receptor transmission	NR	ASD-like behavior Clonazepam ameliorates social behavior	ASD	212
Cntnap2	*Gabra5* KO	Reduced GABAergic interneurons in neocortex, hippocampus, striatum (preferentially PRV)	Epileptiform EEG, abnormal sleep-wake physiology	ASD-like behaviors, hyperactivity	ASD	213

ASD, autism spectrum disorders; Brinp1, BMP/RA-inducible neural-specific protein 1; CNTNAP2, Contactin Associated Protein-Like 2; CKO, conditional knockout; DLX, Distal-less homeobox; EEG, electroencephalogram; En2, engrailed 2; GABA, γ-aminobutyric acid; GABRA5, GABA receptor alpha5; GAD67, glutamate decarboxylase 67; Gpr88, G protein-coupled receptor88; KO, knockout; MGE, median ganglionic eminence; Nkx2.1, NK2 homeobox 1; NPY, neuropeptide Y; NR, not reported; Nse, neuron specific enolase; pFc, pre-frontal cortex; POA, preoptic area; PRV, parvalbumin; PTEN, phosphatase and tensin homolog; PTZ, pentylenetetrazol; PX-RICS, long isoform of RICS (GTPase activating protein for cdc42); RELN, reelin; sIPSC, spontaneous inhibitory postsynaptic currents; SKF83822, dopamine D1 receptor agonist; SN, substantia nigra; SST, somatostatin.

Table 6. Animal models of schizophrenia

Animal models	Pathology (interneurons/ GABA)	Epilepsy phenotype	Cognitive/behavioral/other deficits	Human syndrome	References
Gestational MAM (GD17)	Decreased pFc PRV GABA interneurons	Predisposes to seizures in two-hit models	Impaired relearning in MWM Impaired EDS in ASST Reduced social interaction before puberty Deficit in PPI (at puberty)	Schizophrenia (also models brain malformations)	214–216
Postweaning social isolation	Reduced dendritic spine density, cytoskeletal alteration, and loss of PRV-containing interneurons and reelin in the hippocampus	NR	Impaired novel object recognition, reversal learning in MWM, EDS in the ASST, and fear-motivated conditioned emotional response Increased aggression and social interaction Strain-dependent reduction in PPI	Schizophrenia	216–218
Amphetamine models	No interneuronal problems reported	NR	Deficits in attention and the ASST Persistent deficit in PPI, dose-dependent	Schizophrenia	216,219–221
Disc-1 KO	Reduced hippocampal PRV immunoreactivity in some, but not all mutants	NR	Impaired T-maze performance; impaired spatial working memory in some mutants Reduced social activity (in some strains) Deficits in PPI (in some mutants)	Schizophrenia	216,222
PCP models	Decreased synaptic spines on Fc neurons and cortical and hippocampal PRV-positive interneurons	NR	Deficits in novel object recognition, ASST and T-maze delayed alternation Reduced frequency and duration of primate social behavior No sustained deficit in PPI	Schizophrenia	216,223–226

Ach, acetylcholine; ASST, attention set shifting; EDS, extradimensional shift; GABA, γ-aminobutyric acid; GD17, gestational day 17; DA, dopamine; DISC-1, disrupted-in-schizophrenia 1; KO, knockout; MAM, methylazoxymethanol; MWM, Morris water maze; nAcc, nucleus accumbens; NR, not reported; PCP, phencyclidine; pFc, prefrontal cortex; PPI, prepulse inhibition; PRV, parvalbumin.

pathogenesis of these conditions, is there enough evidence to prove a causative role for each or certain of these disorders?

Can interneuronopathies cause early-life epilepsies?

In support of this statement stand the observations that (1) reduced interneuronal population exists in both genetic (*Arx*) and induced models of IS (multiple-hit) (Table 2), (2) restoration of interneuronal population with early postnatal estradiol administration could prevent epilepsy in the $Arx^{333ins(GCG)7/Y}$ mouse,[72] (3) *Scn1a* mutations disrupt both interneuronal function and physiology and selective deletion of *SCN1A* in PRV interneurons recapitulates features of Dravet syndrome (Table 3). This hypothesis is further supported by the absence of seizures in the $Arx^{-/Y}$ mouse that does not exhibit interneuronopathy, even though monitoring was limited in the study[63] (Table 2). Although defective neuronal migration came into sight as the fundamental cause for lissencephaly, the link between interneuronopathy and epilepsy in the *Lis1* and *Dcx* genes has not yet been studied thoroughly (Table 4).[87–92,116–129] The spectrum of seizures documented in these mice and the natural course of epilepsy vary from epileptic spasms (whether early or late life) to generalized tonic-clonic seizures or other motor seizures (in early or adult life), myoclonic seizures, or nonconvulsive seizures. This phenotypic variability is hardly incongruent with the hypothesis that interneuronopathy can be epileptogenic early in life, because there are typically numerous factors (including biological, epigenetic, genetic networks affected) that could modify the phenotype.

Do interneuronopathies contribute to neurodevelopmental abnormalities and behavioral deficits in the absence of epilepsy?

In the *Arx* or IS models, neurodevelopmental deficits have been reported in those with concurrent epilepsy. In a Dravet syndrome knockin model (R1407X

haploinsufficiency), the observed deficits in sociability and fear memory in adult male mice were restored by single injection of clonazepam, which enhances the deficient GABAergic synaptic transmission, implying that the interneuronal dysfunction was underlying these behavioral deficits.[79] Parallel EEG monitoring for seizures and epileptic abnormalities was not done to exclude that clonazepam's effect was via suppression of epileptic activity. However, a previous study had reported normal interictal EEG in these mice in adulthood, suggesting that this effect was behavioral modification.[130] Still, there is no evidence yet that the clonazepam effect in this model extends beyond the symptomatic control of these behavioral deficits.

Many genes linked to neurodevelopmental and neuropsychiatric diseases are preferentially expressed in developing cortical interneurons in mice, rendering interneurons an interesting therapeutic target.[131] In the *Dcx* and *Lis1* models, the underlying pathology is not pure or preferentially an interneuronopathy to allow conclusions. In the genetic models of ASD, there is strong evidence of underlying dysfunction in the GABAergic signaling, whether due to impaired receptor expression or reduced GABAergic interneurons (Table 5). The resulting inhibition/excitation imbalance in networks involving corticohippocampal, striatonigral, or cerebellar networks is strongly linked with neurodevelopmental and behavioral deficits that are also features of ASD behaviors even in the absence of overt epilepsy. Treatments that enhance GABAergic neurotransmission rescue mice from these behaviors acutely, further corroborating the importance of GABAergic networks in these behaviors. As in Dravet syndrome, however, such effects appear so far to rely on symptomatic control, and there is no evidence yet for or against disease modification.

An interesting twist is presented with the exploration of depolarizing/hyperpolarizing $GABA_A$ receptor signaling due to altered expression and function of cation chloride cotransporters, such as the K^+/Cl^- importer KCC2 (K^+/Cl^- cotransporter 2) and the $Na^+/K^+/2Cl^-$ exporter NKCC1 ($Na^+/K^+/2Cl^-$ cotransporter) (see reviews 7,8,25). Premature appearance of hyperpolarizing $GABA_A$ receptor signaling and prevention of neurotrophic effects of depolarizing $GABA_A$ receptor effects during early development with exposure to the diuretic bumetanide (NKCC1 preferential inhibitor) disrupt the maturation and synaptic integration of cortical neurons, leading to behavioral and cognitive deficits.[132,133] Several clinical reports also exist of improved functional outcomes in children and infants with autism treated with bumetanide.[134–137] Furthermore, in a model of fragile X syndrome, which presents with multiple neurodevelopmental deficits, including ASD symptoms, intellectual disability, and sometimes seizures, there is rather a delayed switch of depolarizing to hyperpolarizing $GABA_A$ receptor signaling.[138] Oxytocin-mediated enhancement of $GABA_A$ receptor inhibition attenuated ASD behaviors in a mouse model of fragile X.[139] However, the poor blood-brain barrier permeability of bumetanide in older age groups renders it unclear whether such effects might be due to direct effects on NKCC1 or indirect effects or other actions. Regardless, these conflicting observations emphasize the importance of investigating the therapeutic effects of new drugs in disease-specific models rather than relying on observations in disease-naive animals. Going beyond the spectrum of neurodevelopmental disorders, in schizophrenia a gain of function mutation of *NKCC1* has been reported,[140] and improvement of hallucinations was noted in a patient treated with bumetanide.[141]

Are interneuronopathies strictly an age-specific etiology of epilepsies and/or neurodevelopmental disorders?

The example of acquired models of schizophrenia (Table 6) is telling in that certain postnatal factors/insults may render interneurons vulnerable at various ages, thus contributing to the pathogenesis of other neurological disorders. Studies in humans and animal models have indicated that more subtle perturbations in the excitatory-inhibitory balance exist in multiple psychiatric conditions,[142] including bipolar disorders and anxiety disorders.[143,144] Interneuronal vulnerability has also been reported in Alzheimer's dementia[145,146] and is a feature of late-onset epilepsies and seizures in both animal models and humans.[147–150] A consistent and profound PRV interneuron imbalance has been demonstrated in the basal ganglia of patients diagnosed with Tourette syndrome, a childhood disorder characterized by motor and vocal tics.[151] Ablation of fast-spiking interneurons in the dorsal striatum of adult mice produced anxiety and elevated grooming, although no EEG study was done in this study.[152] In essence, loss of interneurons or impairment of their functionality may contribute to a variety of seizure or neurological or behavioral deficits at any age, although these effects may depend on numerous factors, including but not limited to type and severity of interneuronal impairment, age-, sex-, brain region–specific factors, other coexistent pathologies or exogenous factors, and genetic substrates.

Do seizures or other etiologies of seizures trigger or deteriorate interneuronopathies and lead to progression of epilepsies and/or associated comorbidities?

Interneuronal loss or dysfunction has been observed in various types of epilepsies and as a result of induced seizures, whether these start in early or later life.[147–150,153] Seizures may also affect the functionality of interneurons by altering $GABA_A$ responses and expression or their intracellular trafficking.[25,33,154–159] In animal studies, it is difficult to dissociate the impact of the inducing factor from the effect of seizures. In clinical studies, additional confounders exist, including but not limited to drugs received, stressors, comorbidities, and limitations in obtaining pathology from true control subjects. The recent advances of stem cell research and interneuronal transplantation, which has

shown some promising effects in certain models,[160,161] offer an interesting therapeutic gain in efforts to clarify the role and contribution of interneuronopathies in epilepsy and neurology in general.

Conclusions

There is abundant evidence that interneuronopathies, here broadly defined as interneuronal deficit or dysfunction, are implicated in the pathogenesis of a large variety of epilepsies and neurodevelopmental, neurological, or neuropsychiatric disorders with remarkable heterogeneity on age of onset, phenotype, natural course, and treatments. In certain cases, the known etiologies (e.g., genetic) are known to preferentially target interneurons, making it rational to perceive these disorders as *primary interneuronopathies*. In other situations, it is more likely that interneuronopathies are the consequence of the ongoing pathology and disease process and can be contributory factors rather that the cause (*secondary interneuronopathies*). Systematic studies are needed to decipher the age-, sex-, or region-specific genetic, biological, and other factors that compromise the interneurons (migration, survival, differentiation, integration, function) to help place these interneuronopathies onto a diagnostic road map that may rationalize therapy development strategies in the various primary and secondary interneuronopathies.

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We have no conflicts of interest to declare. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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