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Interneuron Development and Epilepsy: Early Genetic Defects Cause Long-Term Consequences in Seizures and Susceptibility

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Errors in the generation of the inhibitory GABAergic interneurons of the cerebral cortex and hippocampus have variable consequences. Studies of the molecular pathways of interneuron development reveal genes that are associated with human epilepsies. Animal models of gene variants exhibit seizures and abnormal electroencephalographic activity, providing unique models for discovering better treatments for individual forms of epilepsy.

INTRODUCTION

Alterations in inhibition have been suggested as an underlying cause of epilepsy (1, 2). Local GABAergic interneurons provide much of the inhibition in the cerebral cortex, hippocampus, striatum, and amygdala. Disruptions in neural development—whether genetic, chemical, or physical—can impair interneuron ontogeny, leading to the evolution of unstable neural networks and, ultimately, seizures. Over the past two decades, several animal models of interneuron disruptions have been described that displayed abnormal electroencephalogram activity and seizures, similar to human epilepsies.

Initial genetic studies examined the effects of loss of the specific neurochemical markers that identify the interneuron subpopulations. In the cerebral cortex, the main populations express the calcium binding proteins parvalbumin (PV) and calretinin (CR) or the peptide somatostatin (SST). The calcium-binding protein calbindin (CB) is often used as a marker for embryonic GABA interneurons because PV expression is delayed until the third postnatal week, and most PV cells also express CB. CR and SST are expressed in the embryo and present in GABA interneurons at birth. Mice with null mutations in CB, PV, or calretinin (CR) are largely normal, without behavioral or seizure phenotypes (3). Loss of the gene encoding SST did not alter overall anatomy or prompt spontaneous seizures (4). SST neurons often are immunoreactive for neuropeptide Y (NPY), and in recordings from hippocampal slices, exogenous NPY suppresses excitatory neurotransmission, blocking induced epileptiform activity. Mice lacking NPY presented with mild spontaneous seizures during the adolescent period, followed by remission in the adult. Adult *NPY*-null mice show increased sensitivity and poorer outcomes after chemically induced seizures (5, 6). Thus, the inability to express certain biochemical markers itself can lead to seizure phenotypes.

However, many of the embryonic perturbations that lead to seizures directly affect the generation, migration, and maturation of the GABAergic interneurons. This review is focused on the interneuron ontogeny and disruptions that manifest as epilepsy in animal models. The underlying mechanisms and molecular pathways will be explored and, where possible, translated into the known basis of human neurological disorders. The final section presents the newest research concerning strategies for correcting the insufficient inhibition and providing long-term cures for epilepsies.

Generation and Specification of Forebrain Interneurons

The majority of local GABAergic interneurons of the forebrain are generated in the embryonic striatum in a group of structures known as the ganglionic eminences (GEs) (7) and in the embryonic preoptic area (8–11). The GABAergic interneurons are generated over a prolonged period starting during midgestation (approximately embryonic days (E) 10–17 in the rodent (12, 13) and gestational weeks 10–25 in the human (14)), giving a large window of prenatal susceptibility. The interneurons synthesize GABA using the constitutively expressed glutamic acid decarboxylase 67 (Gad67, encoded by the *Gad1* gene) or the inducible glutamatic acid decarboxylase 65 (Gad65, encoded by the *Gad2* gene). Null mutants of *Gad1* and *Gad2* were generated in the last century. Mice with total loss of *Gad1* die shortly after birth, most likely due to respiratory failure (15), whereas the removal of both *Gad2* alleles (*Gad2⁻/⁻*) is compatible with life, although these mice experience handling and stress-induced seizures and increased mortality (16).

GABAergic interneurons are classified by the expression of biochemical markers, calcium-binding proteins or peptides, their morphology, and electrophysiological characteristics (17, 18). The medial ganglionic eminence (MGE) is the source of PV- and SST-expressing interneurons that are found in the cerebral cortex, hippocampus, and dorsal striatum (10). The lateral ganglionic eminence (LGE) supplies GABAergic interneurons to the olfactory bulbs, as well as generates the medium spiny GABA projection neurons of the striatum (10, 19). Finally, the caudal ganglionic eminence (CGE) is the origin of the CR and vasoactive intestinal peptide (VIP) expressing interneurons and the PV and SST interneurons of the amygdala and the caudalmost cerebral cortex (11). The somatostatin-expressing cells can be further grouped in the cholescystokinin (CCK) and NPY subgroups (20, 21).

The expression of the transcription factors *Dlx1* and *Dlx2* is critical for production of the GABAergic cells in the GE proliferative zone. Loss of both *Dlx1* and *Dlx2* drastically reduces the size of the GE and thus the numbers of GABAergic neurons observed at birth (7, 22). The *Dlx1/2* null mice die shortly after birth, and the survival of the *Dlx1*^{-/-} mice is dependent upon the background strain (23). About 50% of the resulting *Dlx1*^{-/-} mice are able to survive to adulthood (24). Within the first 2 weeks after birth, the GABAergic interneuron profiles in the *Dlx1*^{-/-} mice were similar to wildtype, suggesting normal generation and migration. After 1 month of age, there was a marked reduction in Gad67-expressing cells throughout the cerebral cortex and the hippocampus. Immunohistochemistry analysis showed that the CR, NPY, and SST interneurons were decreased, whereas the PV cells were largely unaffected. Cell death assays imply that reduced interneuron numbers in the *Dlx1*^{-/-} mice are due to cell loss rather than downregulation of GABA expression. Transplantation of *Dlx1*^{-/-} interneurons into a control cerebral cortex demonstrated fewer SST and NPY cells. The remaining interneurons had abnormal morphologies, supporting additional roles for *Dlx1* in interneuron maturation and survival.

Recordings from slices of *Dlx1*^{-/-} mouse hippocampus and neocortex showed reductions in the frequency and amplitude of inhibitory postsynaptic currents (IPSCs), starting at 1 month and progressing with age. The *Dlx1*^{-/-} mice were more susceptible to handling and stress-induced seizures, with nearly 75% showing behavioral seizures. Simultaneous video-EEG monitoring revealed generalized spike and slow-wave discharge events, progressing to high-frequency discharges and myoclonic movements. In humans, polymorphisms located near *DLX1* and *DLX2* genes have been associated with autism susceptibility (25). Considering the comorbidity of autism and epilepsy—as great as 40% in some populations—future studies may discover additional *DLX1* and *DLX2* variants directly connected to seizure disorders.

As transcription factors, Dlx1 and Dlx2 regulate gene transcription to specify interneuron cell fate and identity. Among the characterized targets are *Dlx5* and *Dlx6* (7), *Wnt5a* (26), *Arx* (27), and *Zfhx1b* (also known as *Sip1* or *Zeb2*) (28). *Wnt5a* appears to regulate the expression of GABA, particularly in interneurons of the olfactory bulb (26). While members of the Wnt/β-catenin family have distinct roles in brain development and seizures, a direct link between *Wnt5a* and epilepsy

has not yet been found. By contrast, a genetically targeted loss of a zinc-finger homeobox transcription factor *Zfhx1b* mimics Mowat–Wilson syndrome, a disorder characterized by intellectual disability, epilepsy, and craniofacial and enteric nervous system defects (28). Conditional deletion of *Zfhx1b* in regions that express *Dlx1/2* (or *Nkx2.1*) led to a fate change in the interneurons (29). In the absence of *Zhfx1b* (*Sip1*), fewer cortical interneurons were generated and located dorsally in the embryonic forebrain (28, 29). At postnatal day (P) 15, PV and SST cells in the cerebral cortex were reduced by more than 80%, whereas in the striatum, PV cell numbers were reduced by half, and SST and NPY interneurons were increased by about twofold (28).

In addition to the *Dlx* family of transcription factors, *Nkx2.1* and *Mash1* define molecular pathways that regulate GABAergic interneuron ontogeny (30). *Nkx2.1* is expressed only in the MGE, the major source of the cortical PV and SST interneurons. While the *Nkx2.1*[-/-] mice die at birth, conditional deletion in specific interneuron subpopulations has revealed a role for *Nkx2.1* in epilepsy, dependent upon the time of deletion (31). Pups born with *Nkx2.1* deleted at E9.5 were viable until postnatal day 10; those with the *Nkx2.1* deletion at E10.5 lived until postnatal days 13–17; finally, mice with *Nkx2.1* deleted at E12.5 were viable past postnatal day 30. Mice with deletions at E9.5 and E10.5 presented with overt spontaneous behavioral seizures, including violent tremors, followed by prolonged periods of inactivity. EEG recordings showed abnormal interictal discharges followed by continuous spike-wave rhythmicity during the ictal phase. Mice in which *Nkx2.1* was deleted after E12.5 did not exhibit seizure behavior or abnormal EEG discharges.

Since *Nkx2.1* was suspected to regulate cell fate in the MGE, the GABAergic interneuron populations were characterized. Dramatic deficits in *Gad1* (Gad67)-expressing neurons were found (31). However, individual subpopulations were selectively affected: *Nkx2.1* loss at E10.5 led to gross deficits in PV and SST neurons in all cortical layers, with increased VIP and CR populations. A different scenario was observed after E12.5 *Nkx2.1* deletion, with PV cell deficits and VIP and CR cell excesses only in superficial cortical layers, interneurons in the deep cortical layers being similar to control mice, and SST neurons were not affected in any region. The distinct differences in cortical interneuron populations between the timed mutants indicated that *Nkx2.1* controls a cell fate switch, and in the absence of *Nkx2.1,* the cells generated in the MGE follow fates normally specified by CGE and LGE regions. For example, the reduction of PV and SST cells was due to progenitors adopting the caudal fate and becoming VIP and CR neurons. Medium spiny projection neurons, normally produced by the LGE, were generated in *Nkx2.1* null regions at the expense of striatal interneurons. The changes in interneuron cell fates correspond well with the clinical presentations of chorea, hypotonia, and dyskinesia in patients with *NKX2.1* mutations (32). Considering the severe seizure phenotypes observed in mice with *Nkx2.1* deletions before E12.5, the null mutations are likely incompatible with human survival. Additional, as yet unidentified, alleles may be present in patients with seizure disorders.

In the *Nkx2.1* molecular pathway, the transcription factor *Lhx6* is downstream of *Nkx2.1*, followed by *Sox6* (33). *Sox6*^{-/-}

mice are born alive, but most die within an hour from unknown causes, and the surviving mice have stunted growth and reduced numbers of Gad67 interneurons (34). To overcome the perinatal lethality and retarded growth, *Sox6* was specifically eliminated in MGE interneurons using Cre-*loxP* recombination and the *Lhx6-cre* driver mouse line. The loss of *Sox6* impaired interneuron migration, leading to altered laminar distribution within the cerebral cortex and hippocampus. In addition, the *Sox6* mutants exhibited nearly complete loss of the PV population but overrepresentation of NPY cells (34). In the adult, the few remaining PV cells do not exhibit normal fast-spiking characteristics, instead appearing to be immature PV interneurons. EEG recordings correspond with aberrant interneuron profiles and maturity, demonstrating seizures, abnormal theta oscillations, and increased power in the delta band. *SOX6* has not yet been associated with human neurological disorders, but considering its role in establishing and maintaining inhibition in the hippocampus, allelic variations may be susceptibility factors for epileptogenesis in the medial temporal lobe.

By altering the fate of the cells in the MGE, loss of *Dlx1/2*, *Nkx2.1*, and *Sox6* modified the interneuron profiles within the future striatum and in the cerebral cortical and hippocampal targets, leading to abnormal circuitry and seizures. While initially expressed throughout all domains of the GE, the transcription factor, *COUP-TFI*, becomes restricted to the more caudal regions by E13.5. Eliminating *COUP-TFI* early in development altered the interneuron subtype portfolio without affecting the overall number of Gad67 cells (35). The numbers of PV and NPY neurons were increased, whereas the CR and VIP populations—normally derived from the CGE—were decreased. EEG recordings in adult mice exhibited no differences in normalized power or individual frequency bands. However, the *COUP-TFI* mutant mice were more resistant to seizure induction, either by pilocarpine or PTZ, with increased latencies to the first generalized tonic-clonic seizure. The *COUP-TFI* mutation presents an example of altered interneuron specification that may reduce the likelihood of epileptogenesis.

Interneuron Migration and Maturation Defects

Newly born interneurons leave the proliferative zones and migrate to their final destinations—including the cerebral cortex, hippocampus, amygdala, and olfactory bulbs—or remain in the dorsal striatum. Impaired or delayed migration changes the overall distribution of forebrain GABAergic interneurons, with fewer in target areas such as the cerebral cortex and hippocampus and possibly excessive neurons remaining in the striatum or undergoing cell death. In absence of *Dlx5* or *Dlx5/6*, dorsal migration is delayed, likely due to decreased expression of the migration cue Cxcr4 (36). The *Dlx5/6*$^{-/-}$ mouse is embryonic lethal, but the *Dlx5/6*$^{+/-}$ mouse lives to adulthood with reduced cortical PV neurons, electrographic seizures, and decreased gamma oscillations (30–80 Hz frequency band) (36). *DLX5* mutations have been associated with autism and future variants may link to epilepsy (37).

In multiple mouse models, the loss of *Arx* greatly diminished interneuron migration into the cerebral cortex without altering interneuron fate (38, 39). In patients, *ARX* mutations have been associated with X-linked infantile spasms syndrome (ISSX) and X-linked lissencephaly and ambiguous genitalia (XLAG) disorder, and these phenotypes have been recapitulated to some extent in mouse models. While null mutations are perinatal lethal, conditional mutations or humanized variants of *Arx* demonstrated an array of seizure phenotypes during P7–P11 and in the adult, but not during infancy. The nature of the seizures changed with age, with transient spasms and myoclonic seizures in preweanling mice and tonic–clonic seizures or only electrographic seizures and behavioral arrest in adults (40). In the mouse models, ~50% of heterozygous females were observed to exhibit seizures. This finding prompted further study in humans, revealing new roles for *ARX* mutations in epilepsy and developmental disorders in the previously unrecognized female population. Downstream targets of *ARX* are currently being discovered; one candidate, *MEF2C* was recently reported to be involved in multiple seizure forms and abnormal motor function, placing *MEF2C* within the *DLX1/2* and *ARX* regulatory cascade (41).

Molecular pathways originally identified with roles in axonal and dendritic outgrowth participate in regulation of interneuron migration. Growth factor and receptor pairs—such as brain-derived neurotrophic factor (BDNF) and TrkB, glial cell line-derived neurotrophic factor (GDNF) and GFRα1, hepatocyte growth factor (HGF) and Met, and neuregulin-1 and ErbB4—have roles in interneuron migration (42–44). PV cells are missing in large patches of cortex in mice genetically engineered for loss of GFRα1 in GABAergic interneuron precursors, and the adult mice exhibit decreased inhibition in EEG traces and increased susceptibility and severity to PTZ-induced seizures (45). Similarly, reduced levels of HGF/Met signaling impaired GABAergic interneuron migration and differentiation into PV cells, with eventual loss of the PV population, spontaneous seizures, and increased sensitivity to PTZ induction (46). Axon guidance molecules of the Robo/Slit and Semaphorin/Neuropilin families have roles in embryonic interneuron migration (47, 48), but their involvement in epilepsy has only recently emerged, with the neuropilin-2 null mice being more sensitive to chemically induced seizures.

Correcting Interneuron Deficits to Cure Epilepsy

Identification of critical molecular pathways and candidates has opened the door to correct the abnormalities and alter the trajectory of epileptogenesis away from disorder and towards a cure. In the case of growth factor deficits, short-term supplementation may stabilize the neural network and prevent the subsequent interneuron death and seizure onset. Postnatal supplementation of HGF, by temporary gene overexpression, overcame the endogenous HGF deficits in juvenile mice, halted the interneuron death in adults, and greatly diminished spontaneous and induced seizures (49). Similar approaches, using short-term administration of growth factor receptor agonists, may be sufficient to redirect or halt epileptogenesis progression. Finally, the most severe interneuron dysfunction and seizures arise from mutations that control cell fate. Transplantation of embryonic interneuron progenitor cells into mouse models of human epilepsies holds incredible promise (50).

Highlights

1. Genes that determine interneuron lineage can be susceptibility factors for epilepsy.

2. Profiles of interneuron subtypes are determined in the embryo and altered by specific mutations.

3. Animal models of interneuron disruption can reflect seizure phenotypes of mutations in *ARX*.

4. *COUP-TFI* alleles may represent candidates that are resistant to epileptogenesis.

5. Genes identified from developmental neurobiology are candidates for human disorders.

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