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Review article

Interneuron dysfunction in epilepsy: An experimental approach using immature brain insults to induce neuronal migration disorders

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ABSTRACT

The main elements of the microcircuits in the cerebral cortex are excitatory glutamatergic pyramidal cells and inhibitory γ-aminobutyric acid (GABA) interneurons. Hypofunction/degeneration of GABAergic interneurons has been hypothesized to be a key to the neural circuit dysfunction that underlies epileptogenesis and the development of recurrent spontaneous seizures. Using two experimental animal models of neuronal migration disorders, this review reports that the insults to the immature developing brain causes interneurons to fail to undergo normal processes such as production, migration, and organization. These results represent critical evidence that supports a link between interneuron dysfunction and epilepsy.

1. Introduction

The main elements of the microcircuits in the cerebral cortex are excitatory glutamatergic pyramidal cells and inhibitory γ-aminobutyric acid (GABA) interneurons. Excitatory glutamatergic pyramidal neurons are generated in the cortical subventricular zone and radially migrate to form the cortical plate, while inhibitory GABAergic interneurons originate from the ganglionic eminence and migrate tangentially (Poduri and Volpe, 2018b). Pyramidal cells specialize in transmitting information between different cortical areas and from cortical areas to other regions of the brain, whereas interneurons primarily contribute to local neural assemblies, where they provide inhibitory inputs and shape synchronized oscillations (Klausberger and Somogyi, 2008). The balance between excitation and inhibition is crucial for the cortical function (Maffei et al., 2006; Hensch, 2005; Yizhar et al., 2011) and, consequently, important developmental and physiological mechanisms have evolved to maintain this dynamic equilibrium (Haider et al., 2006). Severe GABAergic deficits can cause pathological hyperexcitability (Kitamura et al., 2002; Butt et al., 2008), which is linked to epilepsy (Galanopoulou, 2010; Poduri and Lowenstein, 2011), and more-subtle perturbations in the excitatory-inhibitory balance can induce multiple psychiatric conditions, including autism, intellectual disability and behavioral disorders (Marin, 2012). The purpose of this review is to present evidence that supports a link between interneuron dysfunction and epilepsy using our experimental animal models of neuronal migration disorders (Takano et al., 2004, 2006; Takano and Matsui, 2015).

2. Induction of neuronal migration disorders by immature brain insult

2.1. Excitotoxic brain injuries (Ibotenate)

Glutamate is the principal excitatory neurotransmitter in the brain and plays an important role in influencing the developmental plasticity of synaptic connections in the nervous system (Lipton and Kater, 1989; Gasic and Hollmann, 1992). Ibotenate is a conformationally-restricted analogue of glutamate that acts as a non-selective agonist of glutamate receptors, including *N*-methyl-d-aspartate receptors (NMDARs) (Madsen and Frolund, 2002). Experimental studies have demonstrated that an intracerebral injection of ibotenate in rodents produces excitotoxic brain lesions mimicking neuronal migration disorders occurring in human fetuses and newborns (Marret et al., 1995a, b; Gressens et al., 1996).

2.1.1. Pathogenic mechanisms of four types of neuronal migration disorders

In addition to genetic factors, environmental factors have been implicated in the etiology of neuronal migration disorders (Larroche et al., 1994; Rosen and Galaburda, 2000). These brain malformations are occasionally recognized as consequences of antenatal or perinatal destructive lesions that lead to disruptions. Three main causes have been suggested: vascular accidents, hemorrhaging and viral infections

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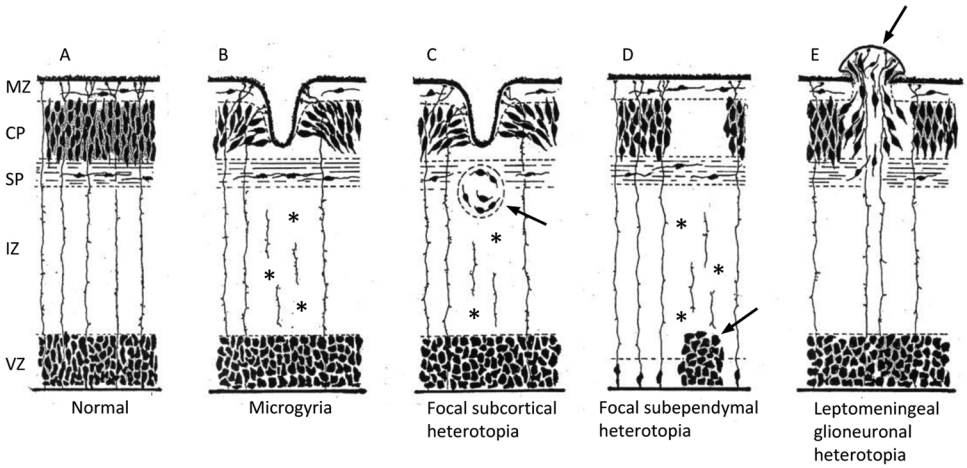

Fig. 1. Histogenetic brain development in the normal and neuronal migration disorders. A: Normal brain, B: Microgyria, C: Focal subcortical heterotopia, D: Focal subependymal heterotopia, E: Leptomeningeal glioneuronal heterotopia. Arrows (C, D, E) indicate each neuronal heterotopia. Asterisks (B, C, D) show disrupted radial glial fibers. MZ, marginal zone; CP, cortical plate; SP, subplate; IZ, intermediate zone; VZ, ventricular zone. Adapted from Takano et al., 2005.

(Norman et al., 1995). In a variety of pathologic conditions, such as stroke and various neurodegenerative disorders, excessive activation of glutamate receptors may mediate neuronal injury or death (Choi, 1985, 1988; Olney, 1990; Lipton and Rosenberg, 1994; Bittigau and Ikonomidou, 1997). NMDARs are ionotropic glutamate receptors that act as cation-selective ion channels regulating Na+, K+, and Ca2+ and have a variety of developmental functions (Waters and Machaalani, 2004; Ritter et al., 2001). These functions include neuronal proliferation (Elizabeth et al., 1994; Gould and Cameron, 1997), cell migration (Komuro and Rakic, 1993; Rakic, 1998), neuronal apoptosis, axonal outgrowth (Ritter et al., 2001), synapse formation and elimination, and synaptic plasticity (Bear et al., 1987; Brooks et al., 1991).

The cortical lesions observed after ibotenate injections have a strong resemblance to the following neuronal migration disorders: (1) microgyria, (2) focal subcortical heterotopia, (3) focal subependymal heterotopia, and (4) leptomeningeal glioneuronal heterotopia (Takano et al., 2004). In the normal brain, newly generated neurons in the ventricular zone migrate along the radial glial fibers to form the cortical plate between the marginal zone and the subplate (Fig. 1A). In contrast, focal excitotoxic brain lesions can induce focal damage of the radial glial fibers and surrounding neural tissues, inducing the collapse of the cortical plate. As the surrounding neurons migrate along the radial fibers, the cortical plate rolls inward and then becomes folded, thereby forming microgyria (Fig. 1B). When cortical damage extends to the subplate, disorganized neural tissue with an abnormal neuronal arrangement is produced over the deeper layers of the cortical plate. When the surrounding neurons migrate along the radial fibers, a small heterotopic cluster is left behind at the cortical plate, forming focal subcortical heterotopia (Fig. 1C). This heterotopia includes a small number of calretinin-expressing neurons originating from the subplate neuronal population (Takano et al., 2004). GABA, calbindin, and calretinin are expressed in tangential migrating cells at different times and in a sequential order, suggesting that the heterotopic neurons constituting the focal subcortical heterotopia originate in the lateral or medial ganglionic eminence of the ventral telencephalon, due to disturbed tangential neuronal migration. When the damage extends to the ventricular zone, then the radial glial fibers become fragmented. As the ventricular zone differentiates into the thinner ependymal layer, and the surrounding neurons migrate along the radial fibers, a conglomerate mass of progenitor cells emerges from the ventricular zone, thus forming focal subependymal heterotopia (Fig. 1D). Leptomeningeal glioneuronal heterotopia is thought to be caused by the excessive growth of radial fibers with unregulated neuronal migration through the disrupted pial glial limitans (Fig. 1E).

2.2. Inhibition of DNA synthesis (Ara-C)

The nucleoside analog cytosine arabinoside (1-β-D-arabinofuranosylcytosine, Ara-C) is one of the most effective chemotherapeutic agents in the treatment of acute myelogenous leukemia and a variety of other hematologic malignancies (Besirli et al., 2003). Ara-C can inhibit DNA synthesis in proliferating cells by being incorporated into elongating DNA strands and causing retardation of DNA elongation, as well as chain termination (Besirli et al., 2003). Disorders of neuronal proliferation are expected to have a major impact on the CNS function and resultant variable brain malformations, including microcephaly (Poduri and Volpe, 2018a).

2.2.1. Extensive neuronal apoptosis

Primary microcephaly is the result of a variety of genetic and chromosomal defects, as well as environmental insults, such as irradiation, infection, and chemical agents (Menkes et al., 2006). Microcephaly can be also accompanied by numerous neuronal migration disorders, including schizencephaly, lissencephaly, pachygyria, polymicrogyria, and gray matter heterotopia (Menkes et al., 2006). The administration of Ara-C to mice during pregnancy gives rise to extensive neuronal apoptosis throughout the cerebral hemisphere, especially in the ventricular and intermediate zones, including in the ganglionic eminence, but relatively weakly in the outer layer of the cortical plate (Fig. 2A, B). These results indicate that Ara-C induces more intensive neuronal apoptosis in immature developing neurons than in postmitotic young neurons settled in the cortical plate (Takano et al., 2006).

2.2.2. Disturbance of interkinetic nuclear migration

The to-and-fro migration of the cells at the ventricular zone occurs in synchrony with the cell cycle, such that after mitosis at the luminal or apical surface of the ventricular zone (M-phase), the nuclei migrate to the outer part of the ventricular zone during the G1 phase and stay at the outer region of the ventricular zone during the S-phase (Kosodo et al., 2011), which results in the accumulation of BrdU (5-bromodeoxyuridine)-positive nuclei in the outer part of the ventricular zone. In the normal brains of 15-day-old mouse embryos, BrdU-positive neuroepithelial cells were found to be accumulated specifically in the outer layer of the ventricular zone (Fig. 2C). However, in the embryonic brains exposed to Ara-C during pregnancy, BrdU-positive cells were nonspecifically and widely scattered in the whole ventricular zone and intermediate zone (Fig. 2D). These differences in the distribution of S-phase neuroepithelial cells appear to be the result of a toxic effect of Ara-C. Thus, the inhibition of DNA synthesis in developing neurons induces a disturbance in interkinetic nuclear migration in the ventricular zone (Takano et al., 2006).

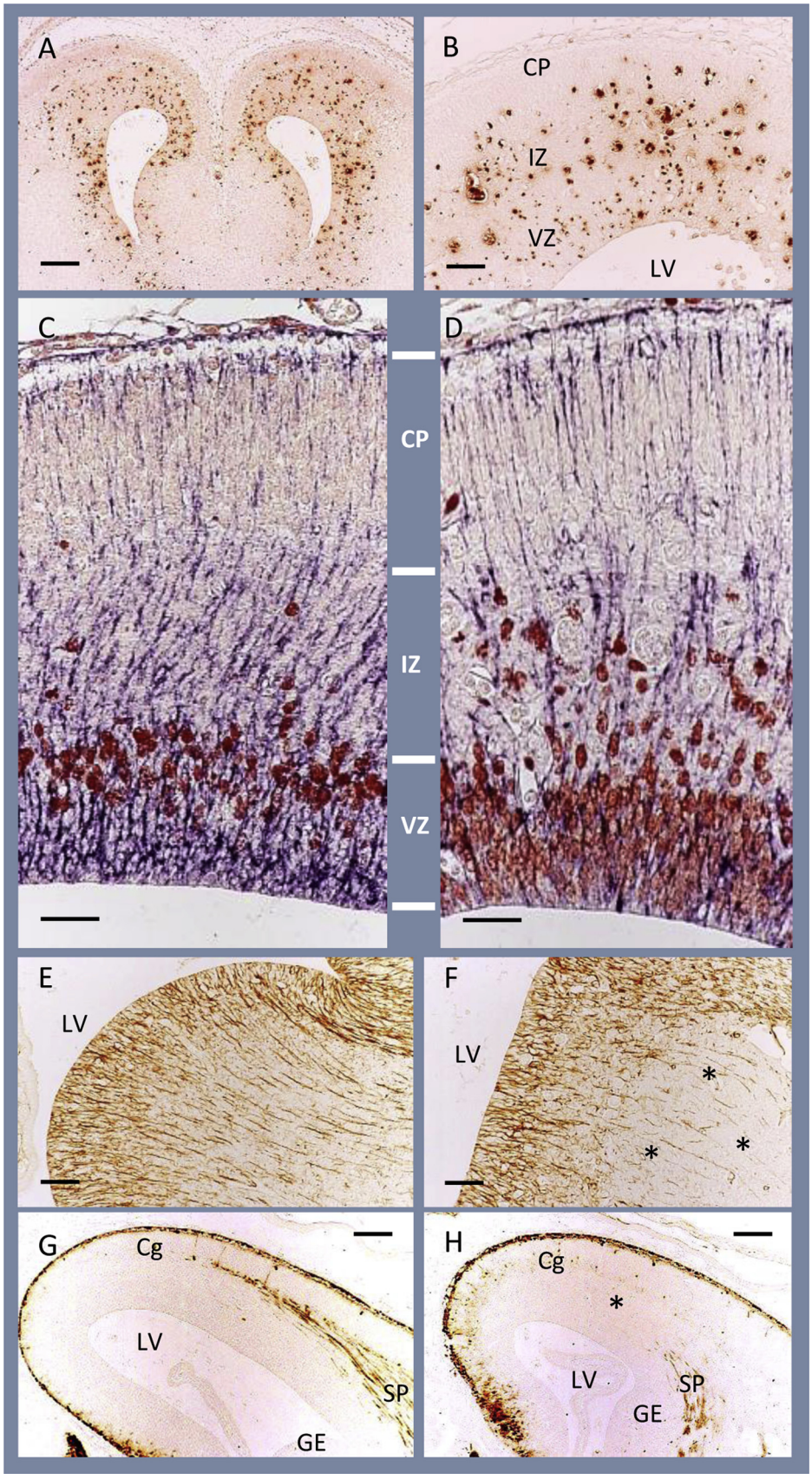

Fig. 2. Developmental brain disorders induced by the inhibition of DNA synthesis. Immunohistochemistry was used to demonstrate the abnormal expression of specific proteins in Ara-C induced neuronal migration disorders. Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end-labeling (TUNEL) reaction enables the detection of cells containing fragmented DNA, indicating apoptosis. 5-bromodeoxyuridine (BrdU) is a thymidine analogue that is incorporated into DNA, showing cells in the S phase of mitosis. Nestin belongs to a distinct sixth class of intermediate filaments and is predominantly expressed in proliferating neuronal progenitor cells. Calretinin is a calcium-binding protein and is abundantly expressed in tangentially migrating interneurons. A, B: TUNEL immunohistochemistry. Intensive neuronal apoptosis throughout the cerebral hemisphere (A), especially in the ventricular and intermediate zones (B) in the embryonic brains exposed to Ara-C during pregnancy. C, D: BrdU-nestin double immunostaining (BrdU, red; nestin, blue). Interkinetic nuclear migration is clear in the normal brain, which shows BrdU-positive nuclei of neuroepithelial cells in the outer layer of the ventricular zone (S-phase position) (C) but is disturbed by the inhibition of DNA synthesis, which shows the non-specific random distribution of BrdU-positive cells in both the ventricular and intermediate zones (D). E, F: Nestin immunohistochemistry. The dense accumulation (E) and disrupted distribution (asterisks in F) of radial glial fibers in the ganglionic eminence of the normal and Ara-C-induced disorder brain, respectively. G, H: Calretinin immunohistochemistry. Tangentially oriented (G) and disrupted subplate fibers (asterisk in H) in the normal and Ara-C-induced disorder cerebral cortex, respectively. Scale bars: (A) 120 μm; (B) 60 μm; (C, D) 40 μm; (E–H) 60 μm. CP, cortical plate; IZ, intermediate zone; VZ, ventricular zone; LV, lateral ventricles; SP, subplate; GE, ganglionic eminence; Cg, cingulum. Adapted from Takano et al., 2006.

2.2.3. Disturbance of tangential neuronal migration

Cortical cells migrating from the lateral ganglionic eminence (LGE) and medial ganglionic eminence (MGE) follow distinct pathways. Initially, to reach the vicinity of the internal capsule—where the corticofugal system terminates at this early age—ganglionic eminence cells use radial glial fibers that extend laterally or ventrolaterally. Subsequently, the ganglionic eminence cells use the axonal plexuses of this system to reach various levels of the developing cortex (Parnavelas, 2000). The calcium-binding protein calretinin is known to be expressed in some tangentially migrating cells. In the cortical neuroepithelium, the spatiotemporal sequence of GABA, calbindin, and calretinin expression has been shown to occur over several embryonic days (Jimenez et al., 2002). In the normal brains of 15-day-old mouse embryos, radial glial fibers were densely accumulated in the ganglionic eminence (Fig. 2E), and calretinin protein was mainly expressed on the tangentially oriented fibers of the subplate, which extended from the internal capsule and reached around the cingulum (Fig. 2G). However, in the embryonic brains exposed to Ara-C during pregnancy, the ganglionic eminence was atrophic with disrupted radial glial fibers (Fig. 2F), and the calretinin-immunoreactive fibers were found to end at the internal capsule and were not detected in the subplate of the frontal or cingulate cortices (Fig. 2H), implying the disruption of the tangential migration route for the ganglionic eminence cells (Takano et al., 2006).

3. Interneuron dysfunction in polymicrogyria

3.1. Epileptogenicity in polymicrogyria

3.1.1. Pathology and clinical manifestations of polymicrogyria

Polymicrogyria is a cerebral cortical malformation characterized by an excessively folded cortical ribbon of miniature thin convolutions, which consists of two pathological subtypes: the unlayered type and the four-layered type (Sisodiya, 2004). In unlayered polymicrogyria, the external molecular layer is continuous and does not follow the profile of the convolutions, and the underlying neurons have radial or vertical distribution, but no laminar organization (Ferrer, 1984). In four-layered polymicrogyria, there are two neuronal layers (2nd and 4th layers) under the molecular layer (1 st layer), separated by an intermediate layer with many fibers and few cells (cell-sparse 3rd layer) (Graham and Lantos, 2002). The polymicrogyric 2nd and 3rd layers are thought to correspond to the normal cortical layers II, III, IV, and V, respectively, and horizontal neuronal lamination is usually spared. In addition, there are clinical subtypes of polymicrogyria that are classified based on differences in extension and topography, and on their association with neurodevelopmental impairment, cognitive deficits, and epilepsy of variable severity (Jansen and Andermann, 2005). Several specific syndromes have been described with characteristic polymicrogyria. The best characterized of these is congenital bilateral perisylvian polymicrogyria (Kuzniecky et al., 1993; Guerrini et al., 1997; Barkovich et al., 1999). Polymicrogyria is a highly epileptogenic lesion. Approximately 80% of patients with this lesion eventually develop seizures, with the majority developing seizures within their first five years (Spreafico et al., 1999). Generalized polymicrogyria is characterized by a significantly lower age at seizure onset in comparison to other bilateral patterns, and patients with bilateral perisylvian polymicrogyria have a significantly lower age at seizure onset in comparison to patients with unilateral perisylvian polymicrogyria. However, the frequency of epilepsy does not differ significantly among any of the major patterns of polymicrogyria, or among the subtypes of polymicrogyria within the same main pattern (Leventer et al., 2010). This may suggest that the epileptogenicity of the polymicrogyric cortex is relatively consistent, regardless of the topography, extent or laterality.

3.1.2. Epileptogenic zone in polymicrogyria

Several clinical investigations have focused on the epileptogenic focus in polymicrogyria. Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies in patients with polymicrogyria showed that the intrinsic epileptogenicity in polymicrogyria may be related to limited areas within the lesion (Kobayashi et al., 2005). Another study combining magnetoencephalography (MEG) and MRI showed that the clusters of dipole sources of the spikes were localized in the polymicrogyric grey matter of the perisylvian cortex (Burneo et al., 2004). A study of intralesional EEG recordings reported that the interictal intralesional activity in the polymicrogyric cortex was characterized by high-frequency spiking, which was clearly different from the continuous rhythmic spike discharges observed in Taylor-type focal cortical dysplasia (TTFCD) (Chassoux et al., 2000). TTFCD, also called focal cortical dysplasia type II (FCD II) according to the classification of Palmini et al. (Palmini et al., 2004), is a distinctive malformation of cortical development characterized by laminar disorganization and dysplastic neurons. Classically, this condition includes the two subtypes of dysplasia (TTFCD-D or FCD IIA) and balloon cells (TTFCD-BC or FCD IIB) based on the presence or absence of balloon cells (Giudice et al., 2006). The epileptogenic zone in polymicrogyria is essentially different from that in TTFCD (Chassoux et al., 2008). In polymicrogyria, resection limited to the lesions would be unlikely to be followed by a favorable outcome; however, in TTFCD, the epileptogenic zone corresponds to the dysplastic tissue, which would likely be confirmed by a large percentage of patients achieving a seizure-free status after the complete resection of the lesion (Chassoux et al., 2000). In conclusion, polymicrogyria is intrinsically epileptogenic. This not only involves the less excitable neural tissue, such as the cell sparse zone, but also a part of a larger epileptic network extending to adjacent and distant cortical areas, including the mesial temporal structures.

3.2. Variable changes of interneurons in polymicrogyria

3.2.1. Mobilization of interneurons to the dysplastic cortex

The inhibitory local circuit interneurons primarily use GABA as a neurotransmitter (Druga, 2009). Most of the cortical inhibitory interneurons in the mammalian cortex are considered to arise from the ganglionic eminence via tangential, rather than radial migration (Anderson et al., 2001). Alterations in the function and number of inhibitory interneurons are one of the causes of the predisposition to seizures. Interneurons in the cortex are highly diverse, and their phenotype is influenced by their local afferent connections, in addition to developmental factors (Gonzalez-Albo et al., 2001). The calcium binding protein parvalbumin, calbindin and calretinin, and somatostatin identify distinct subsets of interneurons that are present in all regions of the mammalian cortex (Conde et al., 1994). The depletion of inhibitory interneurons has been noted in focal cortical dysplasia and may partly explain the excitatory overbalance in these lesions (Thom et al., 2003). This local deficit of interneurons may represent a primary failure of tangential migration or of subsequent differentiation within the region of dysplasia (Thom et al., 2003). The intracerebral injection of ibotenate produces excitotoxic brain lesions that mimic neuronal migration disorders in kittens (Innocenti and Berbel, 1991), and hamsters (Takano et al., 2004). A neuronal tracing study of progenitor cells in the ganglionic eminence using biotinylated dextran amine (BDA) demonstrated that the interneurons were specifically mobilized to the microgyric area out of the ganglionic eminence (Fig. 3A, B) (Sawai et al., 2009; Takano et al., 2010; Takano, 2011). This finding suggests the development of new inhibitory neuronal connections after the onset of excitotoxic brain lesions (e.g., polymicrogyria) that induce cortical dysplasia.

3.2.2. Altered distribution of interneurons around the microgyria

Electrophysiological studies using cortical slices in a rat model of polymicrogyria demonstrated that the epileptiform activity could only be evoked from a focal zone adjacent to the microgyrus (paramicrogyral zone) and not within the microgyrus proper, suggesting that the

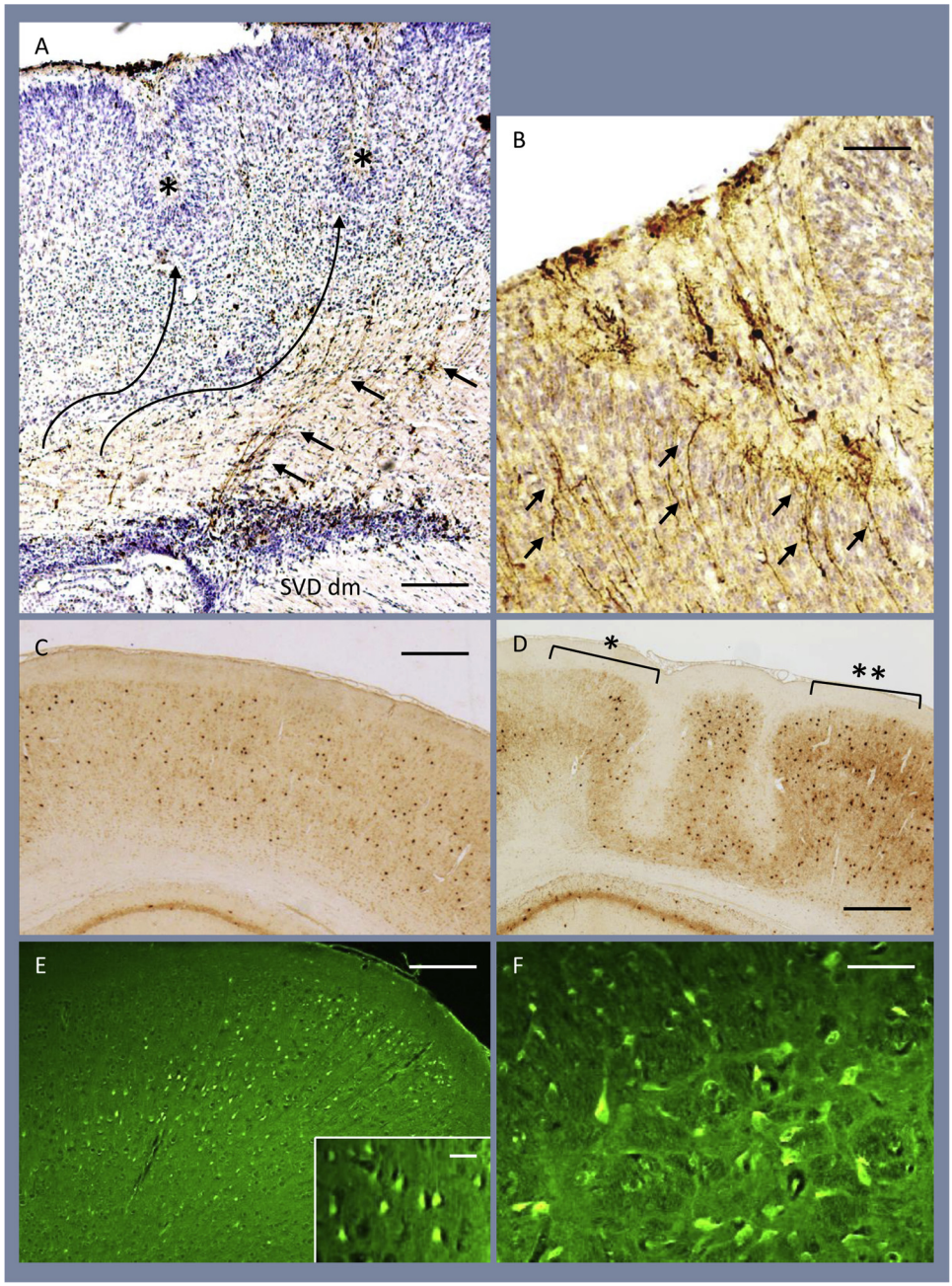

Fig. 3. Interneuron abnormalities induced by excitotoxic brain injury. Neuronal tracing and immunohistochemical studies were performed to examine the variable changes of interneurons. Biotinylated dextran amine (BDA), which yields sensitive and exquisitely detailed labeling of axons and terminals using preferentially anterograde transport, was injected into the ganglionic eminence during the newborn period in this experiment. Parvalbumin is a calcium-binding protein, and all parvalbumin-immunoreactive neurons in the rodent cortex are GABAergic. Fluoro-Jade B (FJB) is an anionic fluorochrome reported to selectively stain degenerating neurons. A, B: BDA immunohistochemistry with hematoxylin double staining. A: BDA immunoreactive cells and fibers (short arrows) are migrating toward the tip of the polymicrogyria (asterisks), extending from the dorsomedial part of the subventricular zone (SVZdm) (long arrows). B: Note the strong accumulation of BDA-labeled unipolar cells within the polymicrogyric cortex with numerous BDA immunoreactive fibers (small arrows) entering this microgyria. C, D: Parvalbumin immunohistochemistry. C: Parvalbumin-positive interneurons are uniformly distributed in the cerebral cortex of normal brain. D: Note the stronger accumulation of interneurons in the lateral part of the polymicrogyric cortex (two asterisks) than those in the medial part of polymicrogyria (asterisk). E, F: FJB staining in polymicrogyria. Small amounts of FJB-positive elements were detected in the cerebral cortex (E) and caudate putamen (F), most of which show non-pyramidal cell morphology, and which are likely to be interneurons (inset in E, and F). Scale bars: (A) 120 μm; (B) 30 μm; (C–E) 400 μm; (F) 80 μm. Adapted from Takano, 2011, 2012; Takano and Matsui, 2015.

epileptiform activity can be generated outside the lesion itself, which is referred to as the paramicrogyral area (Jacobs et al., 1999). Because of the presence of focal cortical dysplasia, the cortical afferents unable to find appropriate targets within the malformed region may instead synapse in the adjacent paramicrogyral area, thus implying that there is an increase in the number of functional excitatory synapses on both the interneurons and pyramidal cells in the paramicrogyral cortex (Jacobs et al., 1999). The temporary downregulation of the parvalbumin expression in the malformed cortex was observed in the freeze-lesion rat model of microgyria (Rosen et al., 1998). On the other hand, the density of GABA- and parvalbumin-positive neurons in the fronto-parietal cortex is not significantly different between lesioned and control animals. Moreover, the density of calbindin-immunoreactive neurons located in the paramicrogyral area was significantly higher (Schwarz et al., 2000). These results indicate the variable presence of less excitable neural tissue within the polymicrogyria. We have demonstrated that parvalbumin-positive interneurons significantly accumulated in the lateral part of the microgyrus, but not the medial part of the microgyrus (Fig. 3C, D). It is unclear whether the increased number of parvalbumin-positive cells in the lateral part of the microgyrus provides an increased perisomatic inhibition of the principal cells. However, these findings suggest that the callosal, thalamic and intracortical afferents to the microgyrus and paramicrogyral area may induce a remarkable imbalance between the excitatory and inhibitory activities of the cortical structures, which may be associated with the epileptogenic mechanism in polymicrogyria (Takano, 2012).

3.2.3. *Selective vulnerability of interneurons to proconvulsant agents*

GAP43, a growth-associated protein, is a presynaptic phosphoprotein of growth cones that is expressed during development and other events of axonal growth, such as the regeneration of injured axons (Benowitz and Routtenberg, 1997; Longo et al., 2005). Developing neurons express high levels of GAP43, which is transported to the growth cones of immature synapses. Its expression in neurons is closely

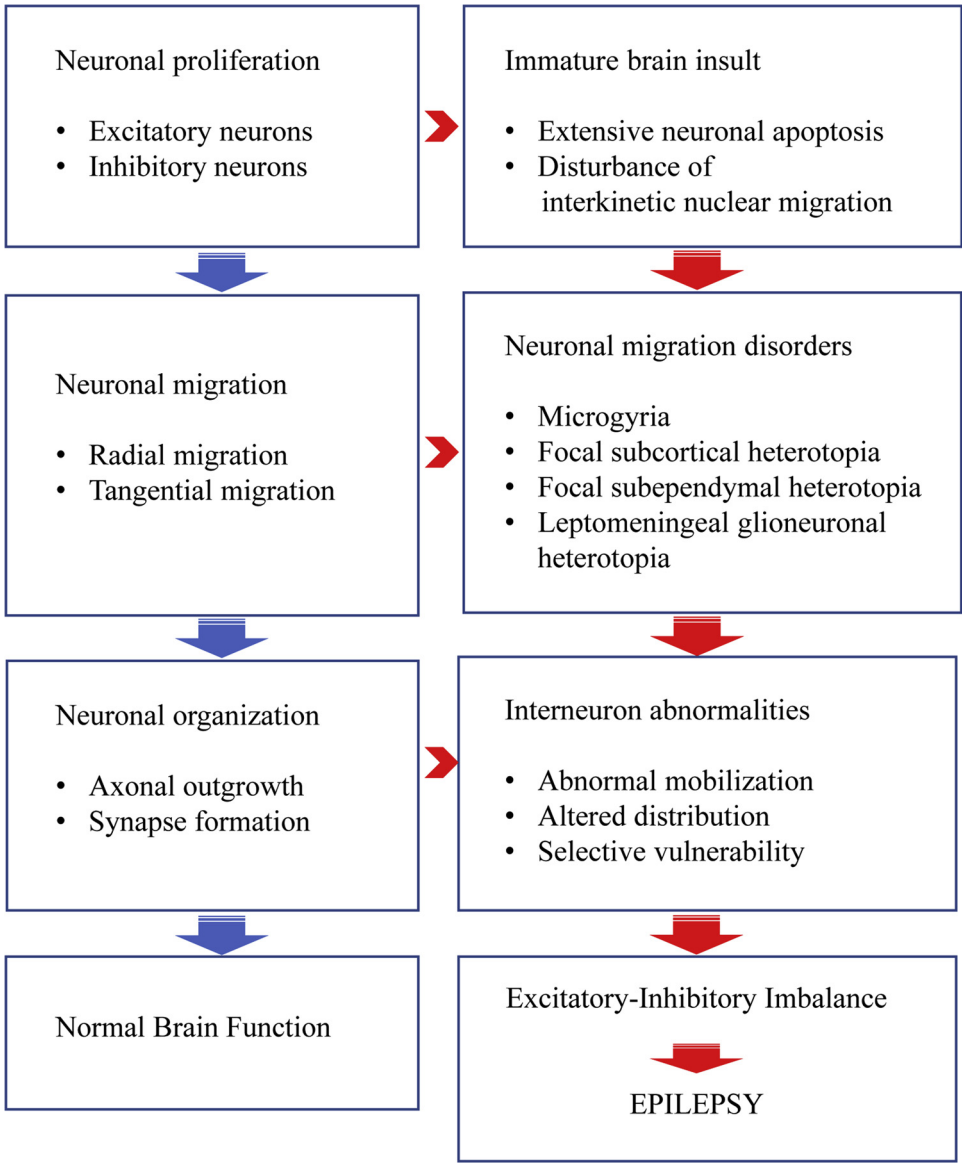

Fig. 4. The disruption of the developmental sequence by immature brain insult. Immature brain insults can induce the failure of interneurons to undergo the entire developmental processes of the brain such as neuronal proliferation, migration and organization. The resultant abnormalities include abnormal mobilization, altered distribution, and the selective vulnerability of the inhibitory cortical interneurons. Thus, the disordered developmental processes are closely associated with the excitatory-inhibitory imbalance and resultant seizure susceptibility inducing epilepsy.

correlated with axonal elongation, synaptogenesis and nerve sprouting during development. Pentylenetetrazole (PTZ) is a well-described pro-convulsant agent used in rat kindling models and in the generation of acute short-lived seizures (Morimoto et al., 2004; Mason and Cooper, 1972). Although the exact mechanisms underlying the pathogenesis of PTZ-induced convulsions remain unclear (Oghlakian et al., 2009), the most accepted theory highlights its action as an antagonist to the picrotoxinin-sensitive site of GABA receptor complex (Chweh et al., 1983; Ramanjaneyulu and Ticku, 1984). Repeated injections of sub-convulsive doses of PTZ elicited significantly higher seizure scores in the polymicrogyria rats in comparison to control rats (Takano and Matsui, 2015). Fluoro-Jade B–positive degenerating neurons after PTZ injection and the subsequent expression of GAP43 were mainly restricted to interneurons in the brain with polymicrogyria; no such neurons were detected in the control brains (Fig. 3E, F). These results imply that the axonal growth and dendritic plasticity observed after the formation of excitotoxic lesions or sub-convulsive chemical injury predominantly occurs in the inhibitory interneurons in the immature brain, which may constitute the basis for the decreased seizure threshold and resultant intractable epilepsy in polymicrogyria.

4. Future directions

More than 30% of cases involve refractory epilepsies in which medical therapies fail to manage the seizures (Engel, 2014). Drug-resistant seizures can be potentially life-threatening and are associated with psychological impairments and a compromised quality of life (Laxer et al., 2014). Patients who undergo surgical removal of seizure foci are more likely to become seizure-free with a better quality of life than those who do not undergo removal (Liu et al., 2018). However, surgical resection can only be done successfully when the seizure focus can be clearly identified and safely removed without lasting consequences (Jobst and Cascino, 2015). Electrical neurostimulation is reported to be effective and acceptably safe (Heck et al., 2014), but it is currently useful only in a fraction of patients with drug-refractory seizures (Pais-Vieira et al., 2016). Transcranial magnetic stimulation is

non-invasive, but there is no powerful evidence to support its efficacy (Lin and Wang, 2017). These limitations in the currently available treatment options for refractory epilepsy call for the development of more effective and restorative therapeutic modalities.

Transplantation of cells, such as cortical GABAergic interneurons, is a strategy currently being examined rigorously in preclinical models of epilepsy (Shetty and Upadhya, 2016; Zhu et al., 2018). A variety of cells have been tested for their proficiency in suppressing seizures following grafting into distinct regions of the brain. These cells include primary GABAergic progenitors from the mouse embryonic MGE (De la Cruz et al., 2011), neural stem cells expanded from the rat embryonic MGE (Waldau et al., 2010), and MGE-like progenitors generated from human embryonic stem cells (Cunningham et al., 2014). Considering the promising results of these experimental investigations, the interneuron replacement therapy would be a safe and effective treatment option against refractory seizures in the future. Further studies will be essential for paving the way for the clinical translation of GABAergic cell grafting for epileptic conditions.

5. Conclusion

The proliferation, migration, and organization of cortical interneurons are determined by a vast array of extrinsic and intrinsic factors that work in concert to assemble a proper functioning cortical inhibitory network. We herein reported that when the immature developing brain is subjected to insult, the interneurons fail to undergo these organizing processes, resulting in several developmental abnormalities as follows: 1) extensive neuronal apoptosis of progenitor cells; 2) disturbed interkinetic nuclear migration and tangential neuronal migration; 3) abnormal mobilization and altered interneuron distribution; and 4) selective vulnerability of the interneurons due to excitotoxic brain injury (Fig. 4). Precisely what compensatory processes generate the cortical excitatory-inhibitory balance has not yet been clarified. However, populations of excitatory and inhibitory synapses must likely be adjusted in a complex and coordinated manner in order to preserve the excitatory-inhibitory balance and prevent neural systems from remaining hypo- or hyper-excitable for prolonged periods. The basic mechanisms underlying seizure suppression should be further explored for the better control of refractory seizures.

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Declaration of Competing Interest

None.

References

Anderson, S.A., Marin, O., Horn, C., Jennings, K., Rubenstein, J.L., 2001. Distinct cortical migrations from the medial and lateral ganglionic eminences. Development 128, 353–363.
Barkovich, A.J., Hevner, R., Guerrini, R., 1999. Syndromes of bilateral symmetrical polymicrogyria. AJNR Am. J. Neuroradiol. 20, 1814–1821.
Bear, M.F., Cooper, L.N., Ebner, F.F., 1987. A physiological basis for a theory of synapse modification. Science 237, 42–48.
Benowitz, L.I., Routtenberg, A., 1997. GAP-43: an intrinsic determinant of neuronal development and plasticity. Trends Neurosci. 20, 84–91.
Besirli, C.G., Deckwerth, T.L., Crowder, R.J., Freeman, R.S., Johnson Jr., E.M., 2003. Cytosine arabinoside rapidly activates bax-dependent apoptosis and a delayed bax-independent death pathway in sympathetic neurons. Cell Death Differ. 10, 1045–1058.
Bittigau, P., Ikonomidou, C., 1997. Glutamate in neurologic diseases. J. Child Neurol. 12, 471–485.
Brooks, W.J., Petit, T.L., Leboutillier, J.C., Lo, R., 1991. Rapid alteration of synaptic number and postsynaptic thickening length by NMDA: an electron microscopic study in the occipital cortex of postnatal rats. Synapse 8, 41–48.
Burneo, J.G., Bebin, M., Kuzniecky, R.I., Knowlton, R.C., 2004. Electroclinical and magnetoencephalographic studies in epilepsy patients with polymicrogyria. Epilepsy Res. 62, 125–133.
Butt, S.J.B., Sousa, V.H., Fuccillo, M.V., Hjerling-Leffler, J., Miyoshi, G., Kimura, S., Fishell, G., 2008. The requirement of Nkx2–1 in the temporal specification of cortical interneuron subtypes. Neuron 59, 722–732.
Chassoux, F., Devaux, B., Landre, E., Turak, B., Nataf, F., Varlet, P., Chodkiewicz, J.P., Daumas-Duport, C., 2000. Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. Brain 123, 1733–1751.
Chassoux, F., Landre, E., Rodrigo, S., Beuvon, F., Turak, B., Semah, F., Devaux, B., 2008. Intralesional recordings and epileptogenic zone in focal polymicrogyria. Epilepsia 49, 51–64.
Choi, D.W., 1985. Glutamate neurotoxicity in cortical cell culture is calcium dependent. Neurosci. Lett. 58, 293–297.
Choi, D.W., 1988. Glutamate neurotoxicity and diseases of the nervous system. Neuron 1, 623–634.
Chweh, A.Y., Swinyard, E.A., Wolf, H.H., 1983. Pentylenetetrazole may discriminate between different types of benzodiazepine receptors. J. Neurochem. 41, 830–833.
Conde, F., Lund, J.S., Jacobowitz, D.M., Baimbridge, K.G., Lewis, D.A., 1994. Local circuit neurons immunoreactive for calretinin, calbindin D-28K or parvalbumin in monkey prefrontal cortex: distribution and morphology. J. Comp. Neurol. 341, 95–116.
Cunningham, M., Cho, J.H., Leung, A., Savvidis, G., Ahn, S., Moon, M., Lee, P.K., Han, J.J., Azimi, N., Kim, K.S., Bolshakov, V.Y., Chung, S., 2014. hPSC-derived maturing GABAergic interneurons ameliorate seizures and abnormal behavior in epileptic mice. Cell Stem Cell 15, 559–573.
De la Cruz, E., Zhao, M., Guo, L., Ma, H., Anderson, S.A., Schwartz, T.H., 2011. Interneuron progenitors attenuate the power of acute focal ictal discharges. Neurotherapeutics 8, 763–773.
Druga, R., 2009. Neocortical inhibitory system. Folia Biol. (Praha) 55, 201–217.
Elizabeth, G.P.D., Cameron, H.A., Mcewen, B.S., 1994. Blockade of NMDA receptors increases cell death and birth in the developing rat dentate gyrus. J. Comp. Neurol. 340, 551–565.
Engel, J., 2014. Approaches to refractory epilepsy. Ann. Indian Acad. Neurol. 17, S12–S17.
Ferrer, I., 1984. A Golgi analysis of unlayered polymicrogyria. Acta Neuropathol. 65, 69–76.
Galanopoulou, A.S., 2010. Mutations affecting GABAergic signaling in seizures and epilepsy. Pflugers Arch. 460, 505–523.
Gasic, G.P., Hollmann, M., 1992. Molecular neurobiology of glutamate receptors. Annu. Rev. Physiol. 54, 507–536.
Giudice, E.D., Bianchi, M.C., Tosetti, M., Varrone, A., Romano, A., Crisanti, A.F., Titomanlio, L., Imperati, F., 2006. Taylor-type focal cortical dysplasia: is the epilepsy always resistant to medical treatment? Epileptic Disord. 8, 289–293.
Gonzalez-Albo, M.C., Elston, G.N., De Felipe, J., 2001. The human temporal cortex: characterization of neurons expressing nitric oxide synthase, neuropeptides and calcium binding proteins and their glutamate receptor subunit profiles. Cereb. Cortex 11, 1170–1181.
Gould, E., Cameron, H.A., 1997. Early NMDA receptor blockade impairs defensive behavior and increases cell proliferation in the dentate gyrus of developing rats. Behav. Neurosci. 111, 49–56.
Graham, D.I., Lantos, P.L., 2002. Greenfield's Neuropathology, 7th ed. Arnold, London, pp. 406–409.
Gressens, P., Marret, S., Evrard, P., 1996. Developmental spectrum of the excitotoxic cascade induced by ibotenate: a model of hypoxic insults in fetuses and neonate. Neuropathol. Appl. Neurobiol. 22, 498–502.
Guerrini, R., Dubeau, F., Dulac, O., Barkovich, A.J., Kuzniecky, R., Fett, C., Jones-Gotman, M., Canapicchi, R., Cross, H., Fish, D., Bonanni, P., Jambaque, I., Andermann, F., 1997. Bilateral parasagittal parietooccipital polymicrogyria and epilepsy. Ann. Neurol. 41, 65–73.
Haider, B., Duque, A., Hasenstaub, A.R., McCormick, D.A., 2006. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. J. Neurosci. 26, 4535–4545.
Heck, C.N., King-Stephens, D., Massey, A.D., Nair, D.R., Jobst, B.C., Barkley, G.L., et al., 2014. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia 55, 432–441.
Hensch, T.K., 2005. Critical period plasticity in local cortical circuits. Nature Rev. Neurosci. 6, 877–888.
Innocenti, G.M., Berbel, P., 1991. Analysis of an experimental cortical network: i) architectonics of visual areas 17 and 18 after neonatal injections of ibotenic acid; similarities with human microgyria. J. Neural Transplant. 2, 1–28.
Jacobs, K.M., Hwang, B.J., Prince, D.A., 1999. Focal epileptogenesis in a rat model of polymicrogyria. J. Neurophysiol. 81, 159–173.
Jansen, A., Andermann, E., 2005. Genetics of the polymicrogyria syndromes. J. Med. Genet. 42, 369–378.
Jimenez, D., Lopez-Mascaraque, L.M., Valverde, F., De Carlos, J.A., 2002. Tangential migration in neocortical development. Dev. Biol. 244, 155–169.
Jobst, B.C., Cascino, G.D., 2015. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA 313, 285–293.
Kitamura, K., Yanazawa, M., Sugiyama, N., Miura, H., Iizuka-Kogo, A., Kusaka, M., Omichi, K., Suzuki, R., Kato-Fukui, Y., Kamiirisa, K., Matsuo, M., Kamijo, S., Kasahara, M., Yoshioka, H., Ogata, T., Fukuda, T., Kondo, I., Kato, M., Dobyns, W.B., Yokoyama, M., Morohashi, K., 2002. Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. Nature Genet. 32, 359–369.
Klausberger, T., Somogyi, P., 2008. Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. Science 321, 53–57.

Kobayashi, E., Bagshaw, A.P., Jansen, A., Andermann, F., Andermann, E., Gotman, J., Dubeau, F., 2005. Intrinsic epileptogenicity in polymicrogyric cortex suggested by EEG-fMRI BOLD responses. Neurology 64, 1263–1266.
Komuro, H., Rakic, P., 1993. Modulation of neuronal migration by NMDA receptors. Science 260, 95–97.
Kosodo, Y., Suetsugu, T., Suda, M., Mimori-Kiyosue, Y., Toida, K., Baba, S.A., Kimura, A., Matsuzaki, F., 2011. Regulation of interkinetic nuclear migration by cell cycle-coupled active and passive mechanisms in the developing brain. EMBO J. 30, 1690–1704.
Kuzniecky, R., Andermann, F., Guerrini, R., 1993. Congenital bilateral perisylvian syndrome: study of 31 patients. The CBPS multicenter collaborative study. Lancet 341, 608–612.
Larroche, J.C., Girard, N., Narcy, F., Fallet, C., 1994. Abnormal cortical plate (polymicrogyria), heterotopias and brain damage in monozygous twins. Biol. Neonate 65, 343–352.
Laxer, K.D., Trinka, E., Hirsch, L.J., Cendes, F., Langfitt, J., Delanty, N., et al., 2014. The consequences of refractory epilepsy and its treatment. Epilepsy Behav. 37, 59–70.
Leventer, R.J., Jansen, A., Pilz, D.T., Stoodley, N., Marini, C., Dubeau, F., Malone, J., Mitchell, L.A., Mandelstam, S., Scheffer, I.E., Berkovic, S.F., Andermann, F., Andermann, E., Guerrini, R., Dobyns, W.B., 2010. Clinical and imaging heterogeneity of polymicrogyria: a study of 328 patients. Brain 133, 1415–1427.
Lin, Y., Wang, Y., 2017. Neurostimulation as a promising epilepsy therapy. Epilepsia Open 2, 371–387.
Lipton, S.A., Kater, S.B., 1989. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. Trends Neurosci. 12, 265–270.
Lipton, S.A., Rosenberg, P.A., 1994. Excitatory amino acids as a final common pathway for neurologic disorders. N. Engl. J. Med. 330, 613–622.
Liu, J.-T., Liu, B., Zhang, H., 2018. Surgical versus medical treatment of drug- resistant epilepsy: a systematic review and meta-analysis. Epilepsy Behav. 82, 179–188.
Longo, B., Vezzani, A., Mello, L.E., 2005. Growth-associated protein 43 expression in hippocampal molecular layer of chronic epileptic rats treated with cycloheximide. Epilepsia 46 (suppl 5), 125–128.
Madsen, U., Frolund, B., 2002. Excitatory and inhibitory amino acid receptor ligand. In: Liljefors, T., Krogsgaard-Larsen, P., Madsen, U. (Eds.), Textbook of Drug Design and Discovery. CRC Press, London, pp. 259–304.
Maffei, A., Nataraj, K., Nelson, S.B., Turrigiano, G.G., 2006. Potentiation of cortical inhibition by visual deprivation. Nature 443, 81–84.
Marin, A., 2012. Interneuron dysfunction in psychiatric disorders. Nature Rev. Neurosci. 13 (January (2)), 107–120. https://doi.org/10.1038/nrn3155.
Marret, S., Mukendi, R., Gadisseux, J.F., Gressens, P., 1995a. Effect of ibotenate on brain development: an excitotoxic mouse model of microgyria and posthypoxic-like lesions. J. Neuropathol. Exp. Neurol. 54, 358–370.
Marret, S., Gressens, P., Gadisseux, J.F., Evrard, P., 1995b. Prevention by magnesium of excitotoxic neuronal death in the developing brain: an animal model for clinical intervention studies. Dev. Med. Child Neurol. 37, 473–484.
Mason, C.R., Cooper, R.M., 1972. A permanent change in convulsive threshold in normal and brain-damaged rats with repeated small doses of pentylenetetrazole. Epilepsia 13, 663–674.
Menkes, J.H., Sarnat, H.B., Flores-Sarnat, L., 2006. Malformations of the central nervous system. In: Menkes, J.H., Sarnat, H.B., Maria, B.L. (Eds.), Child Neurology. Lippincott Williams and Wilkins, Philadelphia, pp. 284–366.
Morimoto, K., Fahnestock, M., Racine, R.J., 2004. Kindling and status epilepticus models of epilepsy: rewiring the brain. Prog. Neurobiol. 73, 1–60.
Norman, M.G., McGillivray, B.C., Kalousek, D.K., Hill, A., Poskitt, K.J., 1995. Congenital Malformations of the Brain: Pathological, Embryological, Clinical, Radiological and Genetic Aspects. Oxford University Press, New York.
Oghlakian, R.O., Tilelli, C.Q., Hiremath, G.K., Alexopoulos, A.V., Najm, I.M., 2009. Single injection of a low dose of pentylenetetrazole leads to epileptogenesis in an animal model of cortical dysplasia. Epilepsia 50, 801–810.
Olney, J.W., 1990. Excitotoxin-mediated neuron death in youth and old age. In: Coleman, P., Higgins, G., Phelps, C. (Eds.), Progress in Brain Research. Elsevier Science Publishers, New York, pp. 37–51.
Pais-Vieira, M., Yadav, A.P., Moreira, D., Guggenmos, D., Santos, A., Lebedev, M., et al., 2016. A Closed loop brain-machine interface for epilepsy control using dorsal column electrical stimulation. Sci. Rep. 6, 32814.
Palmini, A., Najm, I., Avanzini, G., Babb, T., Guerrini, R., Foldvary-Schaefer, N., Jackson, G., Luders, H.O., Prayson, R., Spreafico, R., Vinters, H.V., 2004. Terminology and classification of the cortical dysplasias. Neurology 62, S2–S8.
Parnavelas, J.G., 2000. The origin and migration of cortical neurons: new vistas. Trends Neurosci. 23, 126–131.
Poduri, A., Lowenstein, D., 2011. Epilepsy genetics — past, present, and future. Curr. Opin. Genet. Dev. 21, 325–332.
Poduri, A., Volpe, J.J., 2018a. Neuronal proliferation. In: Volpe, J.J. (Ed.), Volpe'S Neurology of the Newborn. Elsevier, Philadelphia, pp. 100–119.
Poduri, A., Volpe, J.J., 2018b. Neuronal migration. In: Volpe, J.J. (Ed.), Volpe'S Neurology of the Newborn. Elsevier, Philadelphia, pp. 120–144.
Rakic, P., 1998. Images in neuroscience. Brain development, VI: radial migration and cortical evolution. Am. J. Psychiatry 155, 1150–1151.
Ramanjaneyulu, R., Ticku, M.K., 1984. Interaction of pentamethylenetetrazole and tetrazole analogues with the picrotoxinin site of the benzodiazepine-GABA receptor-ionophore complex. Eur. J. Pharmacol. 98, 337–345.
Ritter, L.M., Unis, A.S., Meador-Woodruff, J.H., 2001. Ontogeny of ionotropic glutamate receptor expression in human fetal brain. Dev. Brain Res. 127, 123–133.
Rosen, G.D., Jacobs, K.M., Prince, D.A., 1998. Effects of neonatal freeze lesions on expression of parvalbumin in rat neocortex. Cereb. Cortex 8, 753–761.
Rosen, G.D., Galaburda, A.M., 2000. Single cause, polymorphic neuronal migration disorders: an animal model. Dev. Med. Child Neurol. 42, 652–662.
Sawai, C., Takano, T., Takeuchi, Y., 2009. Experimental neuronal migration disorders following the administration of ibotenate in hamsters: the role of the subventricular zone in the development of cortical dysplasia. J. Child Neurol. 24, 275–286.
Schwarz, P., Stichel, C.C., Luhmann, H.J., 2000. Characterization of neuronal migration disorders in neocortical structures: loss or preservation of inhibitory interneurons? Epilepsia 41, 781–787.
Shetty, A.K., Upadhya, D., 2016. GABA-ergic cell therapy or epilepsy: advances, limitations and challenges. Neurosci. Biobehav. Rev. 62, 35–47.
Sisodiya, S.M., 2004. Malformations of cortical development: burdens and insights from important causes of human epilepsy. Lancet Neurol. 3, 29–38.
Spreafico, R., Avanzini, G., Andermann, F., 1999. Abnormal Cortical Development and Epilepsy. John Libbey and Company, London, pp. 191–201.
Takano, T., Sawai, C., Takeuchi, Y., 2004. Radial and tangential neuronal migration disorders in ibotenate-induced cortical lesions in hamsters: immunohistochemical study of reelin, vimentin, and calretinin. J. Child Neurol. 19, 107–115.
Takano, T., Sawai, C., Sakaue, Y., Takikita, S., Takeuchi, Y., 2005. Experimental cortical dysplasia following ibotenate administration in hamsters: pathogenesis of microgyria and associated gray matter heterotopia. Congenit. Anom. 45, 9–13.
Takano, T., Akahori, S., Takeuchi, Y., Ohno, M., 2006. Neuronal apoptosis and gray matter heterotopia in microcephaly produced by cytosine arabinoside in mice. Brain Res. 1089, 55–66.
Takano, T., Sawai, C., Akabori, S., Takeuchi, Y., 2010. Polymicrogyria without epilepsy by aberrantly migrating inhibitory interneurons. Epilepsy Behav. 18, 505–506.
Takano, T., 2011. Seizure susceptibility in polymicrogyria: clinical and experimental approaches. Epilepsy Res. 96, 1–10.
Takano, T., 2012. Altered distribution of inhibitory interneurons in polymicrogyria. Epilepsy Res. 102, 113–116.
Takano, T., Matsui, K., 2015. Increased expression of GAP43 in interneurons in a rat model of experimental polymicrogyria. J. Child Neurol. 30, 716–728.
Thom, M., Harding, B.N., Lin, W.R., Martinian, L., Cross, H., Sisodiya, S.M., 2003. Cajar-Retzius celle, inhibitory interneuronal populations and neuropeptides Y expression in focal cortical dysplasia and microdysgenesis. Acta Neuropathol. 105, 561–569.
Waldau, B., Hattiangady, B., Kuruba, R., Shetty, A.K., 2010. Medial ganglionic eminence-derived neural stem cell grafts ease spontaneous seizures and restore GDNF expression in a rat model of chronic temporal lobe epilepsy. Stem Cells 28, 1153–1164.
Waters, K.A., Machaalani, R., 2004. NMDA receptors in the developing brain and effects of noxious insults. NeuroSignals 13, 162–174.
Yizhar, O., Fenno, L.E., Prigge, M., Schneider, F., Davidson, T.J., O'Shea, D.J., Sohal, V.S., Goshen, I., Finkelstein, J., Paz, J.T., Stehfest, K., Fudim, R., Ramakrishnan, C., Huguenard, J.R., Hegemann, P., Deisseroth, K., 2011. Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 477, 171–178.
Zhu, Q., Naegele, J.R., Chung, S., 2018. Cortical GABAergic interneuron/progenitor transplantation as a novel therapy for intractable epilepsy. Front. Cell. Neurosci. 12, 167.