Special Issue: Basic Mechanisms of Pediatric Epilepsy

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Developmental Psychologist Jean Piaget once declared that a child is not an adult in miniature. By extension, we can say that the brain of a child is not just an adult brain in miniature. Although the number of cortical neurons is already determined at birth, their positioning, connectivity, and electrophysiological and molecular signatures are far from over. This rapid and continuous transformation bestows young brains with a high capacity for structural and molecular plasticity, particularly within cortical circuits. And while the adult brain is still capable of undergoing plastic changes, they are not as prominent as in young brains.

The developing brain is a very delicate and sensitive organ. Even small errors in cell generation, proliferation, and migration can lead to devastating consequences. This delicate balance can be easily perturbed by physical and metabolic insults, explaining the peculiar susceptibility of developing brains to become hyperexcitable and potentially epileptogenic. It is the toll it pays for being so malleable. Pediatric brains have unique features that make them separate entities which, through a painstaking and protracted process, evolve into adult brains. A number of important differences between young and adult brains have been recognized for a very long time. Morphological and electrophysiological cell properties, connectivity, receptor sensitivity, and subunit composition, are unique to the developing brain. For example, as a result of expression of different subunits, AMPA receptors can be permeable to calcium and NMDA receptors usually have reduced Mg^{2+} sensitivity. In addition, glutamate synaptic activity is incipient in immature brains, whereas GABA synaptic activity is more predominant. An intriguing finding with wide-range neurophysiological and pharmacological consequences is that in immature brains GABA, the classical inhibitory neurotransmitter in the adult brain, can act as a proexcitatory agent by depolarizing cell membranes, due to reduced expression of the mature, K^+-Cl^- cotransporter-2 (KCC2). This implies that in young epileptic brains, drugs that increase GABA function may not be adequate therapeutic agents to control seizures.

A better understanding of a child's brain also can be relevant to understand dysfunction in adult brains. Morbid brain conditions in adults frequently recapitulate processes found in children. Trauma and other brain lesions often recapitulate conditions found in immature brains, including temporal lobe epilepsy (TLE). This is reminiscent of psychoanalytical observations exploring the psyche of children. As noted by A. A. Brill in the Introduction to his translation of Freud's *Totem and Taboo* [1], whenever the individual finds it impossible to dominate the difficulties of the world, there is a regression to the infantile. Thus, the adult brain is the result of his childhood's brain or the sum total of his

early impressions, confirming the old saying that "the child is father to the man."

For years, the book *Basic Mechanisms of Epilepsy* [2] and its sequel *Jasper's Basic Mechanisms of the Epilepsies* [3] have been like the Bible for epileptologists worldwide. However, pediatric epilepsies have rarely received enough attention in terms of understanding basic mechanisms, in spite of their high prevalence. Probably, the only precedent is a Special Issue on "Pediatric Epilepsy and Epilepsy Surgery" edited by Gary W. Mathern in 1999 [4]. After 15 years, we feel it is time for an update of recent progress in the field of pediatric epilepsy. In this Special Issue on Basic Mechanisms of Pediatric Epilepsy, we have assembled contributions, reviews, and original articles by some of the pioneers who have led the way in the examination of pathological conditions that are indigenous or more prevalent in the young brain. Mechanistic studies in animal models of pediatric epilepsy also are included. In no way is this an exhaustive account of all things that can go wrong in the developing brain, and the 13 articles that integrate this issue are not, by any stretch of the imagination, the final word on each theme. We have loosely divided the articles into those that are mostly clinical and deal with human studies and those that are more anchored on basic research studies using animal models.

As a good preamble for this Special Issue, Ivica Kostović and colleagues from the University of Zagreb in Croatia, who have a long-standing trajectory examining developing human brains, contribute a review article examining brain development with particular emphasis on the subplate zone and the role of subplate neurons and connections in Malformations of Cortical Development (MCDs), a group of pathogenic conditions frequently found in histological specimens of children with epilepsy. Cortical dysplasia (CD) is a prime example of cortical development going awry. CD can be considered, paraphrasing Freud, a royal road to the developing brain, albeit in a pathological condition. Sara Abdi-jadid et al. from the University of California in Los Angeles (UCLA) provide a detailed account of what is known to date about CD in children. The UCLA group is one of the pioneer groups using tissue samples resected from epilepsy surgery pediatric patients, particularly CD cases, for slice electrophysiology. Based on these studies, they put forward the dysmaturity hypothesis of CD, which postulates that the interaction between immature and mature cells and networks creates regions of cortical hyperexcitability and epileptic activity.

A very exhaustive review on gray matter heterotopias in humans and in animal models is contributed by Françoise Watrin, Alfonso Represa et al. from INMED in Marseille, France. Genetic factors affecting both neuronal migration and prolifera-

tion are particularly highlighted. An important conclusion reached by these authors is that cortical areas adjacent to the gray matter heterotopia play a consistent and fundamental role in epileptogenesis, implying that plastic changes secondary to the initial lesion are instrumental in the generation of epileptic discharges.

Jie Wu, John F. Kerrigan, and collaborators at the Barrow Neurological Institute (BNI) in Phoenix, Arizona, the only team in the world that has examined electrophysiological cell alterations in human hypothalamic hamartoma (HH) tissue, summarize results obtained in the past 10 years about epileptogenic mechanisms of human gelastic seizures triggered by HH lesions. In their review, they systematically dissect clinical and basic research studies, present an update of current progress, and propose a cellular model that suggests that GABA-mediated excitation contributes to epileptogenesis in HH lesions. Suzan Semaan, Yao (Joyce) Huang, and colleagues at St. Joseph's Hospital, in collaboration with the BNI, have gone further to examine molecular biological mechanisms of epileptogenesis in HH and the role of BDNF in GABA-mediated excitation. In this original research article, they provide experimental evidence demonstrating enhanced TrkB-MAPKs-BDNF signaling and reduced KCC2 levels in HH tissue compared to normal human hypothalamic tissue. This work suggests that multiple BDNF-TrkB signaling pathways are activated in HH. They act independently or collaboratively to downregulate KCC2 expression, which is the key component for GABA-mediated excitation associated with gelastic seizures.

Rasmussen encephalitis (RE) is a rare disorder that affects mostly children. The cause remains unknown, but inflammation in one cerebral hemisphere is the main feature. In this issue, Carlos Cepeda et al. at UCLA examine possible mechanisms of hyperexcitability in RE and reveal, for the first time, a critical role for gap junctions induced by hemichannels linked to the inflammatory process in epileptogenesis. The role of inflammation in epilepsy is now well recognized, and it is hoped that the new light shed on the mechanisms of RE may also be extensive to other epileptic conditions. Indeed, the need for more studies on the role of inflammation in developmental epilepsies is further emphasized in a review article by Nina Dupuis and Stéphane Auvin at the Hôpital Robert Debré in Paris. In their review, they summarize clinical and experimental evidence demonstrating that in developing brains, inflammation contributes to seizure precipitation and, conversely, prolonged seizures induce inflammation.

Roustem Khazipov, Guzél Valeeva, and Ilgam Khalilov from the IN-MED in Marseille and Volodymyr Dzhalala and Kevin Staley from Massachusetts General Hospital in Boston, the two premier laboratories that have provided groundbreaking insights on the role of depolarizing actions of GABA in immature brains, have contributed a review and an original article. In their review, Khazipov et al. use a question and answer format that explains in simple terms the complexities of GABA effects in immature brains and the myriad methodological issues (*in vivo* vs. *in vitro*, type of recording, etc.) that need to be considered before concluding what the sign or outcome of GABA_A receptor activation will be. This excellent review provides very useful information for understanding the dual roles of depolarizing (excitatory) and shunting (inhibitory) actions of GABA in normal brain function and also in epileptic conditions. Similar to conclusions reached by other

investigators dealing with developing cortical networks, the authors propose that correction of chloride homeostasis is a potential strategy for the treatment of neonatal seizures. One of such strategies is the use of bumetanide, a NKCC1 cotransporter blocker. Dzhalala and Staley examined in detail the effects of this agent in a model of epileptogenesis and chronic epilepsy after brain injury using organotypic hippocampal cultures. The authors provide evidence that, while bumetanide produces early (7–14 days in culture) enhancement of the anticonvulsant efficacy of phenobarbital against posttraumatic ictal-like activity, chronic administration (beginning at day 3 in culture) of bumetanide alone or with phenobarbital fails to prevent subsequent epileptogenesis. These results support clinical findings that anticonvulsants can be used to control acute posttraumatic seizures but cannot prevent anticonvulsant pharmacoresistance and epilepsy.

Ozlem Akman, Solomon Moshé, and Aristea Galanopoulou, from Albert Einstein College of Medicine in New York and renowned world experts in age- and sex-specific differences in epileptic activity, examine the effects of early status epilepticus and stress caused by maternal separation on learning, seizure outcomes, and anticonvulsant effects of phenobarbital. They demonstrate that both status epilepticus and maternal separation have sex-specific effects on learning and memory but no significant effects on latency or threshold to clonic seizures. However, they have a sex- and treatment-specific impact on the incidence of spontaneous seizures, hippocampal injury, and mortality.

Absence seizures represent one of the most common forms of pediatric and juvenile epilepsy. Marcello Venzi and Vincenzo Crunelli from Cardiff and Giuseppe Di Giovanni, from both Cardiff and Malta Universities, provide an exhaustive review and critical evaluation of a well-characterized pharmacological model of absence seizures induced by gamma-hydroxybutyrate (GBH), an endogenous brain molecule that also induces a state of sedation. After examining evidence of GBH effects across animal species and humans, the authors conclude that only in rats, GBH has behavioral and EEG events typical of absence seizures and also express the need for more studies on the role of other brain regions, besides the thalamus, in the generation of absence seizures. Traumatic brain injury (TBI) is another well-recognized cause of seizures. How it affects the juvenile brain is for the most part unknown. Here, Trent Anderson and his group from the University of Arizona examine the consequences of TBI in juvenile rats. They found that controlled cortical impact rapidly induces epileptiform activity and enhances cortical synaptic bursting. Detection of epileptiform activity early after injury suggests that it may be an important pathophysiological component and potential marker of developing posttraumatic epilepsy.

Temporal lobe epilepsy is the most frequent form of adult epilepsy, and its prevalence in children is only minor. However, seizures occurring in infancy, for example, febrile seizures, can lead to TLE in adults. For this reason, we decided to include a chapter on TLE as it can be relevant to understanding seizure mechanisms in children. Bo Wen, Jin-Hui Wang, and associates, from the Institute of Biophysics at the Chinese Academy of Sciences in Beijing, examine the mechanisms of seizure termination through endogenous neuronal network activation. In their original research article, they specifically examine the role of inhibitory neurons in endogenous seizure termination using patch-clamp recordings

in seizure-onset cortices from intractable patients with TLE and controls without seizures. They found that a portion of inhibitory neurons in the seizure-onset cortices were upregulated in encoding spikes and controlling their target neurons. These upregulated inhibitory neurons and their output synapses synergistically shortened seizure duration, attenuated its strength, and terminated its propagation. This work provides a potentially novel therapeutic strategy for intractable patients with TLE, namely, simultaneous upregulation of cortical inhibitory neurons and their output synapses.

Our understanding of epileptogenesis in developing brains is still in the early stages. However, we hope that this compendium

helps provide the reader with a wide perspective of this fascinating area of research that, as the young brain, is rapidly evolving. Our purpose also is to raise awareness of the importance of studying the developing brain. Finally, the authors would like to thank CNSNT and its Editor-in-Chief *Ding-Feng Su* and Managing Editor *Buddy Zhou*, for providing initial impetus for compiling this Special Issue and for allowing the use of their forum to highlight a particular subject that deserves more attention by epileptologists and neuroscientists in general. We also thank all the contributors who took time from their busy schedules to write about their seminal findings and enthusiastically embraced this endeavor.

References

1. Freud S. *Totem and Taboo*. Resemblances between the psychic lives of savages and neurotics. Translated by AA Brill. New York: Moffat, Yard & Co, 1918.
2. Jasper HH, Ward AAJR, Pope A. *Basic mechanisms of the epilepsies*. Boston: Little Brown & Co., 1969.
3. Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV. *Jasper's basic mechanisms of the epilepsies*, 4th edn. New York, NY: Oxford University Press, 2012.
4. Mathern GW. (Editor). Special issue on pediatric epilepsy and epilepsy surgery. *Dev Neurosci* 1999;**21**:159–408.