Postnatal Influences on Seizure Susceptibility: Does My Mother Really Matter?

Postnatal Epigenetic Influences on Seizure Susceptibility in Seizure-Prone versus Seizure-Resistant Rat Strains. Gilby KL, Sydserff S, Patey AM, Thorne V, St-Onge V, Jans J, McIntyre DC. *Behav Neurosci* 2009;123(2):337–346. The creation of seizure-prone (Fast) and seizure-resistant (Slow) rat strains via selective breeding implies genetic control of relative seizure vulnerability, yet ample data also advocates an environmental contribution. To investigate potential environmental underpinnings to the differential seizure sensitivities in these strains, the authors compared amygdala kindling profiles in adult male Fast and Slow rats raised by 1) their own mother, 2) a foster mother from the same strain, or 3) a foster mother from the opposing strain. Ultimately, strain-specific kindling profiles were not normalized by cross-fostering. Instead, both strains became more seizure-prone regardless of maternal affiliation (i.e., cross-fostered groups from both strains kindled faster than uncrossed controls). Interhemispheric seizure spread was also facilitated in cross-fostered Slow rat groups and was associated with increased commissural cross-sectional areas, giving them a Fast-like profile. It is important to note, however, that all Fast groups remained significantly more seizure-prone than Slow groups, suggesting that although the postnatal environment strongly influenced seizure disposition in both strains, it did not wholly account for their relative dispositions. Investigation into mechanisms fundamental to cross-fostering-induced seizure facilitation should help prevent postnatal worsening of pathology in already seizure-prone individuals.

COMMENTARY

Genetic influences have been extensively studied as a basis for seizure susceptibility. Mutations at various loci, including those encoding ion channels, ion pumps, neurotransmitter systems, and guidance cues, are associated with increased seizure susceptibility (1). However, sporadic reports between 1975 and 2000 have suggested that nongenetic factors also can affect ictogenesis and seizure expression. Such environmental factors may occur prenatally as well as postnatally and may include maternal care or other early life experiences that influence seizure susceptibility, such as environmental enrichment. Identification of these factors and clarification of their mechanisms may reveal therapeutic strategies that can mitigate both seizures and comorbid cognitive and psychiatric conditions.

Evidence from human studies suggests maternal environmental influences can affect the developing brain. In particular, the hippocampus of humans is very prone to the influence of chronic stress and corticosteroids (2). When in utero,

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preterm infants are commonly exposed to as many as three courses of corticosteroids to promote maturation of the infant's lungs. Children at 3–6 years of age, who had had these multiple courses of prenatal corticosteroids, are three times more likely to have attention deficit disorder with hyperactivity, anxiety, and aggressive–destructive behavior, without necessarily affecting IQ. Similarly, in rodents, prenatal steroids have multiple effects on hippocampal cell proliferation, neurotransmitter turnover, synaptogenesis, and neurotransmitter receptor expression. In response to prenatal stress, corticosteroids decrease BDNF mRNA in the hippocampus, predisposing rat pups to cell death, inflammation, increased seizure susceptibility, and influencing postnatal behavior (2).

Changes in postnatal environment and corticosteroids also affect the degree of neurite outgrowth and synaptic actions, thereby altering the function of neural networks. Koh and colleagues developed an elegant animal model of environmental enrichment and studied the mitigating effects of the enrichment maneuver on gene expression, cell death, and inflammation. They studied environmental enrichment following both induced early life seizures and maternal separation, as neonatal stressors (3). Following early life seizures, diminution of cell death, inflammation, and cognitive deficits was observed in pups with postnatal environment enrichment compared with littermates who had no environmental enrichment (4). Postnatal environmental enrichment was associated with the increased expression of *Bdnf*, activity-regulated cytoskeletal associated protein (*Arc*), *Homer1a*, early growth response (*Egr1*), and serotonin receptors in pups compared with littermates who had no environmental enrichment. Each of these genes is involved in synaptic plasticity, memory consolidation, synaptogenesis, and neurite outgrowth in the developing brain. Thus, changes in the postnatal environment may have definite effects on seizure susceptibility during development.

In this study, Gilby et al. used the kindling model, a reproducible model of focal epileptogenesis, as a basis for studying the role of maternal care on epileptogenesis Through selective breeding, the investigators created rat strains that were either prone or resistant to kindling epileptogenesis (i.e., respectively, fast or slowly kindled rats). They then examined the influence of maternal care in the phenotype of the offspring by comparing pups that were raised by their own mother or by a foster mother from the same or from the opposing strain. Afterdischarge threshold (i.e., amount of current needed to evoke an afterdischarge) and duration, kindling rates, as well as commissural cross-sectional areas were examined.

In cross-fostered strains, pre- and postelectrical kindling afterdischarge thresholds were dramatically elevated in the amygdala. If it is assumed that cross-fostering is a stressor, these data are consistent with previous reports of elevated seizure thresholds after developmental stressors in chemically induced seizures models. However, a marker of rat pup stress, such as cortisol levels, was not measured in this study. Murine developmental stressors have not affected other neurological phenotypes, such as anxiety- or depression-related phenotypes. These phenotypes were examined in multiple mouse strains that are known to have differences in seizure susceptibility. So, it remains to be established whether or not developmental stressors are associated with differential seizure susceptibility in rodent models. However, the findings of Gilby and colleagues argue that the afterdischarge threshold effects may be a combination of postnatal stress and genetic interactions.

Next, Gilby et al. sought to determine whether changes in the source of maternal care affected the rates of electrical spread through the brain to induce kindling epileptogenesis. They found that the cross-fostered groups had increased rates of kindling and a reduced afterdischarge duration to the first generalized tonic–clonic seizure compared with the control groups. These data imply that the interhemispheric spread of the electrical activity (i.e., seizure propagation) was facilitated in cross-fostered groups. The cellular mechanisms of the augmented seizure propagation potentially could involve myriad local changes in inhibitory circuitry (as implied by afterdischarge threshold data), changes in local excitatory synaptogenesis, or changes to network recruitment as a whole. The more rapid interhemispheric spread resulted in faster recruitment of the contralateral (unstimulated) amygdala during kindling, suggesting greater anatomic connectivity.

The electrophysiological phenotypes in the multiple groups may be due to stress-induced changes in axonal outgrowth or synaptogenesis. To investigate anatomic differences among the groups, Gilby et al.: 1) measured the cross-sectional areas of several interhemispheric axonal connections (specifically, the corpus callosum and anterior commissures) and 2) used DiI labeling to assess semiquantitatively the degree of area and cell connectivity between the amygdale of each hemisphere. Both control fast kindled rats as well as cross-fostered, slowly kindled rats have a greater cross-sectional area of the corpus callosum and anterior commissure. The results of the DiI labeling experiments reinforced the findings from the cross-sectional area measurements: the degree of DiI labeling between the amygdala of opposite hemispheres was greater in the control, fast kindled rats compared with the control, slow kindled rats. Results from both anatomic methods imply that the effect of cross-fostering was to increase the anatomic connectivity in slowly kindled rats. Whether or not the outcome of faster interhemispheric spread of seizures is evidence of a morphologic mechanism at work remains unclear.

Developmental stressors produce a variety of neurological sequelae, including but not limited to, alterations in serotonergic, cholinergic, or noradrenergic neurotransmitter systems. The changes in neurotransmitter physiology likely occur in

concert with altered feedback of the hypothalamic–pituitary–adrenal axis and altered ion channel expression. Based on previous work, developmental stressors that increase cortisol should result in decreased BDNF production. The presence of an increased volume of axon bundles within commissures after cross-fostering of pups in the Gilby et al. study would predict the opposite—it ought to show increased BDNF synthesis (5). At this stage in development, increased BDNF promotes the survival and neurite outgrowth of callosal projections neurons. Deletion or rescue of BDNF signaling, respectively, either facilitates or prevents increased seizure susceptibility, neurite outgrowth, epileptogenesis, learning and memory deficits, and behavioral difficulties (6). An alternative hypothesis is that the faster spread of electrical seizures triggered activity-dependent production of BDNF (7). This mechanism would recruit more neurons to elongate their axons, explaining the increased volume of axon bundles within commissures of fast kindled rats versus cross-fostered, slow kindled rats. However, it is easy to envision many other neuritogenic mechanisms via other signaling pathways.

Brain injury in the neonatal period remains a major source of epileptogenesis during the childhood years. Fully, one in four babies treated in intensive care units for neonatal seizures will develop postnatal epilepsy, including the devastating developmental epilepsy, infantile spasms. The model reported by Gilby et al. provide an experiment system that may make it possible to identify the cellular and molecular mechanisms that define prenatal and postnatal influences on seizure susceptibility. Seizure susceptibility is not totally dictated by the genome. Similarly, there is evidence that postnatal environment factors can modify the phenotypes of other neurological disorders. For instance, Dawson published elegant studies demonstrating the potential of environmental enrichment, through intensive early behavioral intervention, to change the course of neurodevelopment in early childhood aged patients with autism spectrum disorder (8). Since the disorder is a proposed human model of altered functional synaptic connectivity, similar postnatal changes or environmental enrichment for infants in the intensive care unit and at risk for postnatal epilepsy may significantly alter seizure susceptibility through nonpharmacological interventions (9). Thus, animal models and further human studies can test both nonpharmacological interventions and also identify therapeutic targets in molecular pathways that may ameliorate or prevent epileptogenesis after injury to the developing brain.

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