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Partners in Crime: How Seizures and Stress Mechanisms Interact To Influence the Structure and Function of the Developing Brain

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Seizures often arise in the setting of an acute injury or insult. In addition, many of the epilepsies are "symptomatic", i.e., they occur in individuals who had sustained injury or insult such as infection, trauma, or stroke. The mechanisms by which diverse factors such as infection or trauma provoke both acute seizures and recurrent, chronic seizures (epilepsy) are not fully understood. To some extent, each of these insults may initiate a unique chain of events that promotes epilepsy. However, these insults also share commonalities that set in motion cellular and molecular changes that promote neuronal hyperexcitability: All these epilepsy- provoking insults are stressful, in that they trigger the release and actions of 'stress-mediating molecules', including glucocorticoids and the intrinsic central nervous system (CNS) stress-activated neuropeptide, corticotropin releasing hormone (CRH). Stress induces release of CRH from hippocampal interneurons, and CRH acts on selective receptors (CRF-R1) to enhance glutamate-mediated neurotransmission. In immature hippocampus, CRH and the CRH receptors are particularly abundant, so that the peptide may excite neurons sufficiently to evoke seizures, followed by dendritic atrophy or death of vulnerable neurons. In animal models, chronic enhancement of CRH levels within the developing hippocampus, may result in enduring reduction of hippocampus-governed learning and memory function. Such levels might be found in infants with chronic CNS stressors including congenital infection, dysplasia, trauma or recurrent seizures. Indeed, drugs that downregulate CRH levels in limbic structures (e.g., ACTH) are potent antiepileptics in the developing CNS. In summary, acute and chronic stress elicits the release of pro-excitatory molecules (CRH), promoting seizures. These further activate the "stress response", leading to a vicious cycle culminating in loss of neuronal function and integrity.