Pathophysiological mechanisms of seizures and epilepsy: A primer

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Abstract

This chapter reviews the cellular and synaptic basis for focal and generalized seizure generation with an emphasis on ion channels and synaptic physiology. This background is useful for understanding the scientific basis of epilepsy and its treatment, as discussed in greater detail in subsequent chapters of this book. A seizure, or epileptic seizure, is a temporary disruption of brain function due to the excessive, abnormal discharge of cortical neurons. The clinical manifestations of a seizure depend on the specific region and extent of brain involvement and may include an alteration in alertness, motor function, sensory perception, or autonomic function, or all of these. Any person can experience a seizure in the appropriate clinical setting (e.g., meningitis, hypoglycemia), attesting to the innate capacity of even a normal brain to support epileptic discharges, at least temporarily. Epilepsy is the condition of recurrent (two or more), unprovoked seizures, usually due to a genetic predisposition or chronic acquired pathologic state (e.g., cerebral dysgenesis, brain trauma). Epilepsy syndrome refers to a constellation of clinical characteristics that consistently occur together, with seizures as a primary manifestation. Features of an epilepsy syndrome might include similar age of onset, electroencephalogram (EEG) findings, etiology, inheritance pattern, natural history of the symptoms, and response to particular antiepileptic drugs. Mechanisms leading to the generation of a seizure (ictogenesis) may differ from those predisposing to epilepsy, the condition of recurrent, unprovoked seizures (i.e., epileptogenesis) (Dichter, 2009). A seizure is characterized by aberrant electrical activity within the brain. Such electrical activity is the net product of biochemical processes at the cellular and subcellular levels occurring in the context of large neuronal networks. Seizures often involve interplay between cortical and subcortical structures (Blumenfeld, 2003). The surface EEG is the primary clinical tool with which normal and abnormal electrical activity in the brain is measured. At the cellular level, the two hallmark features of epileptic activity are neuronal hyperexcitability and neuronal hypersynchrony. Hyperexcitability is the abnormal responsiveness (e.g., lower threshold) of a neuron to excitatory input; a hyperexcitable neuron tends to fire bursts of multiple action potentials instead of just one or two. Hypersynchrony refers to the recruitment of large numbers of neighboring neurons into an abnormal firing mode. Ultimately, a seizure is a network phenomenon that requires participation of many neurons firing synchronously. Conventional EEG techniques can detect cortical areas exhibiting hypersynchronous discharges in the form of interictal sharp waves or spikes. Using specialized EEG recording techniques in humans and animals with epilepsy, bursts of very localized discharges have been detected that are not detected by usual EEG methods (Engel et al., 2009). These so-called “fast ripples” (250 to 600 Hz) reflect abnormal interictal discharges in restricted cortical areas which could synchronize and lead to a seizure (see Chapter 21, this volume).