The word “epilepsy” is derived from the Greek verb ἑπιλαμβάνειν (or ἑπιλαμβάνειν) meaning “to be seized”, “to be taken hold of”, or “to be attacked”. Hippocrates (400 BC) was the first to suggest that epilepsy is a disease of the brain that must be treated. According to the WHO, globally 60 million people have epilepsy, and an estimated 2.4 million are diagnosed with epilepsy each year. There are more than 20 anti-seizure drugs on market, but in about 30% of people with epilepsy, seizures are not controlled by medication.

Epilepsy can be initiated, for example, by an “epilepsy gene”, various types of acute brain insult or chronic neurodegenerative diseases. The epileptogenic process is modulated by an individual’s genetic background, microbe, and exposure (non-genetic exposures of an individual in a lifetime, e.g., life-style, medications etc.). Epileptogenesis continues after epilepsy diagnosis (i.e., occurrence of the first unprovoked seizure) and leads to various outcomes (SUDEP, sudden unexpected death; QoL, quality-of-life; Rx, treatment).

Molecular, Cellular and Neuronal Network Pathologies

- Neurodegeneration
- Anticonvulsant failure
- Microglia
- Mitochondrial dysfunction
- Calcium deposits
- Microvascular remodeling
- Axonal sprouting
- Calcium deposits
- Mitochondrial dysfunction
- Microvascular remodeling
- Axonal sprouting
- Calcium deposits
- Mitochondrial dysfunction
- Microvascular remodeling
- Axonal sprouting

Epileptogenesis and Comorbidogenesis

A framework for the development of animal models of seizures and epilepsy. Model generation begins with the selection of the method of induction (elicitation). The goal is to produce an animal with (a) seizure phenotype(s) corresponding to human seizure type and epilepsy type, (b) comorbidities corresponding to a human epilepsy syndrome, and (c) molecular and cellular pathologies that correspond to alterations in the ictogenic brain area of the corresponding epilepsy type or syndrome.

Brain Pathologies Associated with Epileptogenesis

- Typical pathological findings include neuronal cell death, inflammatory response, including astrocytosis, microglial infiltration and infiltration of T lymphocytes into brain parenchyma; chronic axonal changes, including demyelination and axonal sprouting (may their trajectories in the dentate gyrus); vascular remodeling, including blood-brain barrier dysfunction (pericyte activation), agglutination of iron and calcium.

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Epileptogenesis and Epilepsy

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Terminology

- Seizure: A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures are categorized according to the International League Against Epilepsy (ILAE) classification into three types: generalised onset, focal onset (previously known as partial seizures), and unknown onset.

- Epilepsy: A disease of the brain defined by any of the following conditions: (a) recurrent seizures (2 or more), (b) comorbidities corresponding to a human epilepsy syndrome, (c) multiple etiologies (etiology), (d) progressive nature of the disease, (e) development of neural dysfunction even after cessation of seizures, resulting in:

  1. Epileptogenesis
  2. Comorbidogenesis

Epileptogenesis

- Development and extension of tissue capable of generating spontaneous seizures, resulting in:

  1. Development of an epileptic condition and/or
  2. Progression of the epilepsy after it is established

Epilepsy syndrome

- A cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together. It often has age-dependent features such as age at onset and remission, seizure triggers, diurnal variation, and sometimes prognosis. It may also have distinctive comorbidities such as intellectual and psychiatric dysfunction, together with specific findings on EEG and imaging studies. Specific etiologic, prognostic and treatment implications may also be associated with an epilepsy syndrome.

Unprovoked Epileptic Seizure

Below is an example of an electrographic seizure in a rat that had structural epilepsy induced by traumatic brain injury. As in humans, seizures typically last less than 2-3 minutes. This seizure occurred during the NE stage of sleep. CP4 and CP3 refer to locations of injected electrodes. Such EEG recordings are essential for epilepsy diagnosis.