Epileptogenesis and Epilepsy

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The word "epilepsy" is derived from the Greek verb ἐπιλαμβάνειν (or epilambánein) 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.

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: generalized onset; focal onset (previously known as partial seizures); and unknown onset.

Epilepsy A disease of the brain defined by any of the following conditions:

- At least two unprovoked (or reflex) seizures occurring >24 h apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- Diagnosis of an epilepsy syndrome

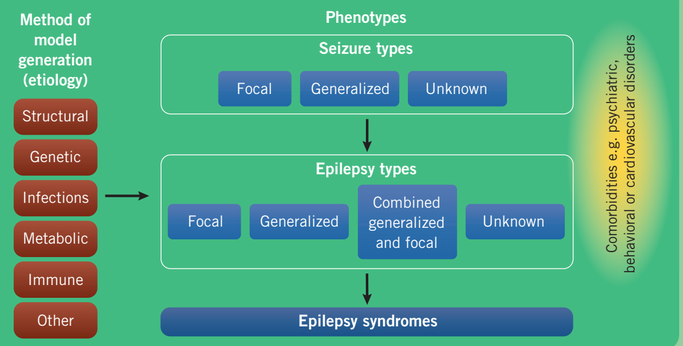
Epileptogenesis Development and extension of tissue capable of generating spontaneous seizures, resulting in:

- Development of an epileptic condition and/or
- 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.

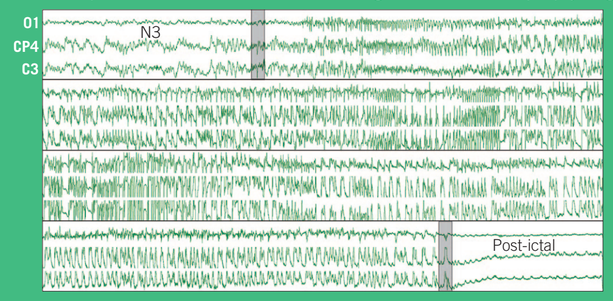
Epileptogenesis and Comorbidogenesis

A framework for the development of animal models of seizures and epilepsy Model generation begins with the selection of the method of induction (etiology). 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.



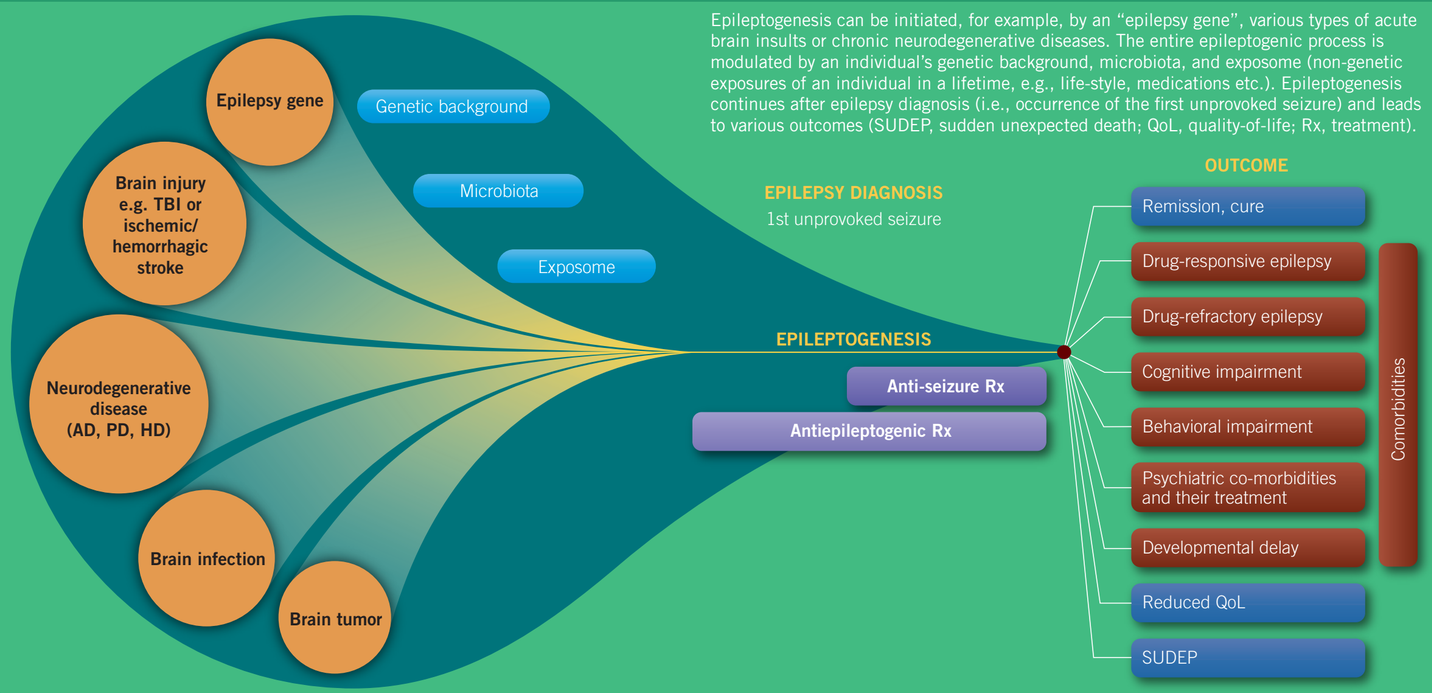
Unprovoked Epileptic Seizure

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 N3 stage of sleep. O1, CP4 and C3 refer to locations of epidural electrodes. Such EEG recordings are essential for epilepsy diagnosis.



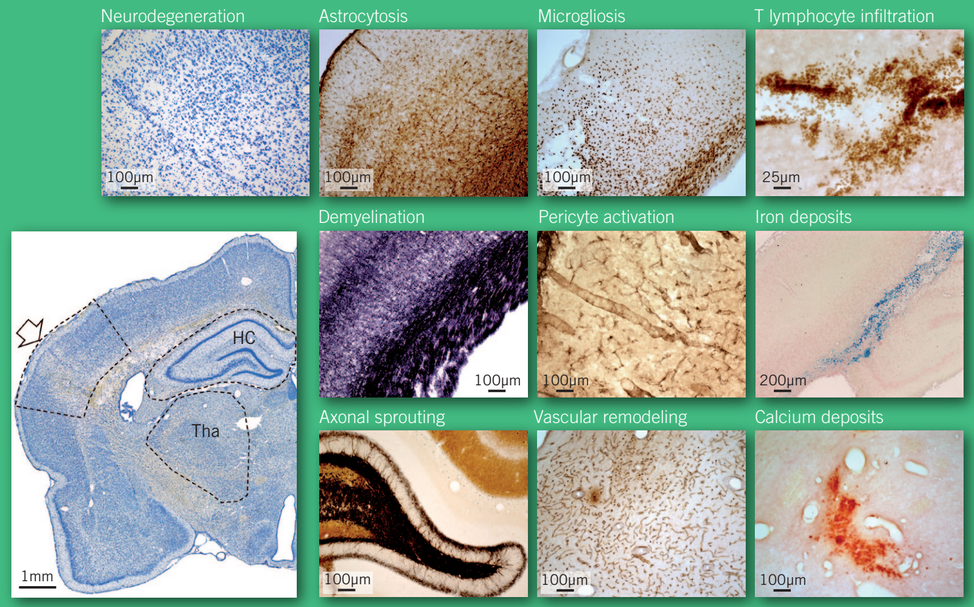
Molecular, Cellular and Neuronal Network Pathologies

Epileptogenesis can be initiated, for example, by an "epilepsy gene", various types of acute brain insults or chronic neurodegenerative diseases. The entire epileptogenic process is modulated by an individual's genetic background, microbiota, and exposome (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).



Brain Pathologies Associated with Epileptogenesis

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



Open arrow, primary injury; HC, hippocampus; Tha, thalamus.
Photomicrographs were taken from the outlined areas of the rat brain.

Disease-modification

Most currently available anti-seizure medicines target sodium channels or the GABAergic system to suppress the excessive neuronal activity in the brain, but do not address the underlying brain pathology. More recently research has focused on identifying new types of treatments that may reverse or prevent the epileptogenic changes in neuronal circuits that arise from a brain insult. The table below highlights treatments that have shown disease-modifying effect in proof-of concept studies in animal models of genetic or structural epilepsies.

α4-integrin-specific Ab	Ketogenic diet
AAF-Nrf2	Losartan
Adenosine	Melatonin
Aspirin	Minocycline
Atipamezole	Minozac
BDNF-FGF-2 gene therapy	mir-134 antagomir
Ceftriaxone	miR-146a mimic
Celecoxib	NRSE-seq decoy OdN
Curcumin	Parecoxib
Etoricoxib	Pentylenetetrazol
Ethosuximide	Rapamycin
Exercise	Sodium selenate
Enriched environment	Statins
Eslicarbazepine	Vigabatrin
Erythropoietin	VX-765+CyP
Fingolimod	WP1066
Fluoxetine	Zonisamide
Furosemide	1NMPP1
Hypothermia	1400W

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Cyclooxygenase
Celecoxib, Resveratrol
Gap Channels
Gap19
GABA Receptors
$GABA_A$
(-)-Bicuculline methochloride, Diazepam, Flupirtine, Furosemide, Ganaxolone, L-838,417, Muscimol, SR 95531
$GABA_B$
(*R*)-Baclofen, CGP 55845, Vigabatrin
Miscellaneous
Pentobarbital, RuBi-GABA, Valproic acid, sodium salt, Zonisamide,
GABA Transporters
Riluzole, (*S*)-SNAP 5114
Glutamate (Ionotropic) Receptors
AMPA
GYKI 52466, NBQX disodium salt
Kainate
CNQX disodium salt
NMDA
Felbamate, Memantine, (+)-MK 801
Glutamate (Metabotropic) Receptors
Group I
(*S*)-3,5-DHPG, MPEP, VU 0360172
Group II
LY 341495 disodium salt, LY 379268 disodium salt
Group III
CPPG
Glutamate Transporters
DL-TBOA, Ceftriaxone
HMG-CoA Reductase
Atorvastatin, Simvastatin
Na^+/Ca^{2+} Exchanger
SN-6
PPAR Receptors
GW 7647, Rosiglitazone
Translocation, Exocytosis & Endocytosis
Levetiracetam
Voltage-gated Calcium Channels
(±)-Bay K 8644, Gabapentin, Isradipine, Nefiracetam, Nitrendipine, Nilvadipine, Pregabalin
Voltage-gated Chloride Channels
CaCCinh-A01
Voltage-gated Potassium Channels
Retigabine, XE 991
Voltage-gated Sodium Channels
Carbamazepine, QX 314 chloride, Riluzole, Veratridine

Abbreviations
AD, Alzheimer's disease
EEG, electroencephalography
PD, Parkinson's disease
HD, Huntington's disease
Rx, treatment
SUDEP, sudden unexpected death
TBI, traumatic brain injury
QoL, Quality-of-life

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