UNDERSTANDING EPILEPSY: from the infected brain cells to seizures

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Learning objectives

- Describe the possible direct mechanisms leading to a stress of the neuron and its hyperexcitability during infection.
- Describe the possible indirect mechanisms, via glial cells, leading to a stress of the neuron and its hyperexcitability during infection.
- Explain neurochemical factors leading to epileptogenic patterns.
- Describe membrane and synapse involvement leading to epileptogenesis after an infectious stress of the brain.
Whatever the cause, when a group of neurons is, directly or indirectly stressed:

- Necrosis
- Apoptosis
- Disturbance

- Death

- Loss / Reduction of function(s)

- Hyperexcitability.
  - Exaggeration;
  - If synchronised
  - Seizure
Neuron & its environment

Direct attack of the neuron and consecutive reactions

Indirect attack of the neuron via microcytes and astrocytes and consecutive neuronal reactions

Neurone " pensant "
Astrocyte " intendant "
Astrocyte " pipelette "
Astrocyte " entretien "
Cellules " Sécurité "
Neurons & Glial cells

1. Oligodendrocyte / cell. Schwann
2. Microglie
3. Astrocyte / cell. satellite
4. Cellule épendymale
MICROCYTES

✓ Derived from blood monocytes
✓ Synthèse de cytokines
✓ Production of excitatory Glutamate-like substances.
  i.e.: during Brain-HIV.
  No neuron CD-4 receptor
Protective or stressful co-operation

ASTROCYTES

Cytokines Inductors

MICROGLIA

Gliosis

Production of cytokines

Immune reaction

Adherence

Demyelination

BBB Rupture

Inflammation + fever

TNF-α
Disturbed Neuronal Environment via microcytes and Astrocytes

• **Ionic balance**
  – Accumulation of $K^+$
  – Membrane $Na^+\/K^+$ ATPase
  – $+$ Ion passive transport

• **Acido-basic homeostasis, pH**
  Intra-Astrocyte alcaline environment;
  Intra-Neuron and extracellular acid environment

• **Regulation of extracellular environment**
  Astrocyte swelling
  $\rightarrow$ brain swelling and suffering
If disturbed, the neurons suffer
EPILEPTOGENESIS

Neurobiological Factors
- Unbalance
  - Membranes
  - VD Ion Channels
- Synapses
  - LD ionic channels
  - GABA (inhibition)
  - Glutamate (excitation)

Electrophysiological Consequences
- Hyperexcitability
- Hypersynchronism
- Epileptic discharges

Clinical Consequences
- Seizure
Physiopathology of seizure

Ionic Channels: Hyperexcitability

Synapses: Amplification of signal

Neuronal Networks: Hypersynchronism
Genes mutations in many epileptic syndromes i.e. BFNS, FC+, JME

Voltage Dependant Channels

Na+, K+, Ca++

Ligand Dependant Channels

Cl-

POTENTIAL PREDISPOSING GENETIC FACTORS LEADING TO HYPERSENSITIVE MEMBRANES
Glutamatergic Neurotransmission

3 Types of receptors
1) AMPA/KA  2) NMDA  3) Metabotropic
Synapse receptors

Excitatory: AMPA, NMDA, Kainate...

Inhibitory: GABA-A...

Modulators: mGluR...
GABA-B...

Channel Receptors
Metabotropic Receptors
MECHANISMS of EXCITOTOXICITY
Role of intra-neuronal Ca++

**Increased production of Glutamate or Glu-like**

- Ka/AMPA receptors
- NMDA receptors
- Metabotropic receptors

**Increased production of Glutamate or Glu-like**

- Na+
- Osmotic stress
- Ions entry
- Mitochondries
- Proteine kinase
- Protease
- Lipase
- NO synthase
- Endonuclease
- Membrane Phospholipids
- NO
- Free Radicals

**Neuronal Stress**

- Lysis
- Synaptic transmission
- Cytoskeleton
- Neuronal Necrosis or Apoptosis
- Early Genes
- Neuronal Necrosis or Apoptosis
- Seizure?
ROLE of GLUTAMATE and GLUTAMATE-Like PRODUCTS

EARLY RESPONSE
Glutamate receptors, Ca\(^{++}\), AMPc, Kinase, Early genes, Transcription factors, Modified cell functionning

Hyperexcitability + Synchronisation

LATE RESPONSE
Chimiokines, cytokines, membranes lipids
Neurones
Neurotrophines
Neurogenesis
Reosynaptogenesis
Survival
TNF \(\alpha\), IL1\(\beta\), NFk \(\beta\)

Toxicity
Neuronal death
MICROGLIA
ASTROCYTES

Inflammatory reaction

Glial reaction

i.e. FC \(\rightarrow\) Temporal lobe
Epilepsy

Templar lobe
Epilepsy
Unbalance status

INHIBITION vs EXCITATION

GABA / GLUTAMATE
Neurons

Network
Leading to seizures

Generalised

Focal
MANAGEMENT: the infection + the seizures
Infectious particles attack either the neurons (if possible), or the glial cells, finally leading to neuronal death or stress;

Normally the astrocytes and the microcytes co-operate for protecting the neurons. But when they are outdated, they become the source of an epileptogenic process.

Glutamate and glutamate-like substances are overexpressed or produced during an infectious stress and lead to unbalanced status between excitatory and inhibitory Neurotransmitters.

Ca$^{++}$ and other ions abnormal flux is the final result of all these disturbances and the shutter of abnormal epileptogenic spikes.
Baldy-Moulinier M et al; Physiopathology of epilepsy, Ann Fr Anesth Reanim, 2001; 20:97-107


Hult B et al; Neurobiology of HIV; Int Rev Psych, 2008, 1, 3-13

ILAE Classification, 2017; ilae.org