TC Epilepsy – WCN 2019

UNDERSTANDING EPILEPSY:
from the infected brain cells to seizures

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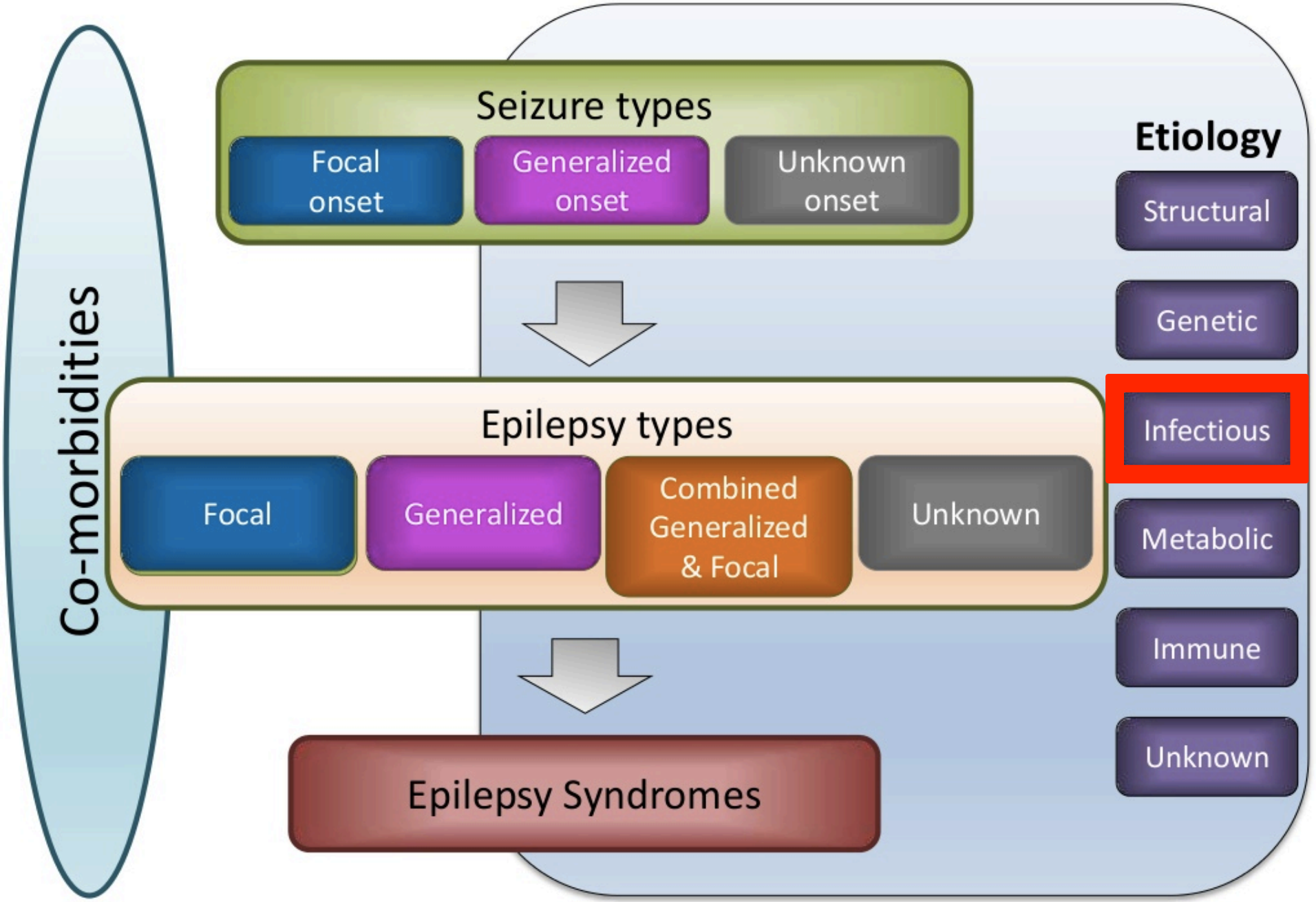
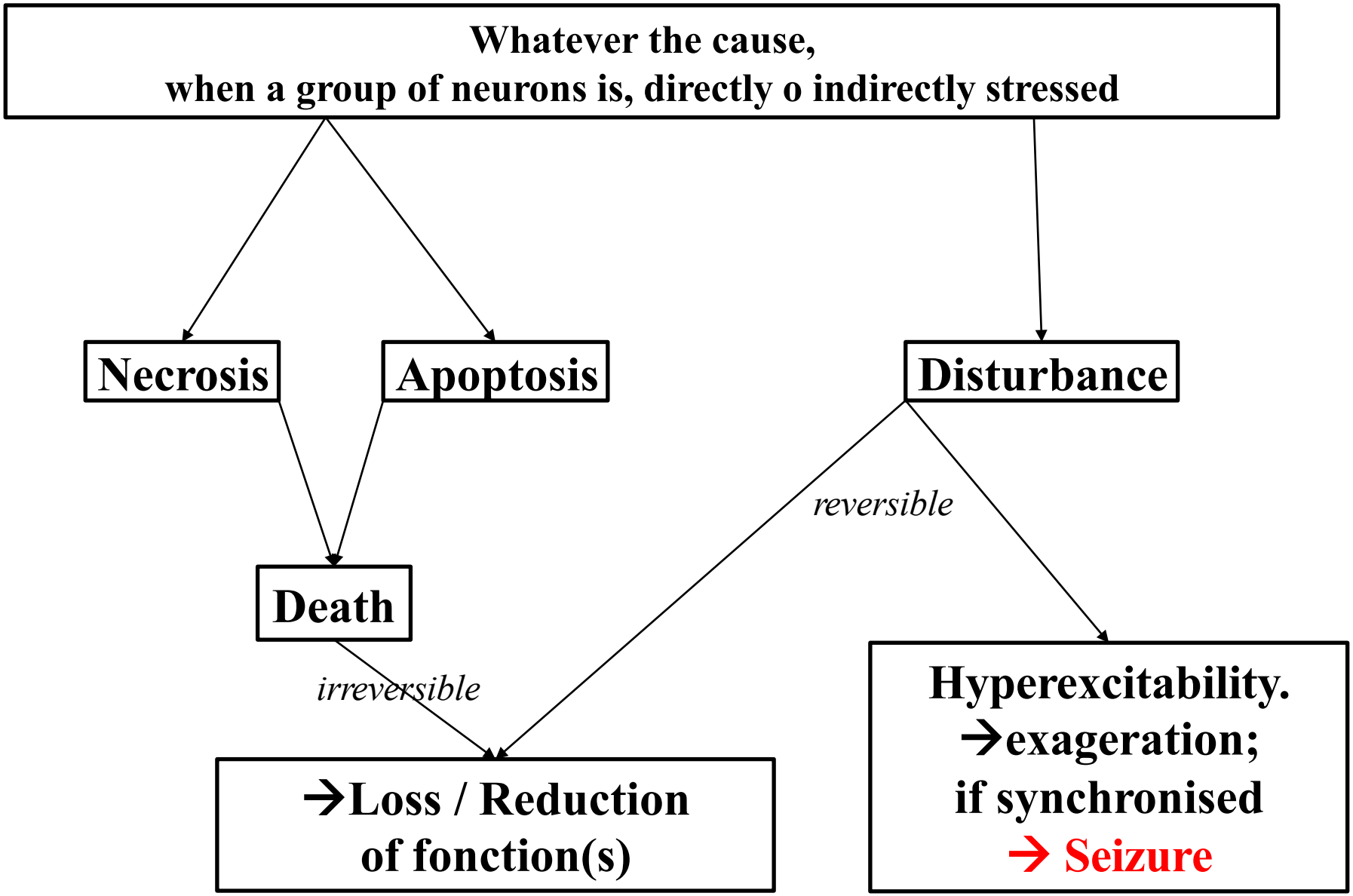
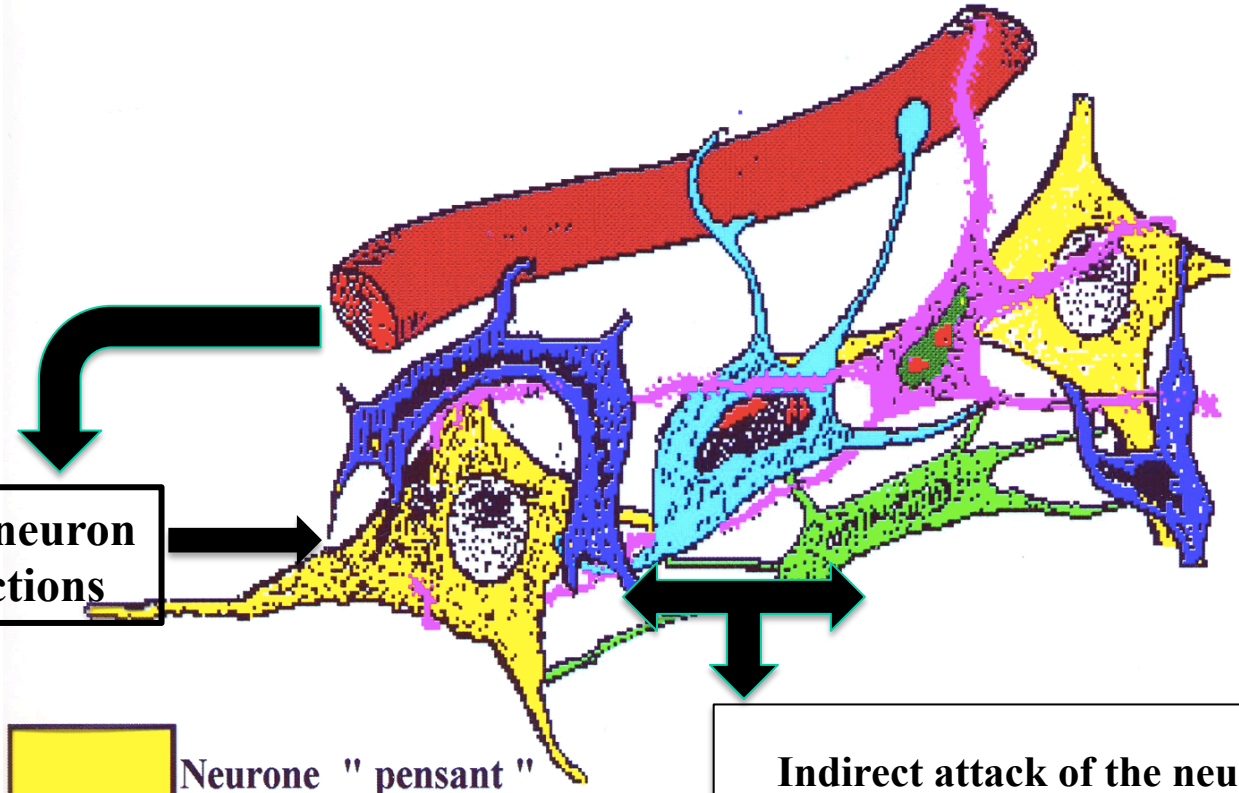
Learning objectives

- 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


Co-morbidities
Seizure types
Focal onset
Generalized onset
Unknown onset
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes


Whatever the cause,
when a group of neurons is, directly o indirectly stressed
Necrosis
Apoptosis
Disturbance
reversible
Death
irreversible
Hyperexcitability.
→exageration;
if synchronised
→ Seizure
→Loss / Reduction
of fonction(s)

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 "

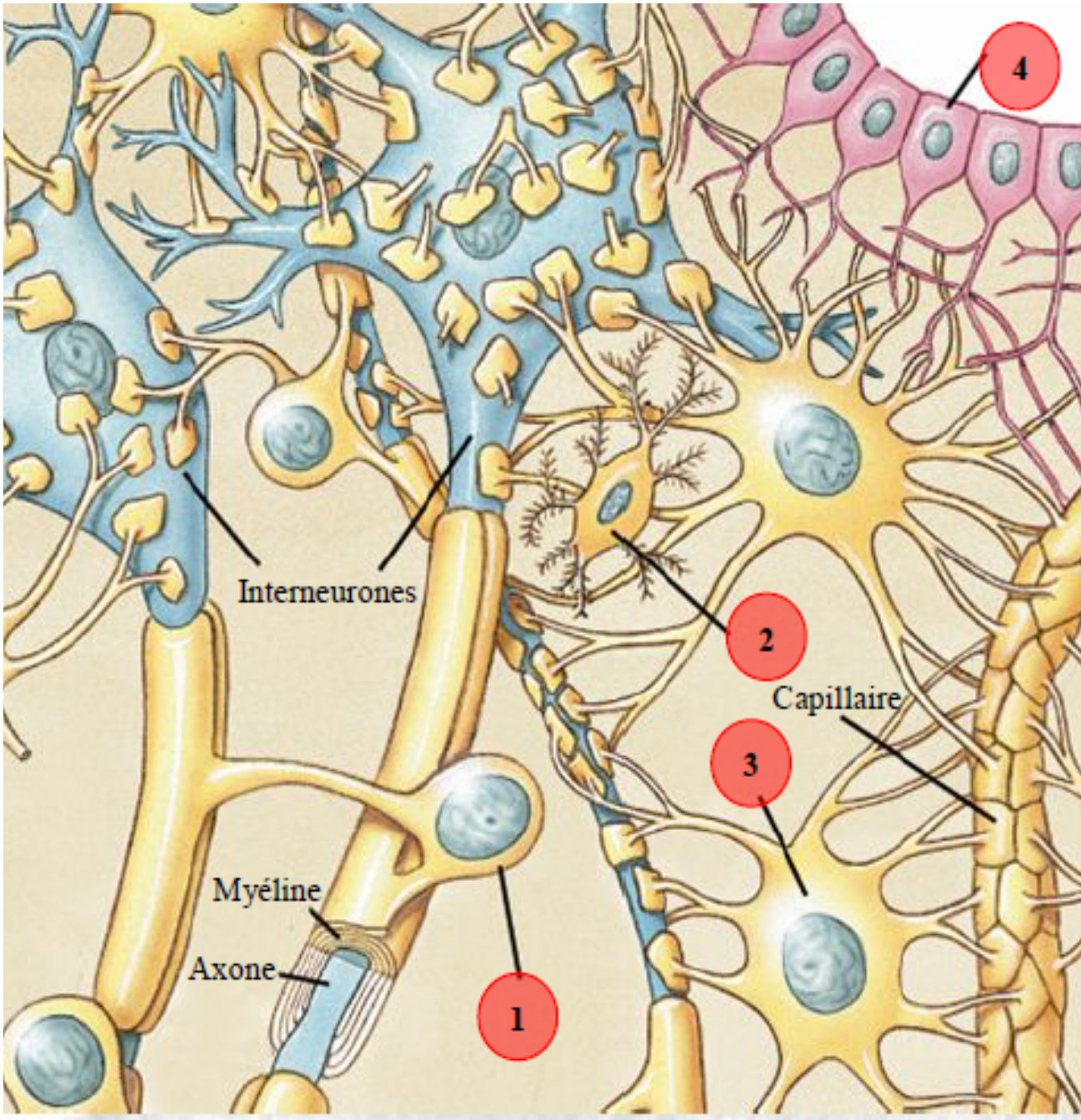
Astrocyte " pipelette "

Astrocyte " entretien "

Cellules " Sécurité "

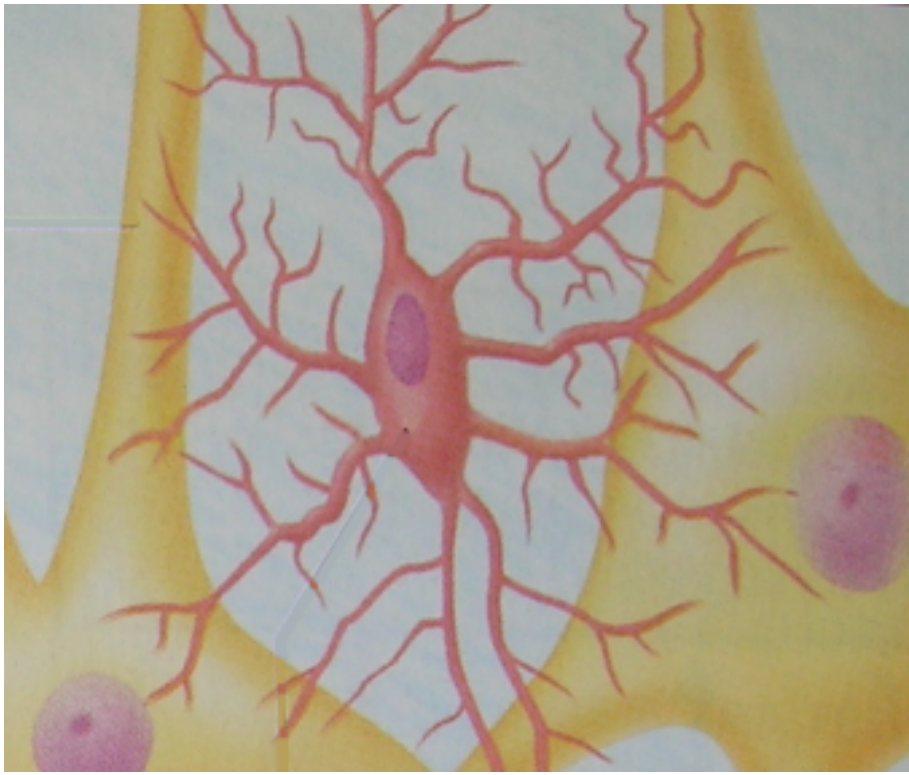
Neurons & Glial cells

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

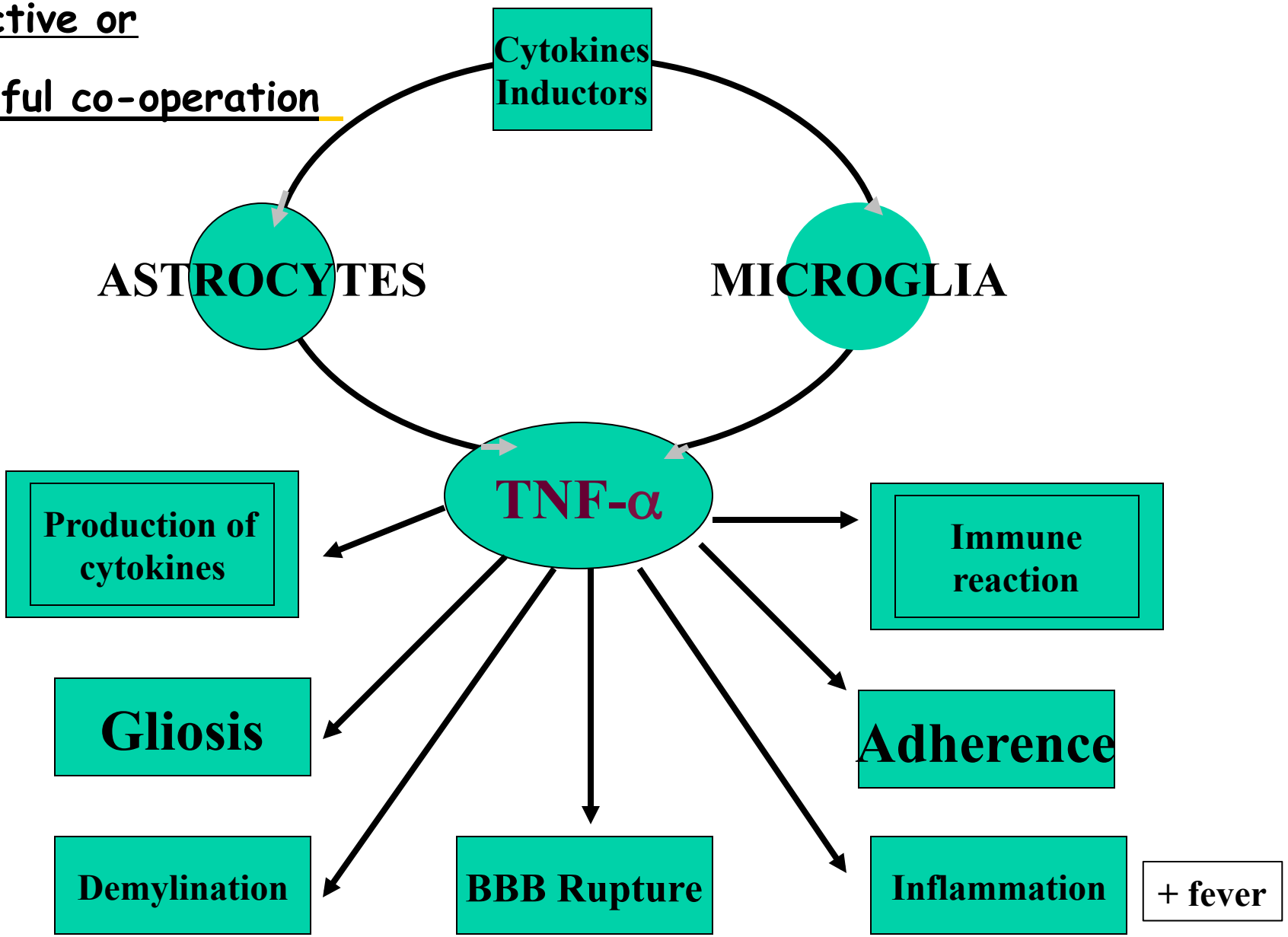


MICROCYTES

- ✓ **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



Disturbed Neuronal Environment via microcytes and Astrocytes

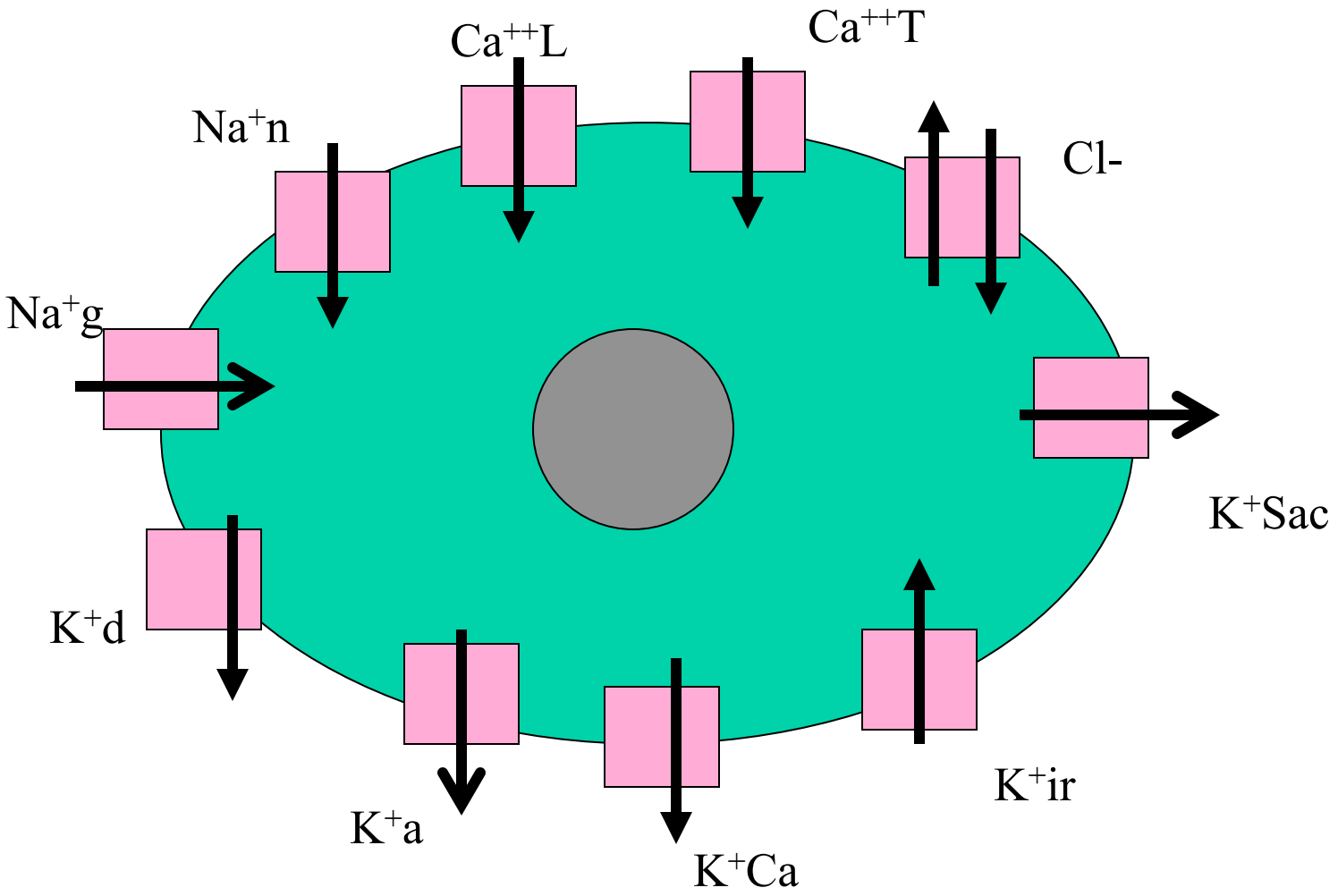
- **Ionic balance**
  - Accumulation of K^+
  - Membrane Na^+/K^+ ATPase
  - + Ion passive transport
- **Acido-basic homeostasis, pH**

  Intra-Astrocyte alcaline environment;
  Intra-Neuron and extracellular acid environment
- **Regulation of extracellular environment**

  Astrocyte swelling

  → brain swelling and suffering

ASTROCYTES membrane ion channels



If disturbed, the neurons suffer

EPILEPTOGENESIS

Neurobiological **Factors**

Electrophysiological **Consequences**

Clinical

Unbalance

- Membranes

VD Ion Channels

- Synapses

LD ionic channels

GABA (inhibition)

Glutamate (excitation)

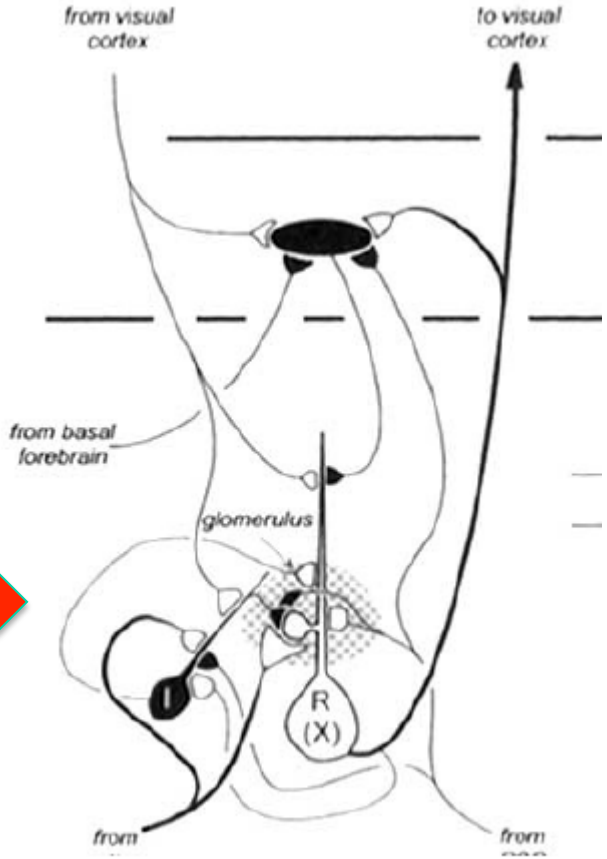
Hyperexcitability
Hypersynchronism

Epileptic discharges

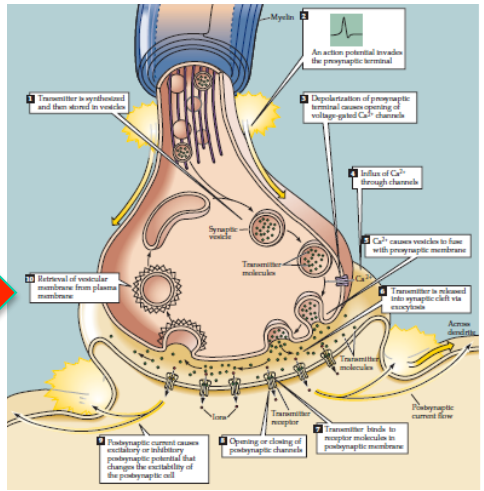
Seizure

Physiopathology of seizure

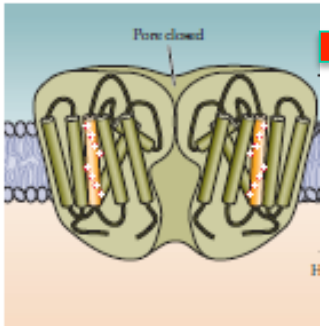
Neuronal Networks:
Hypersynchronism



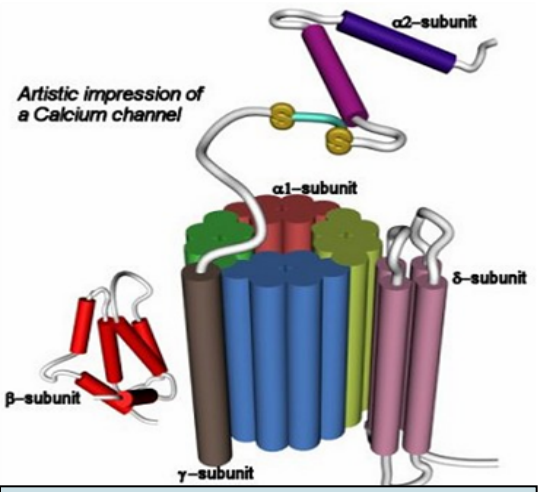
Synapses:
Amplification of signal



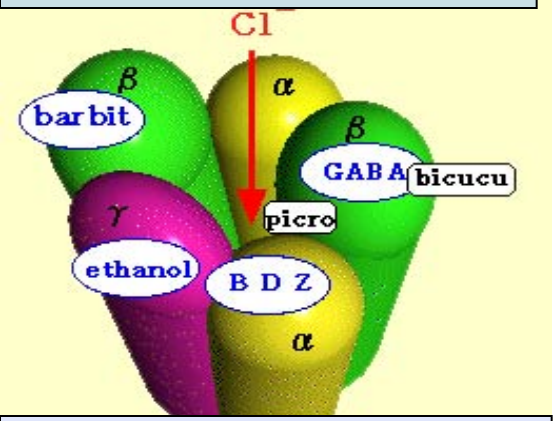
Ionic Channels:
Hyperexcitability



POTENTIAL PREDISPOSING GENETIC FACTORS LEADING TO HYPERSENSITIVE MEMBRANES



Ca++ Channel



Chloride Channel

Genes mutations in many epileptic syndromes
i.e. BFNS, FC+, JME

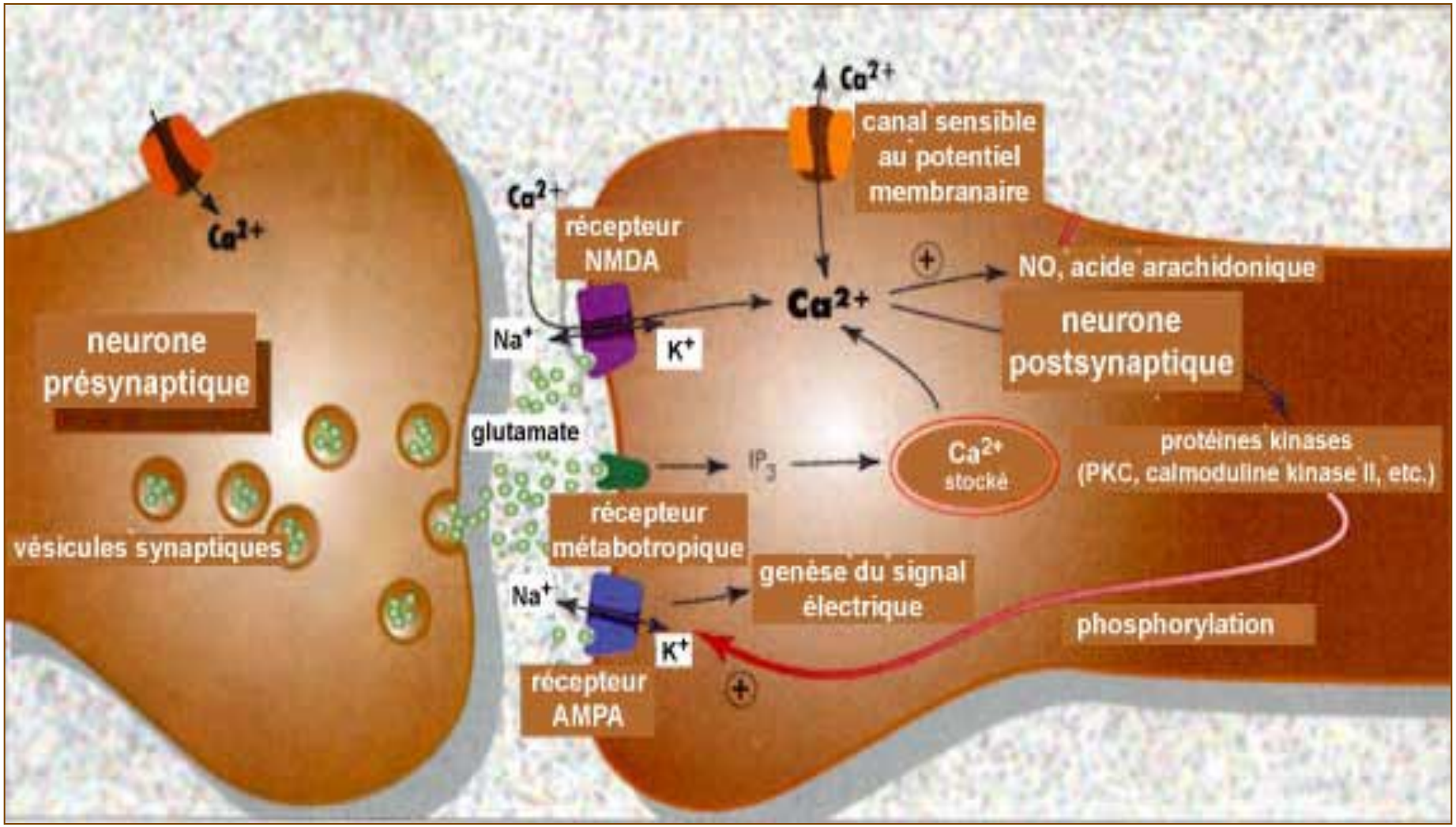
Voltage Dependant Channels

Na+, K+, Ca++

CANALOPATHIES

Ligand Dependant Channels
Cl-

Glutamatergic Neurotransmission



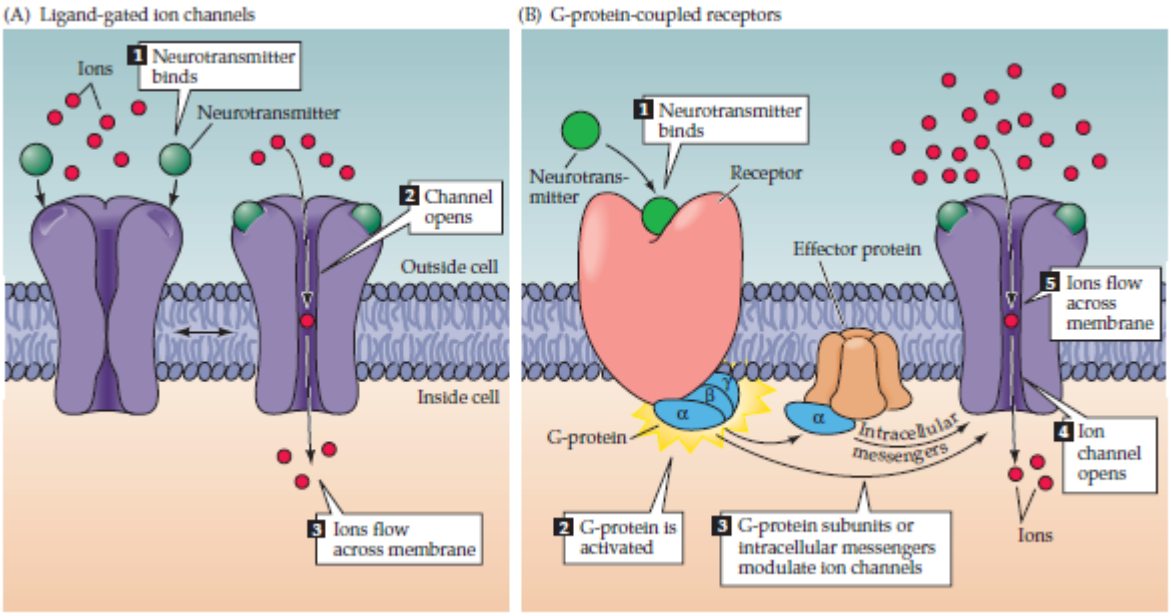
3 Types of receptors

1) AMPA/KA 2) NMDA 3) Metabotropic

Synapse receptors

Excitatory:
AMPA,
NMDA,
Kainate…

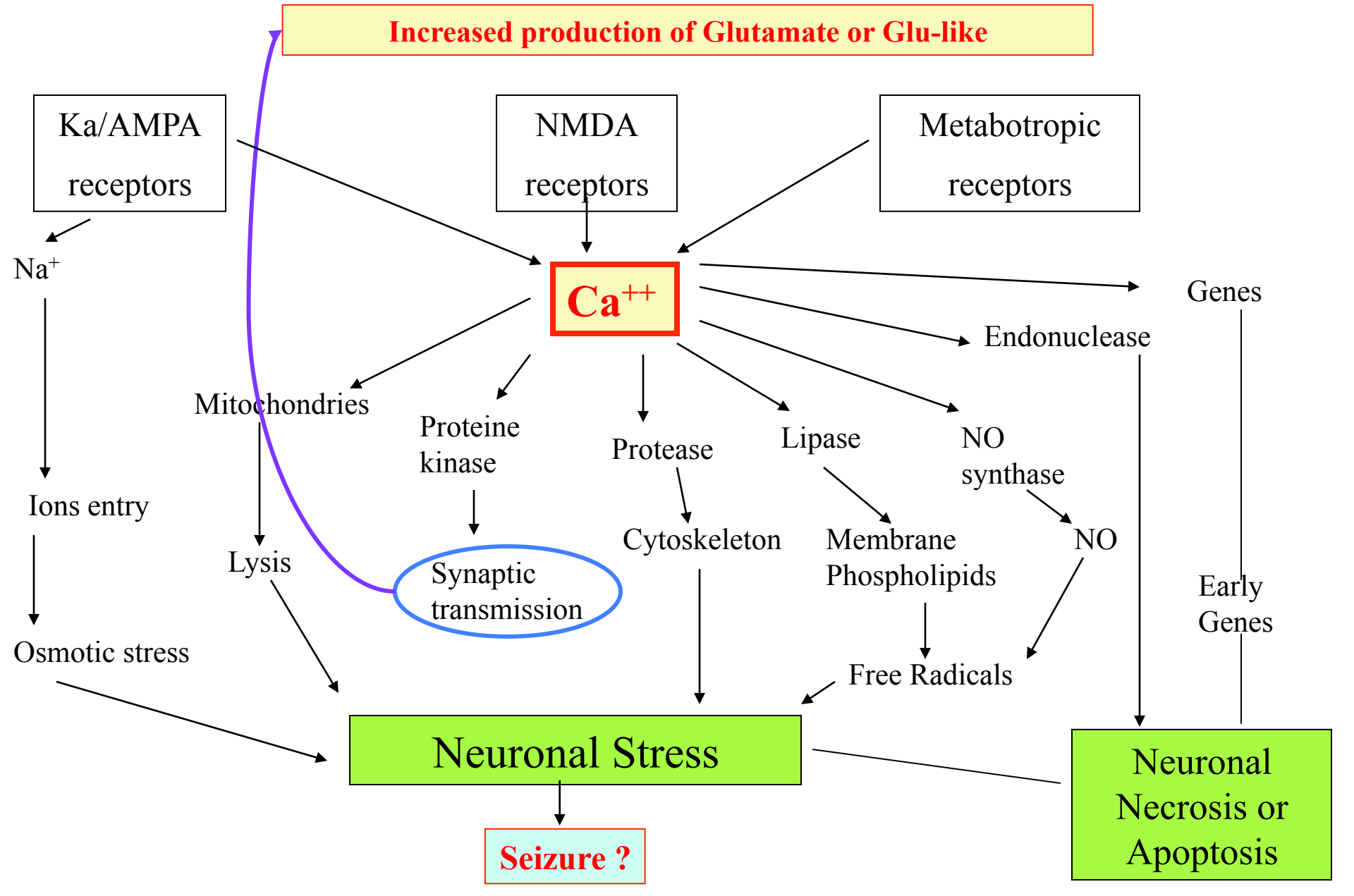
Inhibitory:
GABA-A…



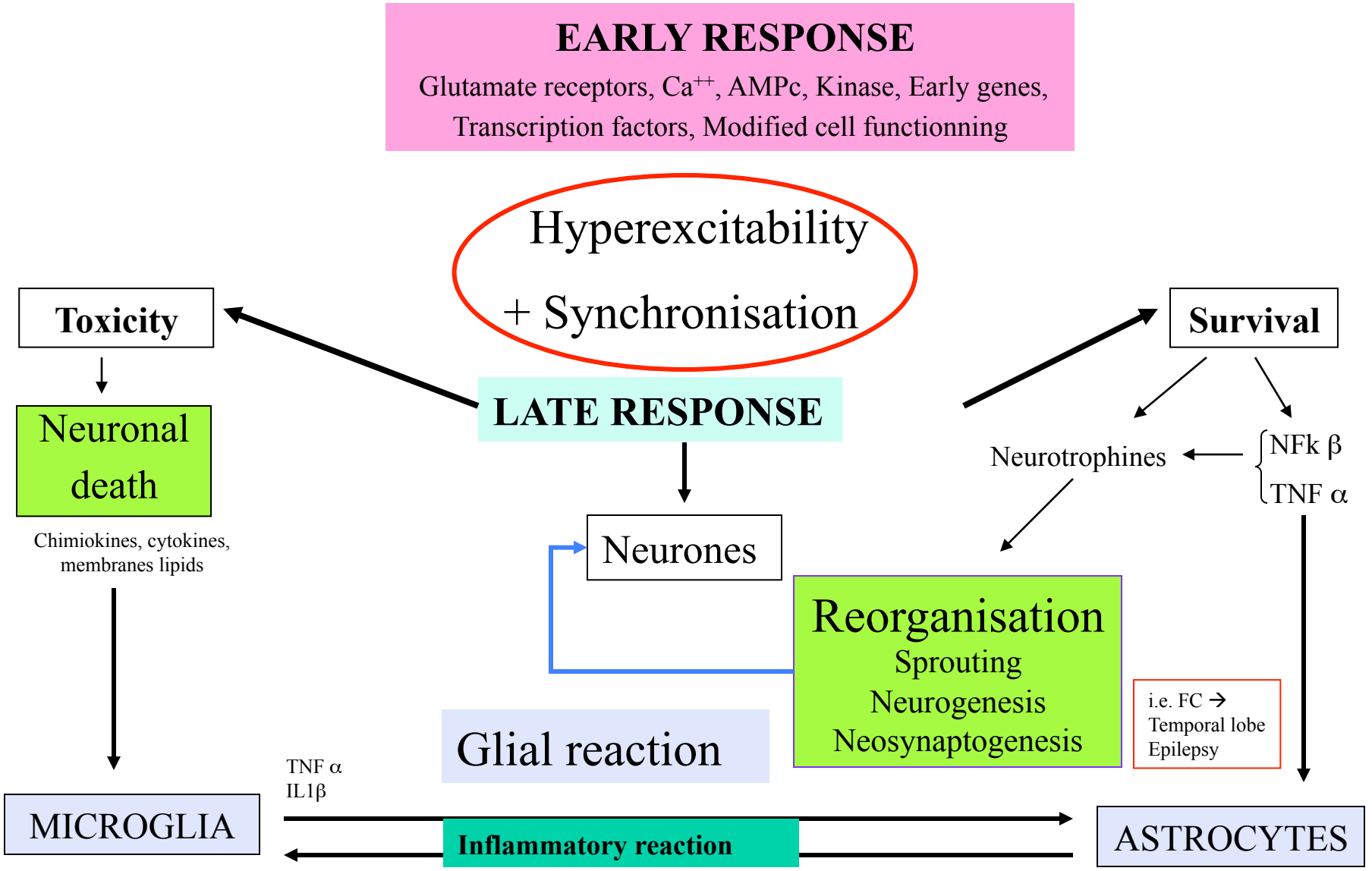
Channel Receptors **Metabotropic Receptors**

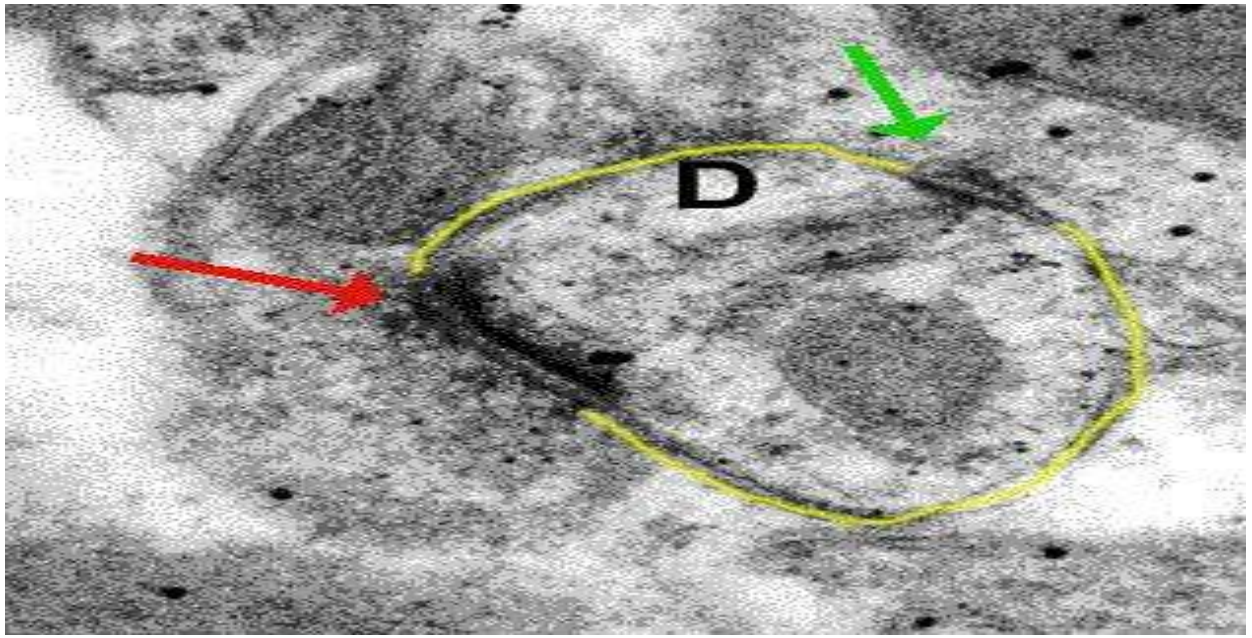
Modulators:
mGluR…
GABA-B…

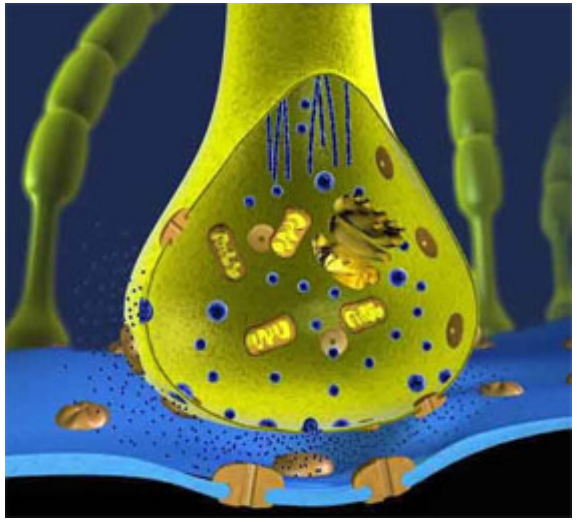
MECHANISMS of EXCITOTOXICITY
Role of intra-neuronal Ca^{++}



ROLE of GLUTAMATE and GLUTAMATE-Like PRODUCTS



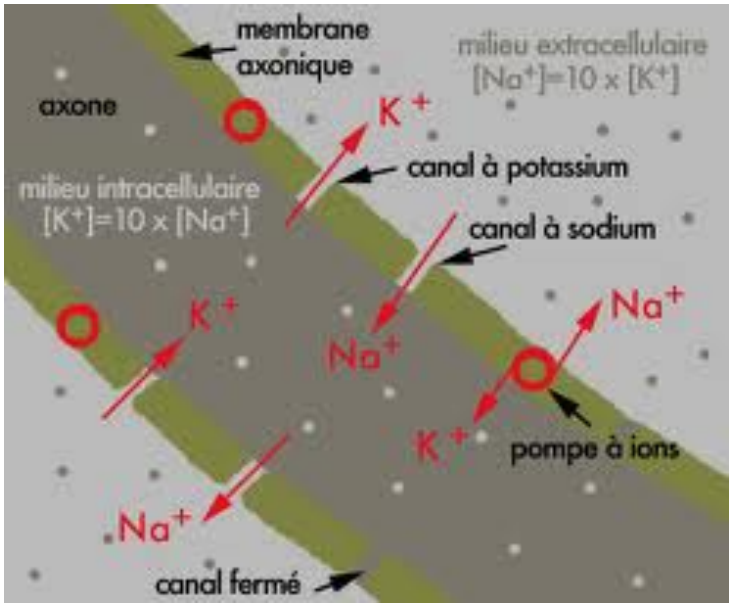




Unbalance status

INHIBITION vs EXCITATION

GABA / GLUTAMATE

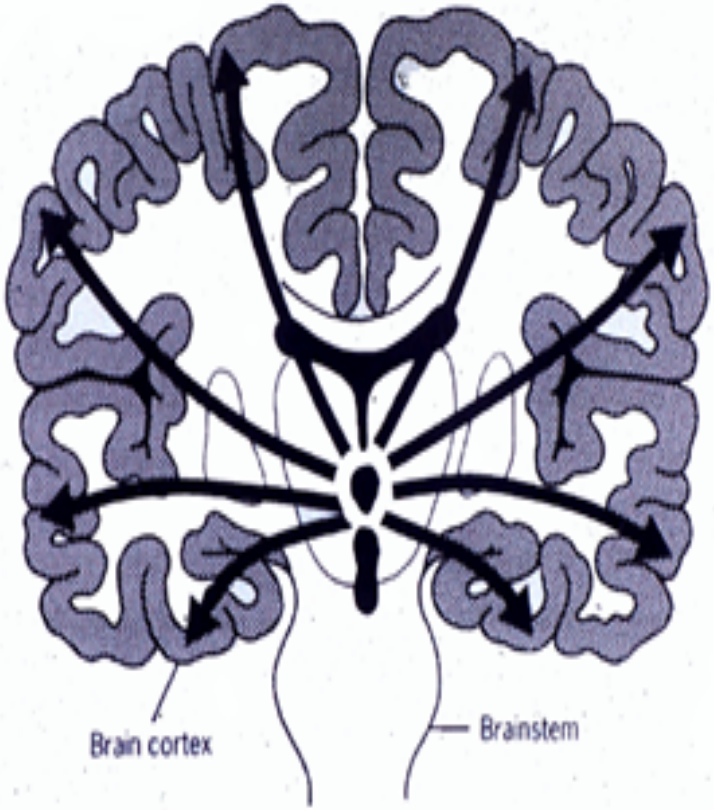


Neurons

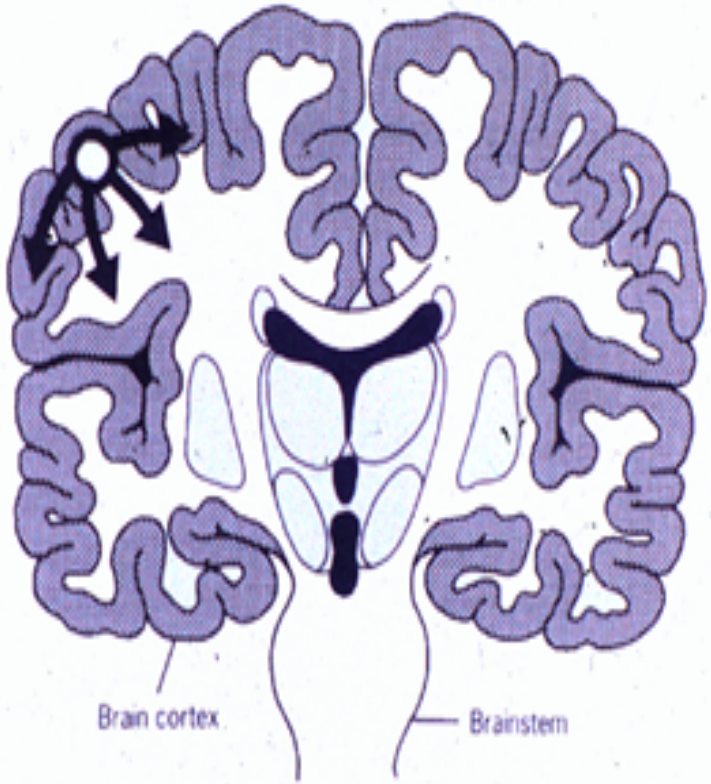
Network

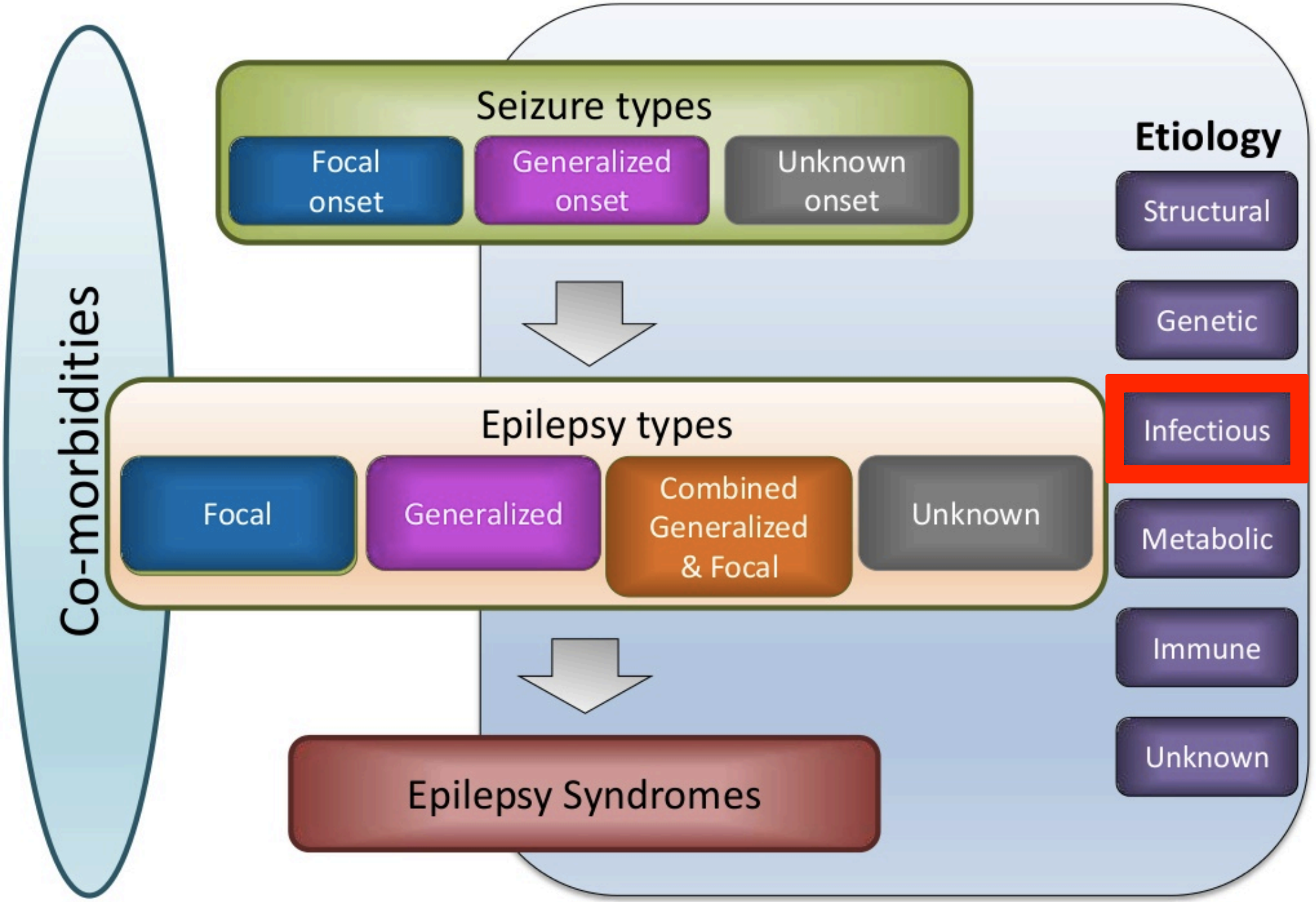
Leading to seizures

Generalised



Focal

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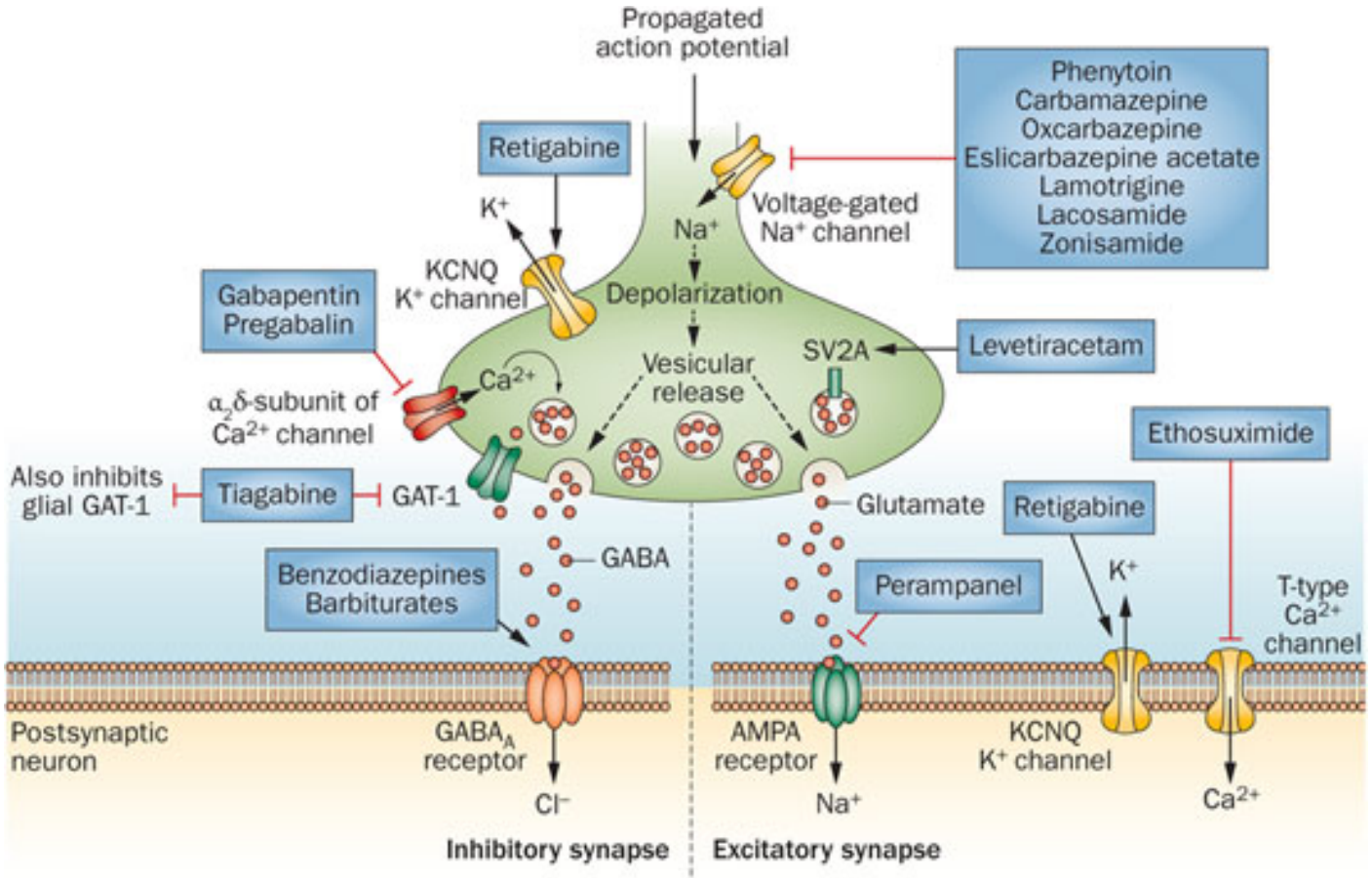
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes

MANAGEMENT: the infection + the seizures



Not illustrated:

- Vigabatrin → ↓ GABA degradation

and drugs with multiple mechanisms:

- Valproate → ↑ GABA turnover, ↓ Na^+ channels, ↓ NMDA receptors
- Topiramate → ↓ Na^+ channels, ↓ AMPA/kainate receptors, ↑ $GABA_A$ receptors
- Felbamate → ↓ Na^+ channels, ↑ $GABA_A$ receptors, ↓ NMDA receptors

Key Messages

- 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 subtances 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

References

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