Are There Sharing Mechanisms of Epilepsy, Migraine and Neuropathic Pain?

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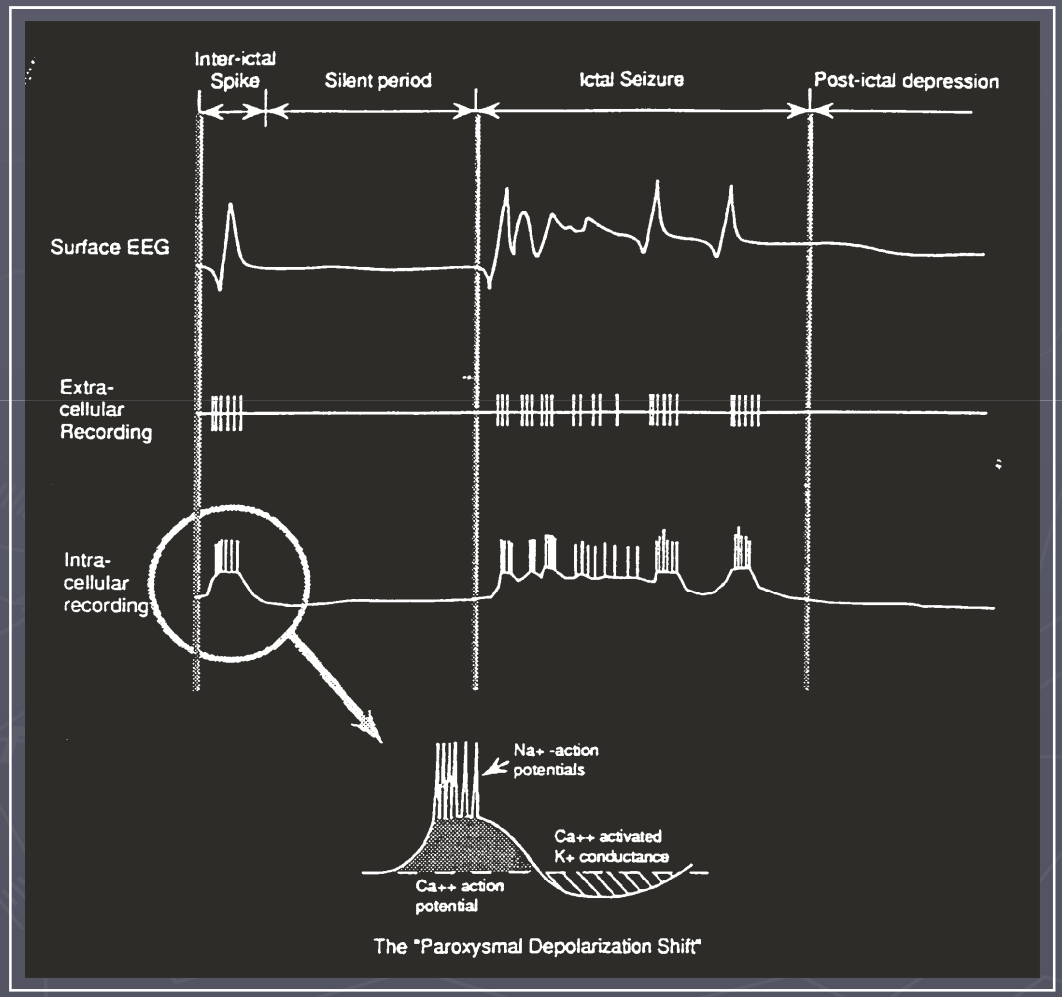
Basic mechanisms underlying seizures and epilepsy

- Seizure: the clinical manifestation of an abnormal and excessive excitation and synchronization of a population of cortical neurons
- Epilepsy: a tendency toward recurrent seizures unprovoked by any systemic or acute neurologic insults
- Epileptogenesis: sequence of events that converts a normal neuronal network into a hyperexcitable network

Cellular mechanisms of seizure generation

- Excitation (too much)
  - Ionic—inward Na^{+}, Ca^{++} currents
  - Neurotransmitter—glutamate (AMPA, NMDA)
- Inhibition (too little)
  - Ionic—inward Cl^{-}, outward K^{+} currents
  - Neurotransmitter—GABA

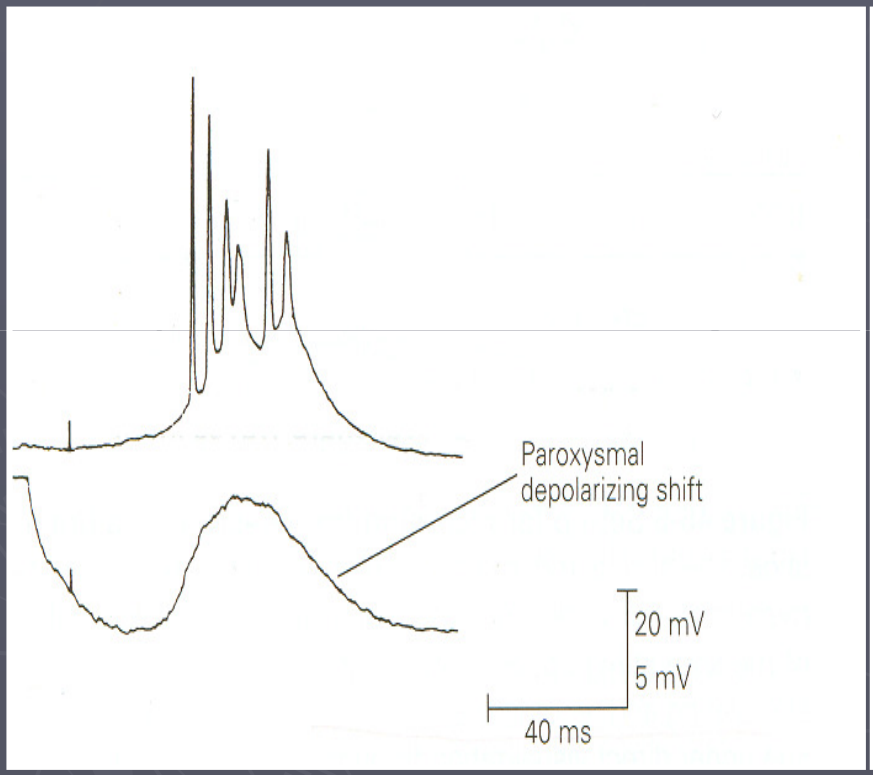
The "Interictal Spike and Paroxysmal Depolarization Shift (PDS)"

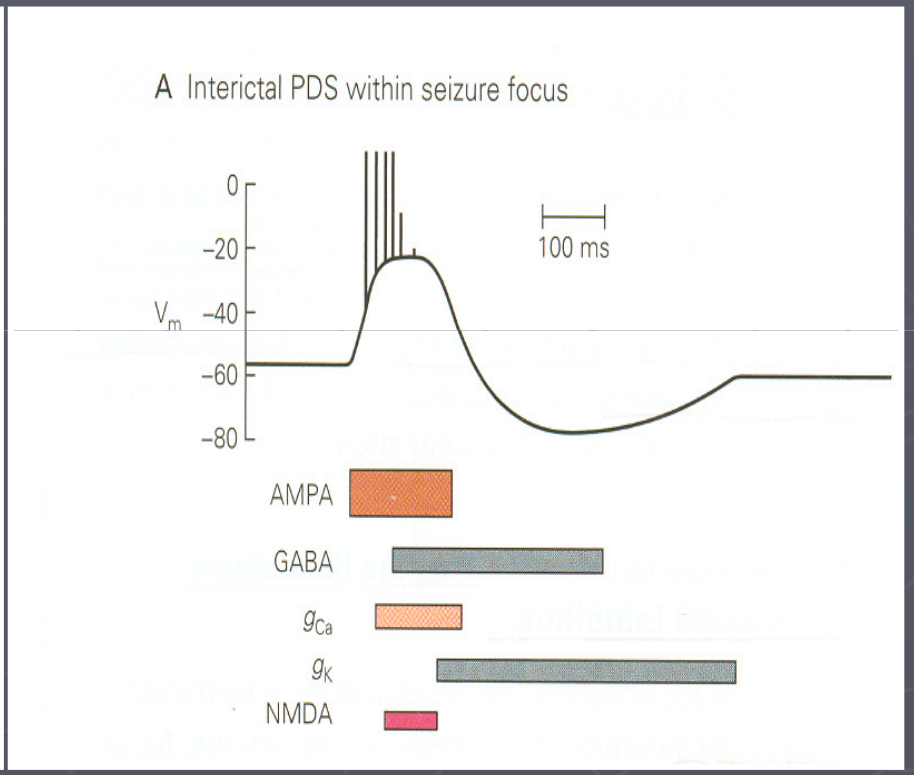


Ayala et al., 1973

Intracellular and extracellular events of the PDS underlying the interictal epileptiform spike detected by surface EEG

Paroxysmal depolarizing shift (PDS)

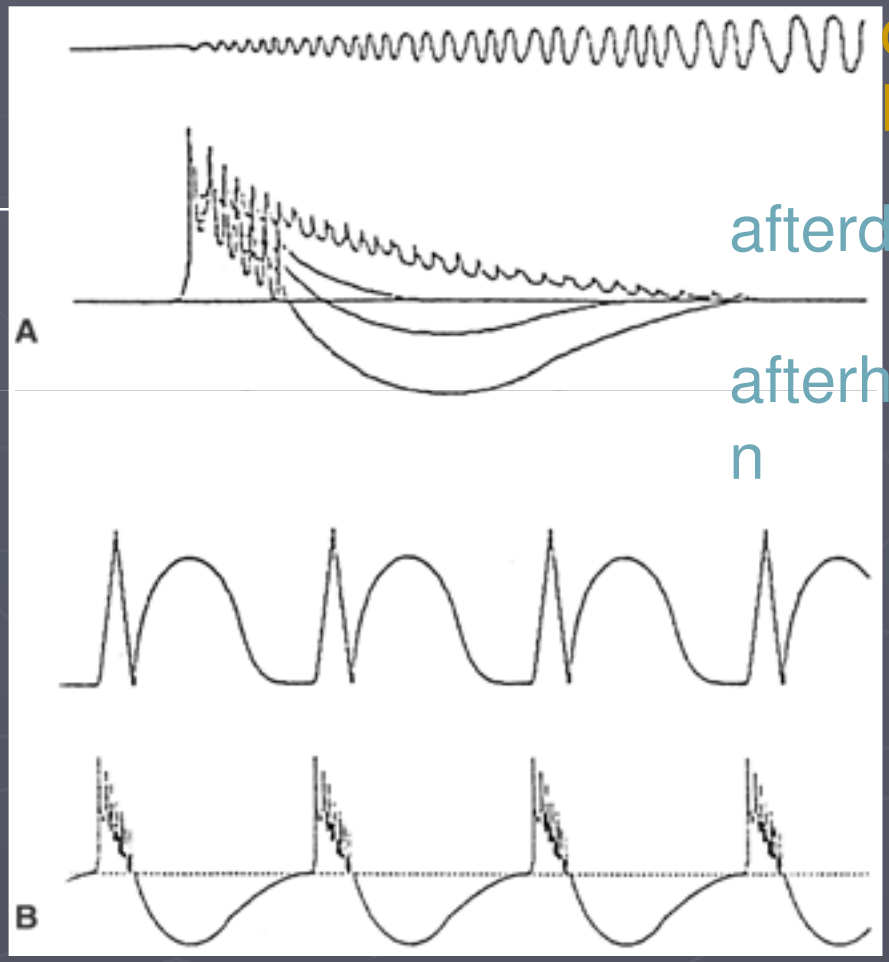




PNAS 2002; *Adv Neurol* 1986

Paroxysmal depolarizing shift (PDS)

Paroxysmal depolarizing shift



development of hypersynchrony

afterdepolarization

afterhyperpolarization

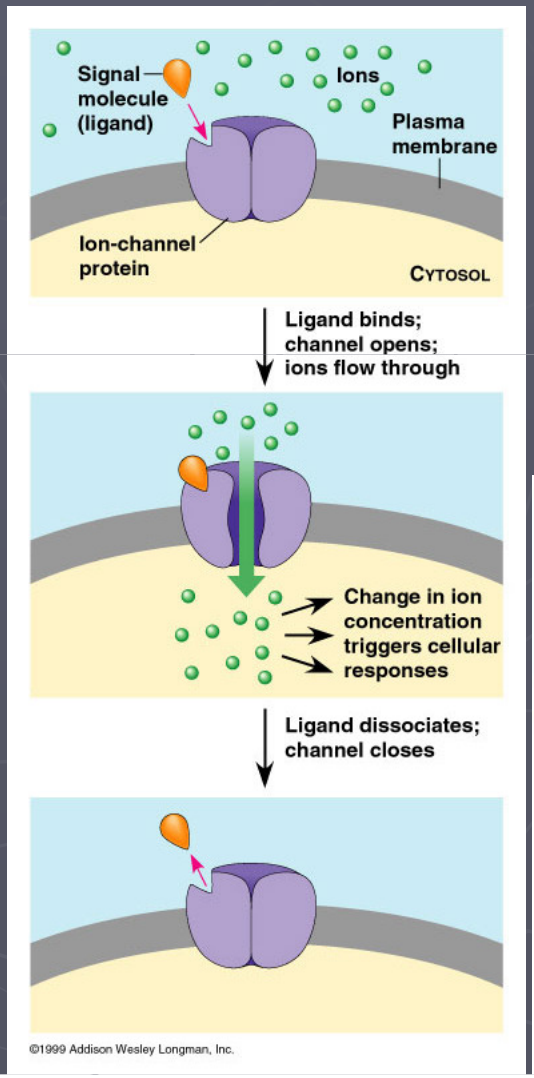
Spike-and-wave discharge

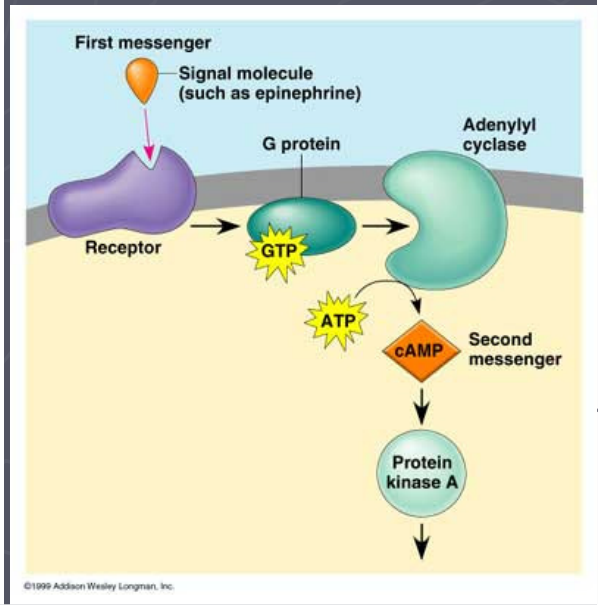
Recurrent depolarizations

Electroencephalogr Clin Neurophysiol 1990

Neuronal (Intrinsic) factors modifying neuronal excitability

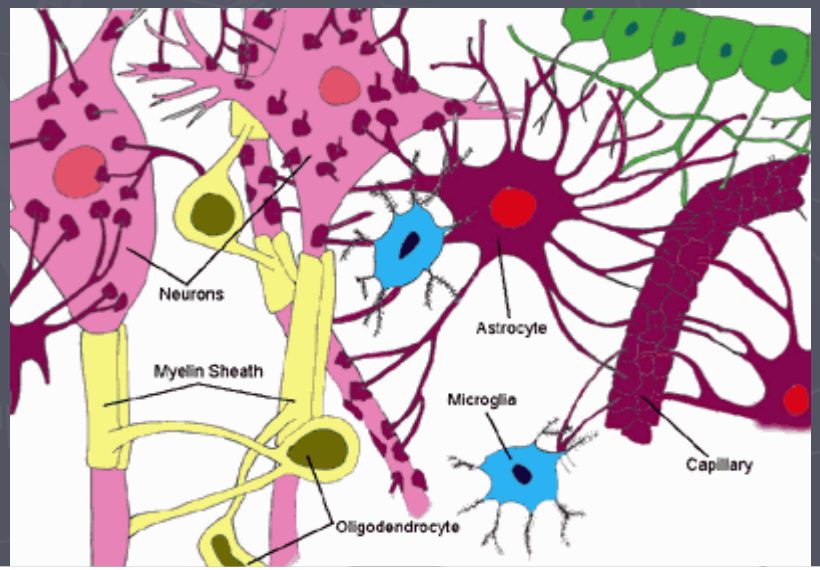
- Ion channel type, number, and distribution
- Biochemical modification of receptors
- Activation of second-messenger systems
- Modulation of gene expression

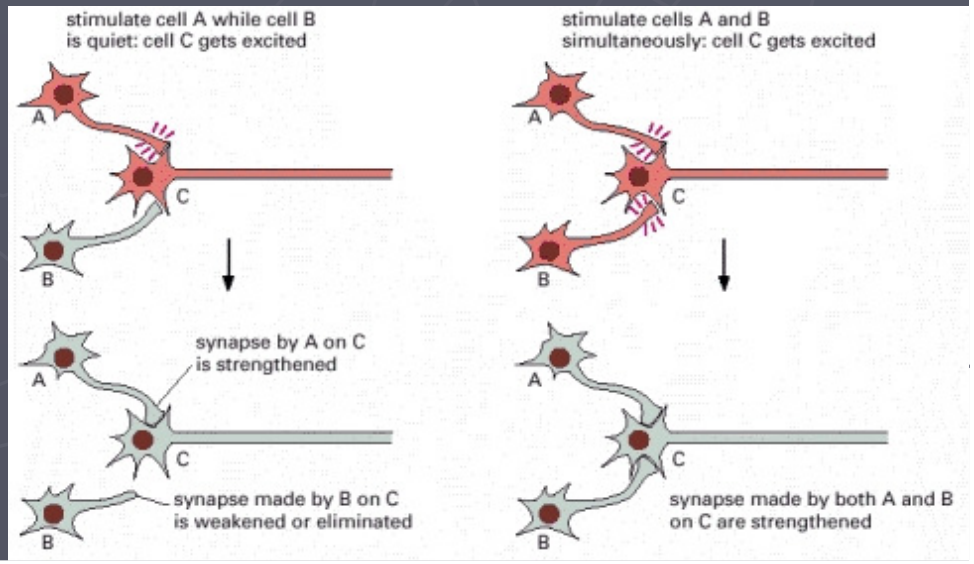




Extra-neuronal (extrinsic) factors modifying neuronal excitability

- Changes in extracellular ion concentration
- Remodeling of synapse location or configuration by afferent input
- Modulation of transmitter metabolism or uptake by glial cells

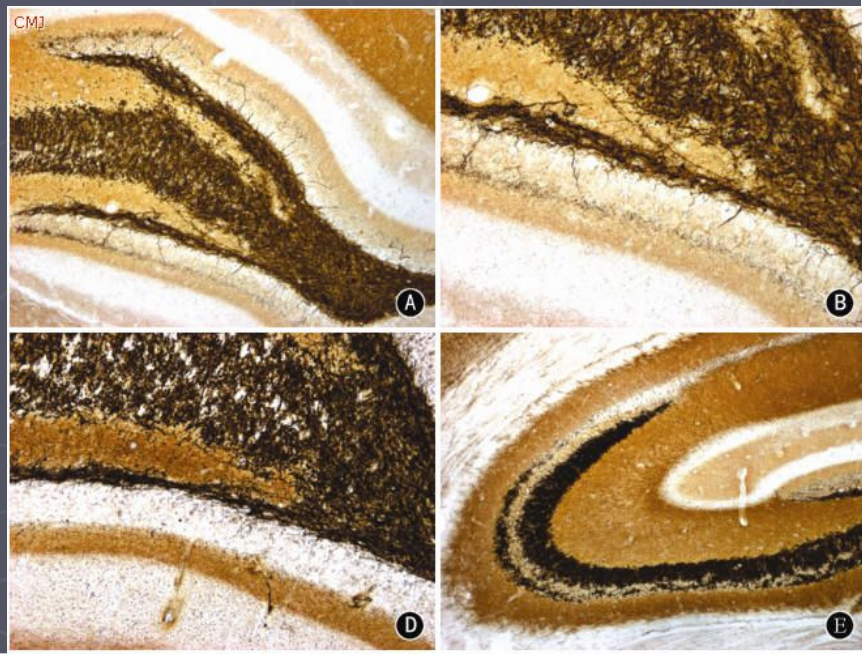




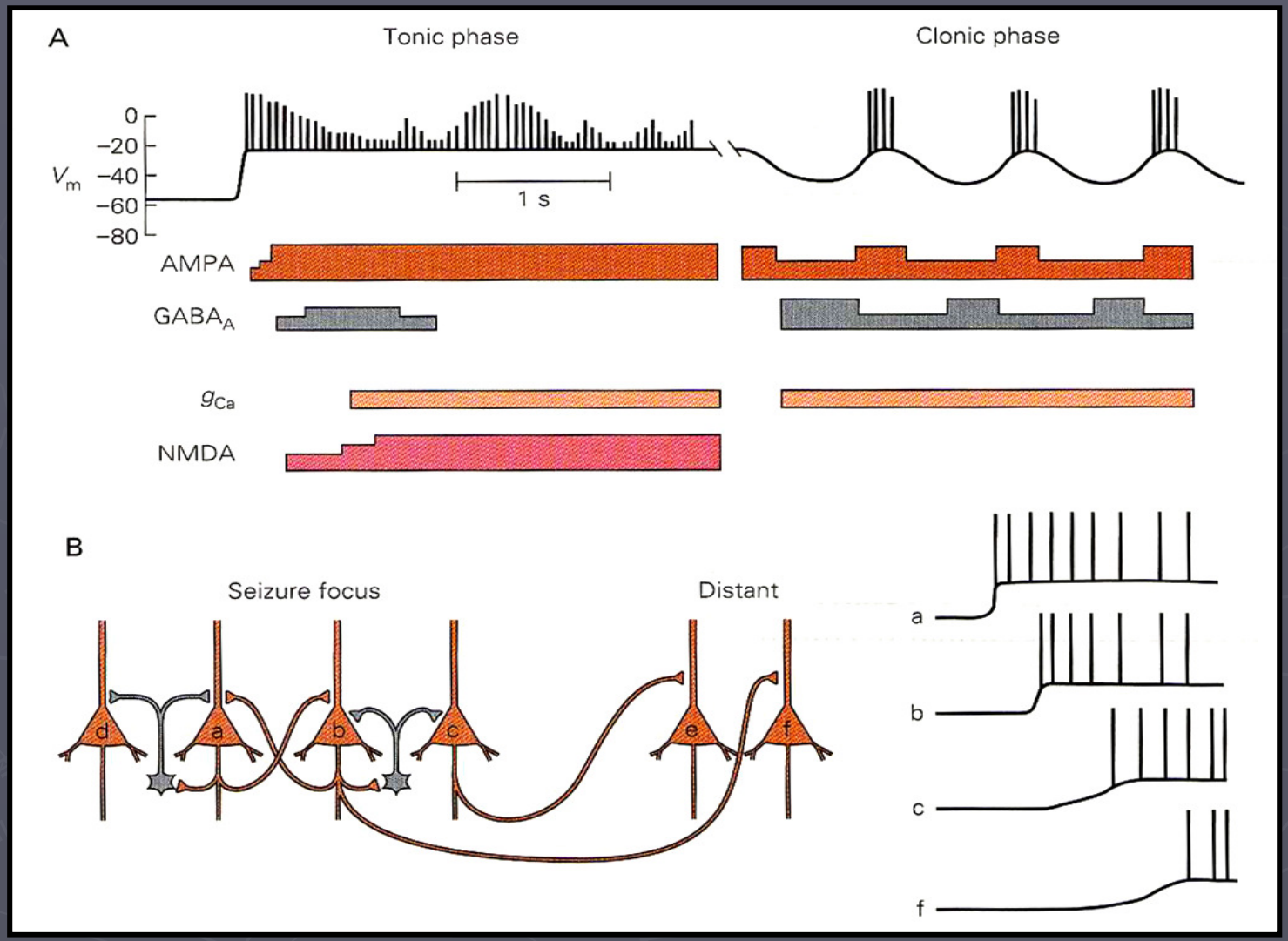
Mechanisms of generating hyperexcitable networks

- Excitatory axonal "sprouting"
- Loss of inhibitory neurons
- Loss of excitatory neurons "driving" inhibitory neurons

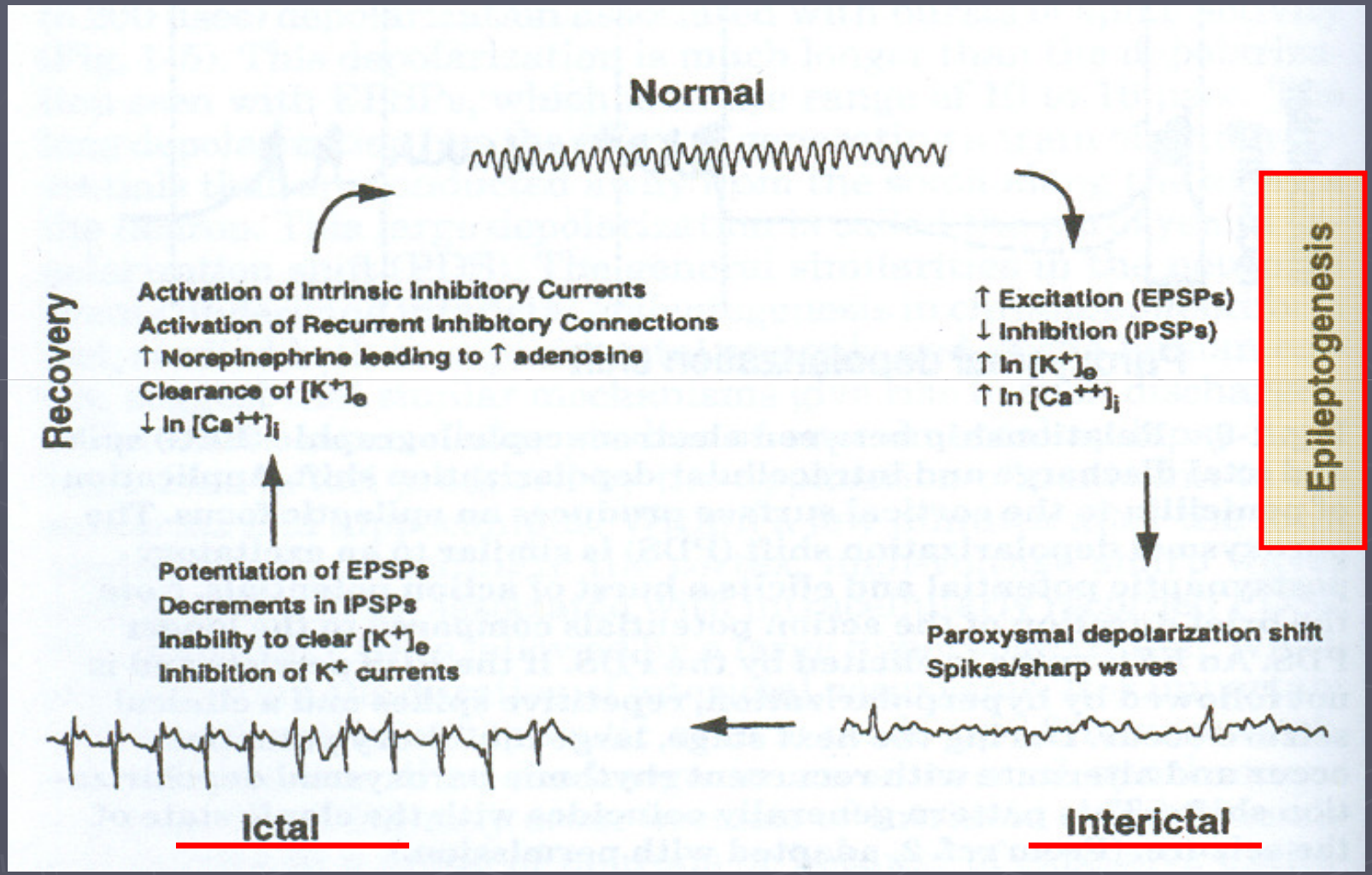
Xu et al., 2006



Loss of the afterhyperpolarization and surround inhibition accompanies the onset of a partial seizure



Interictal and ictal events



Intern Pediatr 1996; *The treatment of epilepsy* 2005

Neuropathic pain disorders

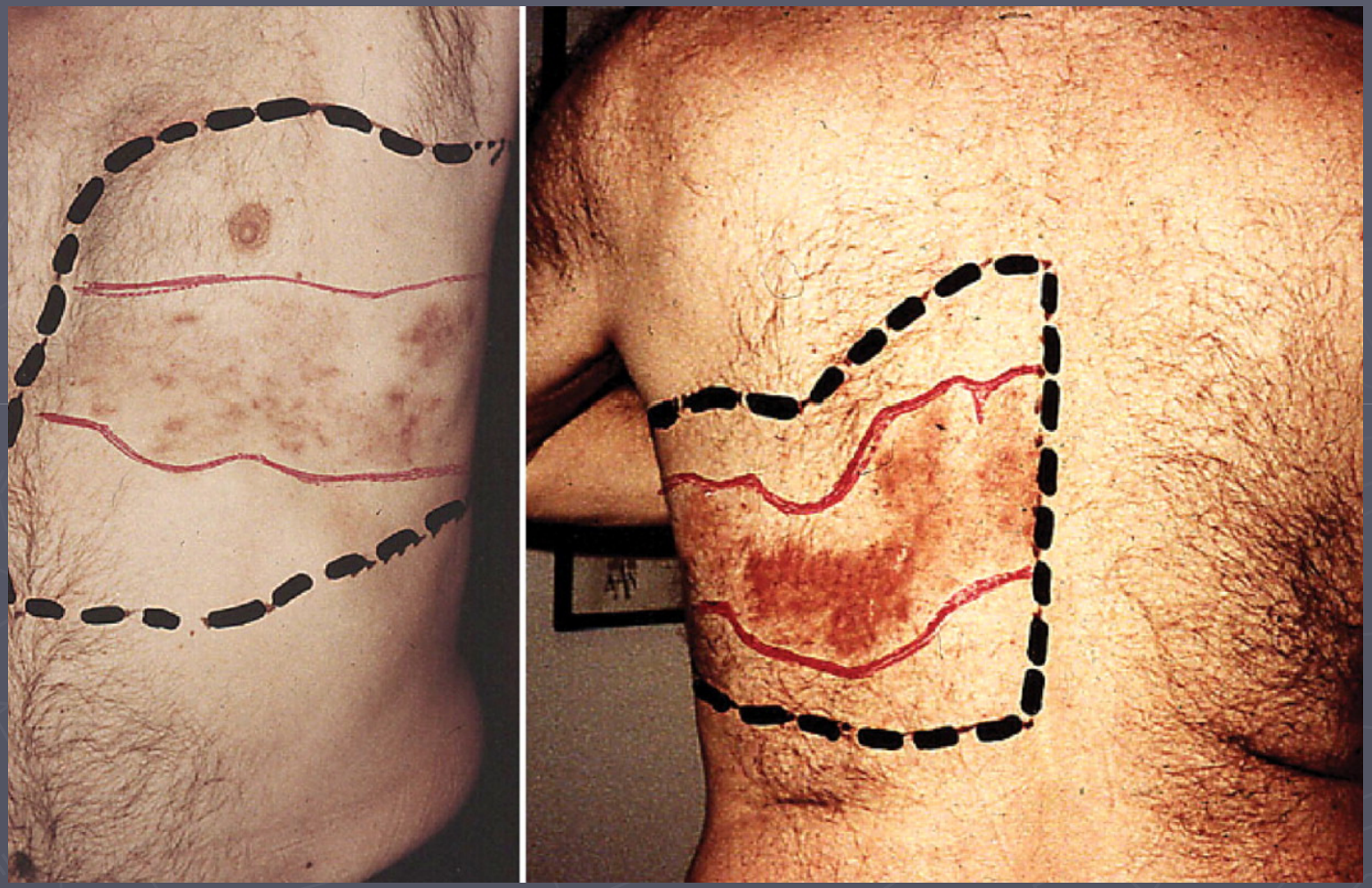
- Painful diabetic neuropathy
- Postherpetic neuralgia
- Trigeminal neuralgia
- Complex regional pain syndrome
- Radiculopathies
- Painful HIV-associated neuropathy
- Central poststroke pain
- Spinal cord injury
- Deafferentation syndromes (eg, phantom limb pain)
- Migraine headache

Neuropathic pain

- Characterized by a neuronal **hyperexcitability** in damaged areas of the nervous system
- Pathophysiological processes ranging from cellular to intranuclear level
- Molecular changes include abnormal expression of sodium channels, increased activity at glutamate receptor sites, changes in GABA-ergic inhibition and an alteration of calcium influx into cells

(Jensen, 2002)

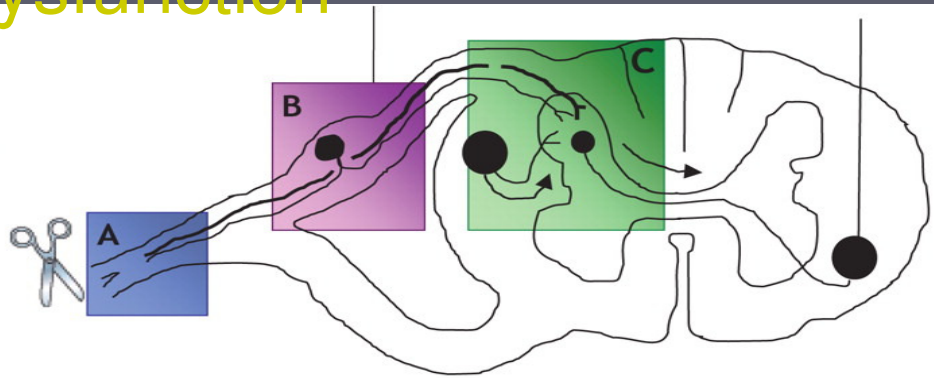
Man with postherpetic neuralgia in the left fifth and sixth thoracic dermatomes

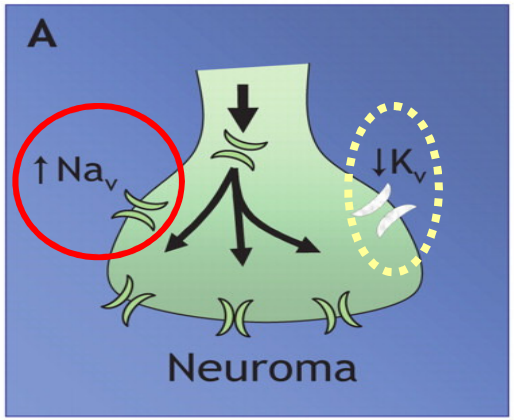


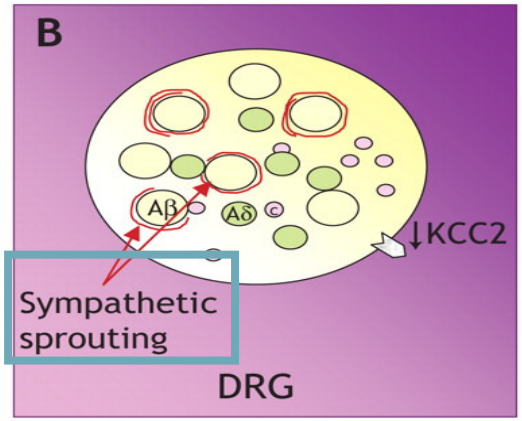
Gilron et al., 2006

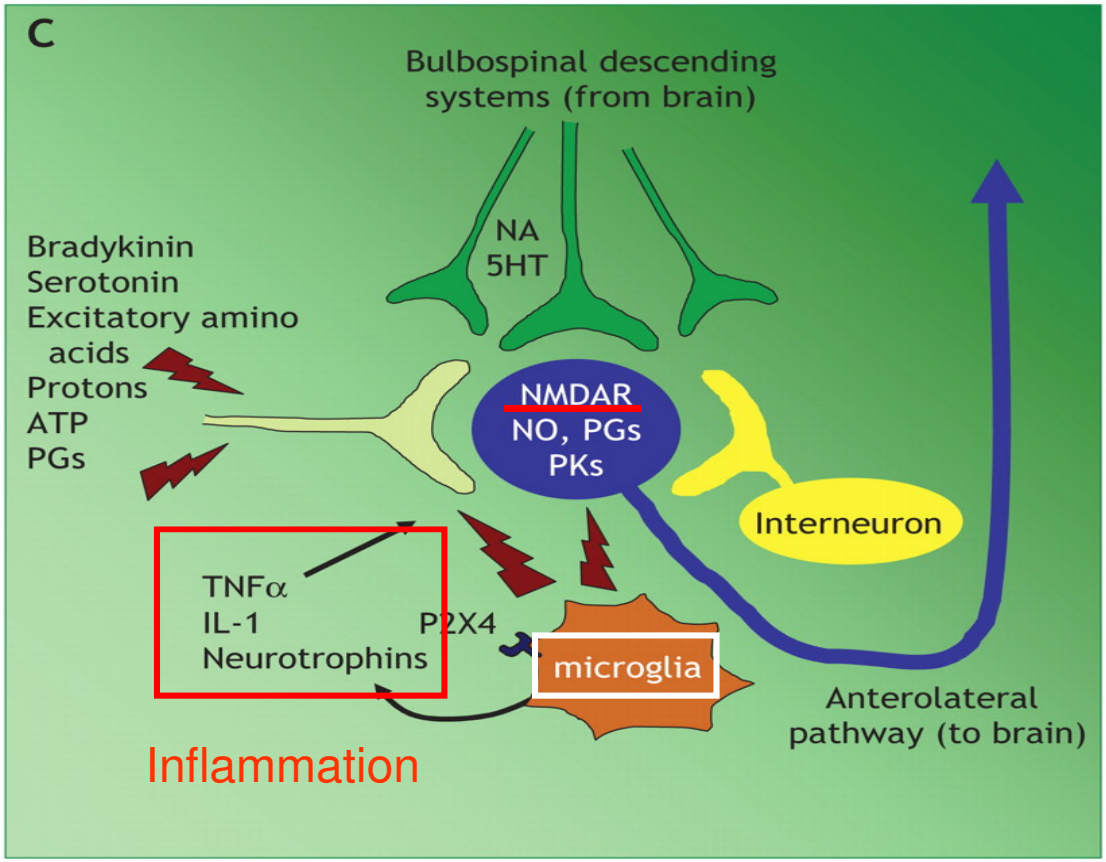
Neuropathic pain arises following nerve injury or dysfunction

Injury-induced nerve changes in the periphery, dorsal root ganglia and spinal cord contribute to neuropathic pain syndromes

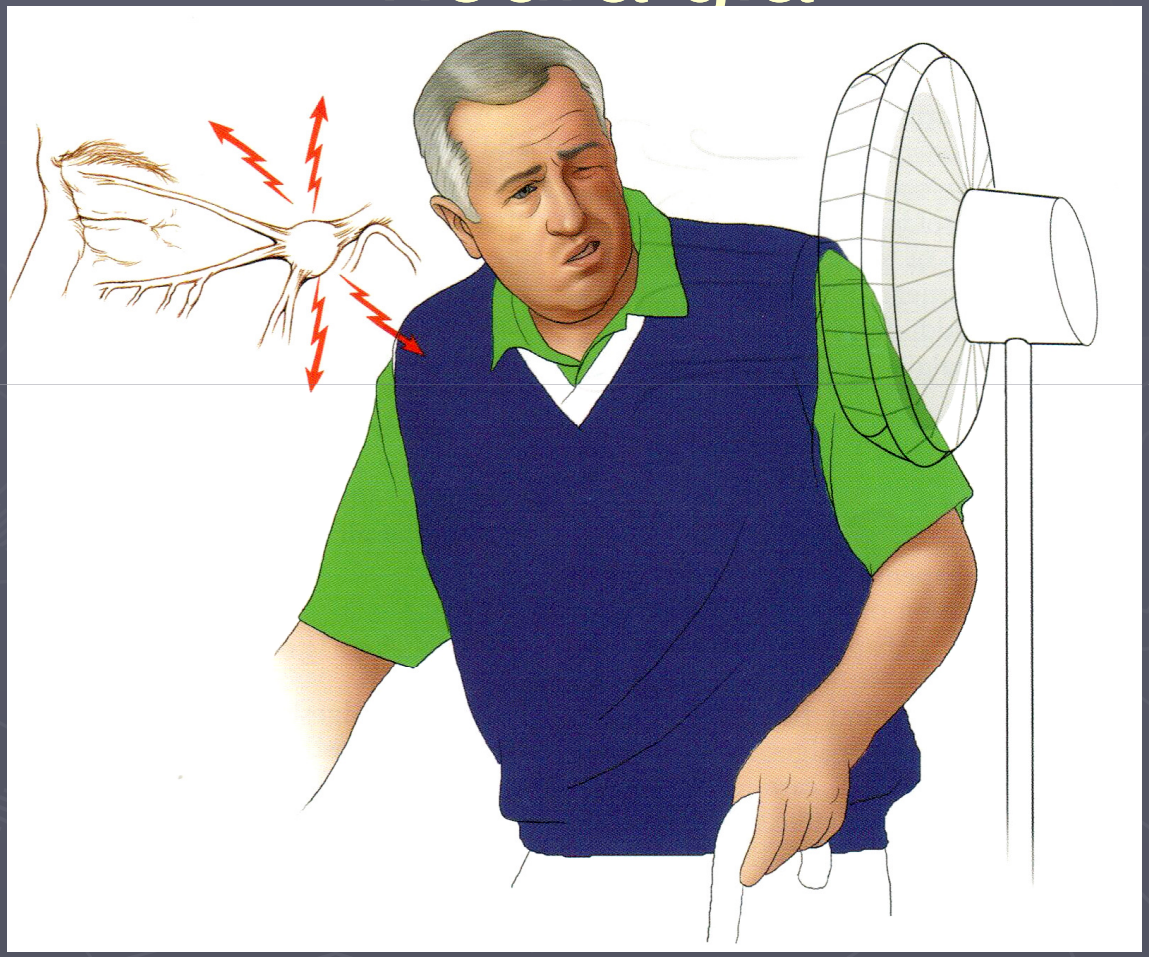






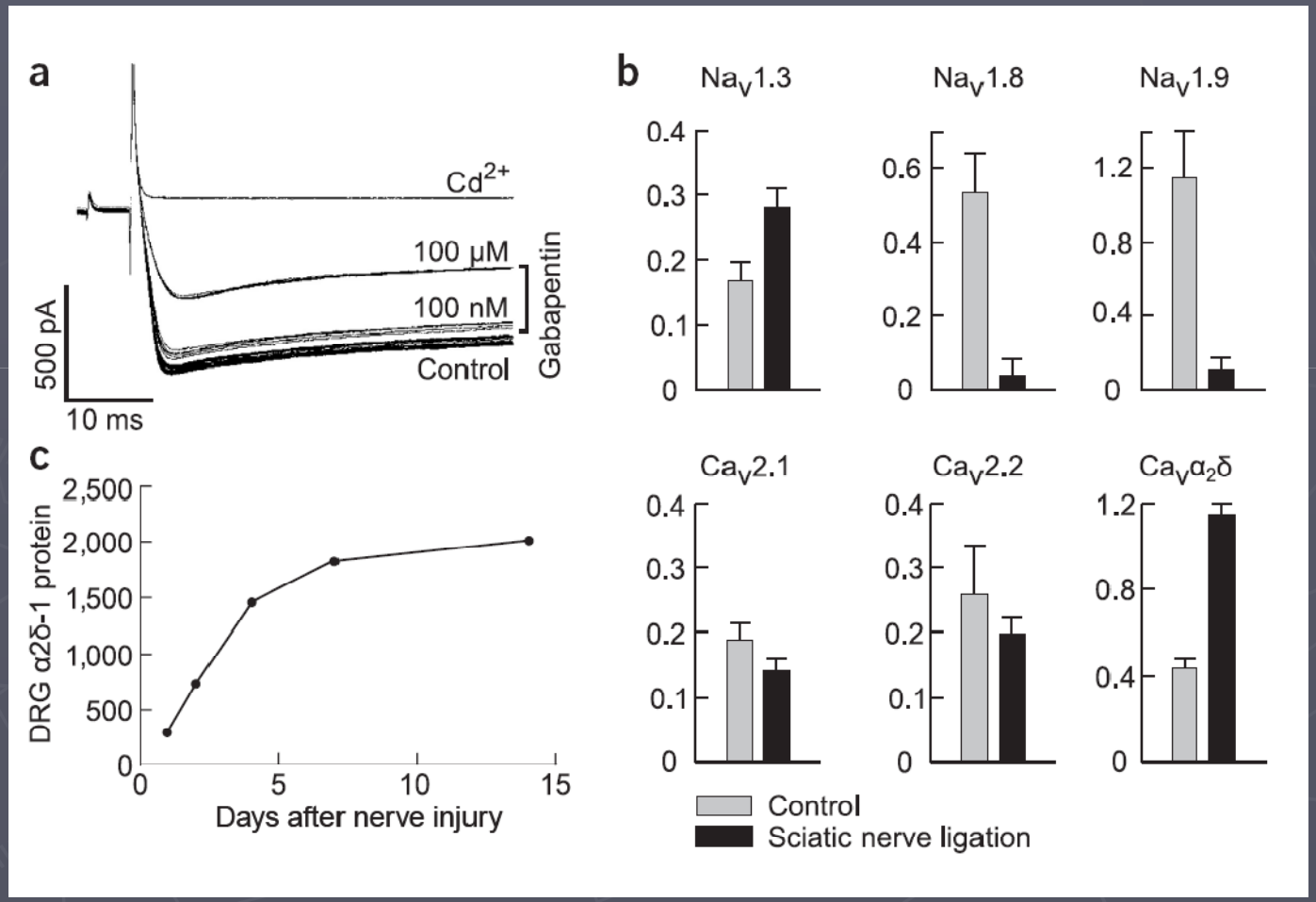


Allodynia and dysesthesia are characteristic of postherpetic neuralgia



Waldman. Atlas of common pain syndromes

Ca^{2+} channel subunit plasticity in chronic pain models



Luo et al., 2002

Role of Na^+ channels

- Plasticity in Na^+ channel expression is accompanied by electrophysiological changes that poise these cells to fire spontaneously or at inappropriately high frequencies, often from ectopic sites
- An increase in tetrodotoxin-sensitive $Na_v1.3$ (type III) Na+ channels in the cell bodies of sensory neurons
- redistribution of $Na_v1.8$ and $Na_v1.9$
- expression of β3 (an auxiliary Na^+ channel subunit)

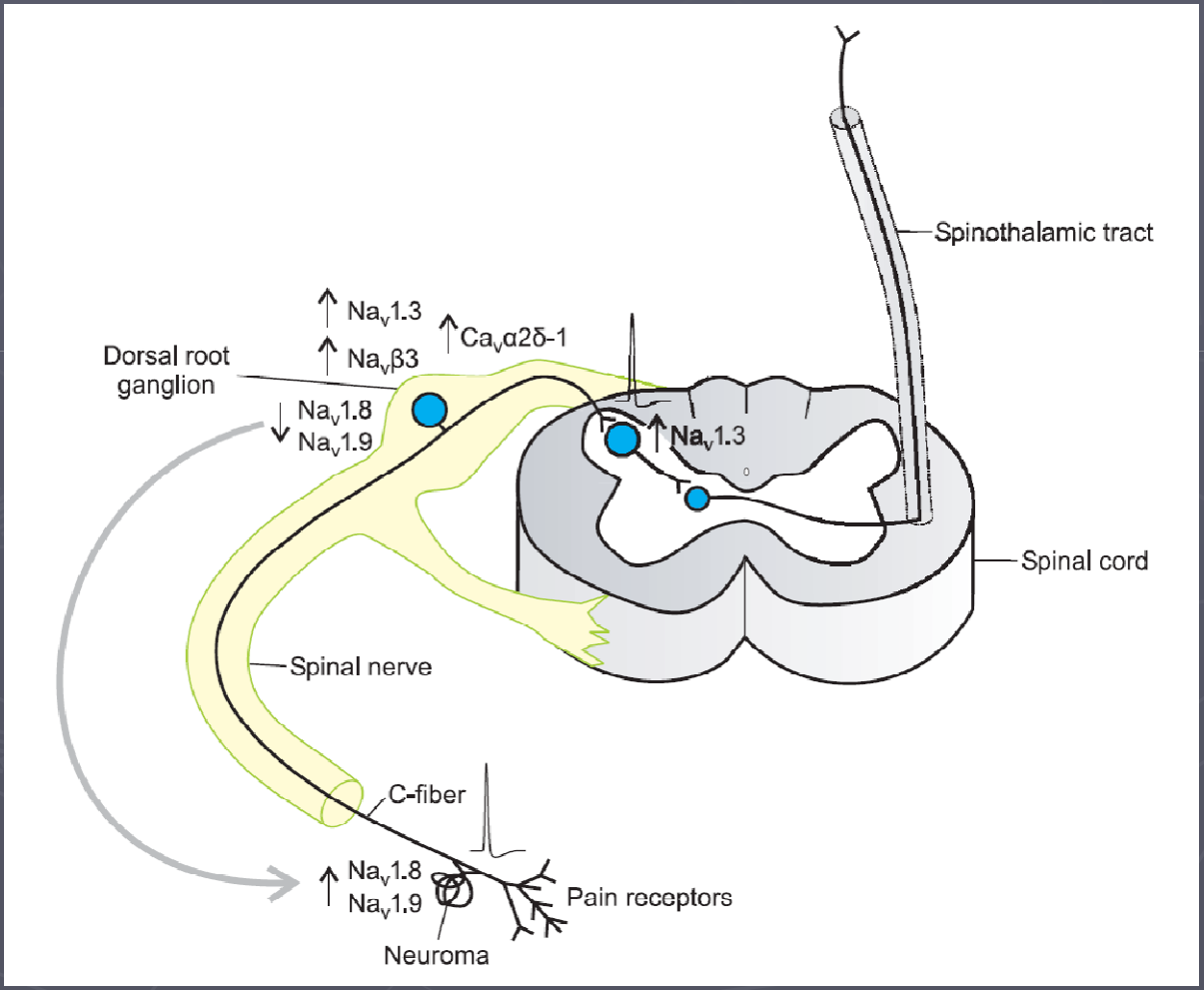
Role of Ca^{2+} channels-α2δ

- Selective alterations in the expression of Ca^{2+} channel subunits occur in some models of chronic neuropathic pain
- After peripheral nerve ligation injury the α2δ-1 subunit in dorsal root ganglion neurons is markedly upregulated in association with the development of tactile allodynia
- The allodynia in this model is sensitive to gabapentin: Gabapentin binds with high affinity to α2δ-1 and α2δ-2 and is thought to inhibit high voltage–activated Ca^{2+} currents through channels that contain these subunits

Role of Ca^{2+} channels-T type

- T-type low voltage–activated Ca^{2+} channels are involved in the transmission of neuropathic pain signals from peripheral nociceptors and in the spinal cord
- Recent evidence from α1G knockout mice indicates that bursting in thalamocortical neurons mediated by T-type Ca^{2+} channels has an inhibitory role in pain transmission
- Consequently, at the level of the thalamus, T-channel blockers would be expected to reduce this endogenous antinociceptive action of the Ca^{2+} current, balancing any beneficial effect exerted in the periphery

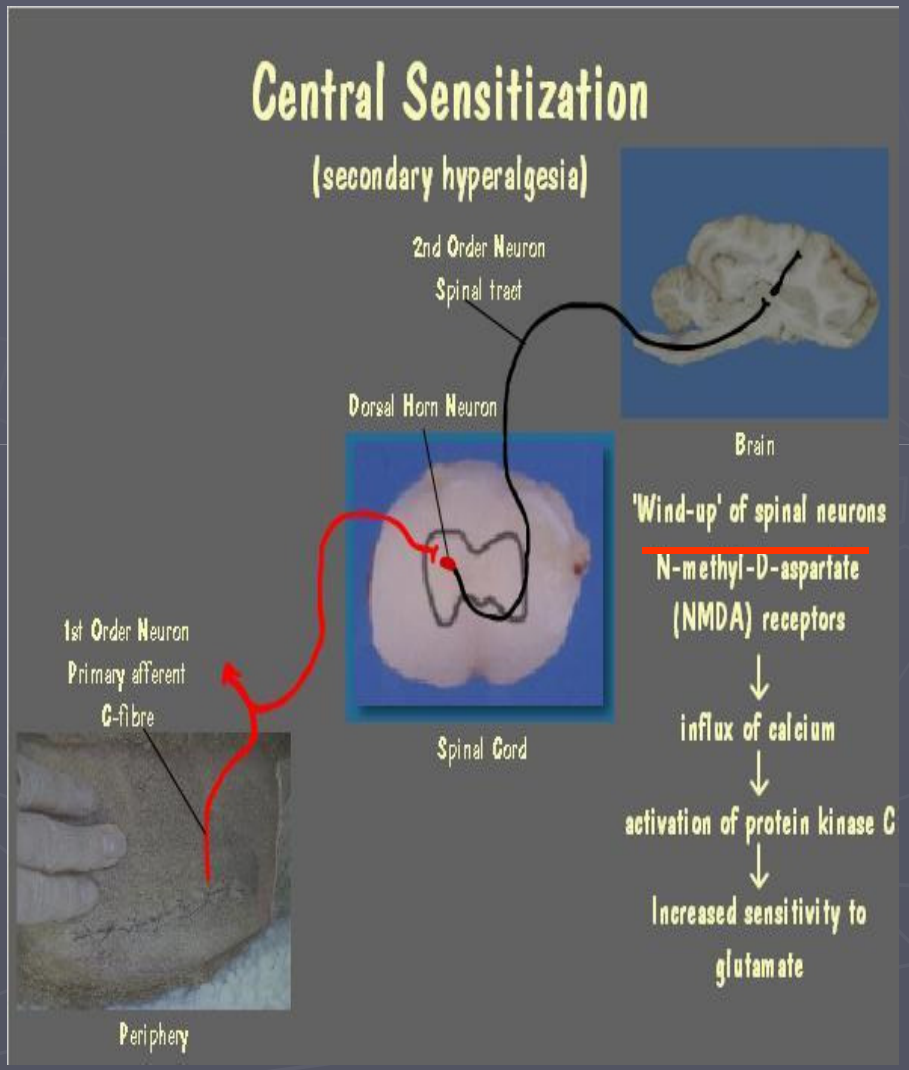
Alterations in voltage dependent Na^+ and Ca^{2+} channel subunits after chronic nerve injury associated with neuropathic pain



Rogawski and Loscher, 2004

Wind-up in neuropathic pain

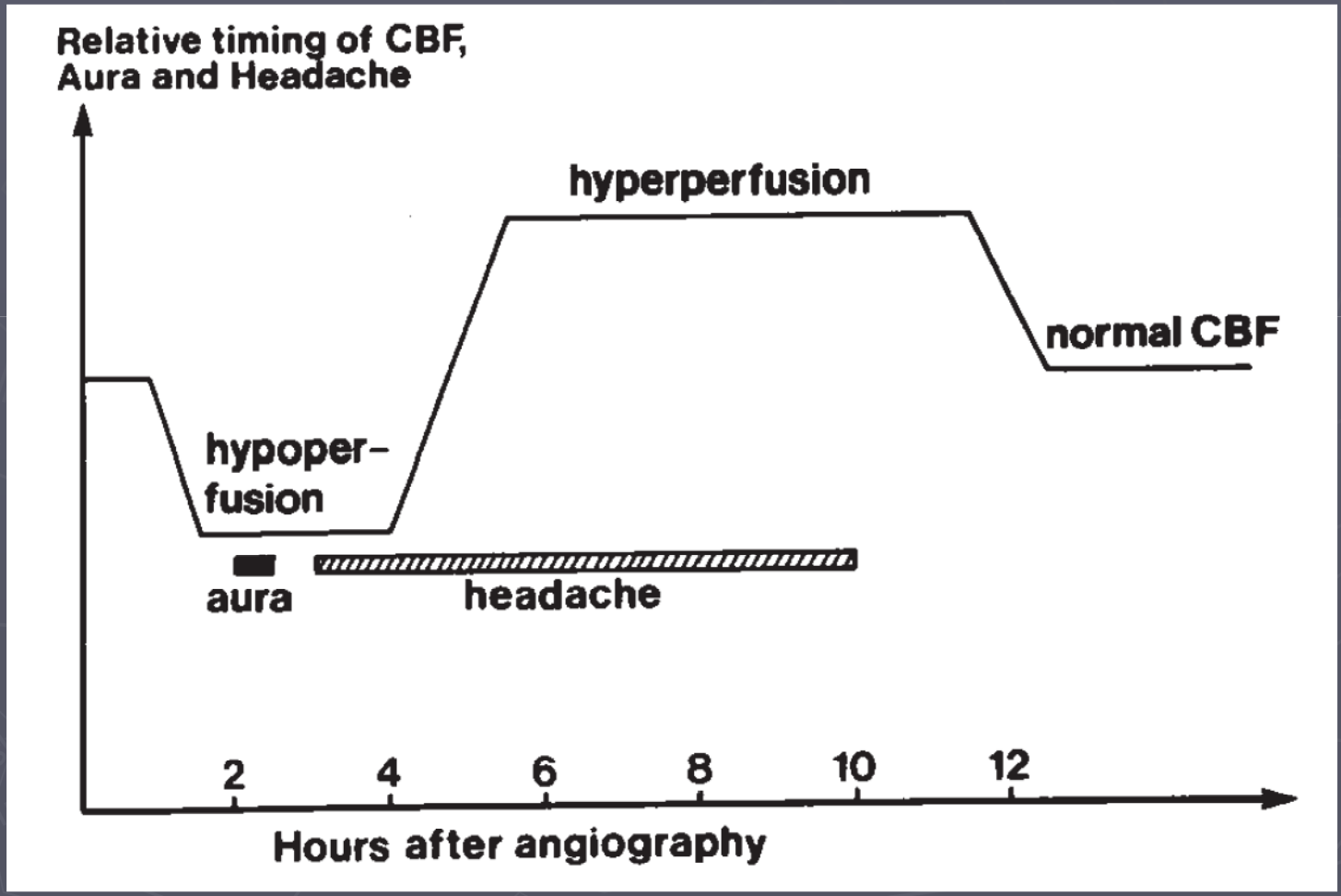
- Spinal cord neurons show a progressive increase in responsiveness with repeated activation of C-fibers, known as ‘wind-up’, underlie the phenomenon of ‘central sensitization’
- In spinal dorsal horn neurons, Ca^{2+}-dependent plateau potentials have been implicated in the generation of wind-up



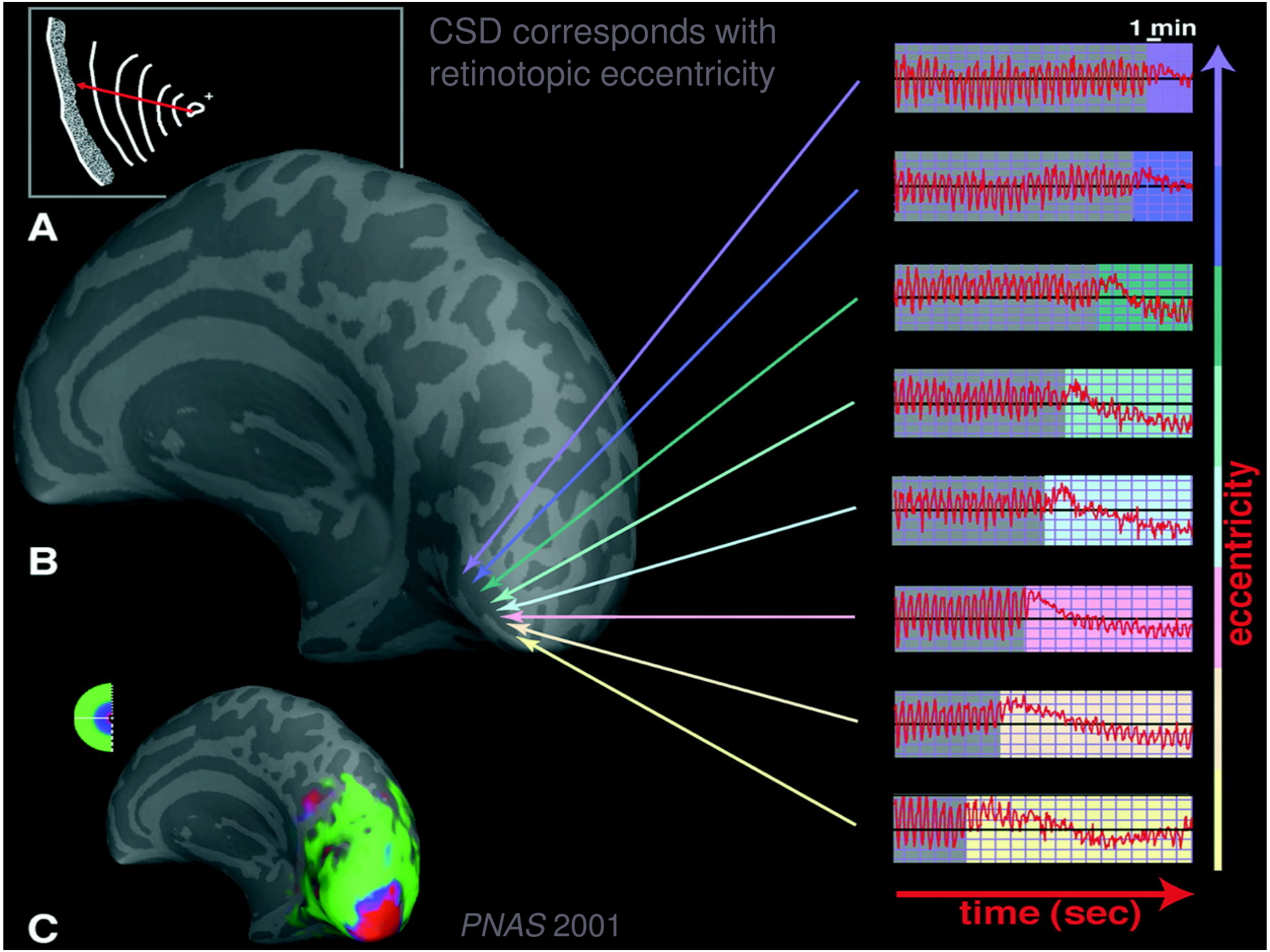
Migraine

- Characterized by episodic pain, and the paroxysmal nature of the disorder is reminiscent of epilepsy
- Pain in migraine results from the activation of trigeminovascular afferents from the meninges, which become sensitized in a way similar to their sensitization in other neurogenic pain states
- Mechanisms involve inflammation, vasodilation and altered pain sensation- altered excitability

Changes in cerebral blood flow in relation to the occurrence of the aura and headache



Ann Neurol 1990


CSD corresponds with
retinotopic eccentricity
1 min
A
B
C
eccentricity
time (sec)
PNAS 2001

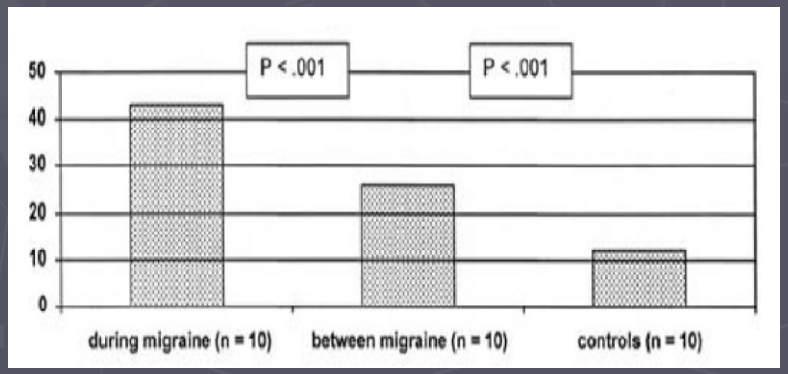
Migraine

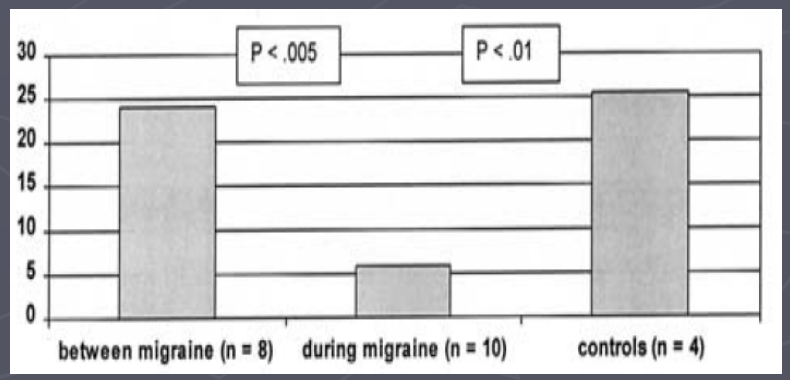
- The trigeminovascular system is activated by cortical spreading depression, which results from neocortical hyperexcitability
- Cortical hyperexcitability: an imbalance between GABAergic inhibition and glutamatergic excitation
- The cortical excitability could be related to excessive excitatory transmitter release resulting from alterations in Ca^{2+} channel function, as occurs in familial hemiplegic migraine—an autosomal-dominant form of migraine associated with mutations in the Ca^{2+} channel α1A subunit

Migraine headache

at least three mechanisms:

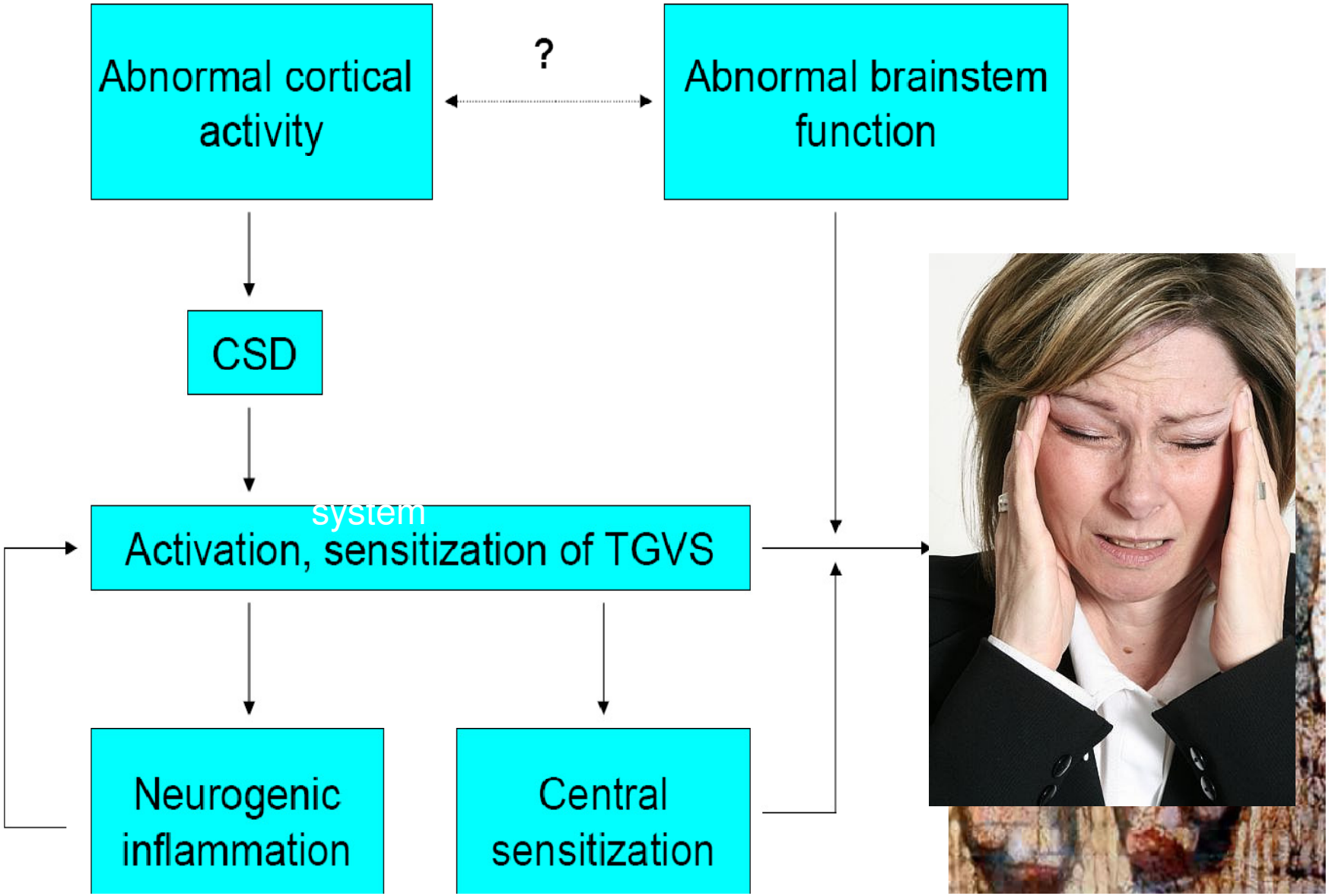
- extracranial arterial vasodilation
- extracranial neurogenic inflammation
- decreased inhibition of central pain transmission
- an imbalance between GABAergic inhibition and glutamatergic excitation, may play in the pathophysiology of migraine





Headache 1980; *Comp Ther* 2002

Proposed pathophysiological mechanisms in the generation of a migraine



Neuropathic pain and epilepsy: similarities

- Alterations in Na^+ channel expression, including upregulation of $Na_v1.3$ and changes in β subunits, in both neuropathic pain and epilepsy
- Central sensitization and kindling (glutamate receptors)
- Ectopic neuronal firing
- Susceptibility to sodium channel blockers
- May have common causes-such as head injury

Perspective

- Considerable advances have come from studies using models of neuropathic pain and epilepsy
- It is now recognized that hyperalgesia and allodynia develop as a result of the pathological plasticity of Na^{+} and Ca^{2+} channels (the redistribution of channels within neurons and alterations in the expression of specific subunits)

Perspective

- The enhanced pathological excitability can be counteracted by AEDs that act specifically on channels responsible for the injury related abnormal activity-this action occurs in a use-dependent fashion such that pathological high-frequency firing is affected more than ordinary activity
- The underlying mechanisms through which the drugs act in neuropathic pain are similar to those in epilepsy