BASIC PAIN PATHOPHYSIOLOGY

and why the medications we prescribe work!

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Disclosures: None

CATEGORIES OF PAIN

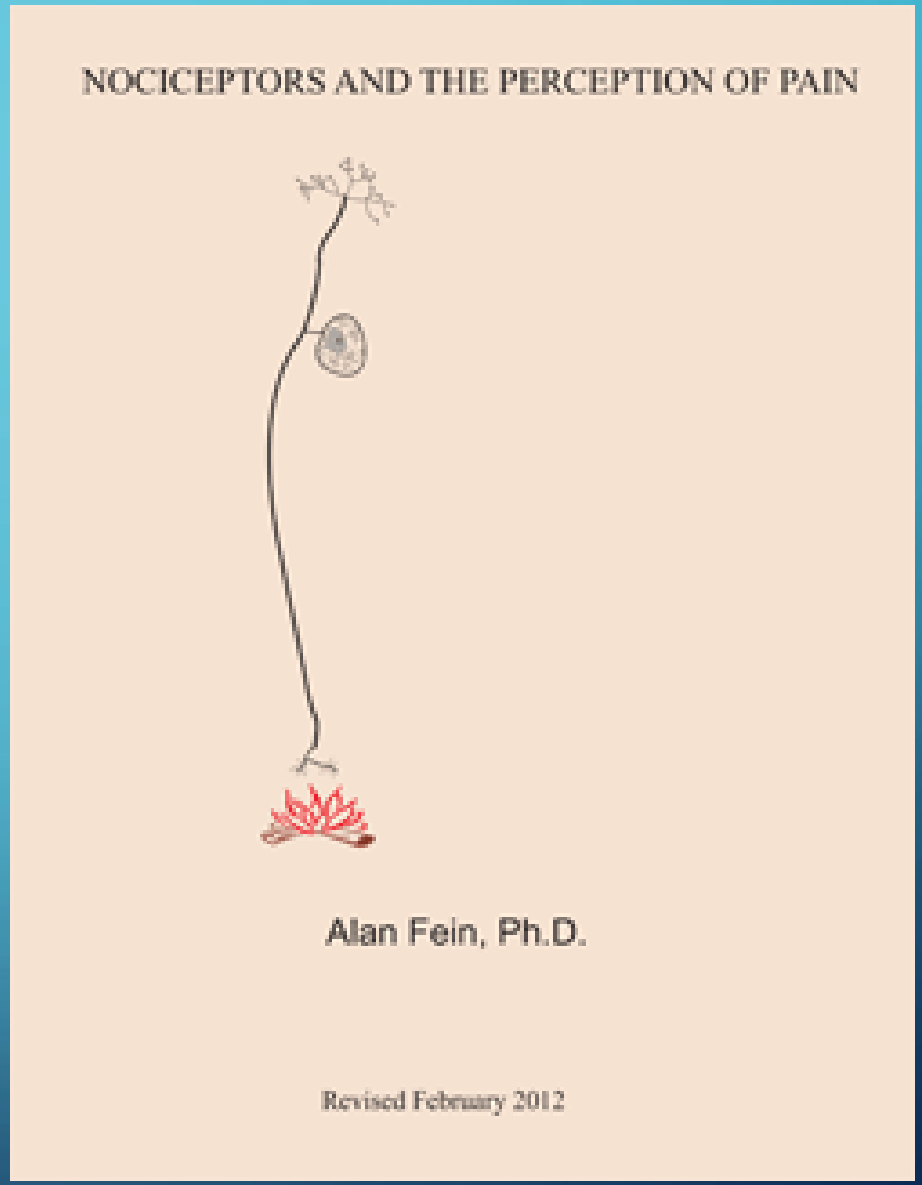
- Nociceptive
- Inflammatory
- Neuropathic
- Centralized

NOCICEPTIVE PAIN

Results from peripheral tissues injury, damage, or disease.

Protective at first and adaptive for survival

Considered pathologic when pain continues after peripheral tissue healing



Nociceptive Pain

- Arthropathies (e.g. rheumatoid arthritis, osteoarthritis, gout, post-traumatic arthropathies, mechanical neck and back syndromes
- Myalgia (e.g. myofascial pain syndromes)
- Skin and mucosal ulceration
- Nonarticular inflammatory disorders (e.g. polymyalgia rheumatica)
- Ischemic disorders
- Visceral pain (pain of internal organs and viscera)

INFLAMMATORY PAIN

Results from peripheral tissues injury, damage, or disease.

Protective at first and adaptive for survival

Considered pathologic when pain continues after peripheral tissue healing

NEUROPATHIC PAIN

Results from injury, damage, or disease to peripheral nervous structures or sensory pathways in the spinal cord or brain

Always pathologic no matter the duration

Neuropathic Pain Etiology: Peripheral vs Central Syndromes

Peripheral syndromes

- Metabolic
- Infectious
- Toxic
- Traumatic
- Neurodegenerative
- CRPS

Central syndromes

- Injuries
- Thalamic/ischemic
- Phantom limb

CENTRALIZED PAIN

-Reflects aberrant function in various CNS pathways

-Not associated with any common peripheral tissue injury

-Now thought to account for fibromyalgia, irritable bowel syndrome and other chronic conditions.

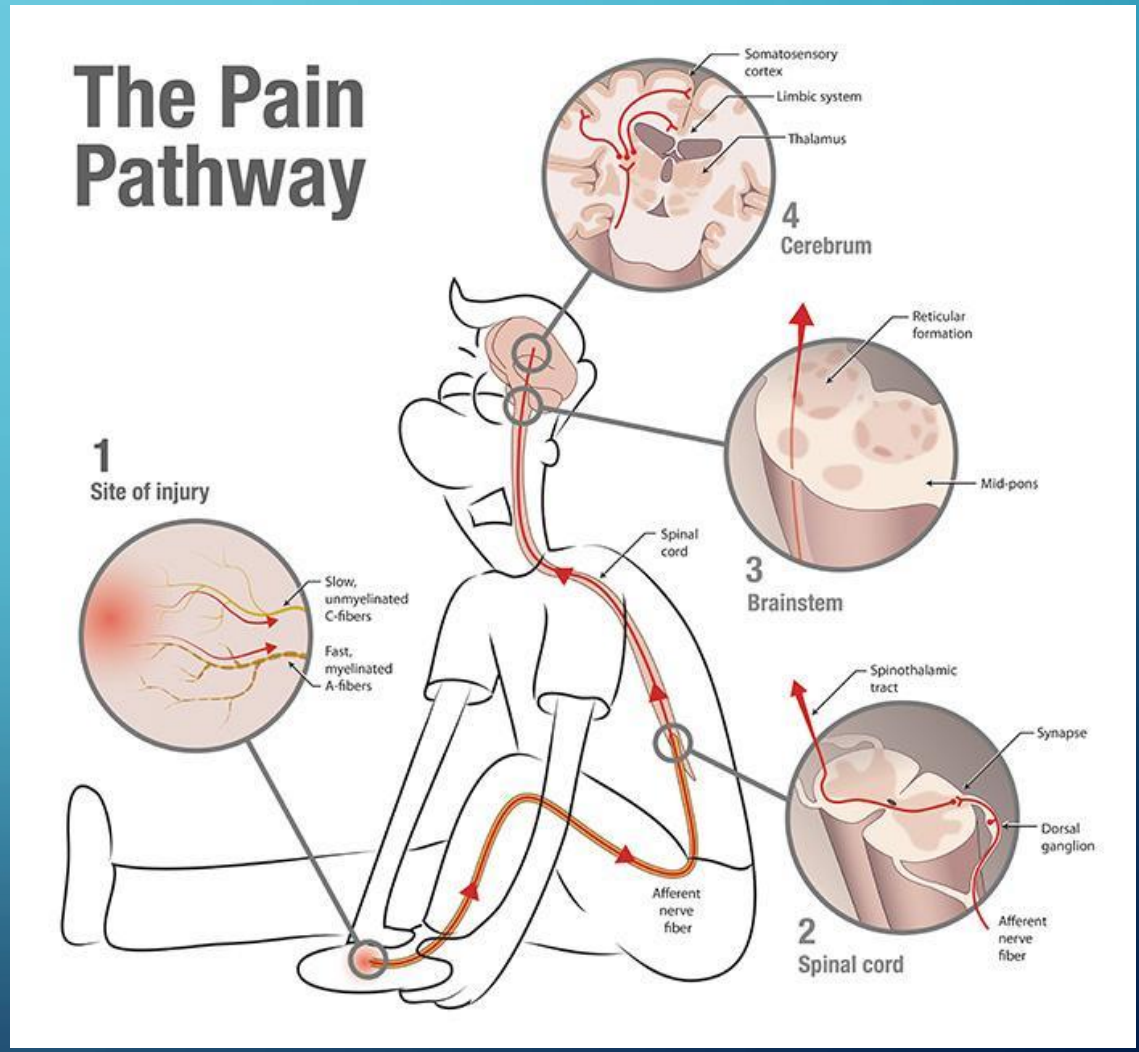
MANY CASES OF PAIN HAVE A MIXTURE

NEW PARADIGMS OF PAIN

- Pain is not an accurate measure of tissue state
- Pain is modulated by multiple factors across somatic psychologic and social domains
- The relationship between pain and tissue state further weakness as pain persists
- Pain represents a conscious correlate of implicit perception that tissue is in danger, not the actual tissue state and not the actual threat to the tissue.

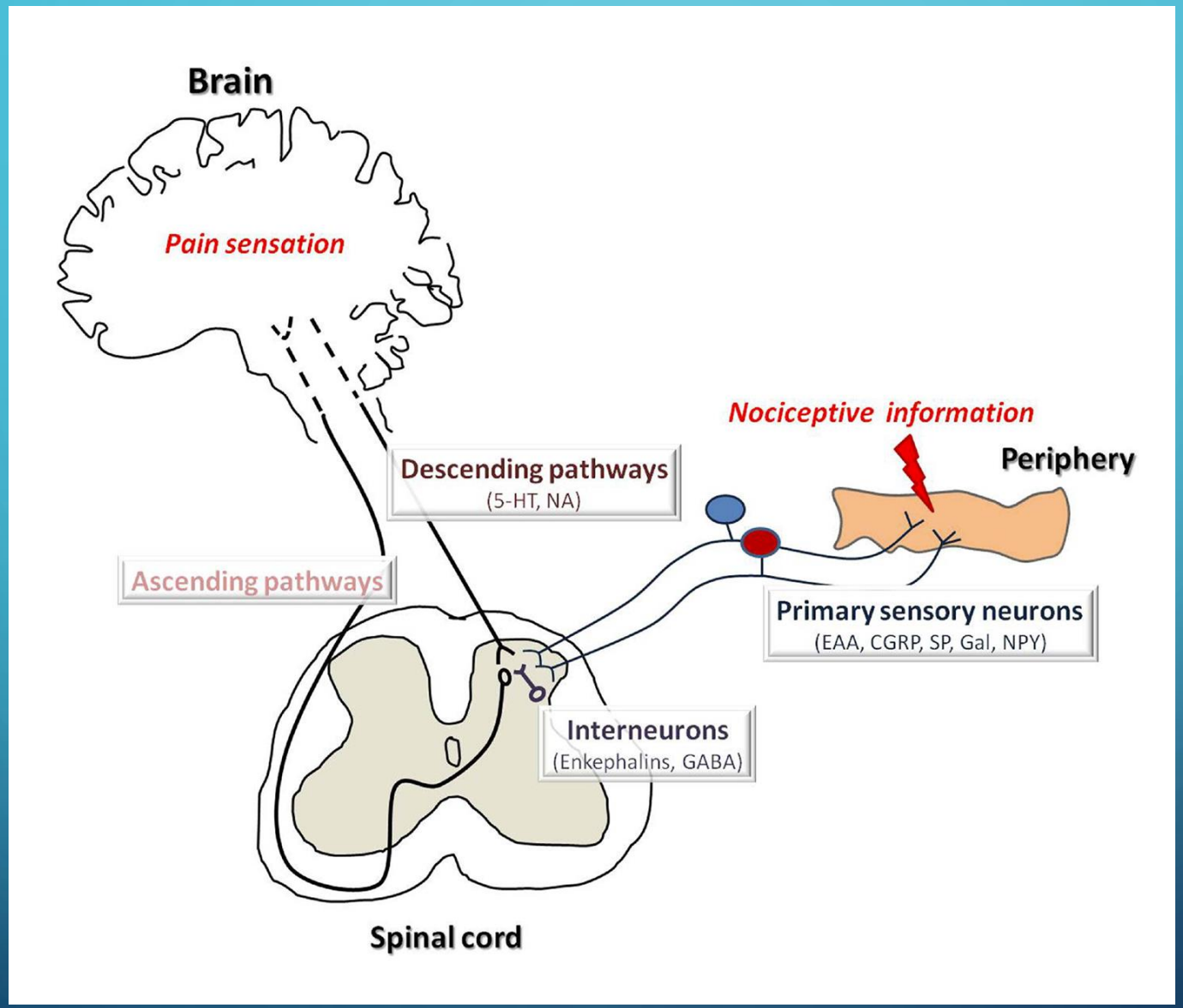
PAIN PHYSIOLOGY

- Pain begins with peripheral tissue injury, infection, or peripheral nerve injury
- Impulses are transmitted to the brain through pathways involving the damaged tissue, peripheral nerves, spinal cord, brainstem, and cerebrum.



PERIPHERAL NOCICEPTION

- Nociceptors are specialized high-threshold afferent (sensory) neurons.
- Activation by noxious stimuli transduces energy into action potentiation, transmitted to the spinal cord along axon containing C (non-myelinated) or A-delta (myelinated) nerve fibers (EMG IMPLICATION)
- Receptors also signal noxious stimuli, including transient receptor potential and acid sensing ion channels and K+ channels.


Brain
Pain sensation
Nociceptive information
Periphery
Descending pathways
(5-HT, NA)
Ascending pathways
Primary sensory neurons
(EAA, CGRP, SP, Gal, NPY)
Interneurons
(Enkephalins, GABA)
Spinal cord

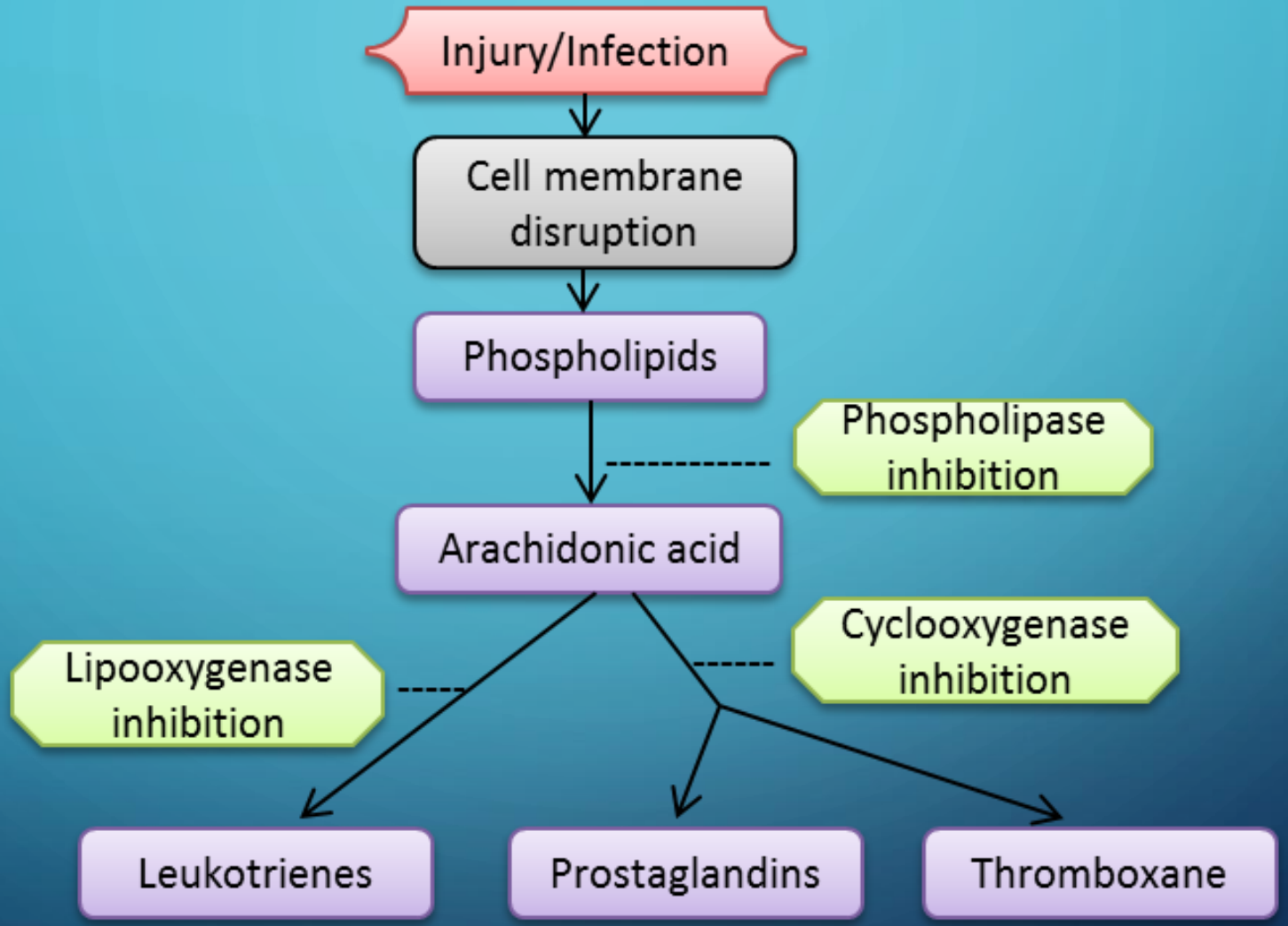
INFLAMMATORY PAIN

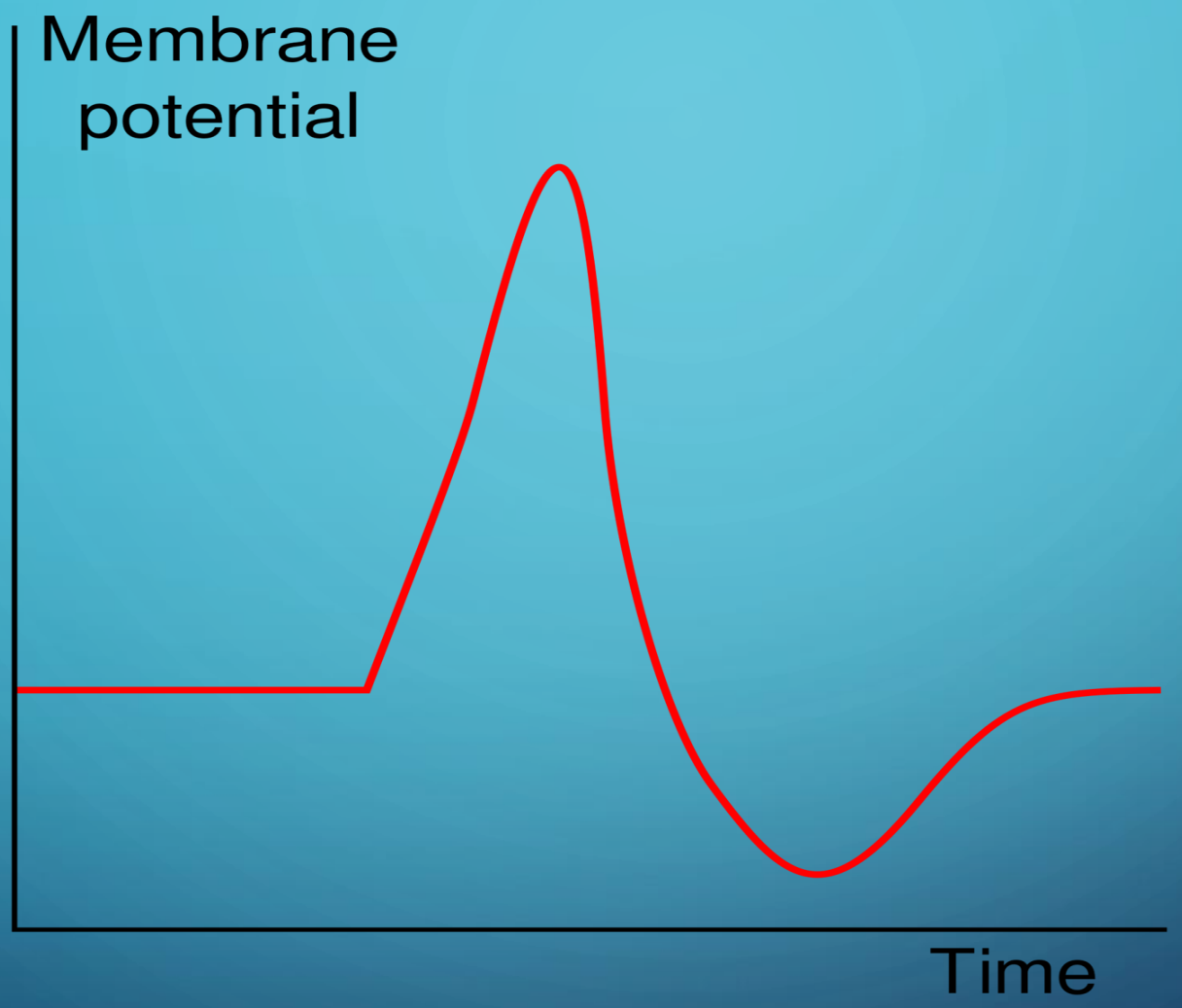
- Tissue injury or infection prompts release of chemical mediators that trigger inflammatory response
  - COX-2, mast cells, others (NSAIDS indication)

Chemical mediators activate sensitive nociceptors via ligand gated ion channels or metabotropic receptors.

INFLAMMATION CASCADE

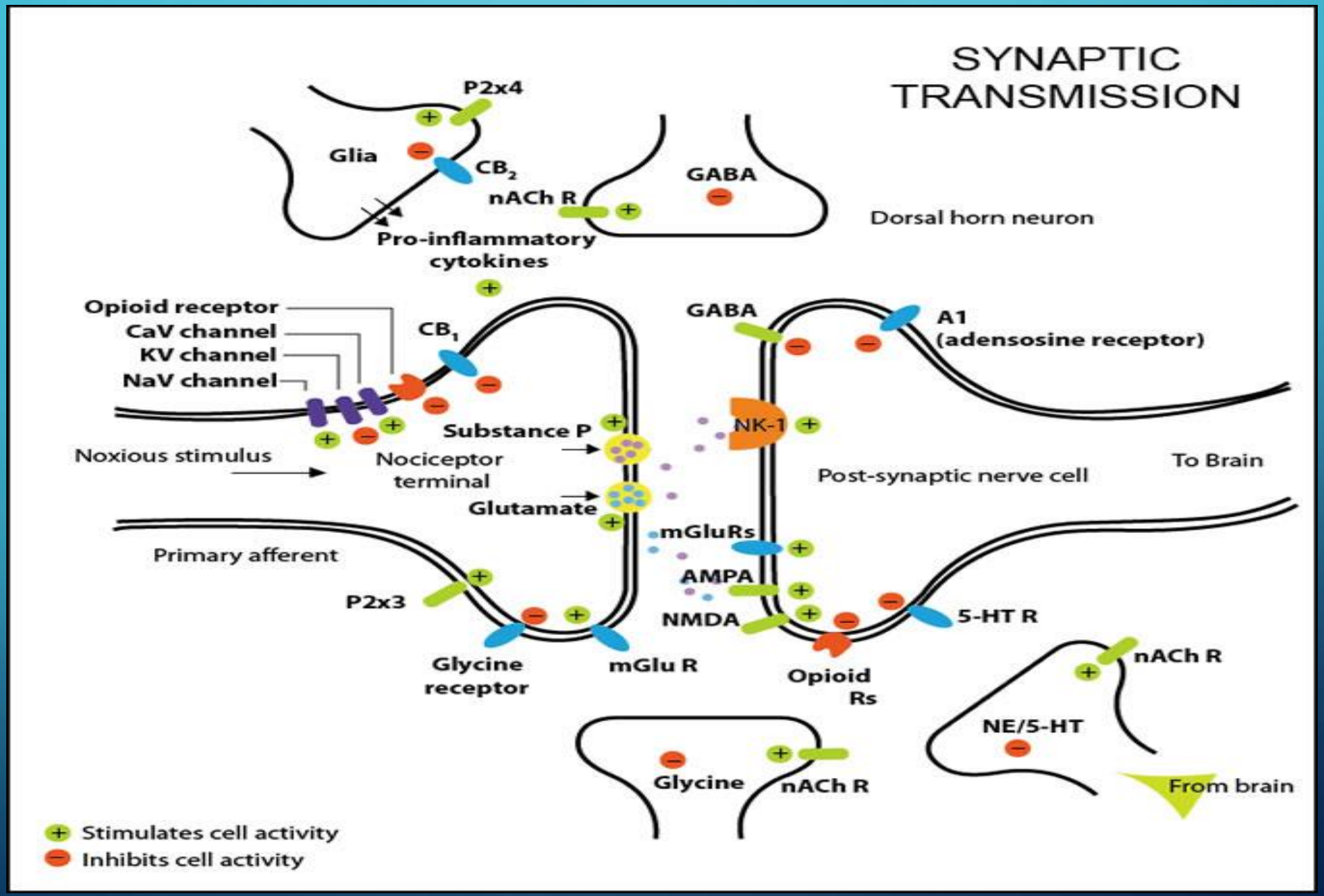
- Nociception activation induces cascade sensitizing nociceptors and altering voltage gated sodium kinetics and thresholds.
- Substance P, Calcitonin, Gene-related peptide (CGRP), and other neuropeptides released from peripheral terminals to recruit serum factors and inflammation cells at the injury site to produce neurogenic edema. (CGRP receptor antagonist use)


Injury/Infection
Cell membrane disruption
Phospholipids
Phospholipase inhibition
Arachidonic acid
Lipooxygenase inhibition
Cyclooxygenase inhibition
Leukotrienes
Prostaglandins
Thromboxane


Membrane
potential
Time

SPINAL CORD TRANSMISSION

- Peripheral nociceptive signal transmitted to the dorsal root ganglion, where it synapses with a central neuron.
- Neuron terminals release excitatory neurotransmitters accordingly.
  - Glutamate
  - Aspartate
  - Substance P
  - CGRP
  - Brain-derived neurotrophic factor (BDNF)


SYNAPTIC TRANSMISSION
P2x4
Glia
CB2
nACh R
GABA
Dorsal horn neuron
Pro-inflammatory cytokines
Opioid receptor
CaV channel
KV channel
NaV channel
CB1
GABA
A1 (adensosine receptor)
NK-1
Substance P
Noxious stimulus
Nociceptor terminal
Post-synaptic nerve cell
To Brain
Glutamate
mGluRs
Primary afferent
AMPA
P2x3
NMDA
5-HT R
Glycine receptor
mGlu R
Opioid Rs
nACh R
NE/5-HT
Glycine
nACh R
From brain
Stimulates cell activity
Inhibits cell activity

SPINAL CORD TRANSMISSION

- The signal can be modulated by peripheral or descending spinal pathway neurons
- Inhibitory mechanisms in the dorsal horn are activated to reduce excitatory response to persistent peripheral input
  - Endorphins
  - Enkephalins
  - Serotonin
  - Norepinephrine

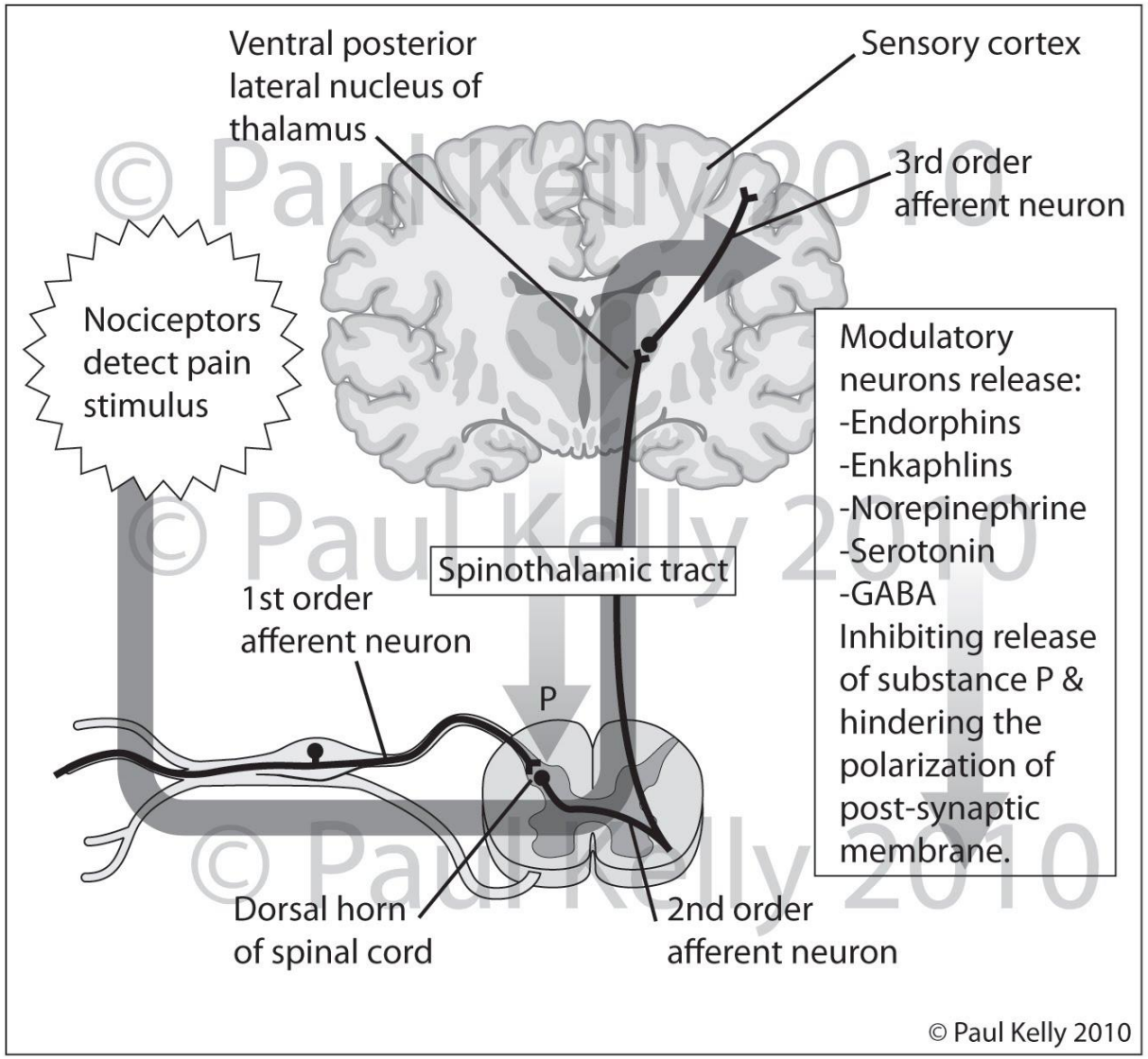


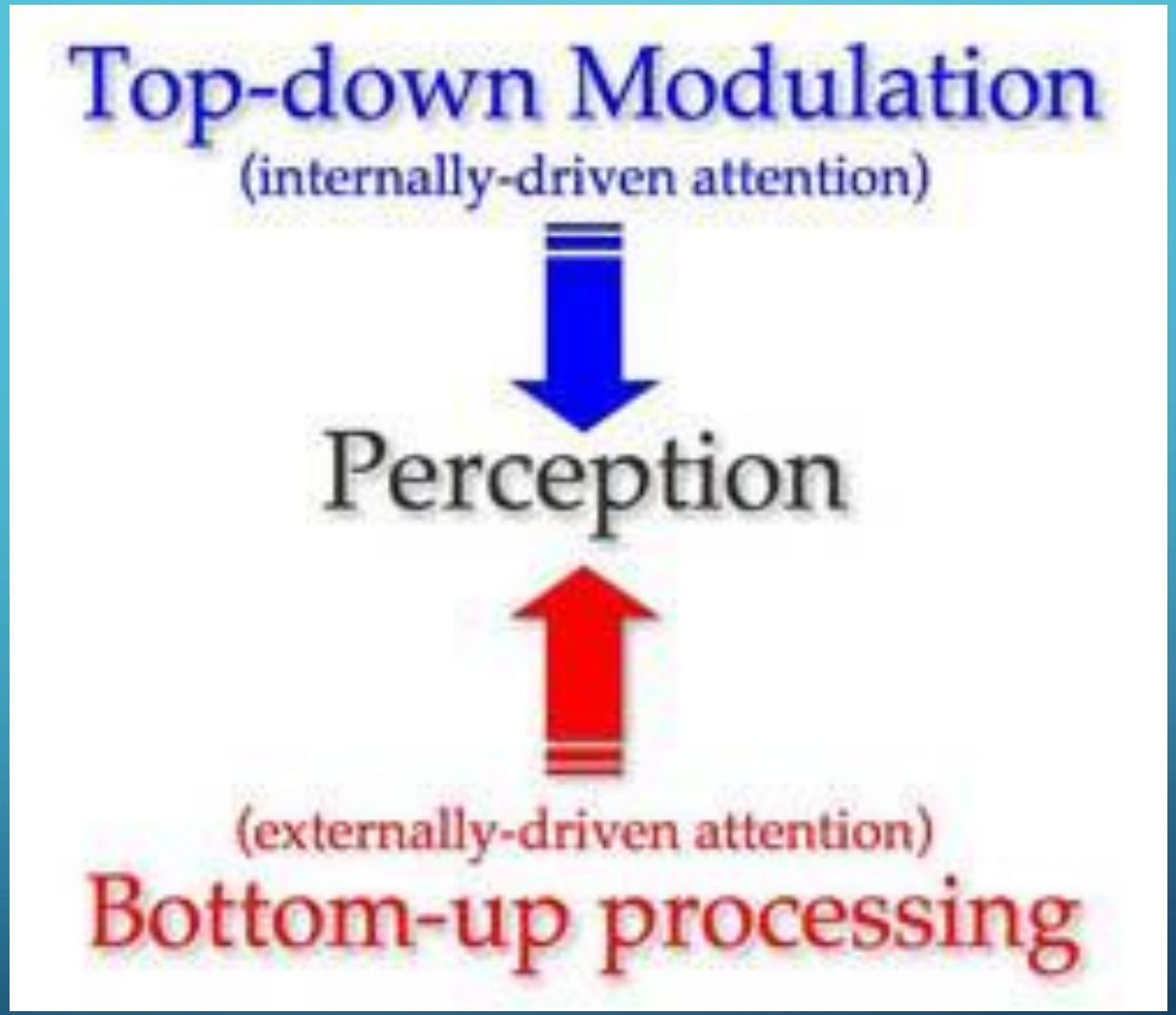
Figure #: Acute Pain Mechanism

BRAIN PROJECTIONS OF PAIN PATHWAYS

- Pain signal relayed through spinal pathways into midbrain, forebrain, and cortex
- Distinct qualities of pain experience are mediated by activation of specific brain regions receiving ascending projections.
- Signal processing in the brainstem, thalamus, and cerebral cortex results in pain perception

DESCENDING MODULATORY PAIN PATHWAYS

- Descending pathways from the cortex, thalamus, or brainstem extend down the spine to the dorsal horns.
- The descending signal (now experienced as pain) is routed down descending pathways to the dorsal horn receiving peripheral inputs to dampen pain perception by modulating signal transmission through pre- and post-synaptic actions on intrinsic interneurons.
- Relative balance between descending inhibition and facilitation varies by type and intensity of stimulus and by time from injury.
- Serotonergic and noradrenergic pathways contribute to this. (think: TCAs, SNRIs)


Top-down Modulation
(internally-driven attention)
Perception
(externally-driven attention)
Bottom-up processing

DEVELOPMENT OF CHRONIC PAIN

- Progression from acute to chronic pain coincides with development of alteration of pain pathways and brain regions that modulate aspects of pain processing.
- Psychosocial factors contribute
- When chronic pain is alleviated, some brain regions and mediated functions become normalized, other regions may remain impaired, making clinical improvement and restoration of function difficult.
- Important to *TREAT* pain

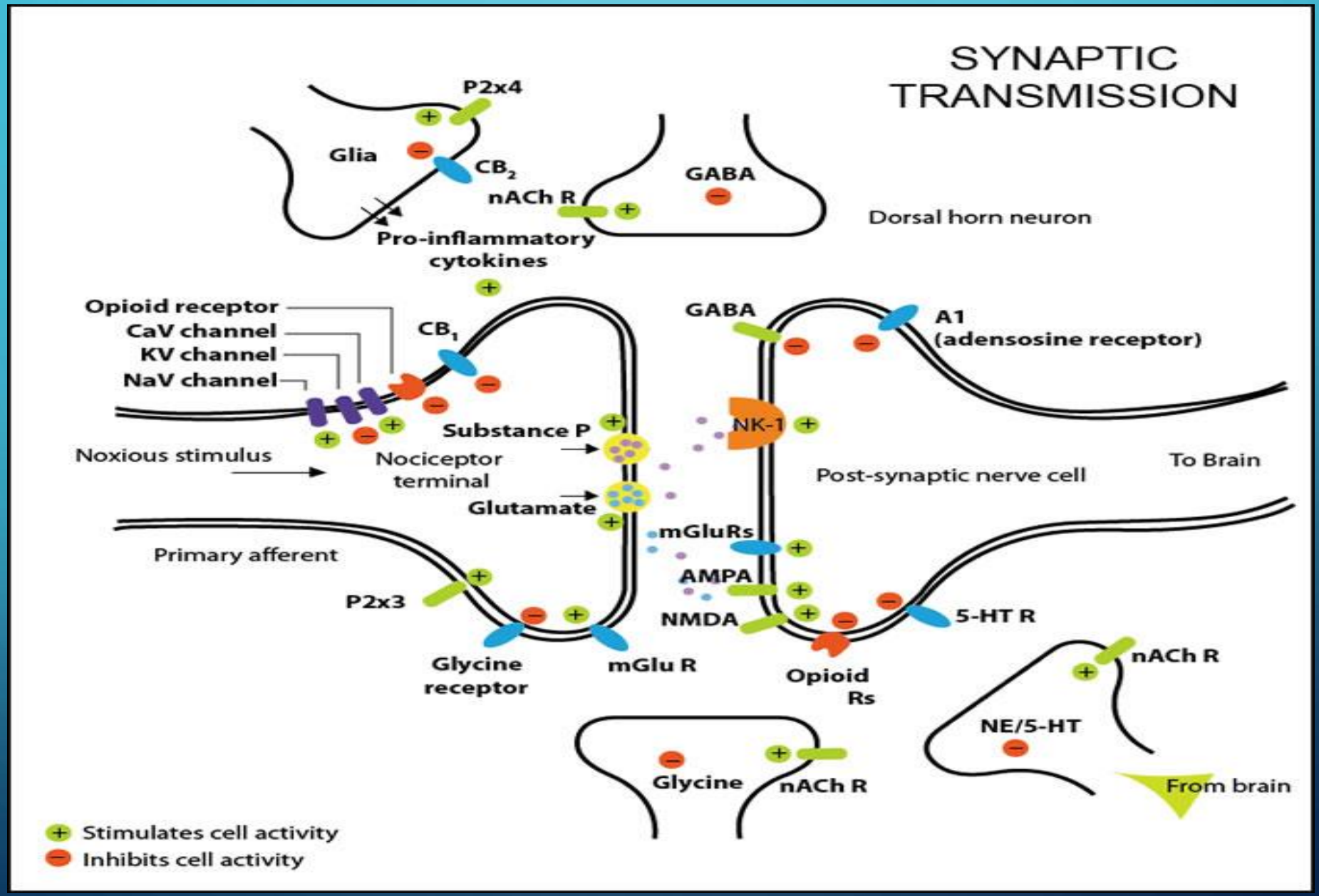
PERIPHERAL SENSITIZATION

- Develops at the site of peripheral nerve injury
- Nociceptors' nerve endings develop lowered threshold and heightened response to tissue stimuli that trigger activation

- EX: complex regional pain syndrome

CENTRAL SENSITIZATION

- Amplification of neural signaling within the CNS that elicits pain hypersensitivity.
- Low peripheral input may be required to maintain a painful state.
- Occurs when post synaptic terminals of ascending neurons in dorsal horn become altered by nociceptive barrage, which surge excitatory signaling trasmitters and modulates (Glutamate, Substance P, CGRP, BDNF).
- This activates intracellular signaling pathways of glutamate receptors N-methl-D-aspartate (NMDA) and AMPA.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From brain
Stimulates cell activity
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CENTRAL SENSITIZATION

- Activation of NMDA and AMPA lowers the threshold and opening characteristics of the channels and results in increased CNS neuron excitation, which increases pain transmission and develops central sensitization.
- NMDA receptor activation in the spinal cord is greatest contributor to central sensitization.
  - Alters signaling pathways
  - Amplifies nociceptive responses
  - Can induce functional antagonism to opioids
- NMDA receptor sites possess binding sites for NMDA antagonists (think: Ketamine, dextromethorphan, amantadine, Levorphanol,

CENTRAL SENSITIZATION

- Central sensitization promotes transition from acute to chronic pain.
- Underlying neuroplasticity occurs (cellular process of neuronal cytoarchitecture alteration through physical remodeling.)
- Brain regions become activated, including emotional processing of pain, pain modulation, pre-motor activity and pain cognition.
- Cascading changes in brain circuitry enhance pain pathway sensitivity , alters sensory, motional and modulatory pathways
- Generate new behaviors, such as increased pain responses, depression , and altered cognition.

Central sensitization

Dependent on NMDA activation

- A short-term (wind-up) and long-term potentiation of pain signals
- Associated with the induction of specific genes (C-fos)
- Specific features:
  - Increased neurotransmitter release
  - Expansion of receptive field size
  - Increase in magnitude and duration of responses
  - Changes in response thresholds
  - New nerve growth


PAIN
8
7
6
9
10
11
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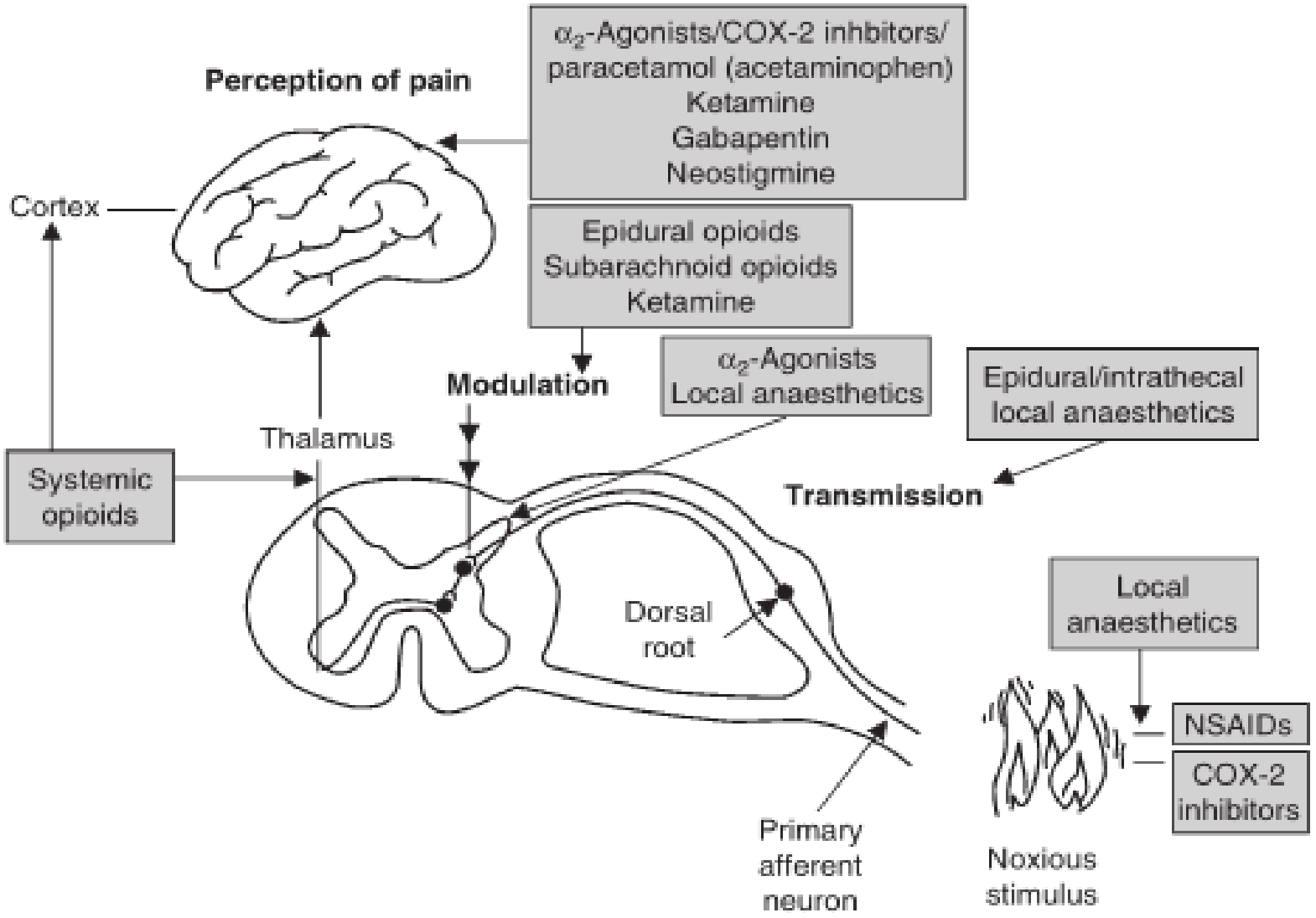
CENTRAL SENSITIZATION

- Treatment
  - Combined modalities with different mechanisms to target peripheral nociceptors and top-down and bottom up mechanisms.
    - Top-down: opioids, combined noradrenanaline reuptake inhibitor drugs
    - Bottom-up: Topically applied analgesics, interventions that target metabolic and neurotrophic factors
  - Cognitive behavioral therapy with pain neuroscience education
  - Exercise therapy


Perception of pain
α2-Agonists/COX-2 inhbitors/
paracetamol (acetaminophen)
Ketamine
Gabapentin
Neostigmine
Cortex
Epidural opioids
Subarachnoid opioids
Ketamine
Modulation
α2-Agonists
Local anaesthetics
Epidural/intrathecal
local anaesthetics
Thalamus
Systemic
opioids
Transmission
Local
anaesthetics
Dorsal
root
NSAIDs
COX-2
inhibitors
Primary
afferent
neuron
Noxious
stimulus

PSYCHOLOGICAL FACTORS

- Depressive symptoms, pain catastrophizing, and fear avoidance are thought to enhance facilitory pathways in the CNS, resulting in sensitization of dorsal horn spinal cord neurons and the development of exaggerated pain perception.
  - Decreases adaptive pain responding
  - Promotes alteration of neural process related to pain attention and response.
  - More likely in trauma patients

PSYCHOLOGICAL FACTORS

Emotional stress increases neurotransmission of inflammatory mediates: substance P, IL-1, and IL-6, which elevate corticosteroid levels

NEUROSCIENCE FINDINGS

- Neuroimaging shows patients with chronic LBP develop alterations in brain structure, function, and chemistry.
- Subacute pain is associated with large changes in hippocampal functional connectivity, which may explain learning difficulties and emotional abnormalities associated with chronic pain.

HERITABLE FACTORS

- Pain sensitivity is heritable to some degree, which genetic contribution accounting for about 50% of pain variance.