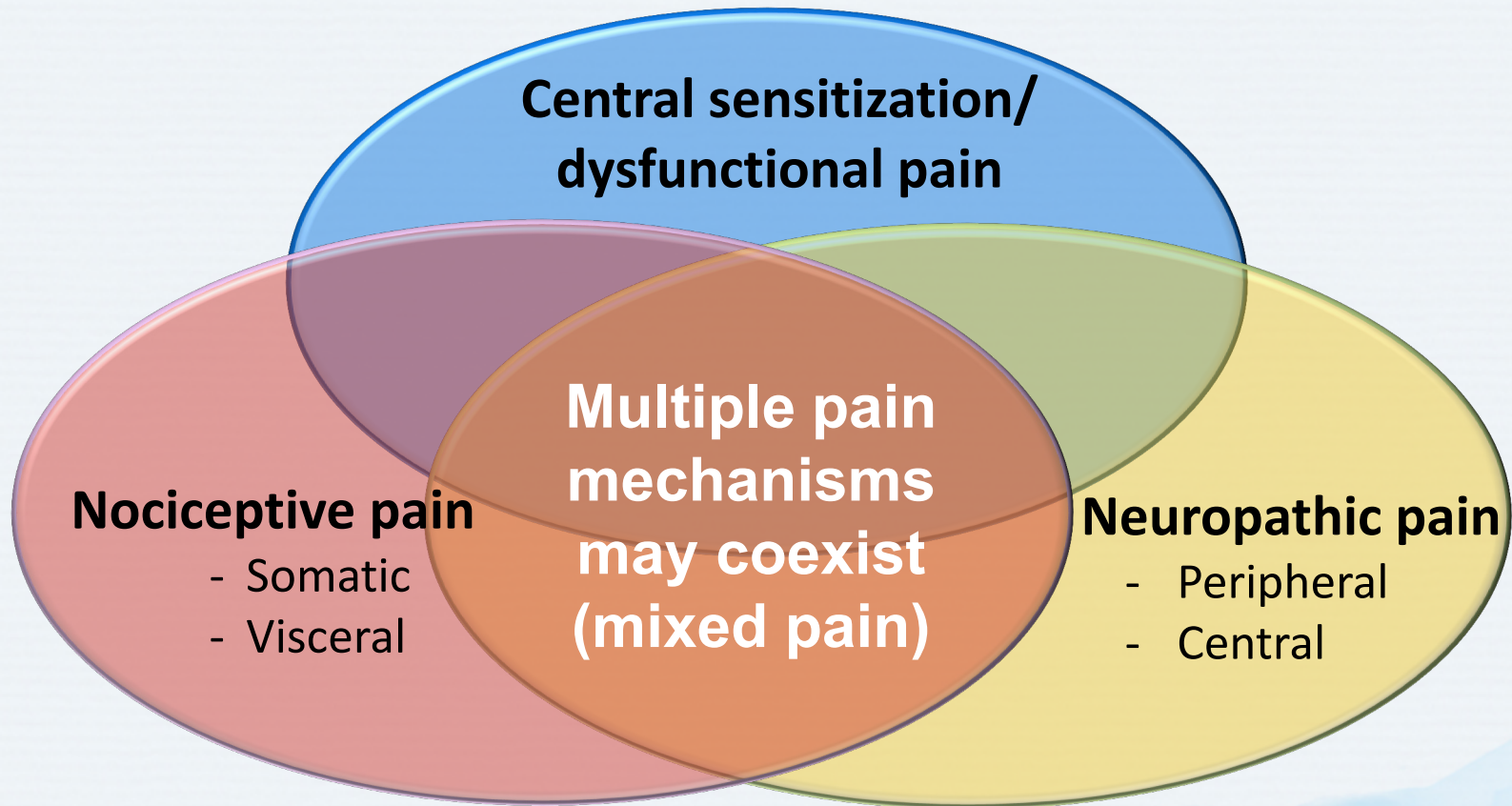

PATHOPHYSIOLOGY

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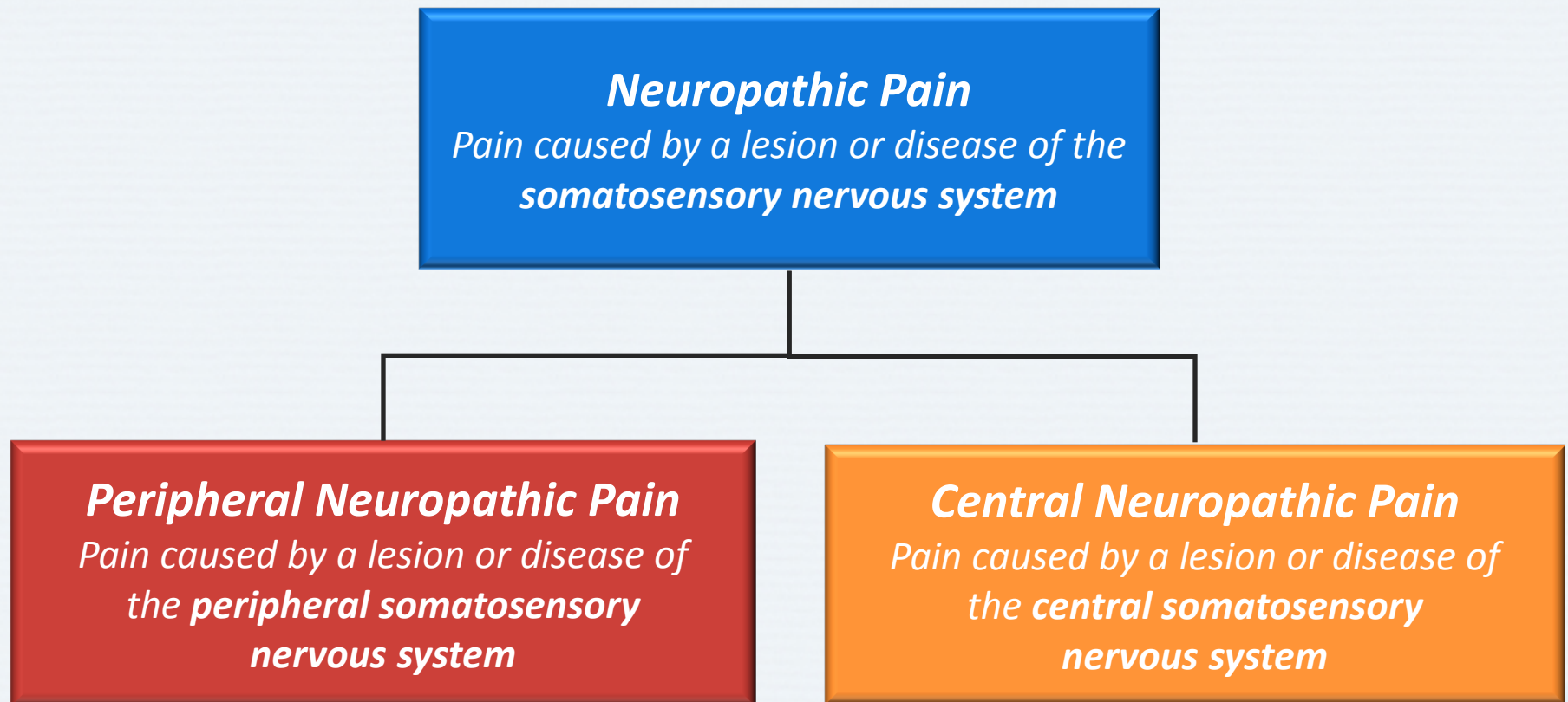
Overview

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Pathophysiological Classification of Pain



What is neuropathic pain?



Nociceptive vs. Neuropathic Pain

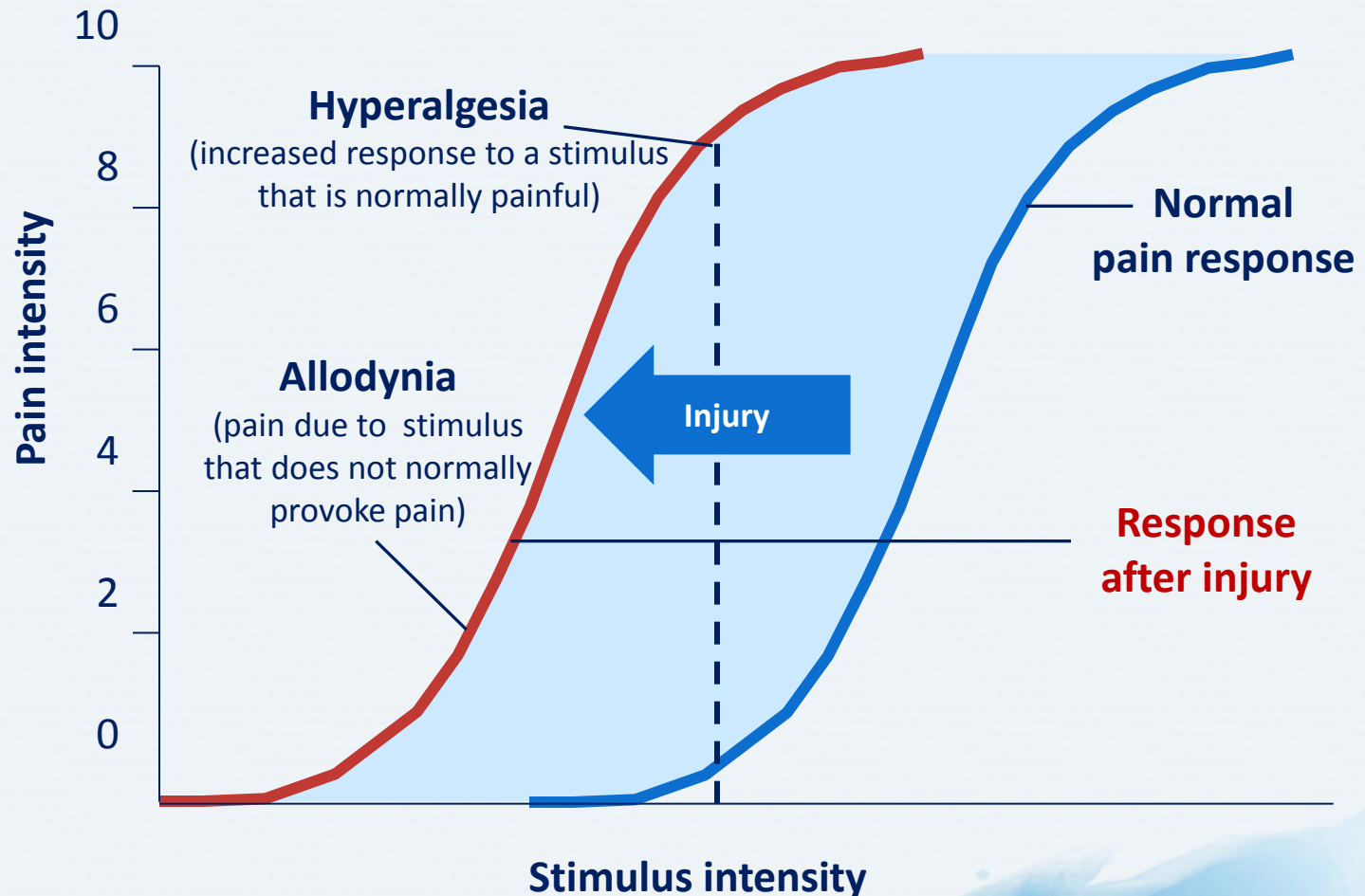
Nociceptive

- Usually aching or throbbing and well-localized
- Usually time-limited (resolves when damaged tissue heals), but can be chronic
- Generally responds to conventional analgesics

Neuropathic

- Pain often described as tingling, shock-like, and burning – commonly associated with numbness
- Almost always a chronic condition
- Responds poorly to conventional analgesics

Neuropathic Pain Is Characterized by Changes in Pain Response to Painful Stimuli



Etiology

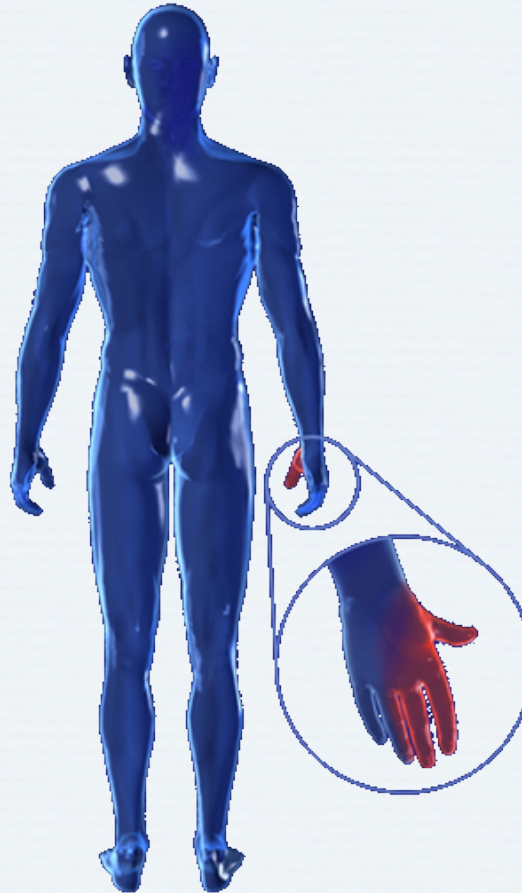
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Neuropathic Pain Conditions May Affect Various Parts of the Somatosensory Nervous System

Lumbar Radiculopathy¹



Carpal Tunnel Syndrome²



Diabetic Peripheral Neuropathy³



1. Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90;
2. Michelsen H, Posner MA. *Hand Clin* 2002; 18(2):257-68;
3. Perkins T, Morgenlander JC. *Postgrad Med* 1997; 102(3):81-2, 90-2, 102-6.

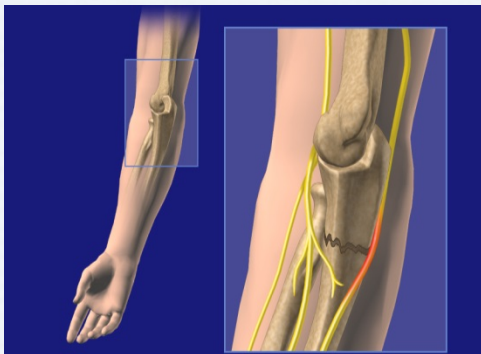
Neuropathic Pain Has a Wide Variety of Etiologies



Shingles



Diabetic neuropathy



Nerve trauma



Surgery



Radiculopathy

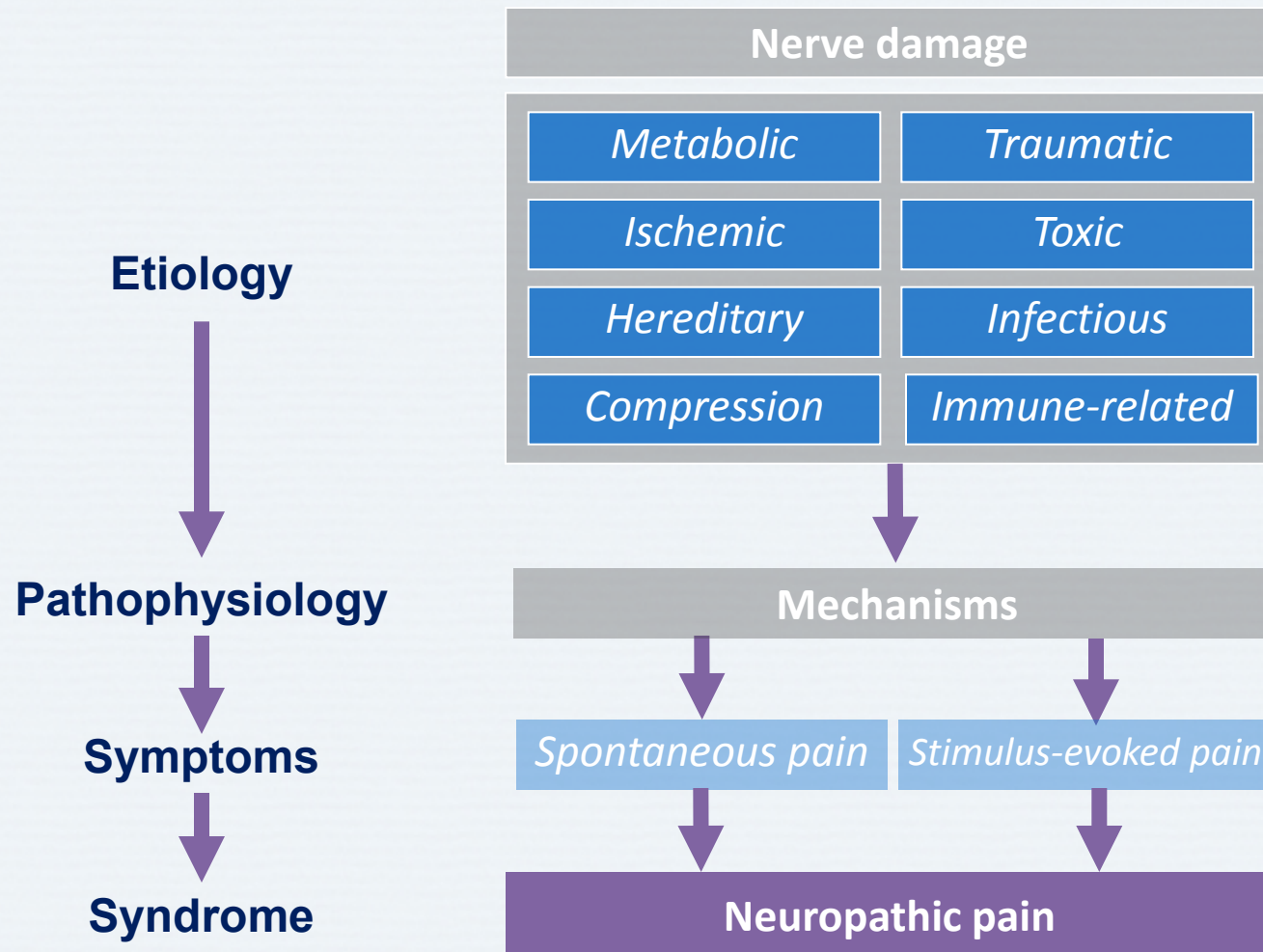
Complex Regional Pain Syndrome

- *What is it?*
 - Exaggerated response to trauma, characterized by intense prolonged pain, delayed recovery of function, vasomotor disturbances and trophic changes
 - Causes are unclear, but may include exaggerated local inflammatory response, nerve injury and involvement of the central and peripheral somatosensory nervous systems
- *How common is it?*
 - Thought to occur in 1 in 2000 cases of limb trauma
- *How should it be treated?*
 - Physiotherapy is the mainstay of treatment
 - Combination of pharmacological agents may be necessary

Pathophysiology

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Development of Neuropathic Pain



Pathophysiology of Neuropathic Pain

Peripheral mechanisms

- Membrane hyperexcitability
- Ectopic discharges
- Transcriptional changes

Central mechanisms

Hyperexcitability

**Loss of
inhibitory controls**

Reorganization

Sensitization

- Peripheral
- Central

**Neuropathic
pain**

Mechanisms of Neuropathic Pain in Diabetic Peripheral Neuropathy

Peripheral Mechanisms

- Changes in sodium channel distribution and expression
- Changes in calcium channel distribution and expression
- Altered neuro-peptide expression
- Sympathetic sprouting
- Loss of spinal inhibitory control
- Altered peripheral blood flow
- Axonal atrophy, degeneration or regeneration
- Damage to small fibers
- Increased glycemic flux

Central Mechanisms

- Central sensitization
- Changes in the balance of facilitation/inhibition with descending pathways
- Increased thalamic vascularity

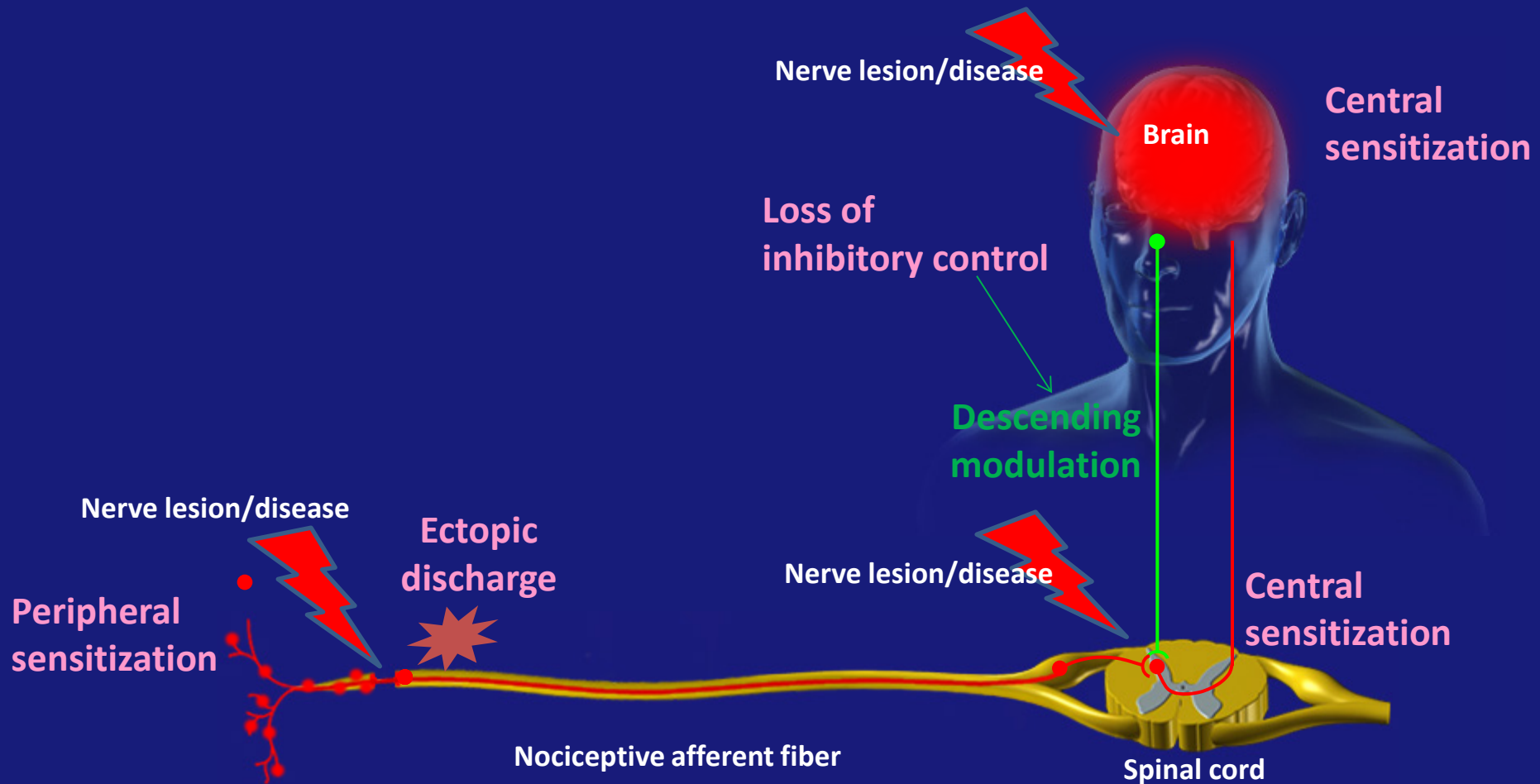
Sensory Processing and Neuropathic Pain

Nerve function	Stimulus	Primary afferent	Sensation	Mechanism
Normal	Innocuous Mechanical	A β	Normal touch	Normal function
	Noxious Mechanical Thermal Chemical	A δ nociceptor C nociceptor	Normal sharp pain Normal burning pain	
Decreased	Innocuous Mechanical	A β	Tactile hypoesthesia	Decreased transmission of impulses
	Noxious Mechanical Thermal Chemical	A δ nociceptor C nociceptor	Mechanical Heat or cold hypoalgesia	
Increased	Innocuous Mechanical	A β	Dynamic mechanical allodynia	Many theories (e.g., sensitization)
	Noxious Mechanical Thermal Chemical	A δ nociceptor C nociceptor	Mechanical Heat or cold hyperalgesia	Many theories (e.g., wind-up, peripheral sensitization)

Neuropathic Pain: A β , A δ and C Fibers

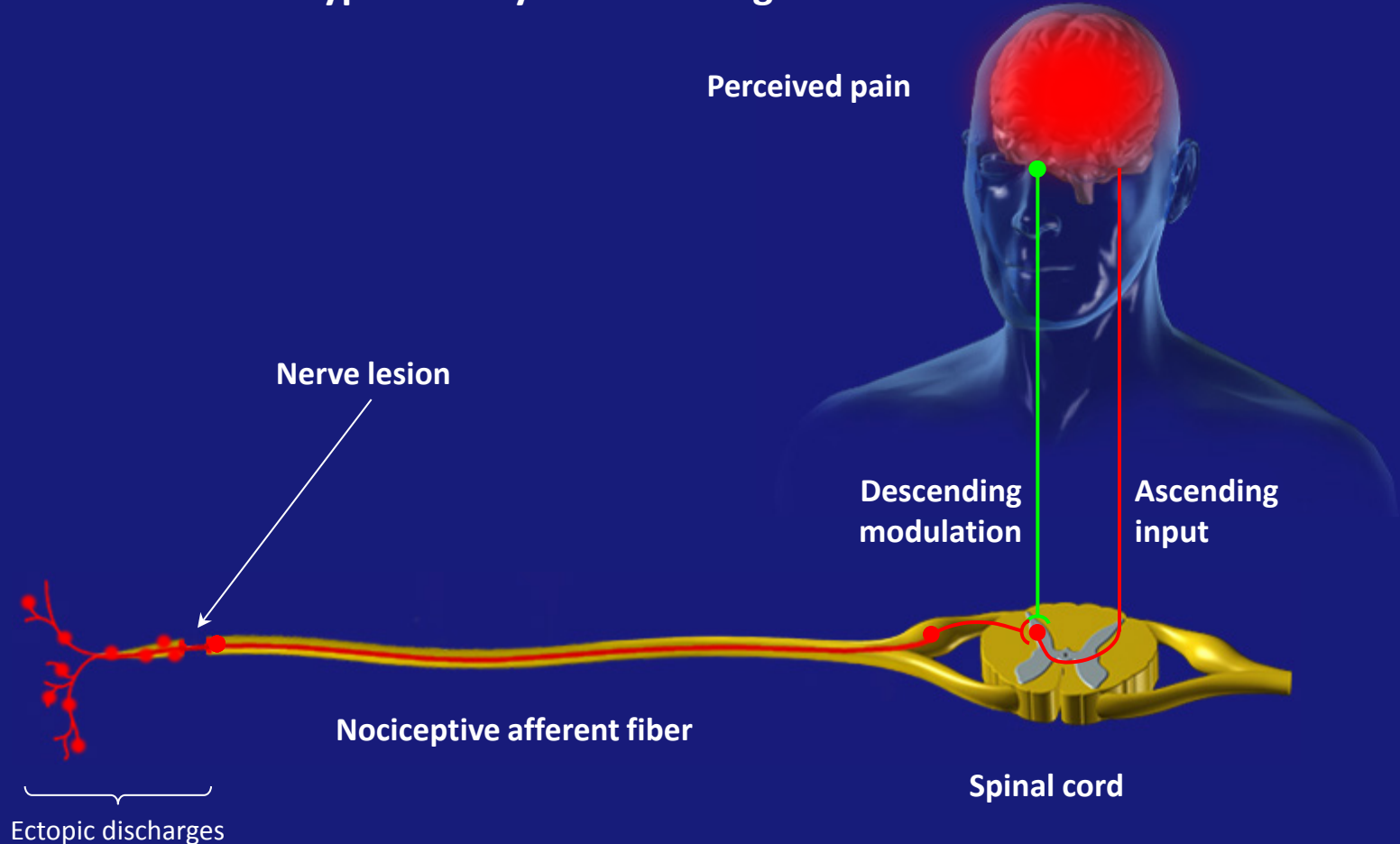
Characteristic	A β fibers	A δ fibers	C fibers
Diameter	Large	Larger	Small
Myelination	Yes	Yes	No
Conduction velocity	Rapid	Intermediate	Slow
Activation stimuli	Non-noxious mechanical	Noxious	Noxious

Mechanisms of Neuropathic Pain



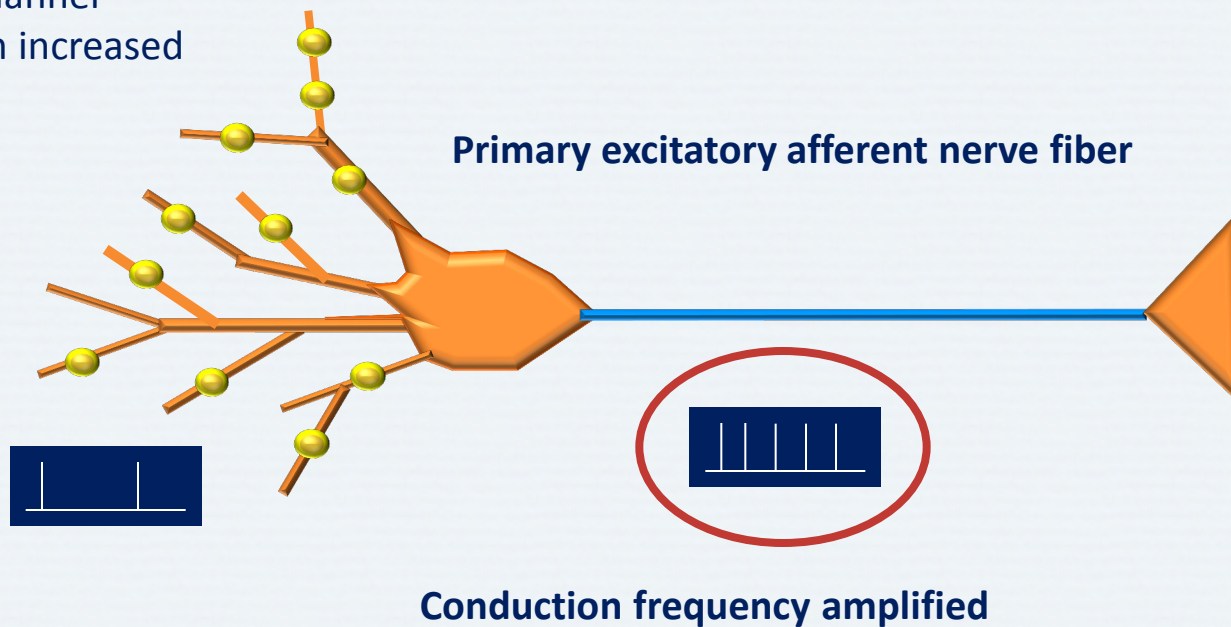
Ectopic Discharges

Nerve lesion induces hyperactivity due to changes in ion channel function.

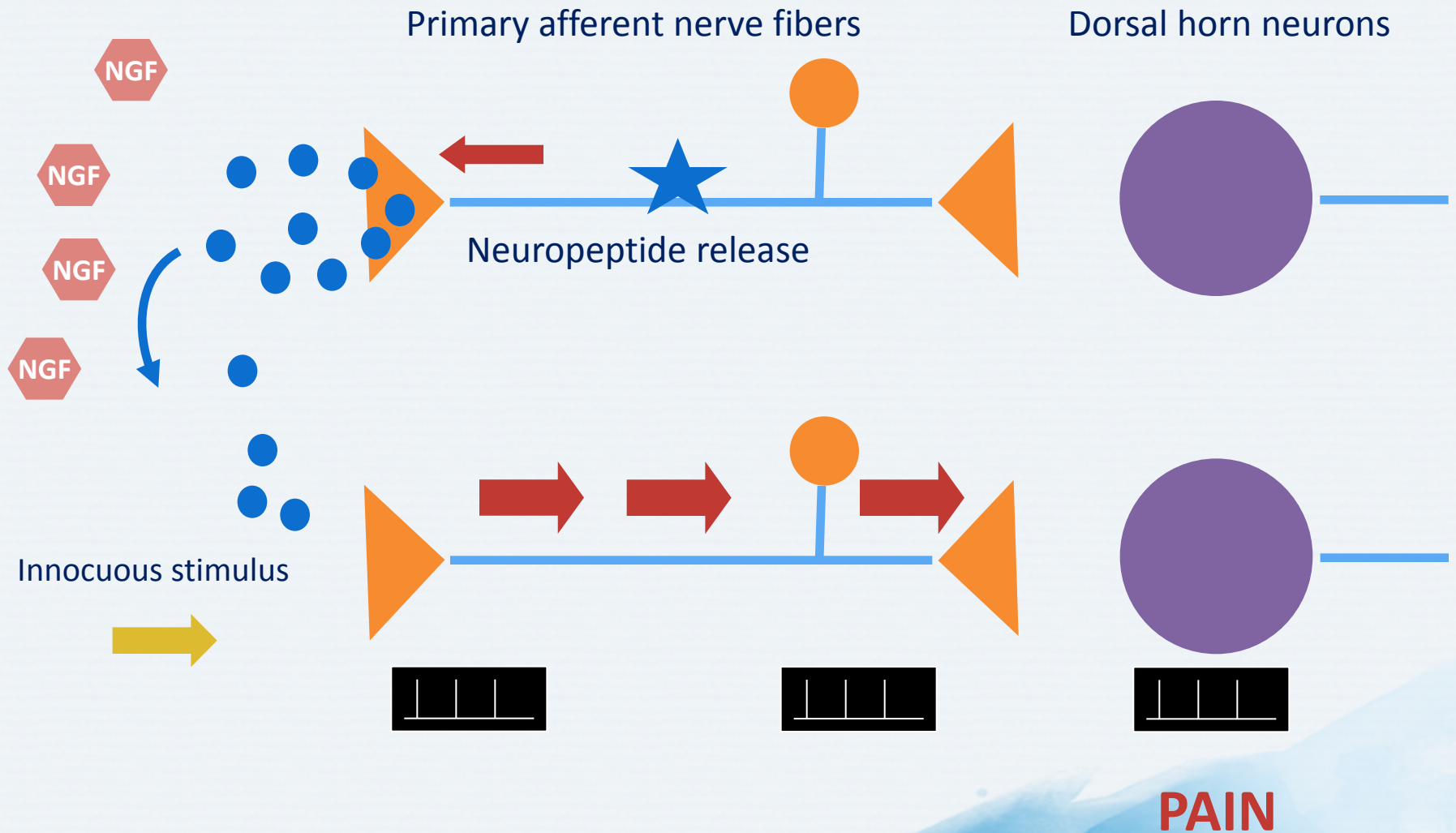


Ectopic Discharges

- Sodium channel expression increased

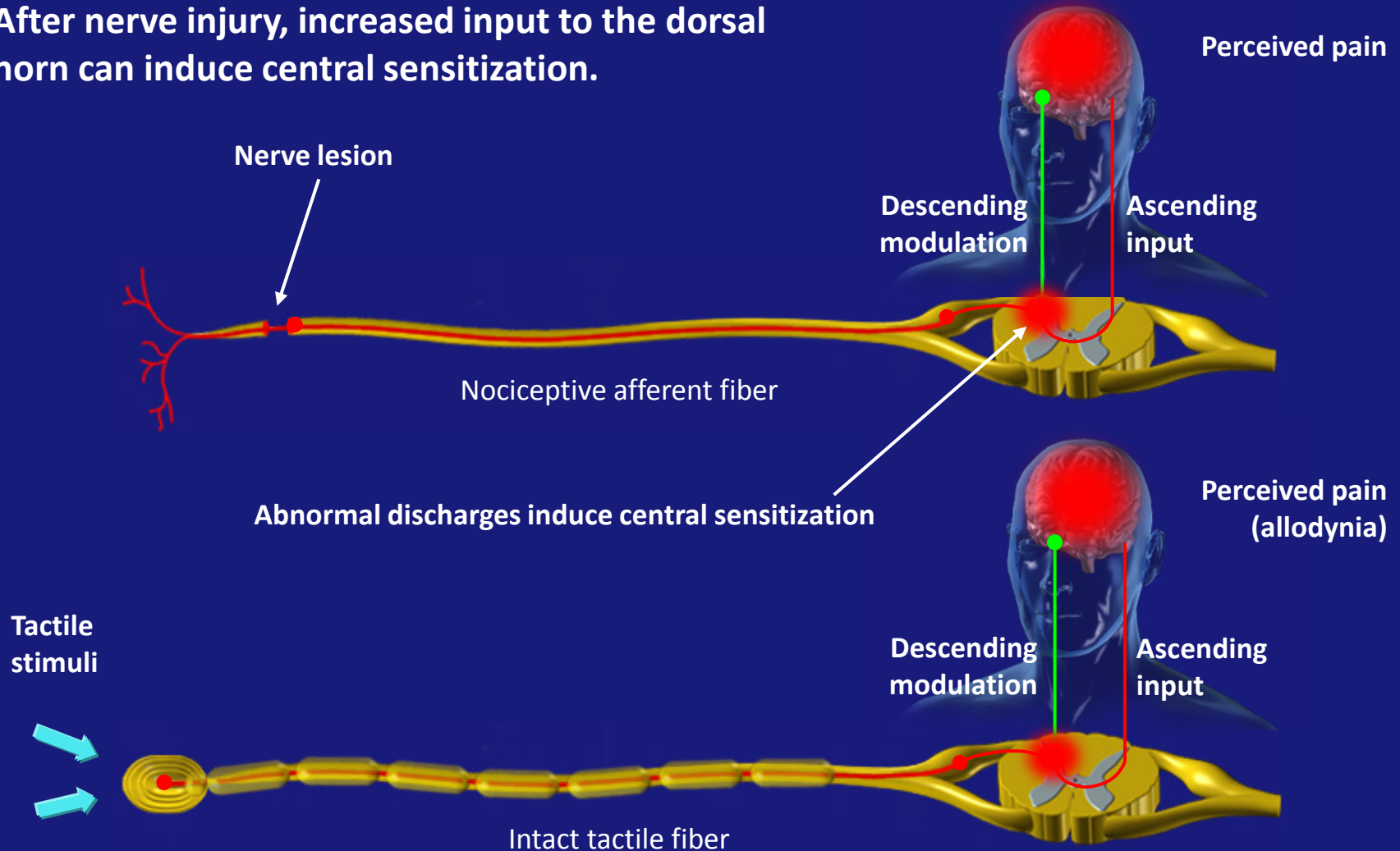


Peripheral Sensitization



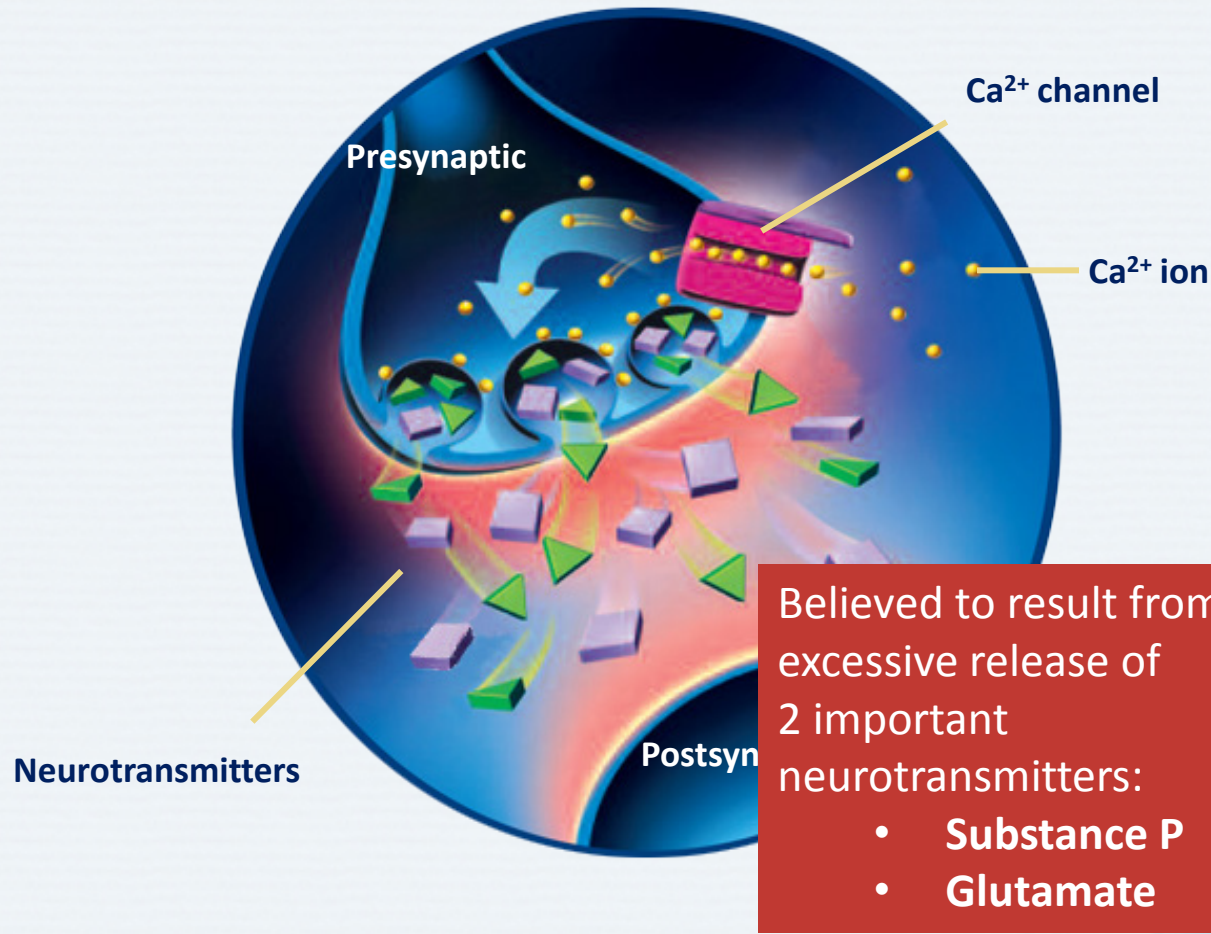
Central Sensitization

After nerve injury, increased input to the dorsal horn can induce central sensitization.

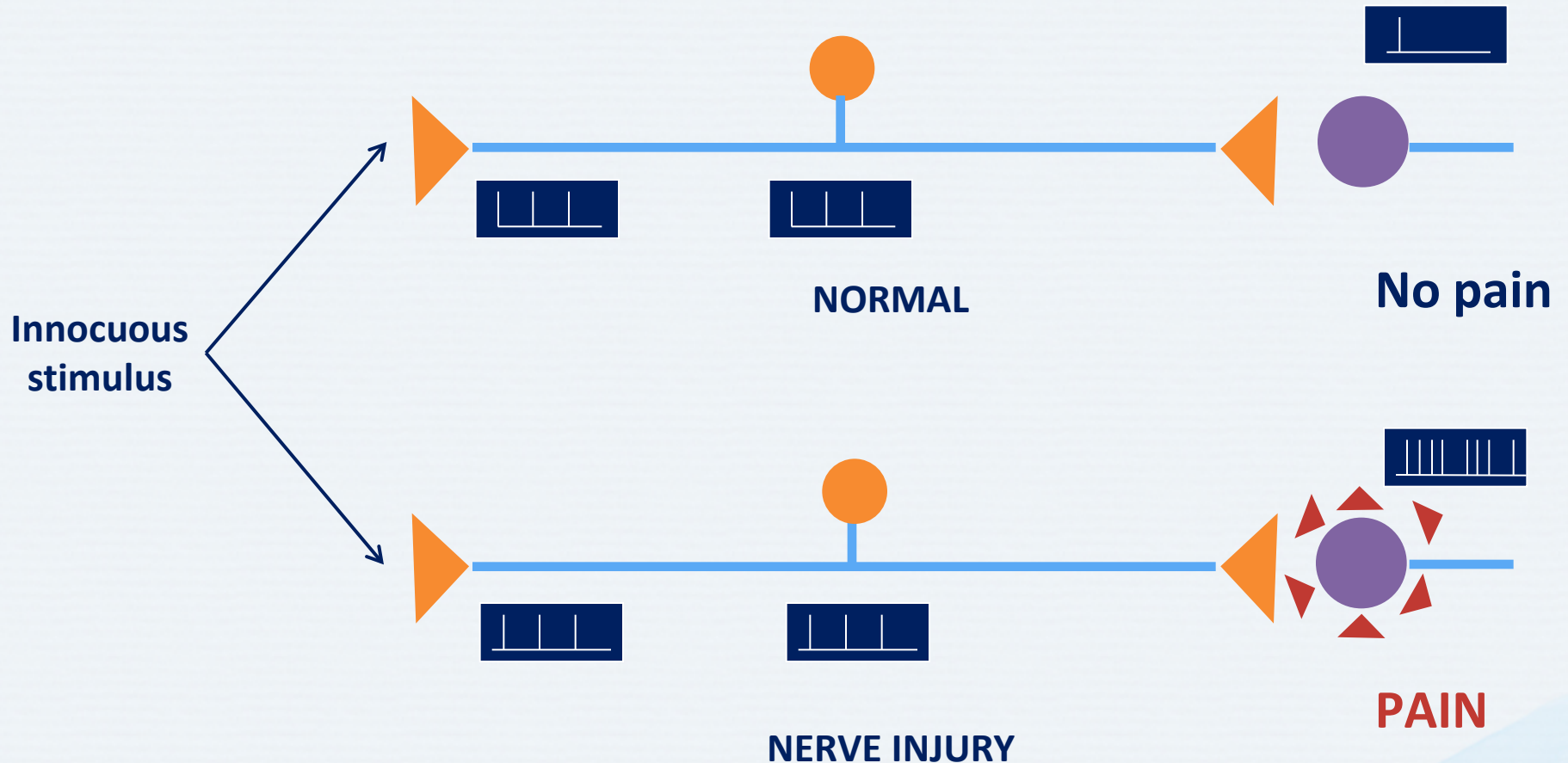


Adapted from: Campbell JN, Meyer RA. *Neuron* 2006; 52(1):77-92; Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10):1979-86; Henriksson KG. *J Rehabil Med* 2003; 41(Suppl):89-94; Larson AA et al. *Pain* 2000; 87(2):201-11; Marchand S. *Rheum Dis Clin North Am* 2008; 34(2):285-309; Rao SG. *Rheum Dis Clin North Am* 2002; 28(2):235-59; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14; Staud R, Rodriguez ME. *Nat Clin Pract Rheumatol* 2006; 2(2):90-8; Vaerø H et al. *Pain* 1988; 32(1):21-6; Woolf CJ et al. *Ann Intern Med* 2004; 140(6):441-51.

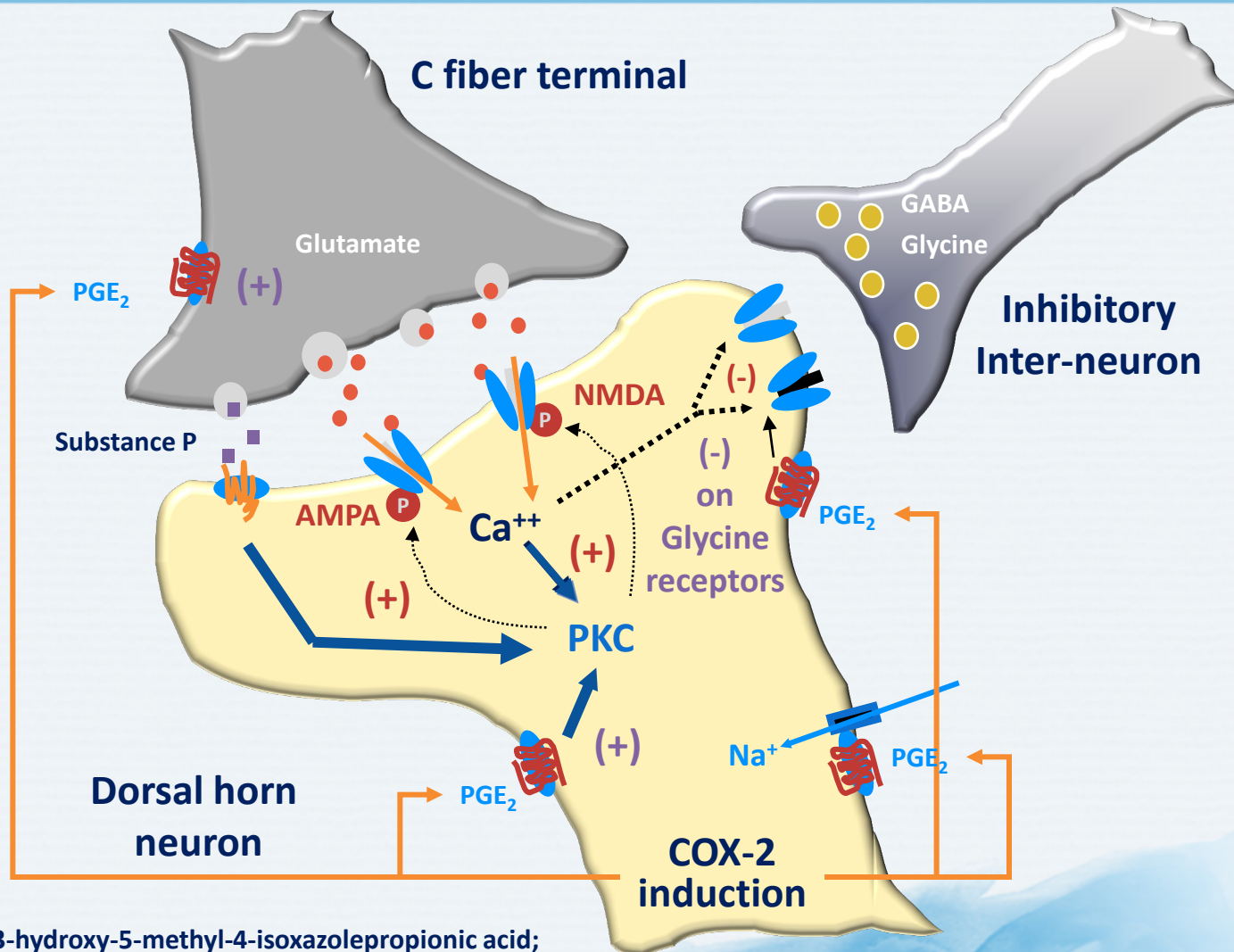
Central Sensitization



Central Sensitization after Nerve Injury



Central Sensitization

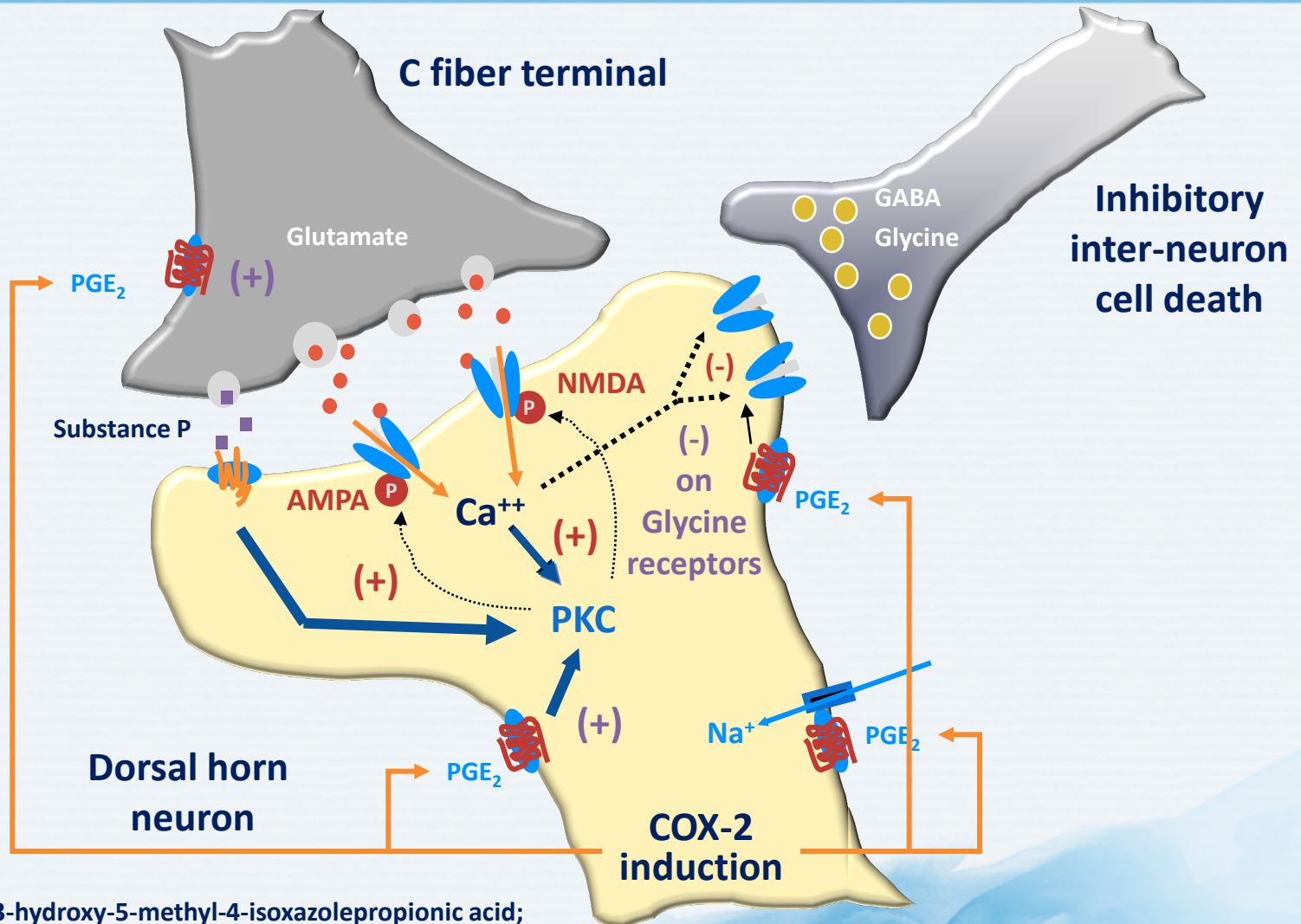


AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;

GABA = γ -aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Central Sensitization

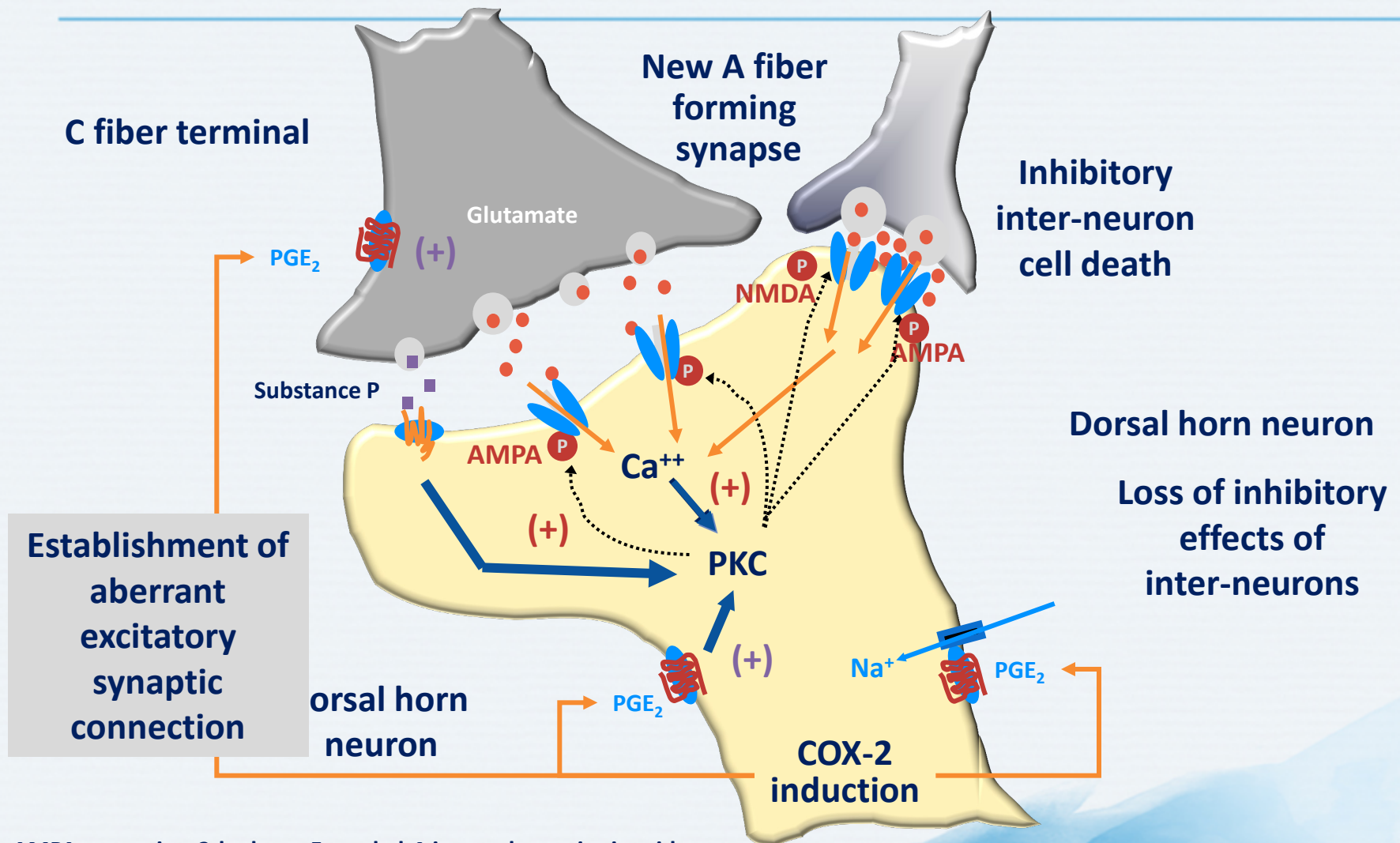


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Central Sensitization



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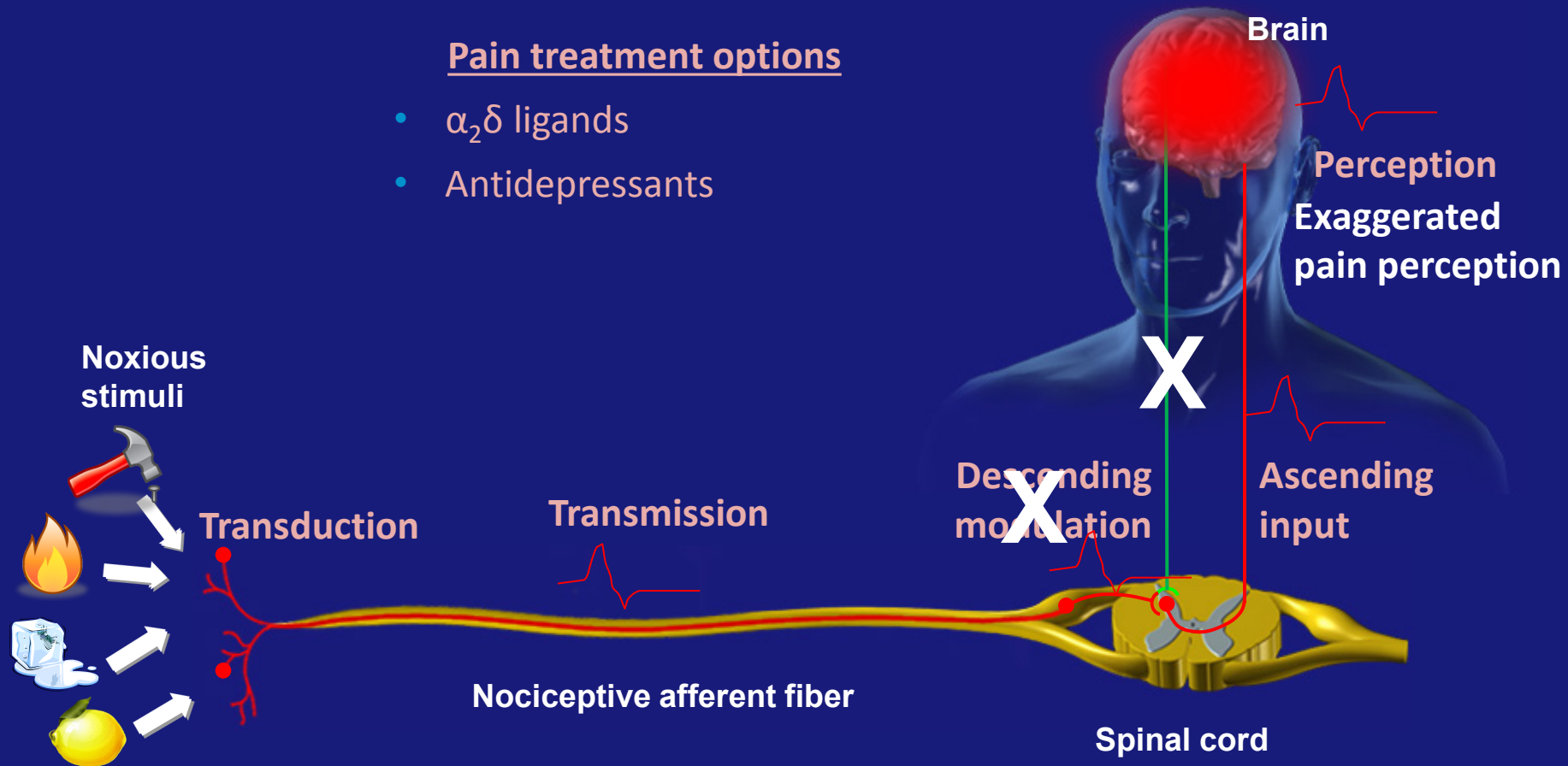
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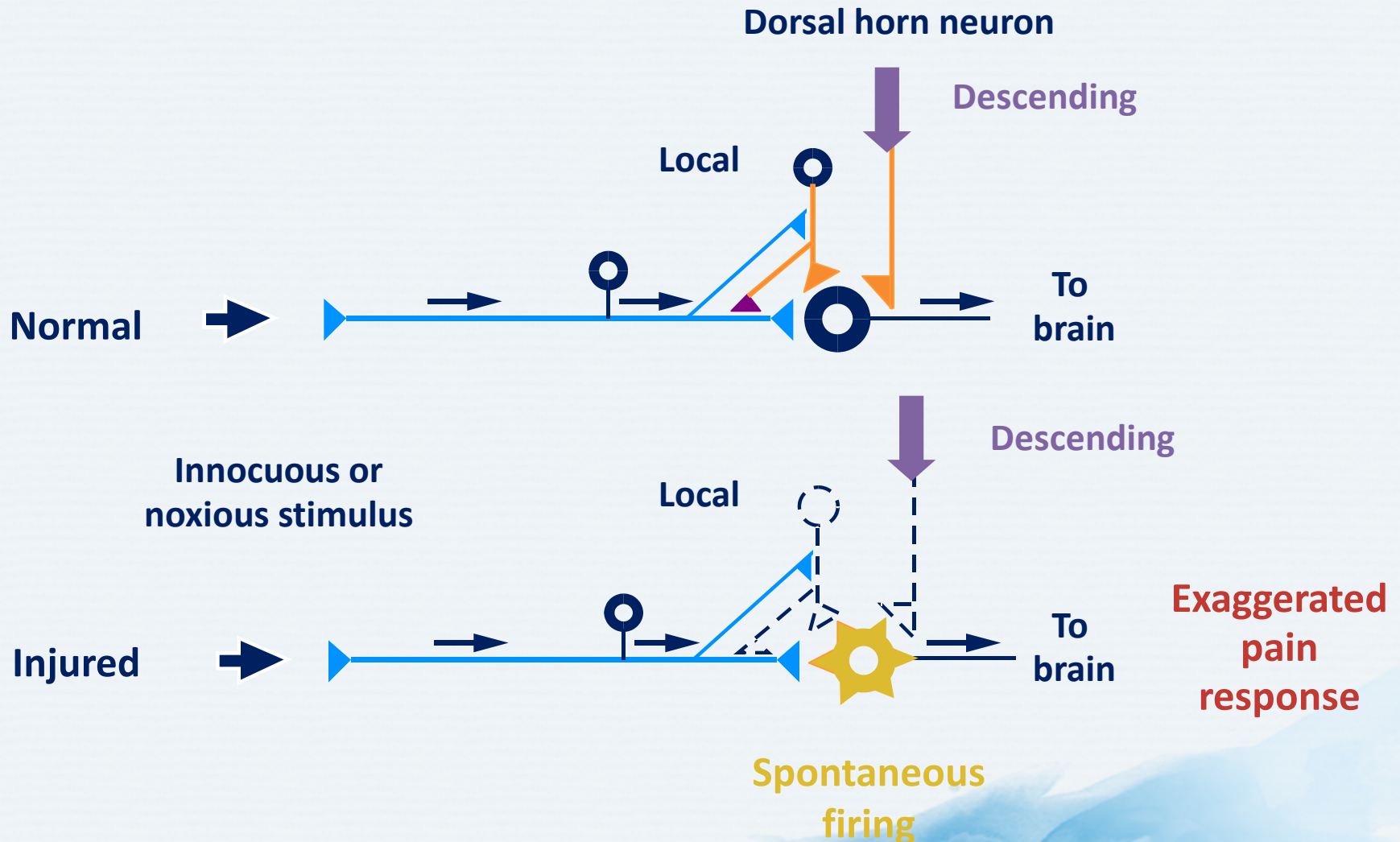
Loss of Inhibitory Control: Disinhibition

Pain treatment options

- $\alpha_2\delta$ ligands
- Antidepressants



Loss of Inhibitory Controls



Summary

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Pathophysiology: Summary

- Neuropathic pain is pain caused by a lesion or disease of the somatosensory system
 - It is characterized by positive and negative sensory symptoms
 - Peripheral and central mechanisms mediate neuropathic pain independent of etiology
 - Hyperexcitability
 - Sensitization
 - Loss of inhibitory controls
- 