# PATHOPHYSIOLOGY

## Overview

### Pathophysiological Classification of Pain

### Central sensitization/ dysfunctional pain

### Nociceptive pain

- Somatic
- Visceral

Multiple pain mechanisms may coexist (mixed pain)

#### **Neuropathic pain**

- Peripheral
- Central

Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90; Jensen TS *et al. Pain* 2011; 152(10):2204-5; Julius D *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Ross E. *Expert Opin Pharmacother* 2001; 2(1):1529-30; Webster LR. *Am J Manag Care* 2008; 14(5 Suppl 1):S116-22; Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

### What is neuropathic pain?

Neuropathic Pain Pain caused by a lesion or disease of the somatosensory nervous system

Peripheral Neuropathic Pain Pain caused by a lesion or disease of the peripheral somatosensory nervous system Central Neuropathic Pain Pain caused by a lesion or disease of the central somatosensory nervous system

International Association for the Study of Pain. *IASP Taxonomy, Changes in the 2011 List.* Available at: <u>http://www.iasp-pain.org/AM/Template.cfm?Section=Pain\_Definitions</u>. Accessed: July 15, 2013.

### Nociceptive vs. Neuropathic Pain

### Nociceptive

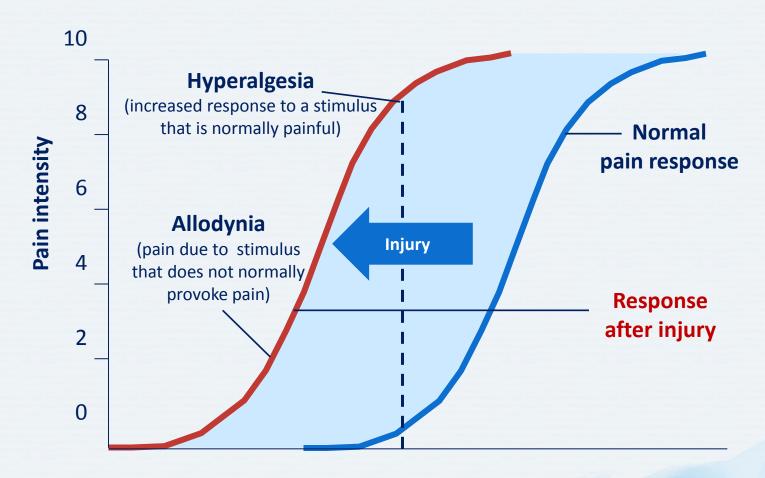
- Usually aching or throbbing and well-localized
- Usually time-limited (resolves when damaged tissue heals), but can be chronic
- Generally responds to conventional analgesics

### Neuropathic

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

Dray A. *Br J Anaesth* 2008; 101(1):48-58; Felson DT. *Arthritis Res Ther* 2009; 11(1):203; International Association for the Study of Pain. *IASP Taxonomy*. Available at: <u>http://www.iasp-pain.org/AM/Template.cfm?Section=Pain\_Definitions</u>. Accessed: July 15, 2013; McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain*. 5th ed. Elsevier; London, UK: 2006; Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

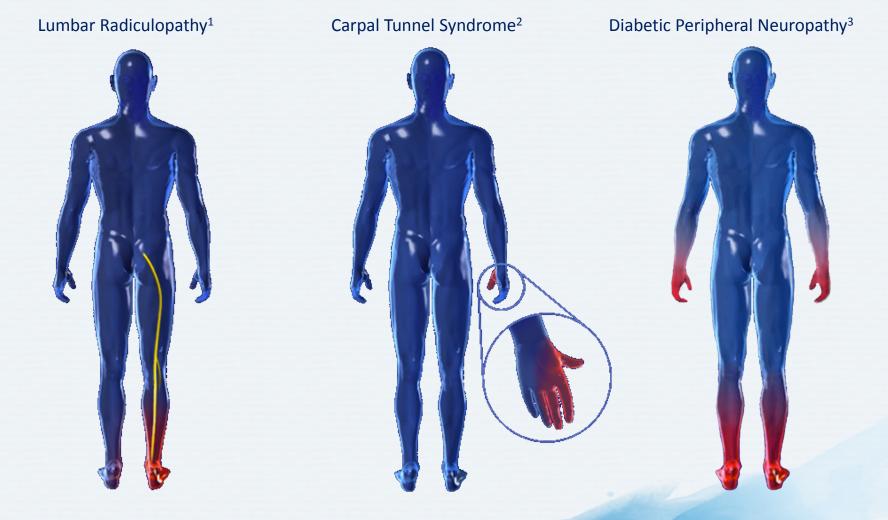
### Neuropathic Pain Is Characterized by Changes in Pain Response to Painful Stimuli



**Stimulus intensity** 

# Etiology

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



Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90;
Michelsen H, Posner MA. *Hand Clin* 2002; 18(2):257-68;
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**







#### Radiculopathy

Nerve trauma

Surgery

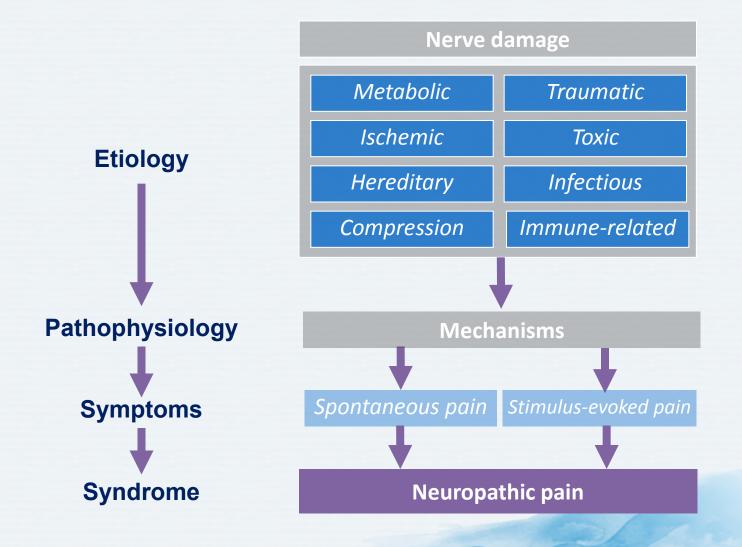
Baron R *et al. Lancet Neurol* 2010; 9(8):807-19; McMahon SB, Koltzenburg M. *Wall and Melzack's Textbook of Pain*. 5th ed. Elsevier; London, UK: 2006.

## **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

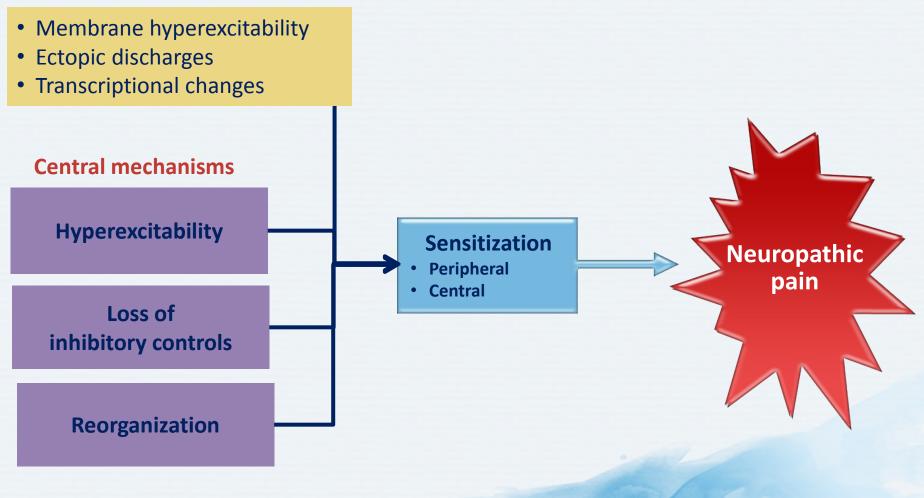
### **Development of Neuropathic Pain**



Woolf CJ, Mannion RJ. Lancet 1999; 353(9168):1959-64.

## Pathophysiology of Neuropathic Pain

#### **Peripheral mechanisms**



Moisset X, Bouhassira D. *Neuroimage* 2007; 37(Suppl 1):S80-8; Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

# 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	Αβ	Normal touch	Normal function
	Noxious Mechanical Thermal Chemical	Aδ nociceptor C nociceptor	Normal sharp pain Normal burning pain	
Decreased	Innocuous Mechanical	Αβ	Tactile hypoanesthesia	Decreased transmission of impulses
	Noxious Mechanical Thermal Chemical	Aδ nociceptor C nociceptor	Mechanical Heat or cold hypoalgesia	
Increased	Innocuous Mechanical	Αβ	Dynamic mechanical allodynia	Many theories (e.g., sensitization)
	Noxious Mechanical Thermal Chemical	Aδ nociceptor C nociceptor	Mechanical Heat or cold hyperalgesia	Many theories (e.g., wind-up, peripheral sensitization)

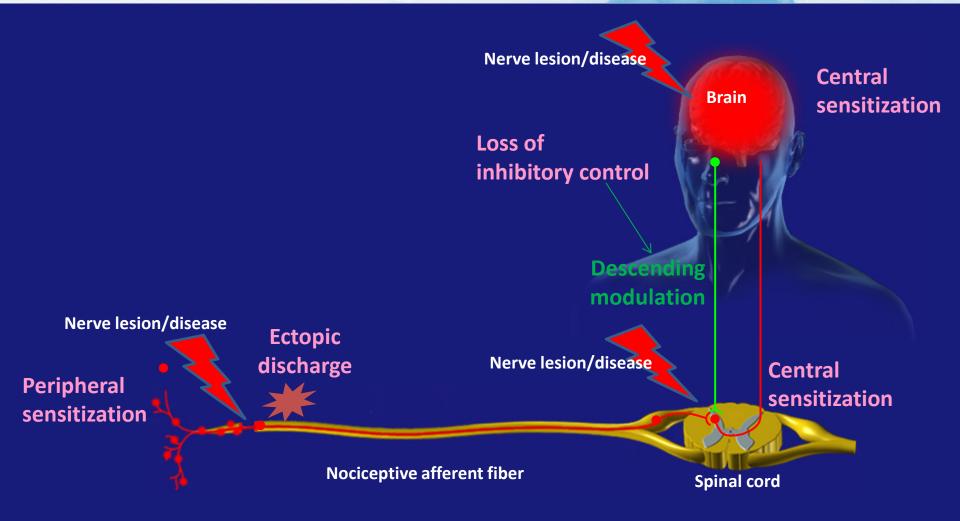
Adapted from: Doubell TP *et al.* In: Wall PD, Melzack R (eds). *Textbook of Pain*. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999.

## Neuropathic Pain: A $\beta$ , A $\delta$ and C Fibers

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

Dworkin RH. Clin J Pain 2002; 18(6):343-9; Raja SN et al. In: Wall PD, Melzack R (eds). Textbook of Pain. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999.

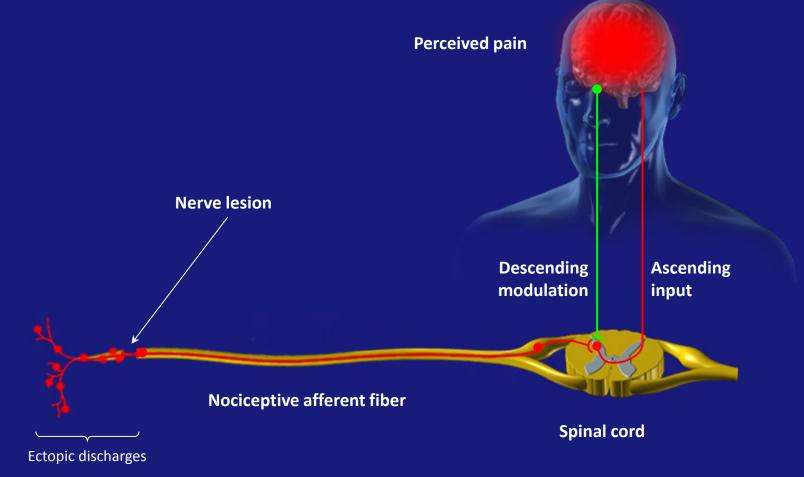
## **Mechanisms of Neuropathic Pain**



Gilron I *et al. CMAJ* 2006; 175(3):265-75; Jarvis MF, Boyce-Rustay JM. *Curr Pharm Des* 2009; 15(15):1711-6; Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

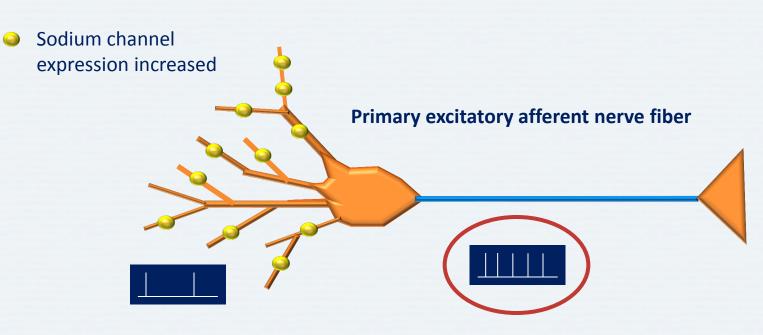
## **Ectopic Discharges**

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



England JD *et al. Neurology* 1996;47(1):272-6; Ochoa JL, Torebjörk HE. *Brain* 1980; 103(4):835-53; Sukhotinsky I *et al. Eur J Pain* 2004; 8(2):135-43; Taylor BK. *Curr Pain Headache Rep* 2009; 13(3):208-14;

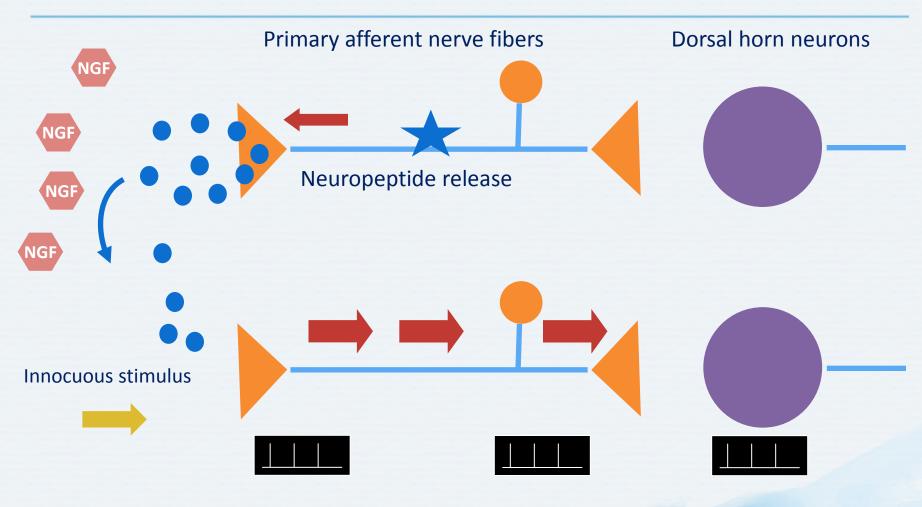
### **Ectopic Discharges**



**Conduction frequency amplified** 

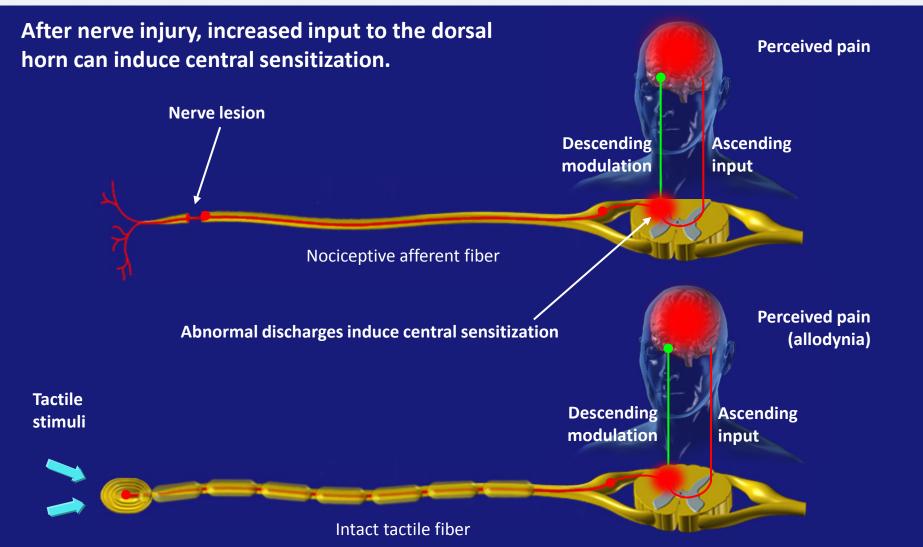
England JD *et al. Neurology* 1996; 47(1):272-6; Ochoa JL, Torebjörk HE. *Brain* 1980; 103(4):835-53; Sukhotinsky I *et al. Eur J Pain* 2004; 8(2):135-43; Taylor BK. *Curr Pain Headache Rep* 2001; 5(2):151-61.

### **Peripheral Sensitization**

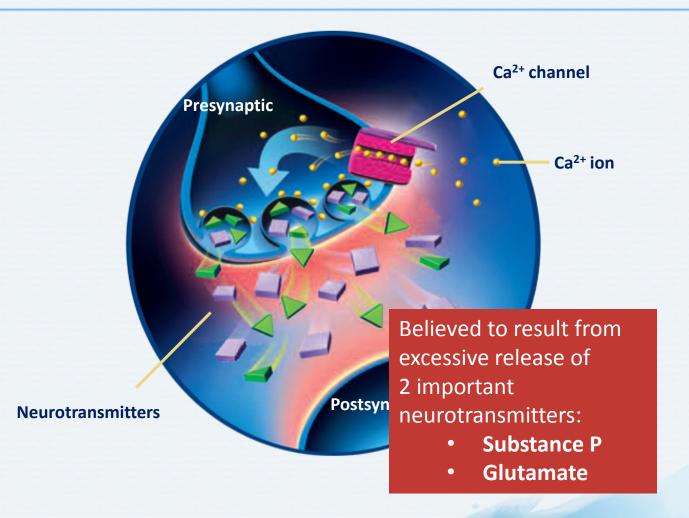


PAIN

Ørstavik K et al. Brain 2003; 126(Pt 3):567-78; Woolf CJ, Mannion RJ. Lancet 1999; 353(9168):1959-64.

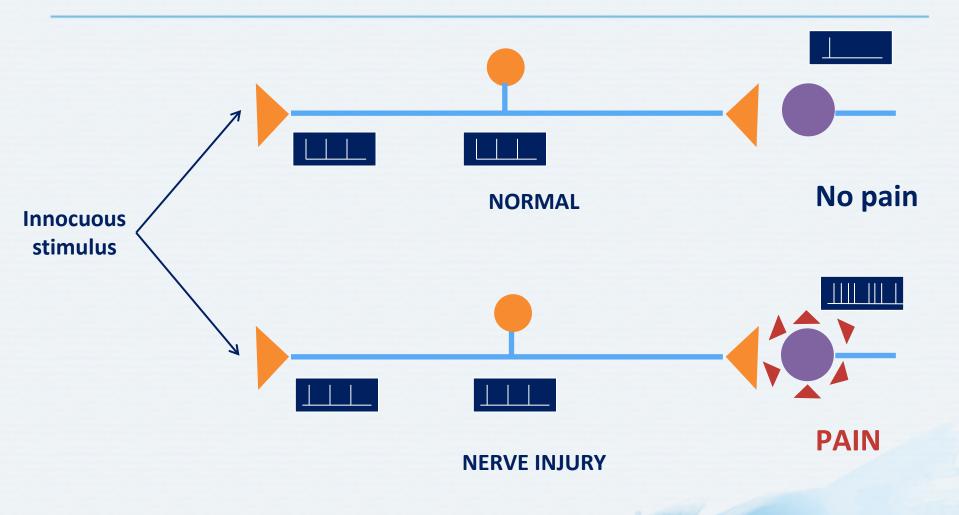


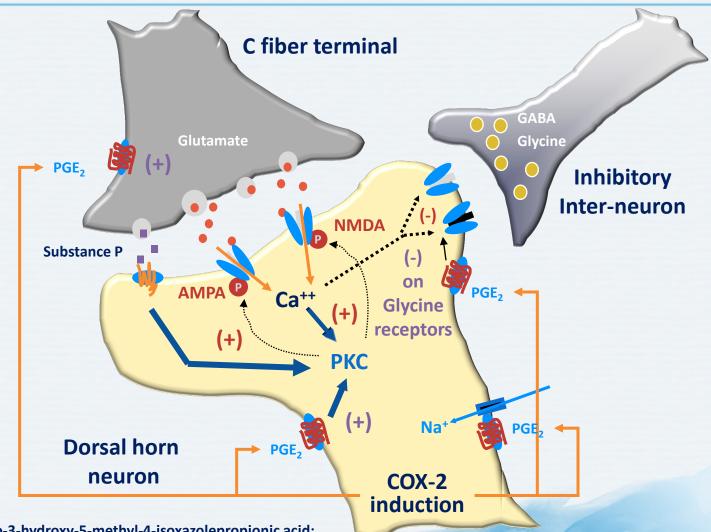
Adapted from: Campbell JN, Meyer RA. *Neuron* 2006; 52(1):77-92; Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10)1979-86; Henriksson KG. *J Rehabil Med* 2003; 41(Suppl):89-94; Larson AA *et al. Pain* 2000; 87(2):201-11; Marchand S. *Rheum Dis Clin North Am* 2008; 34(2):285-309; Rao SG. *Rheum 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; Vaerøy H *et al. Pain* 1988; 32(1):21-6; Woolf CJ *et al. Ann Intern Med* 2004; 140(6):441-51.



Costigan M et al. Annu Rev Neurosci 2009; 32:1-32; Costigan M et al. In: Siegel GJ et al (eds). Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 7th ed. Elsevier Academic Press; Burlington, MA: 2006; Staud R. Arthritis Res Ther 2006; 8(3):208-14.

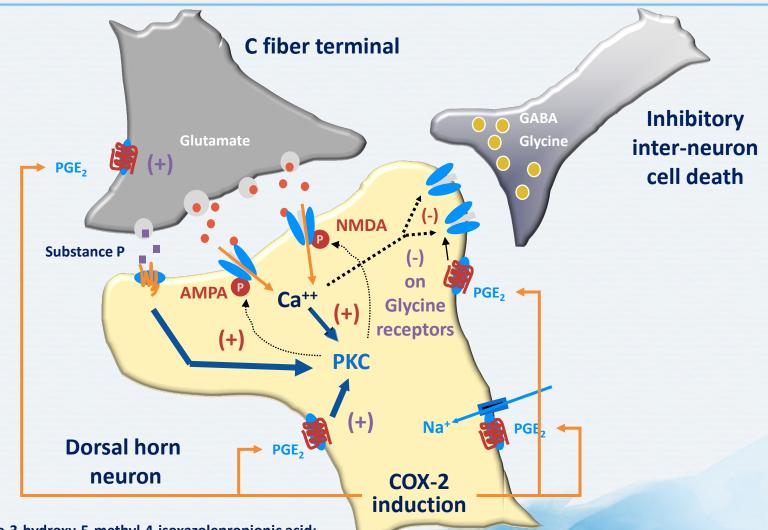
### **Central Sensitization after Nerve Injury**





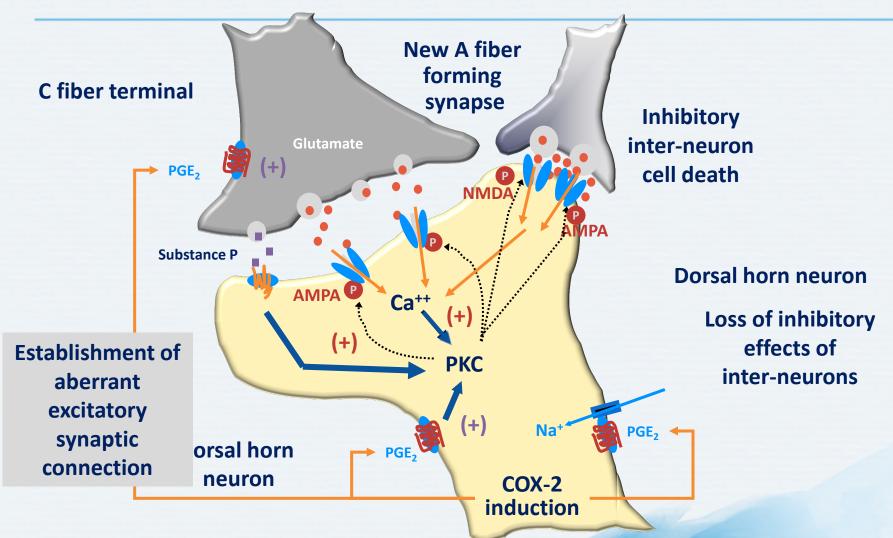
AMPA =  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;

**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.



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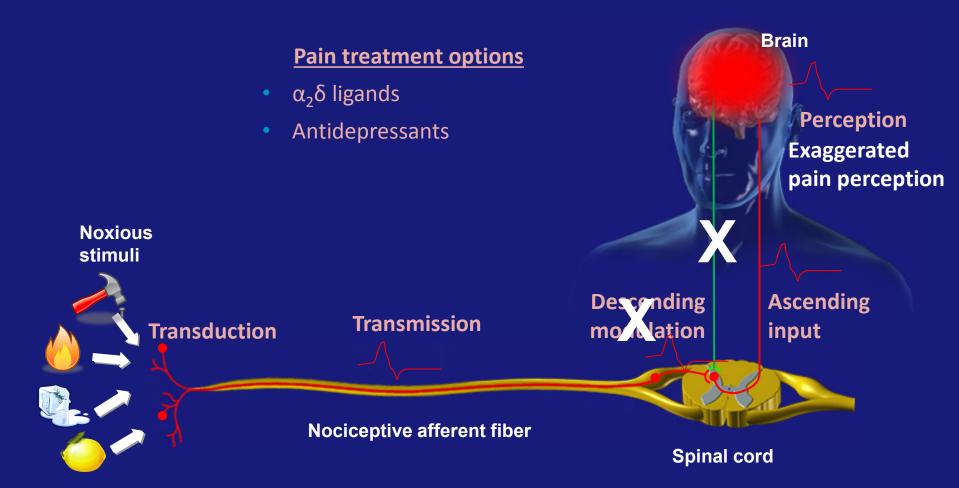
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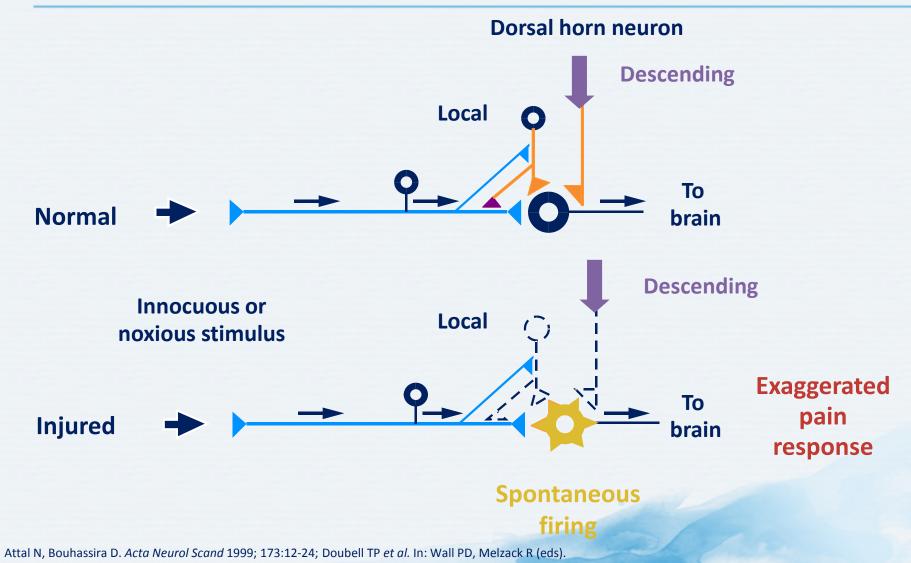
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# Loss of Inhibitory Control: Disinhibition



Attal N, Bouhassira D. Acta Neurol Scand 1999; 173:12-24; Doubell TP et al. In: Wall PD, Melzack R (eds). Textbook of Pain. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999; Woolf CJ, Mannion RJ. Lancet 1999; 353(9168):1959-64.

### Loss of Inhibitory Controls



Textbook of Pain. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999; Woolf CJ, Mannion RJ. Lancet 1999; 353(9168):1959-64.

## Summary

### 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