PATHOPHYSIOLOGY

Overview

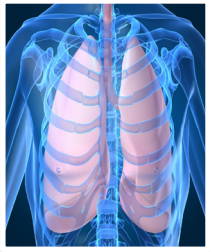
What is pain?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

International Association for the Study of Pain (IASP) 2011

International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. Accessed: July 15, 2013.

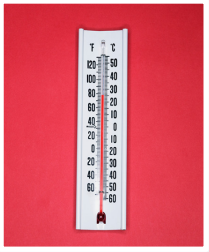
Pain Is the 5th Vital Sign



Respiration

Pulse

Blood pressure



Temperature

Pain

Phillips DM. *JAMA* 2000; 284(4):428-9.

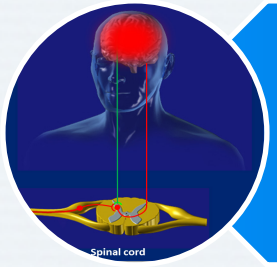
Overview of Pain

Protective role: vital early warning system

- Senses noxious stimuli
- Triggers withdrawal reflex and heightens sensitivity after tissue damage to reduce risk of further damage

Unpleasant experience:

- Suffering – physical, emotional and cognitive dimensions
- Continuous unrelieved pain can affect physical (e.g., cardiovascular, renal, gastrointestinal systems, etc.) and psychological states

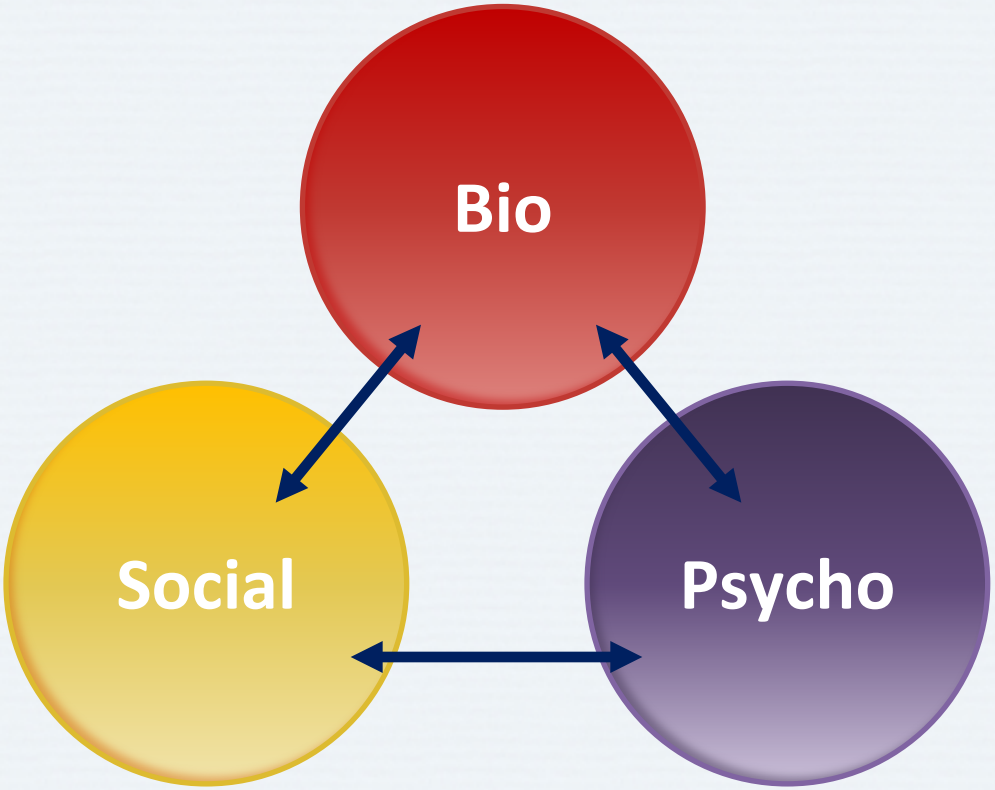


Maladaptive response:

- Neuropathic and central sensitization/dysfunctional pain
- Not protective
- Lessens quality of life

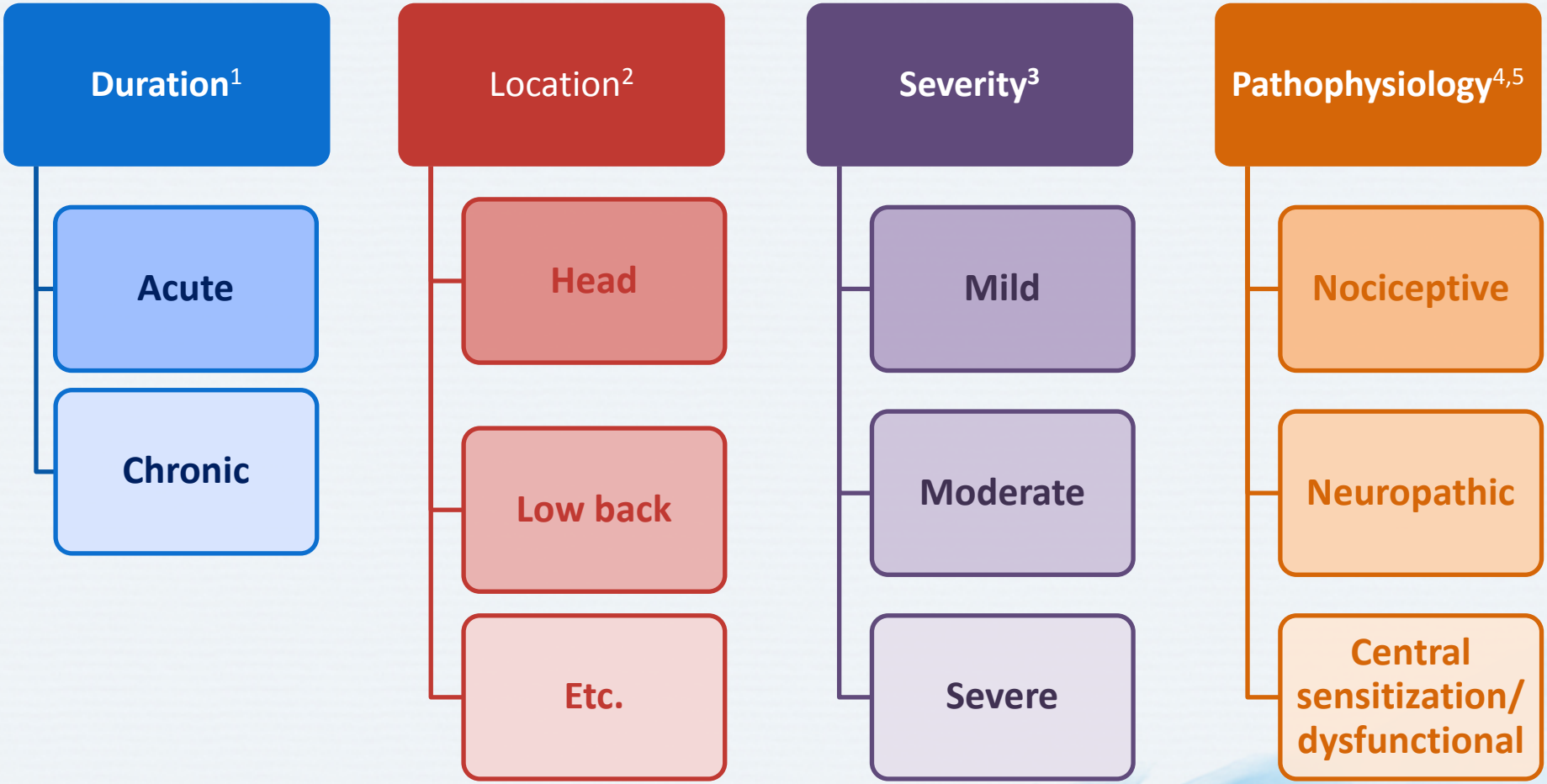
Costigan M *et al*. *Annu Rev Neurosci* 2009; 32:1-32; Wells N *et al.* In: Hughes RG (ed). *Patient Safety and Quality: An Evidence-Based Handbook for Nurses.* Agency for Healthcare Research and Quality; Rockville, MD: 2008; Woolf CJ *et al. Ann Intern Med* 2004; 140(6):441-51.

Biopsychosocial Model of Pain



Gatchel RJ *et al. Psychol Bull* 2007; 133(4):581-624.

Pain Classification



1. McMahon SB, Koltzenburg M. In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
2. Loeser D *et al* (eds). *Bonica's Management of Pain*. 3rd ed. Lippincott Williams & Wilkins; Hagerstown, MD: 2001;
3. Hanley MA *et al. J Pain* 2006; 7(2):129-33; 4. Jensen TS *et al. Pain* 2011; 152(10):2204-5; 5. Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

The Pain Continuum

Insult

Time to resolution

Acute pain → **Chronic pain**

Normal, time-limited response to 'noxious' experience (less than 3 months)

- Usually obvious tissue damage
- Serves a protective function
- Pain resolves upon healing

Pain that has persisted beyond normal tissue healing time (usually more than 3 months)

- Usually has no protective function
- Degrades health and function

Acute pain may become chronic

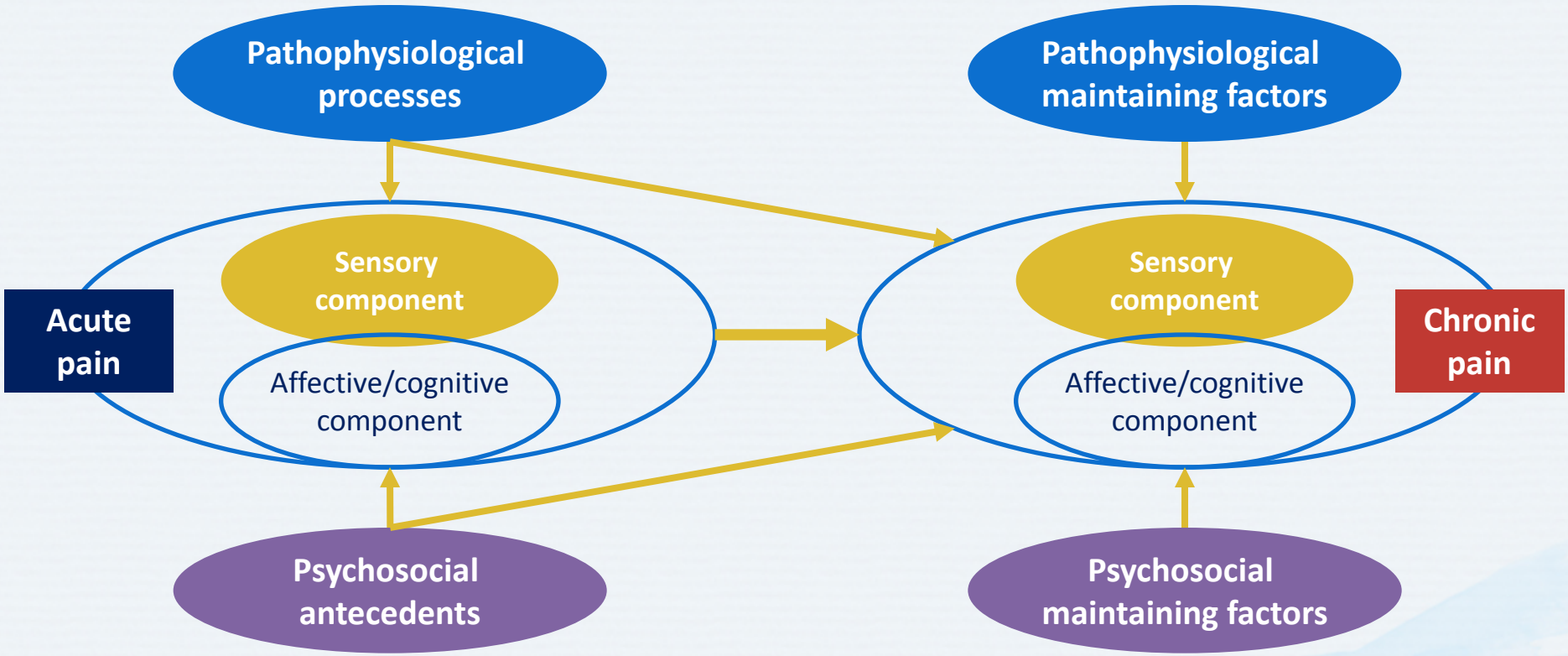
Chapman CR, Stillman M. In: Kruger L (ed). *Pain and Touch*. Academic Press; New York, NY: 1996; Cole BE. *Hosp Physician* 2002; 38(6):23-30;
International Association for the Study of Pain. *Unrelieved Pain Is a Major Global Healthcare Problem.*
Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Press_Release&Template=/CM/ContentDisplay.cfm&ContentID=2908. Accessed: July 24: 2013;
National Pain Summit Initiative. *National Pain Strategy: Pain Management for All Australians.*
Available at: http://www.iasp-pain.org/PainSummit/Australia_2010PainStrategy.pdf. Accessed: July 24, 2013;
Turk DC, Okifuji A. In: Loeser D *et al* (eds.). *Bonica's Management of Pain*. 3rd ed. Lippincott Williams & Wilkins; Hagerstown, MD: 2001.

Acute vs. Chronic Pain

Acute	Chronic
• Sudden, sharp, intense, localized • Usually self-limited (<6 months) • May be associated with physiologic changes (e.g., sweating, increased heart rate, elevated blood pressure)	• Gnawing, aching, diffuse • No definite beginning or end • Varies in intensity; may remit briefly • Associated with psychological and social difficulties • Acute pain may be superimposed

Siddall PJ *et al.* In: Cousins MJ, Bridenbaugh PO (eds). *Neural Blockade in Clinical Anesthesia and Management of Pain.* 3rd ed. Lippincott Williams & Wilkins; Philadelphia, PA: 1998; Thienhaus O, Cole BE. Classification of pain. In: Weiner R. *Pain Management: A Practical Guide for Clinicians*. CRC Press; Boca Raton, FL: 2002.

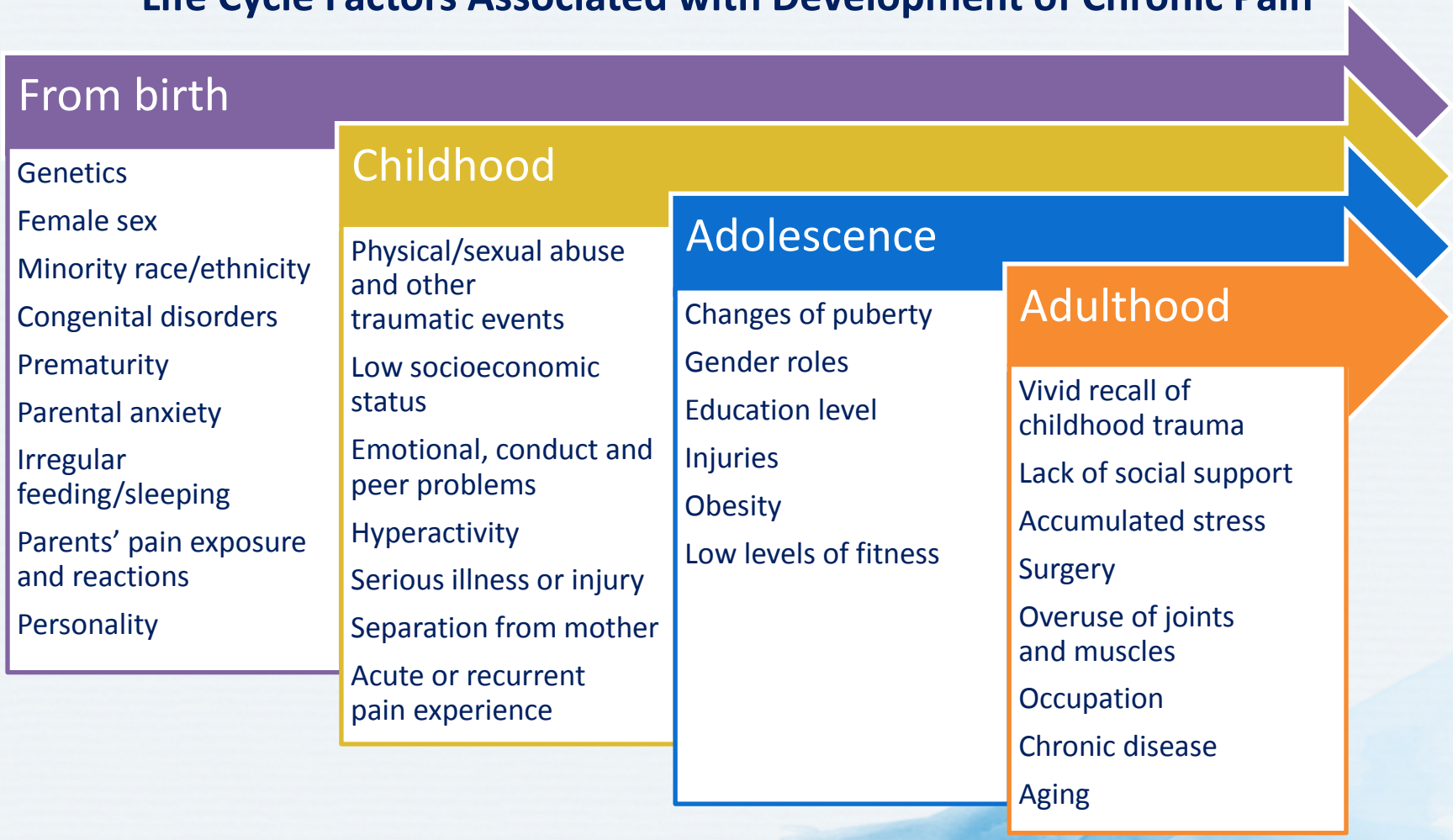
Acute Pain Can Become Chronic



Dworkin RH. *Pain Forum* 1997; 6(2):127-36.

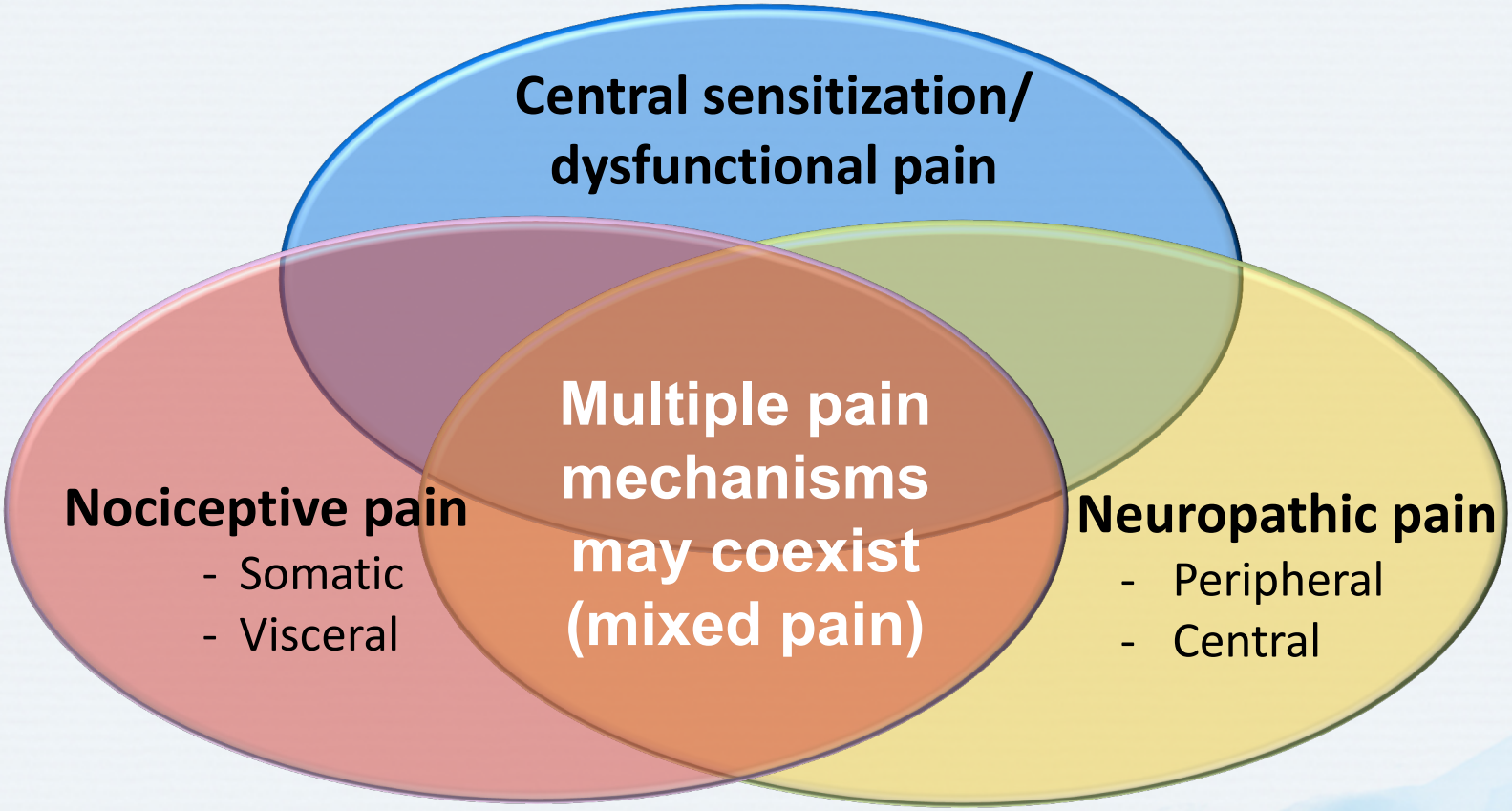
Acute Pain Can Become Chronic

Life Cycle Factors Associated with Development of Chronic Pain



Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* The National Academies Press; Washington, DC: 2011.

Pathophysiological Classification of Pain



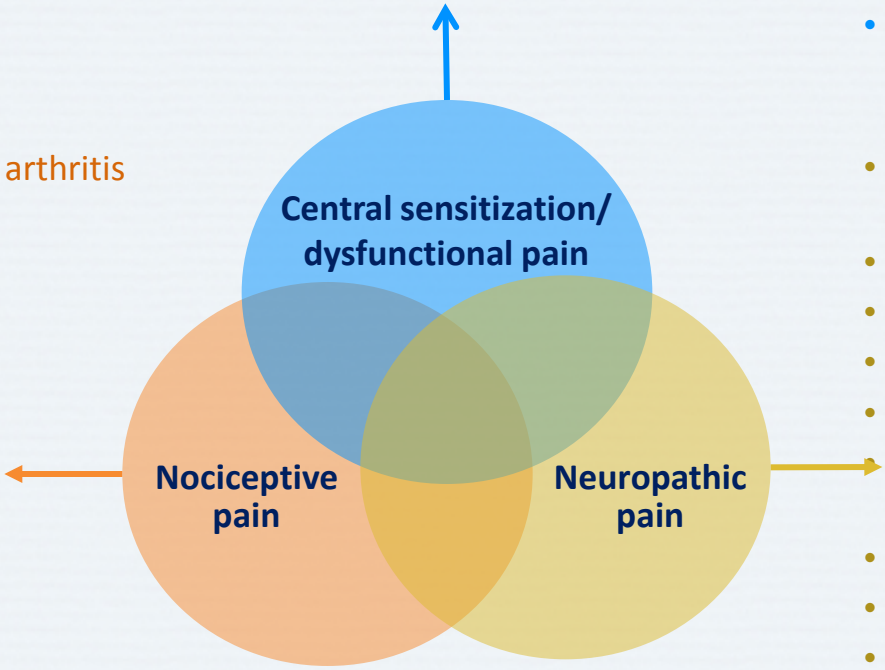
Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90; Jensen TS *et al. Pain* 2011; 152(10):2204-5;
Julius D *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
Ross E. *Expert Opin Pharmacother* 2001; 2(1):1529-30; Webster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

Several Pathophysiologies May Contribute to Chronic Pain

- Fibromyalgia
- Irritable bowel syndrome
- Functional dyspepsia
- Interstitial cystitis

- Neck and back pain (no structural pathology)
- Myofascial pain (temporomandibular joint disorder)

- Pelvic pain syndrome
- Restless leg syndrome
- Headaches
- Complex regional pain syndrome

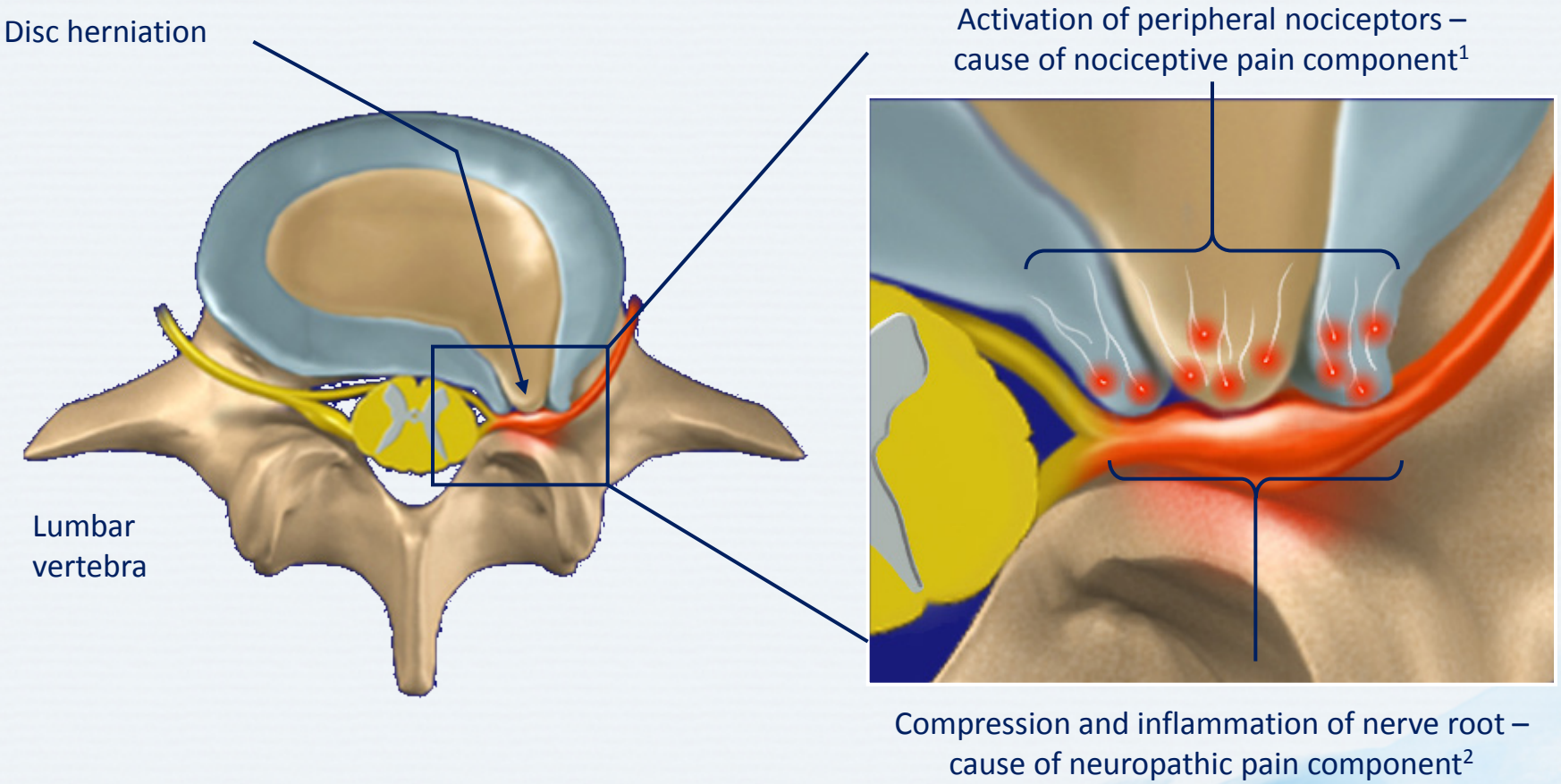


- Osteoarthritis, rheumatoid arthritis
- Tendonitis, bursitis
- Gout
- Inflammatory myositis
- Sjogren's syndrome
- Cushing's disease
- Tumor-related nociceptive pain
- Neck and back pain + structural pathology
- Sickle-cell disease
- Crohn's disease

- Postherpetic neuralgia, diabetic peripheral neuropathy
- Sciatica/stenosis
- Entrapment syndromes
- Spinal cord injury pain
- *Tumor-related neuropathy*
- *Chemotherapy-induced* neuropathy
- Small fiber neuropathy
- Post-stroke pain
- Multiple sclerosis pain
- Persistent postoperative pain

Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-S15.

Example of Coexisting Pain: Herniated Disc Causing Low Back Pain and Lumbar Radicular Pain



1. Brisby H. *J Bone Joint Surg Am* 2006; 88(Suppl 2):68-71.
2. Freynhagen R, Baron R. *Curr Pain Headache Rep* 2009; 13(3):185-90.

Etiology

Many Common Conditions are Painful

- Headache, migraine
- Trauma
- Musculoskeletal injury
- Muscle spasm
- Carpal tunnel syndrome
- Low back pain
- Osteoporosis
- Arthritis*
- Systemic lupus erythematosus
- Gout
- Herpes zoster
- Postherpetic neuralgia
- Peripheral neuropathy
- Fibromyalgia
- Cancer
- Surgery

***Includes osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis**

Merskey H *et al* (eds). *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms.* 2nd ed. IASP Press; Seattle, WA: 1994.

Pathophysiology

What is nociceptive pain?

Definition

- Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
- Can be somatic or visceral

Pain Quality

- Usually aching or throbbing
- Usually time-limited (resolves when damaged tissue heals)
- Usually well localized if somatic
- May be referred if visceral
- Can become chronic

Felson DT. *Arthritis Res Ther* 2009; 11(1):203; International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. 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.

Characteristics of Nociceptive Pain

Type of pain	Nociceptor location	Potential stimuli	Pain localization
Superficial somatic pain	Skin Subcutaneous tissue Mucous membranes	External mechanical, chemical or thermal events Dermatologic disorders	Well localized
Deep somatic pain	Muscles Tendons Joints Fasciae Bones	Overuse strain Mechanical injury Cramping Ischemia Inflammation	Localized or diffuse and radiating
Visceral pain	Visceral organs*	Organ distension Muscle spasm Traction Ischemia Inflammation	Well or poorly localized

***Visceral organs include the heart, lungs, gastrointestinal tract, pancreas, liver, gallbladder, kidneys and bladder.**

American Pain Society. *Pain: Current Understanding of Assessment, Management, and Treatments.* Available at: http://www.americanpainsociety.org/education/content/enduringmaterials.html. Accessed: October 8, 2013.

Examples of Nociceptive Pain

Type of Pain	Pain Quality	Signs and Symptoms	Examples
Superficial somatic pain	Sharp, pricking or burning sensation	Cutaneous tenderness Hyperalgesia Hyperesthesia Allodynia	Sun, chemical or thermal burns Skin cuts and contusions
Deep somatic pain	Usually dull or aching, cramping	Tenderness Reflex muscle spasm Sympathetic hyperactivity**	Arthritis pain Tendonitis Myofascial pain
Visceral pain*	Deep aching or sharp stabbing pain, which is often referred to cutaneous sites	Malaise Nausea Vomiting Sweating Tenderness Reflex muscle spasm	Colic Appendicitis Pancreatitis Peptic ulcer disease Bladder distension

***Visceral organs include the heart, lungs, gastrointestinal tract, pancreas, liver, gallbladder, kidneys and bladder.**
****Symptoms and signs of sympathetic (autonomic) nervous system hyperactivity include increased heart rate, blood pressure, and respiratory rate; sweating pallor; dilated pupils; nausea; vomiting dry mouth; and increased muscle tension.**

American Pain Society. *Pain: Current Understanding of Assessment, Management, and Treatments.* Available at: http://www.americanpainsociety.org/education/content/enduringmaterials.html. Accessed: October 8, 2013.

Somatic vs. Visceral Pain

Somatic

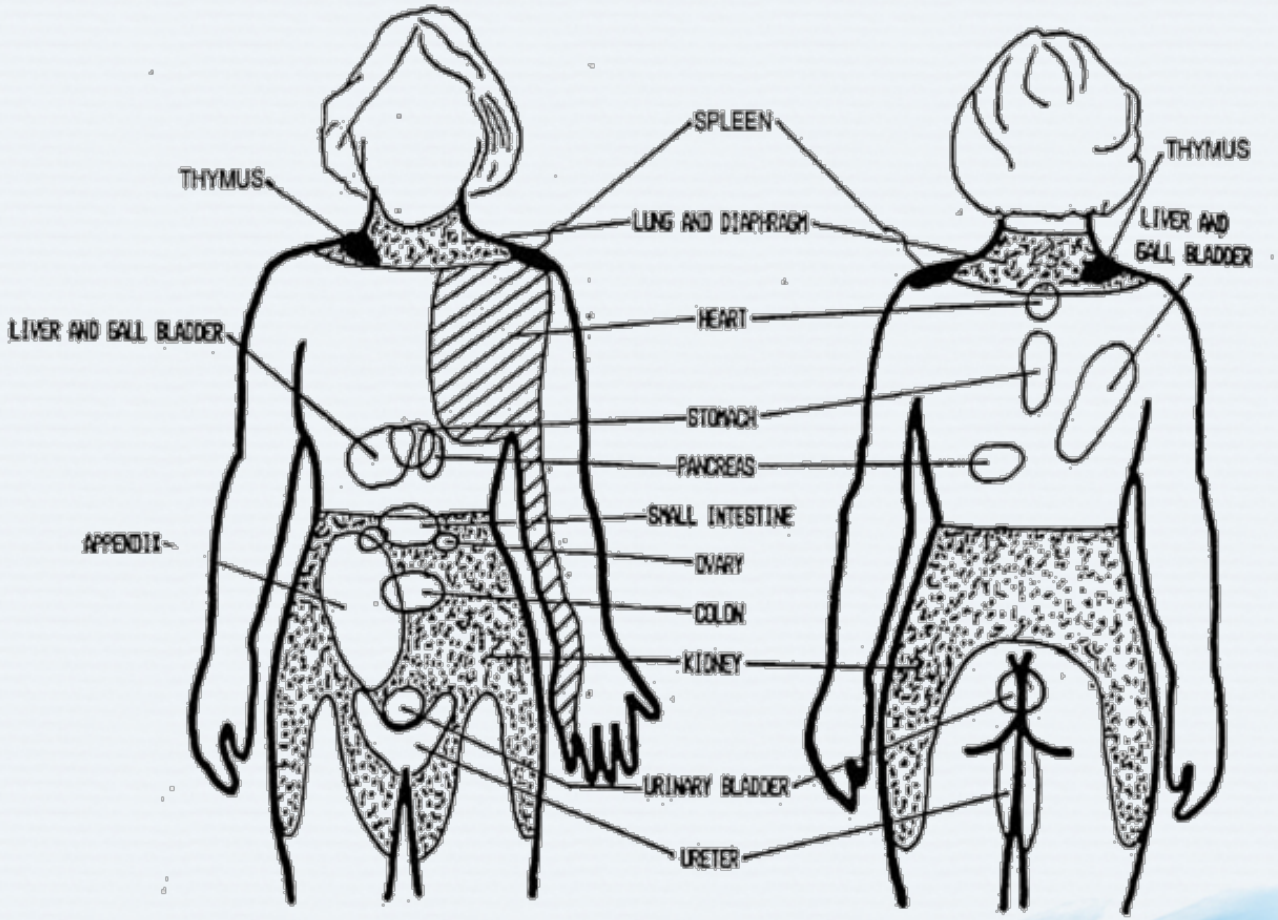
- Nociceptors are involved
- Often well localized
- Usually described as throbbing or aching
- Can be superficial (skin, muscle) or deep (joints, tendons, bones)

Visceral

- Involves hollow organ and smooth muscle nociceptors that are sensitive to stretching, hypoxia and inflammation
- Pain is usually referred, poorly localized, vague and diffuse
- May be associated with autonomic symptoms (e.g., pallor, sweating, nausea, blood pressure and heart rate changes)

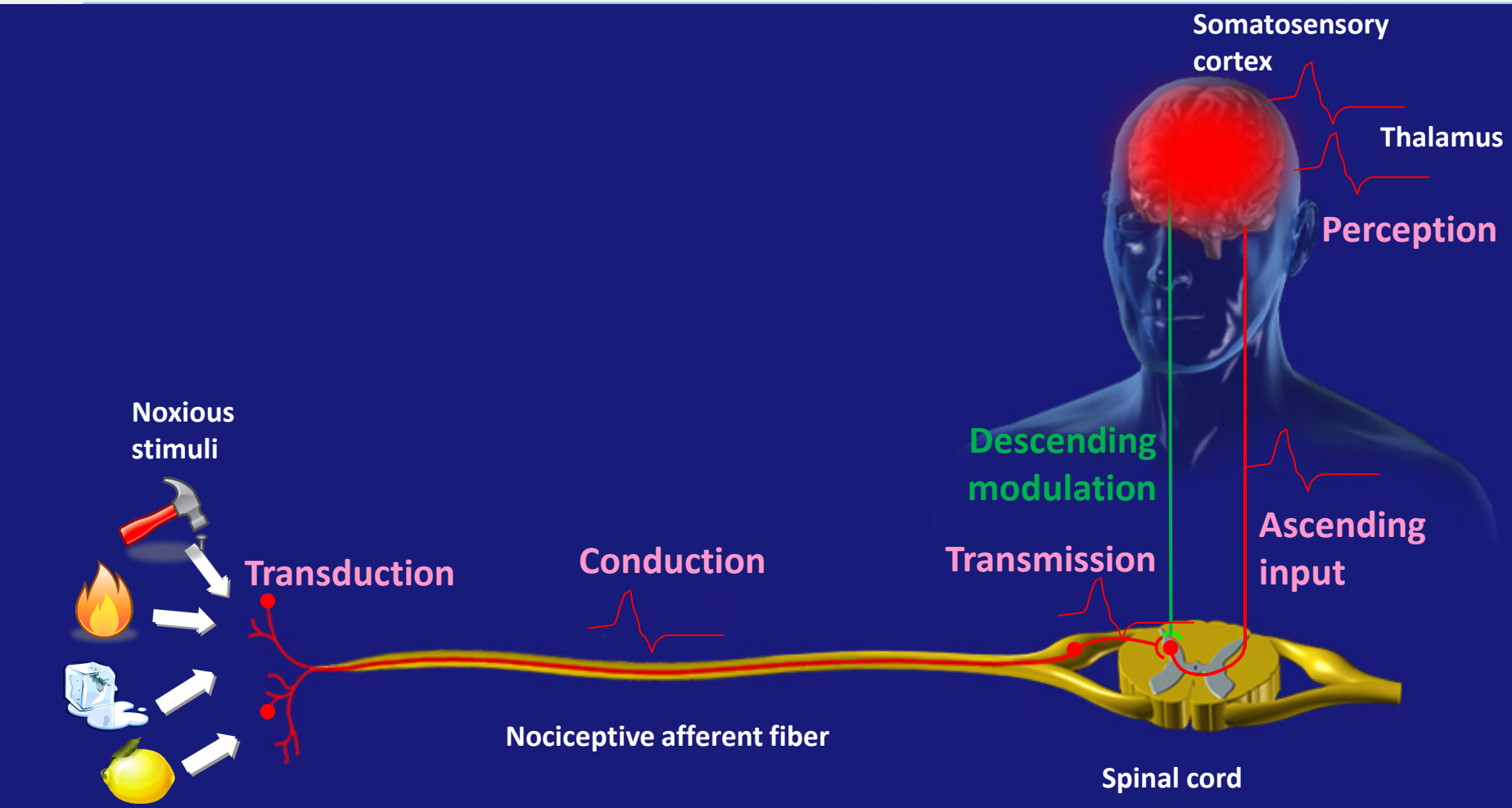
McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
Sikandar S, Dickenson AH. *Curr Opin Support Palliat Care* 2012; 6(1):17-26.

Referred Pain



Hudspith MJ *et al.* In: Hemmings HC, Hopkins PM (eds). *Foundations of Anesthesia*. 2nd ed. Elsevier; Philadelphia, PA: 2006;
Schmitt WH Jr. *Uplink* 1998; 10:1-3.

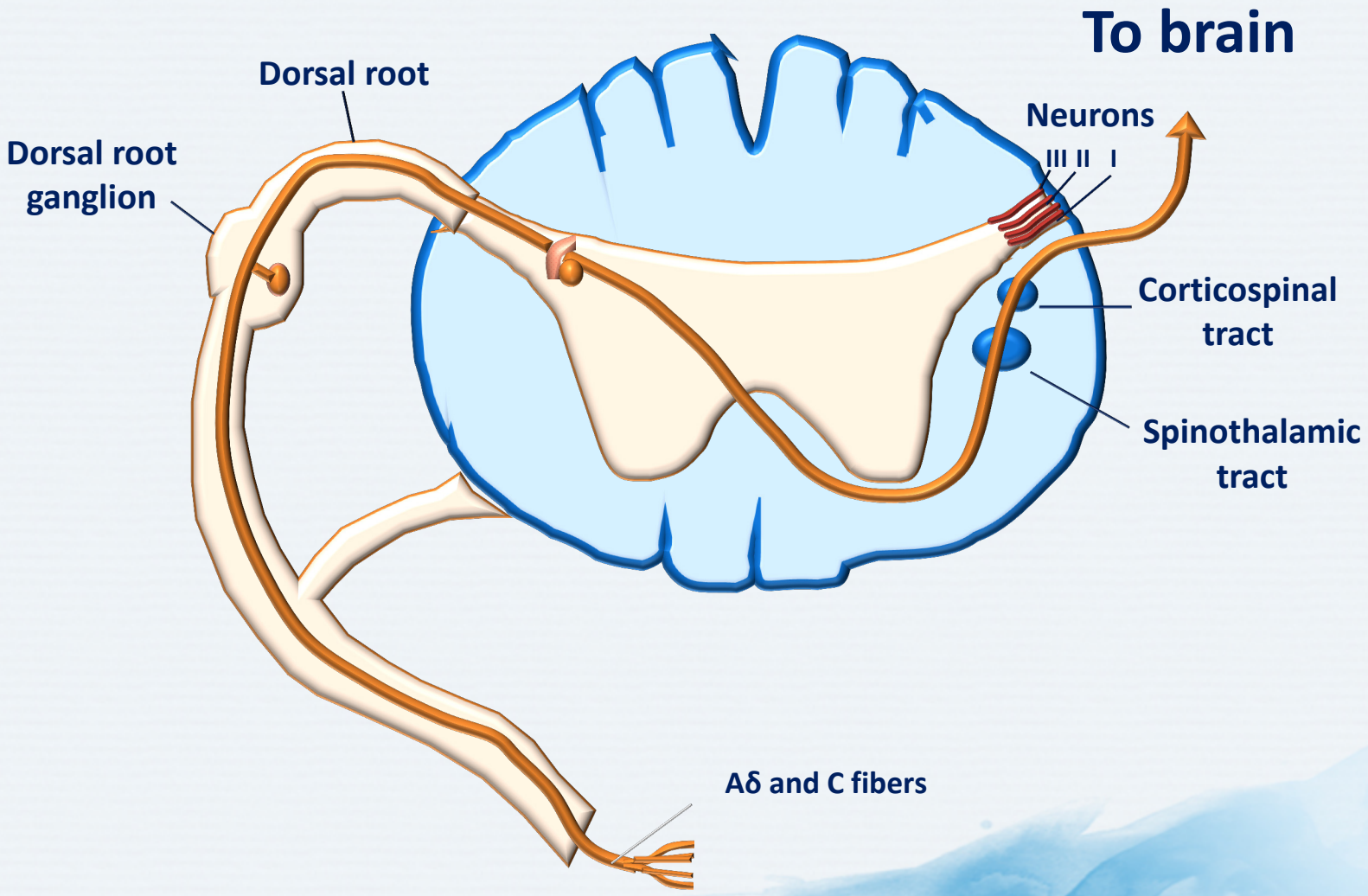
Nociception: Neural Process of Encoding Noxious Stimuli



Consequences of encoding may be autonomic (e.g., elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

Nociception



Dubin AE, Patapoutian A. *J Clin Invest* 2010; 120(11):3760-72; Fields HL *et al. Neurobiol Dis* 1998; 5(4):209-27; Williams SJ, Purves D. Neuroscience. Sinauer Associates; Sunderland, MA: 2001..

Primary Nociception Is Accomplished through Peripheral Nociceptors: C Fibers and Aδ Fibers

Characteristic	Aδ fibers	C fibers
Receptive fields	Small	Broad
Diameter	Large	Small
Myelination	Yes	No
Receptors	Nociceptors Thermoreceptors Mechanoreceptors	Nociceptors High threshold mechanoreceptors
Conduction velocity	Rapid (10–30 m/s)	Slow (0.5–2.0 m/s)
Activation stimuli	Thermal Mechanical	Polymodal

Dubin AE, Patapoutian A. *J Clin Invest* 2010; 120(11):3760-72; Fields HL *et al. Neurobiol Dis* 1998; 5(4):209-27;
Williams SJ, Purves D. Neuroscience. Sinauer Associates; Sunderland, MA: 2001..

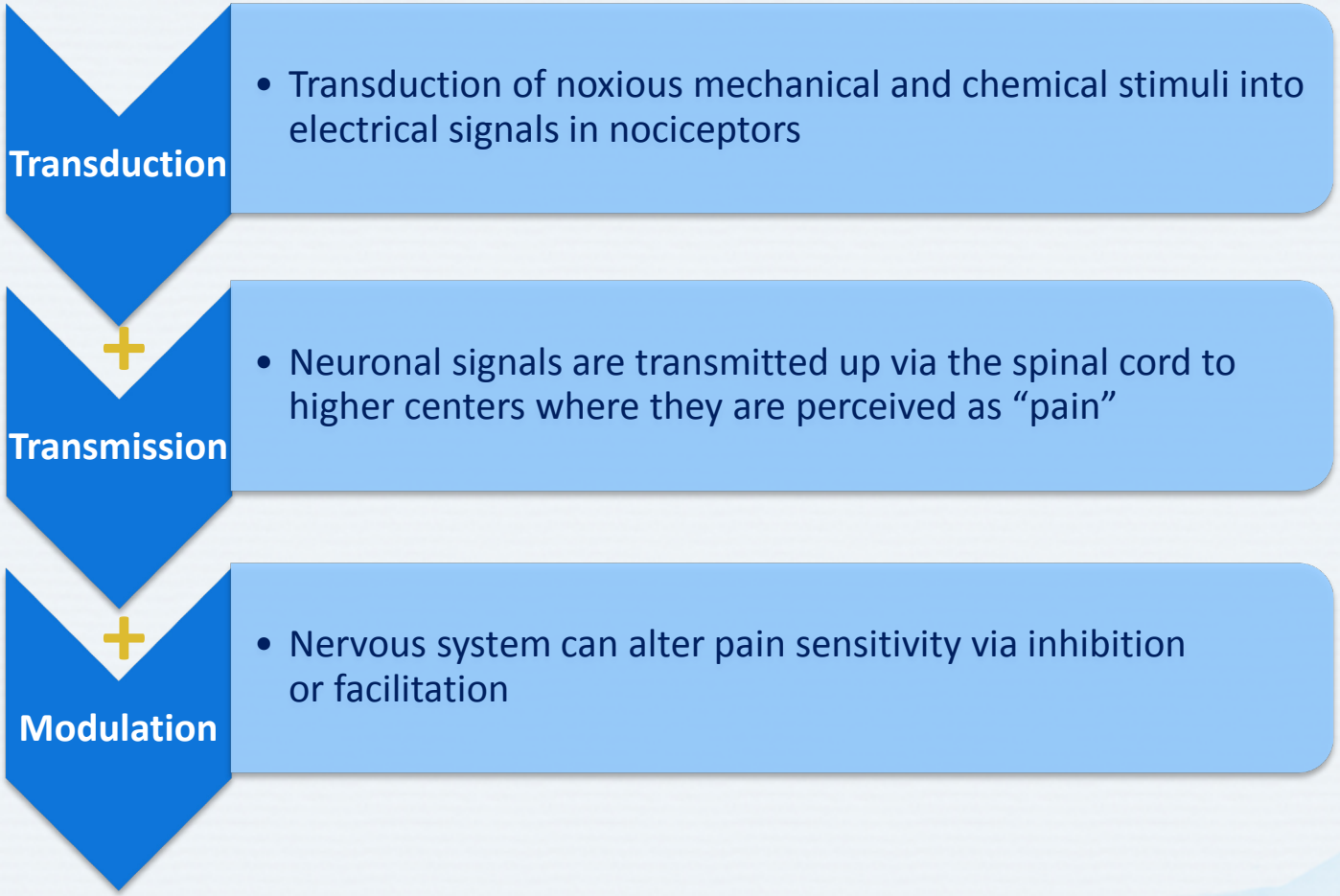
Peripheral Nociceptors in Chronic Pain

- Sustained inflammation causes prolonged stimulation of C fibers
- Gene transcription altered at dorsal root ganglia and dorsal horn neurons
  - Vanilloid receptor 1 (VR1) and SNS/PN3 sodium channels increase on nociceptors
- Prolonged elevation of nociceptor excitability, chronic pain persisting after initial injury healed
- Similar changes can follow peripheral nerve injury

VR1 detects noxious heat and is also sensitive to capsacin.
SNS/PN3 allows sodium to enter neuron, thus decreasing firing threshold.

Messeguer A *et al. Curr Neuropharmacol* 2006; 4(1):1-15; Tate S *et al. Nature Neurosci* 1998; 1(8):653-55.

Nociceptive Pain



Caterina MJ *et al. Nature* 1997; 389(6653): 816-24; Julius D. Basbaum AI. *Nature* 2001; 413(6852):203-10; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Transduction via Endogenous Mediators

Noxious stimuli

- Mechanical
- Thermal
- Chemical

Mediators

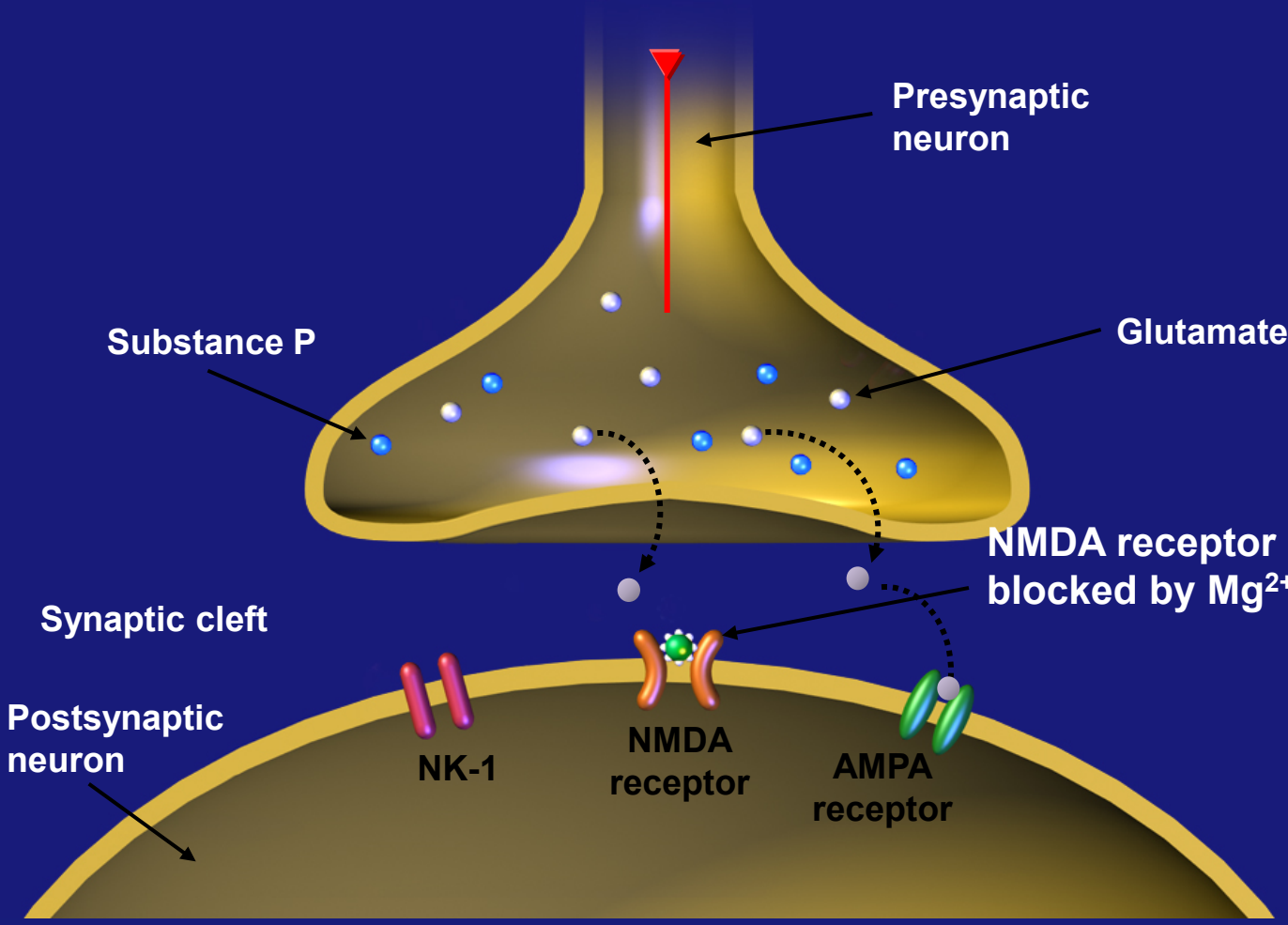
- Prostaglandins
- Leukotrienes
- Substance P
- Histamine
- Bradykinin
- Serotonin
- Hydroxyacids
- Reactive oxygen species
- Inflammatory cytokines and chemokines

Receptors/channels on nociceptors

Julius D, Basbaum AI. *Nature* 2001; 413(6852):203-10; Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-68.

Transmission via Neurotransmitters

1. Impulses reach terminals of presynaptic neuron
2. Glutamate is released into synaptic cleft
3. Glutamate binds to AMPA receptor
4. Impulse is transmitted to postsynaptic neuron



AMPA = 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; NK = neurokinin; NMDA = N-methyl-D-aspartate

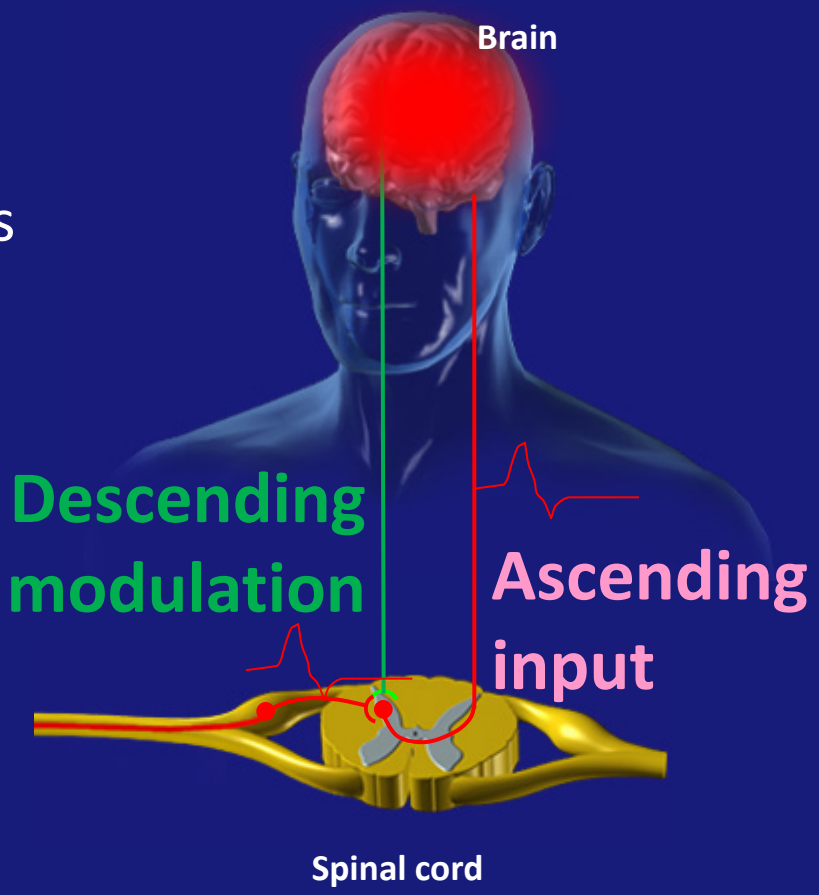
Fields HL *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Julius D, Basbaum AI. *Nature* 2001; 413(6852):203-10; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-68.

Pain Modulation

- Pain is modulated via **ascending nociceptive** and **descending inhibitory/facilitatory** spinal tracts

Ascending Nociceptive
C fibers Aδ fibers

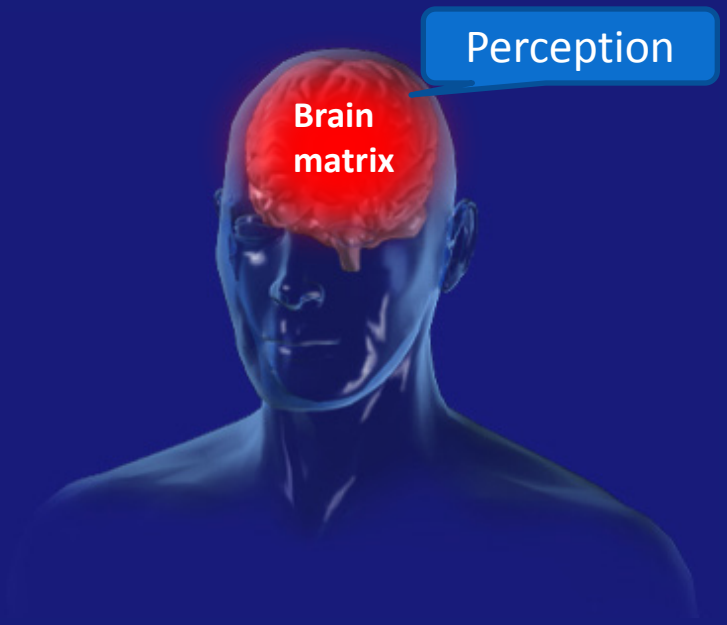
Descending Inhibitory/facilitatory
Serotonin Norepinephrine Dopamine



Benarroch EE. *Neurology* 2008 ; 71(3):217-21; Fields HL *et al.* In: McMahon SB, Koltzenburg M (Eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

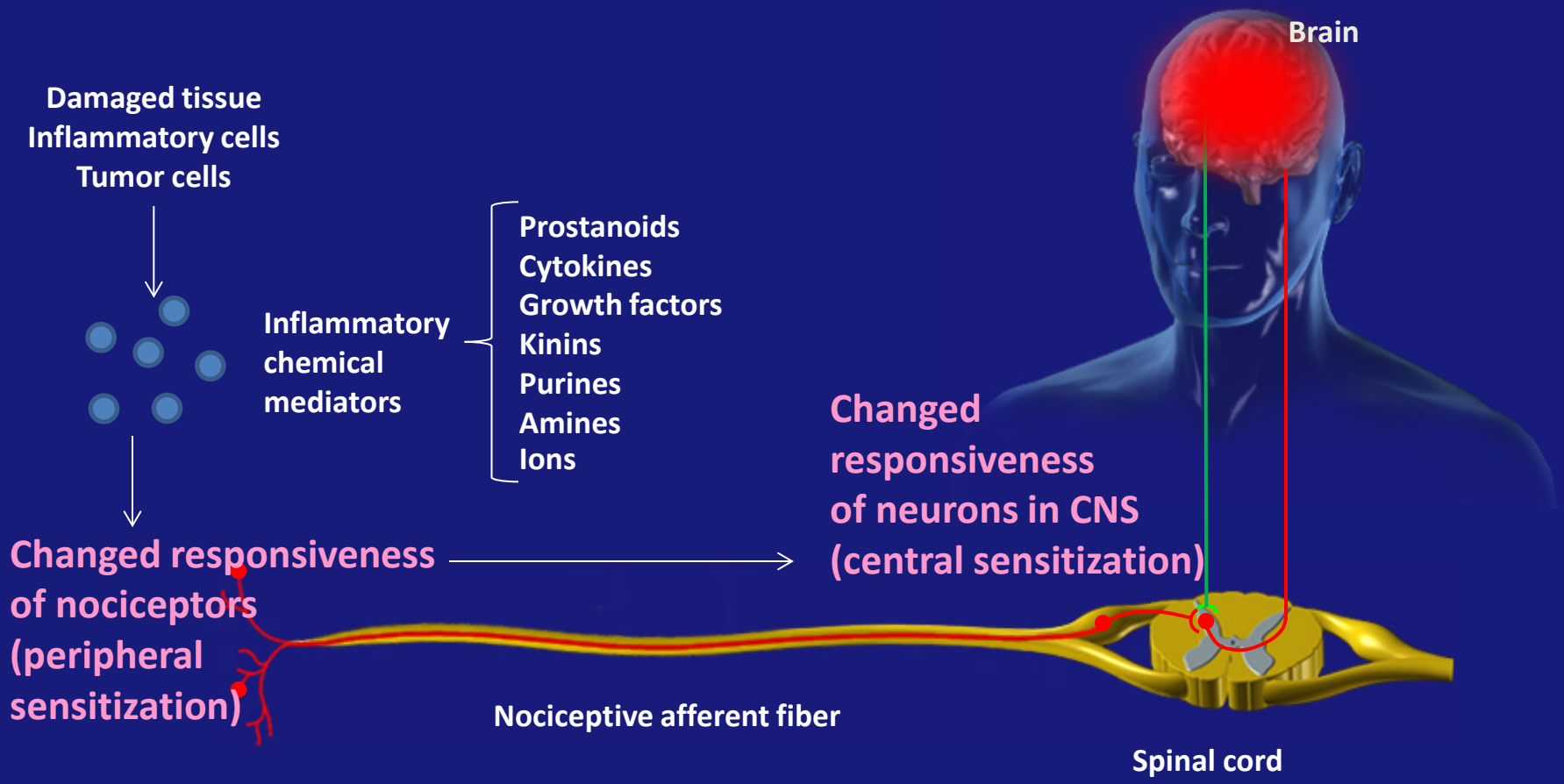
Pain Perception

- Spinal cord transmits pain signals to specific nuclei in the thalamus, and from there to wide variety of regions in the brain – collectively known as the "pain matrix"
- Pain perception can also be altered without any external stimuli (i.e., through emotion, distraction, placebo, etc.)



Tracey A, Dickenson A. *Cell* 2012; 148(6):1308-e2.

Inflammation



CNS = central nervous system

Scholz J, Woolf CJ. *Nat Neurosci* 2002; 5(Suppl):1062-7.

What is neuropathic pain?

Definition

- Pain caused by a lesion or disease of the somatosensory nervous system
- Can be peripheral or central

Pain Quality

- Burning
- Lancinating
- Electric shock-like
- Often diffuse
- Frequently with allodynia and/or hyperalgesia

Chong MS, Bajwa ZH. *J Pain Symptom Manage* 2003; 25(5 Suppl):S4-11; Cruccu G *et al. Eur J Neurol* 2004; 11(3):153-62; Dray A. *Br J Anaesth* 2008; 101(1):48-58; International Association for the Study of Pain. *IASP Taxonomy.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. 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.

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***

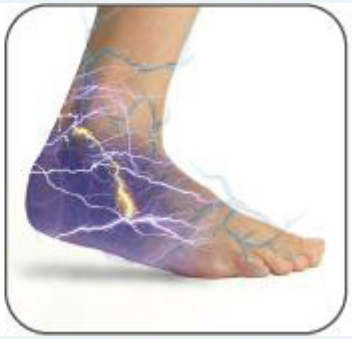
International Association for the Study of Pain. *IASP Taxonomy, Changes in the 2011 List.* Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions. Accessed: July 15, 2013.

Common Descriptors of Neuropathic Pain

Burning

Tingling

Pins and needles

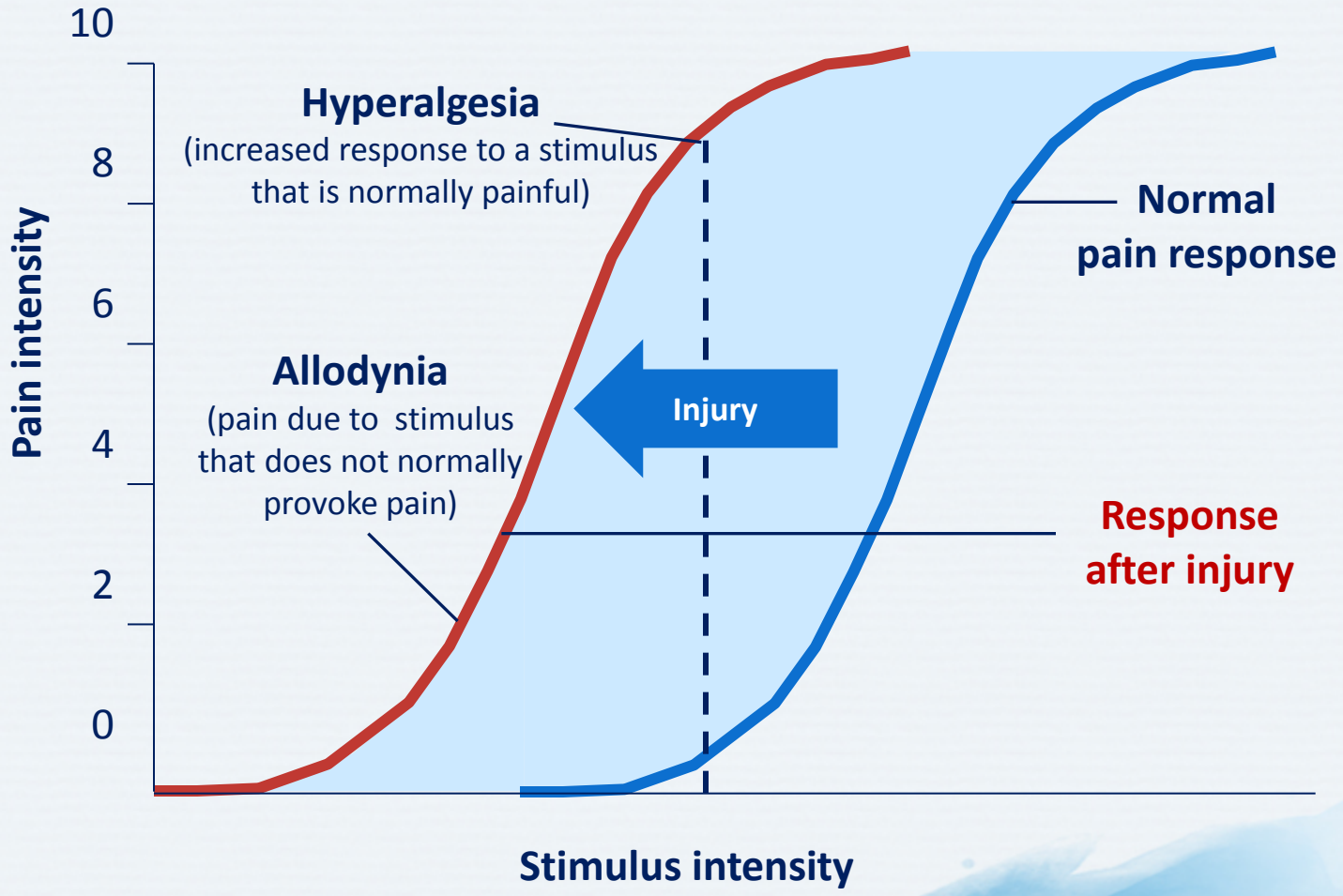


Electric shock-like

Numbness

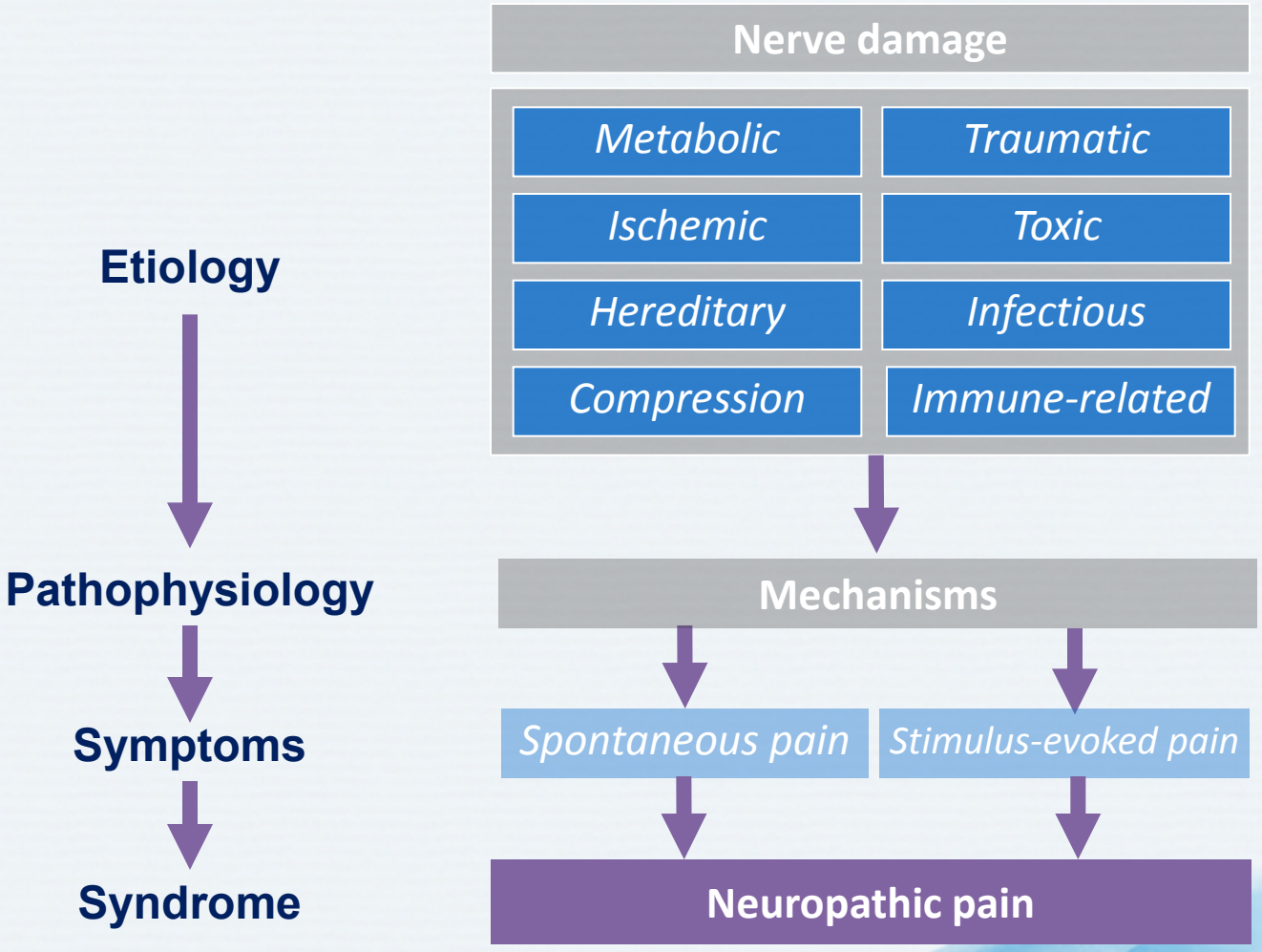
Baron R *et al. Lancet Neurol* 2010; 9(8):807-19; Gilron I *et al. CMAJ* 2006; 175(3):265-75.

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



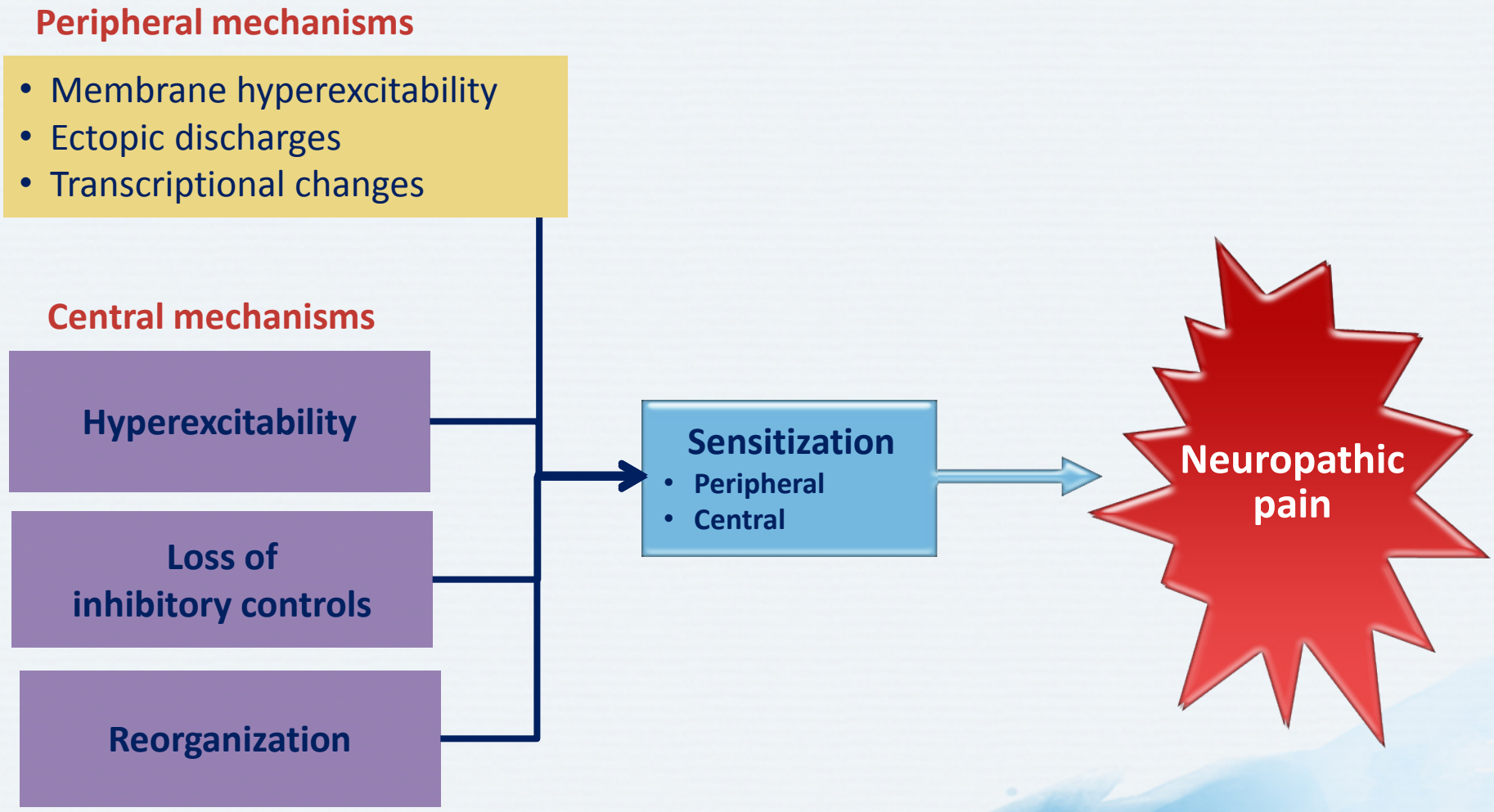
Adapted from: Gottschalk A *et al. Am Fam Physician* 2001; 63(10):1979-84.

Development of Neuropathic Pain



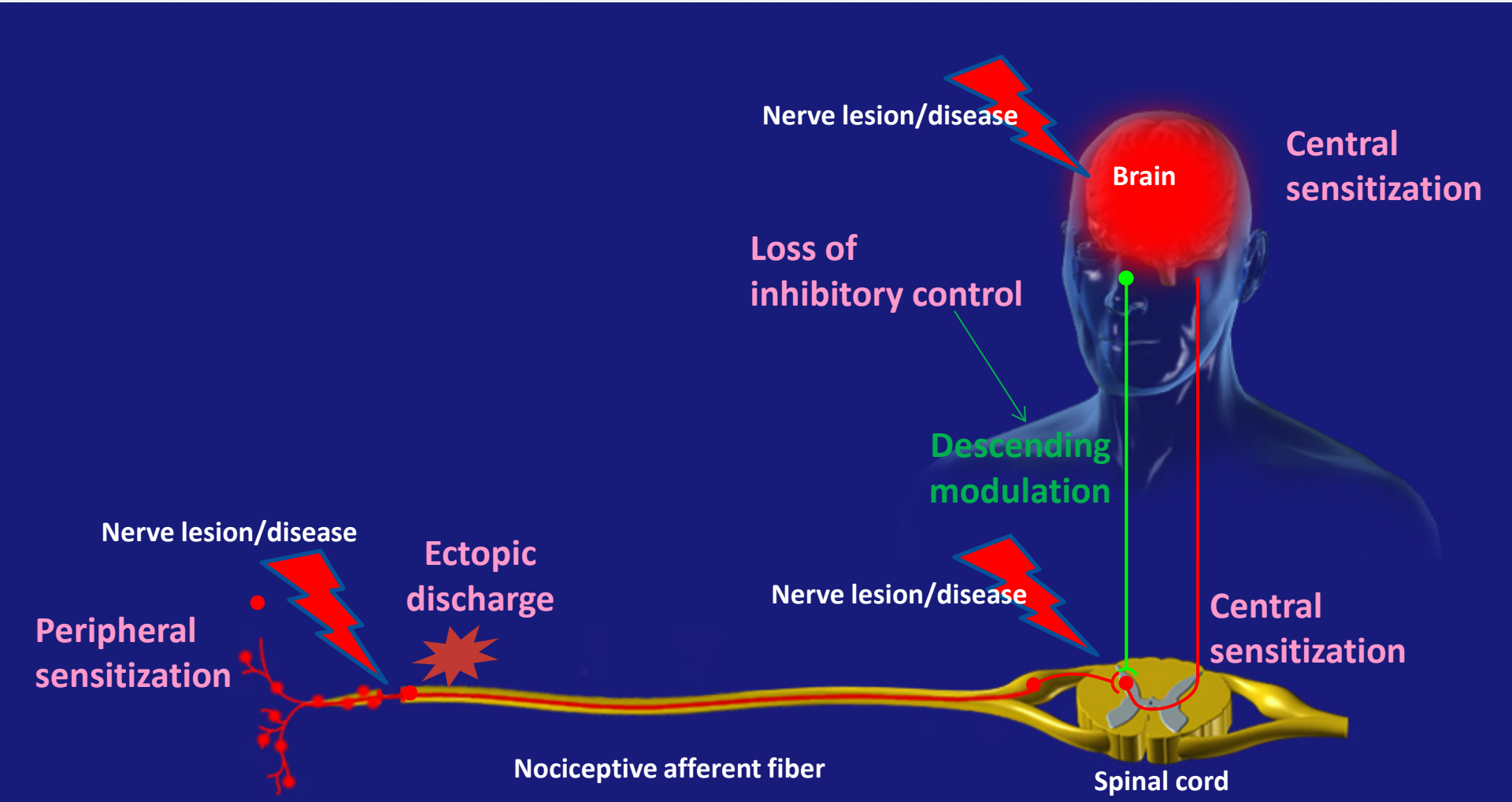
Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

Pathophysiology of Neuropathic Pain



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



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.

Neuropathic Pain: Aβ , Aδ 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.

Sensory Processing and Neuropathic Pain

Nerve function	Stimulus	Primary afferent	Sensation	Mechanism
Normal	Innocuous Mechanical	Aβ	Normal touch	Normal function
	Noxious Mechanical Thermal Chemical	Aδ nociceptor C nociceptor	Normal sharp pain Normal burning pain	
Decreased	Innocuous Mechanical	Aβ	Tactile hypoanesthesia	Decreased transmission of impulses
	Noxious Mechanical Thermal Chemical	Aδ nociceptor C nociceptor	Mechanical Heat or cold hypoalgesia	
Increased	Innocuous Mechanical	Aβ	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.

What is central sensitization/ dysfunctional pain?

Definition

- Amplification of neural signaling within the CNS that elicits pain hypersensitivity

Examples

- Fibromyalgia
- Irritable bowel syndrome
- Interstitial cystitis
- Temporomandibular joint pain
- May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis

Pain Quality

- Burning
- Lancinating
- Electric shock-like
- Often diffuse
- Frequently with allodynia and/or hyperalgesia

CNS = central nervous system

Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

Clinical Features of Central Sensitization/Dysfunctional Pain

Pain

- Pain all over body
- Muscles stiff/achy
- Headaches
- Pain in jaw
- Pelvic pain
- Bladder/urination pain

Anxiety/depression

- Sad or depressed
- Anxiety
- Stress makes symptoms worse
- Tension in neck and shoulder
- Grind/clench teeth

Fatigue

- Do not sleep well
- Unrefreshed in morning
- Easily tired with physical activity

Other symptoms

- Difficulty concentrating
- Need help with daily activities
- Sensitive to bright lights
- Skin problems
- Diarrhea/constipation

Mayer TG *et al. Pain Pract* 2012; 12(4):276-85.

Neuronal Plasticity

Changes in neuron function, chemical profile or structure as a result of painful stimulation and nerve damage

Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-8.

Neuronal Plasticity and Pain Pathogenesis

- Neuronal plasticity can cause pain[1,2]
  - Neuropathic pain is pain felt in absence of nociceptor stimulation
    - From a lesion or disease affecting the somatosensory system
- Amplified pain perception due to changes in pain processing in CNS[1,3]
  - Characterized by hyperalgesia and allodynia[2]

CNS = central nervous system

1. Costigan M *et al. Annu Rev Neurosci* 2009; 32:1-32;
2. Woolf CJ. *Ann Intern Med* 2004; 140(6):441-51;
3. Staud R. *Arthritis Res Ther* 2006; 8(3):208-14.

Neurons Detecting and Transmitting Pain Display "Plasticity"

- Plasticity can be defined as:
  - Capacity to change function, chemical profile or structure
  - Response to painful stimuli and inflammation
- All contribute to altered sensitivity to pain

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

3 Forms of Neuronal Plasticity

Activation

- Rapid onset, substantial, readily reversible
- **Autosensitization and wind-up**

Modulation

- Follows repeated intense stimuli
- Substantial, slowly reversible
- **Peripheral and central sensitization**

Modification

- Follows prolonged, intense stimuli or nerve damage
- Very long-lasting
- **Persistent, pathological (neuropathic) pain**

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

Autosensitization

- Repeated stimulation of vanilloid receptors in nociceptors by heat, capsaicin or acidic pH cause
  - Rapid increase in receptor sensitivity
  - Increase in substantial but readily reversible “autosensitization”

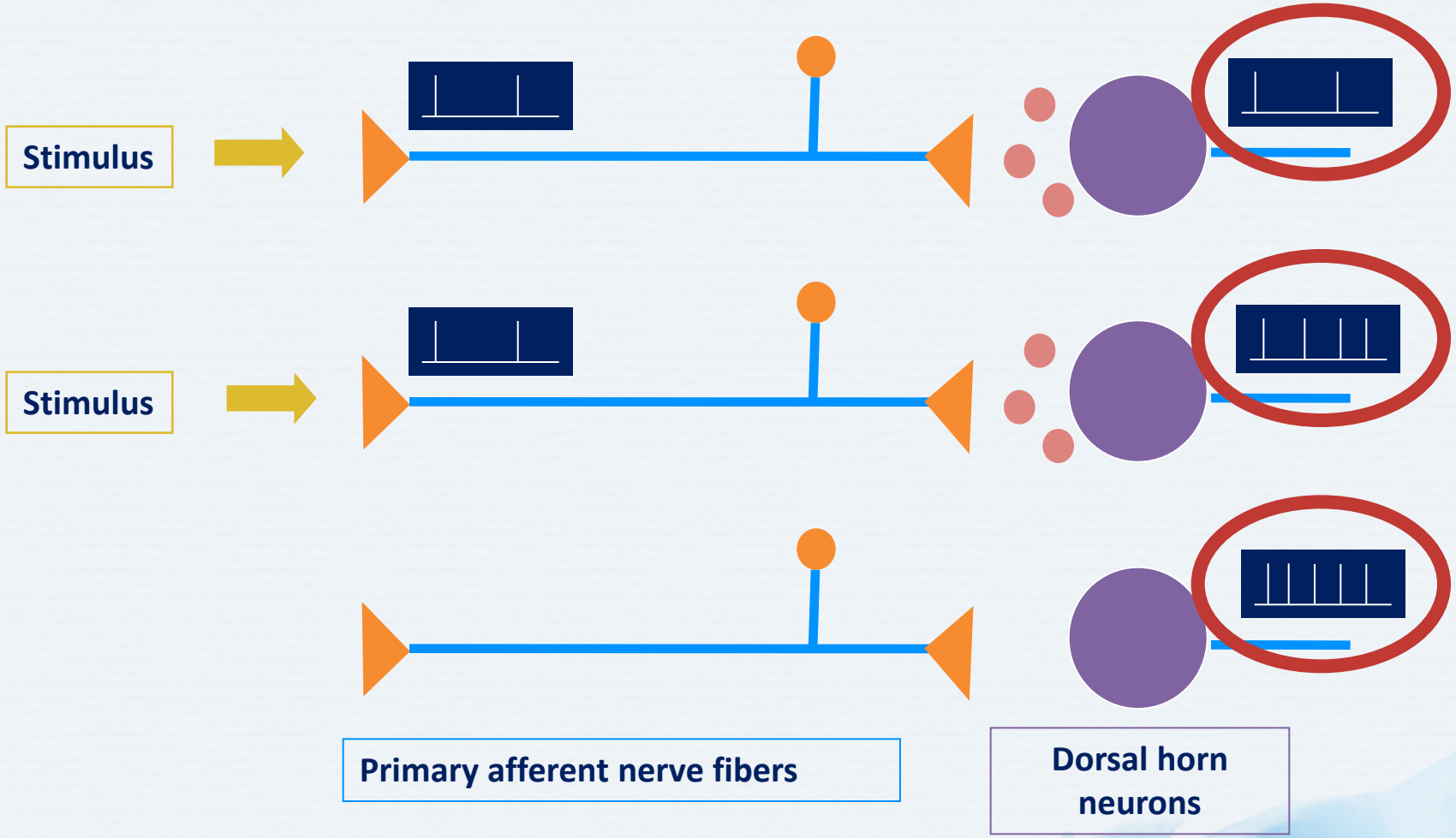
Caterina MJ *et al. Nature* 1997; 389(6653):816-24; Guenther S *et al. Eur J Neurosci* 1999; 11(9):3143-50; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Wind-Up

- Dorsal horn: intense or sustained noxious stimuli cause:
  - Release of neuromodulators (e.g., substance P) and glutamate
  - Long-lasting slow excitatory postsynaptic potentials and cumulative depolarization
  - Cascade of events further potentiate depolarization
  - Net result: “wind-up” of action potential discharge

Caterina MJ *et al. Nature* 1997; 389(6653):816-24; Guenther S *et al. Eur J Neurosci* 1999; 11(9):3143-50; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

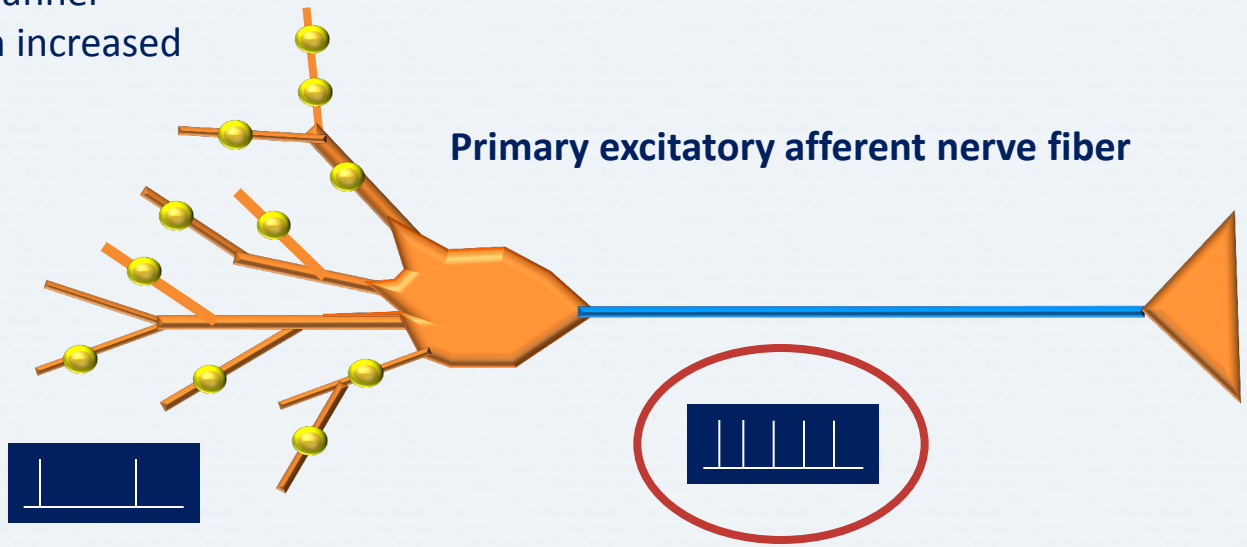
Wind-Up



Doubell TP *et al.* In: Wall PD, Melzack R (eds). *Textbook of Pain*. 4th ed. Harcourt Publishers Limited; Edinburgh, UK: 1999; Mannion RJ, Woolf CJ. *Clin J Pain* 2000; 16(3 Suppl):S144-56; Siddall PJ, Cousins MJ. *Spine (Phila Pa 1976)* 1997; 22(1):98-104; Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

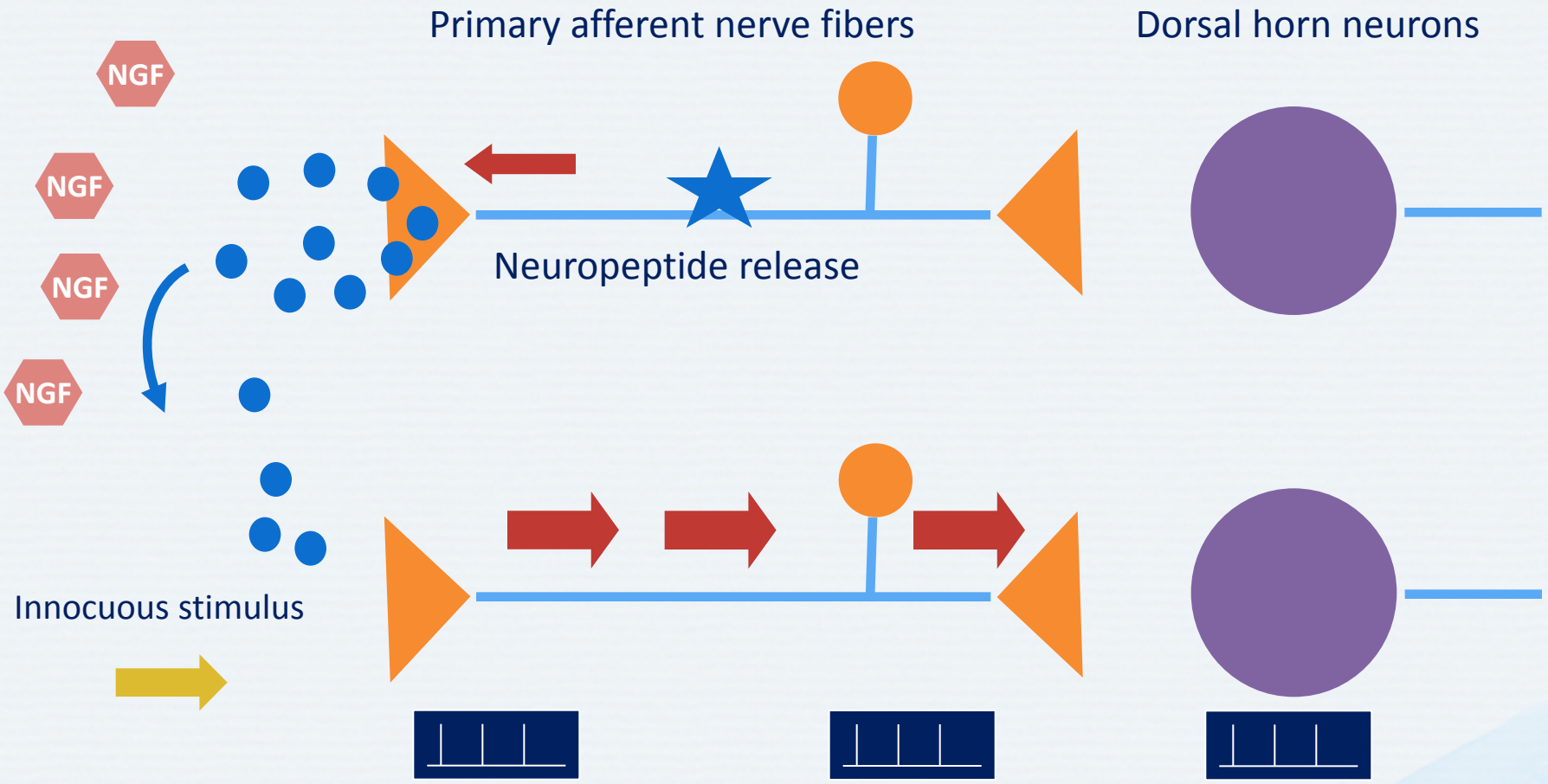
Ectopic Discharges

- Sodium channel expression increased



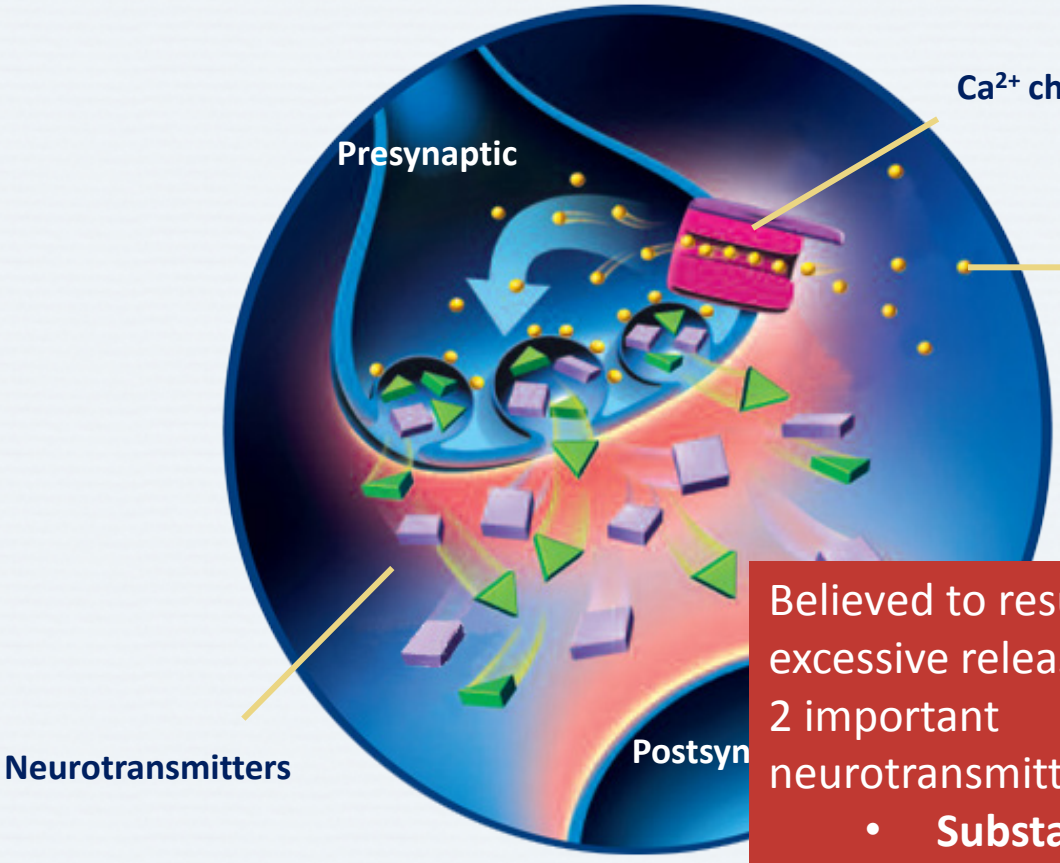
England JD *et al. Neurology* 1996; 47(1):272-6; Ochoa JL, Torebjörk HE. *Brain* 1980; 103(4):835-53; Sukhotinsky I *et al. Eur J Pain* 2004; 8(2):135-43; Taylor BK. *Curr Pain Headache Rep* 2001; 5(2):151-61.

Peripheral Sensitization



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

Central Sensitization

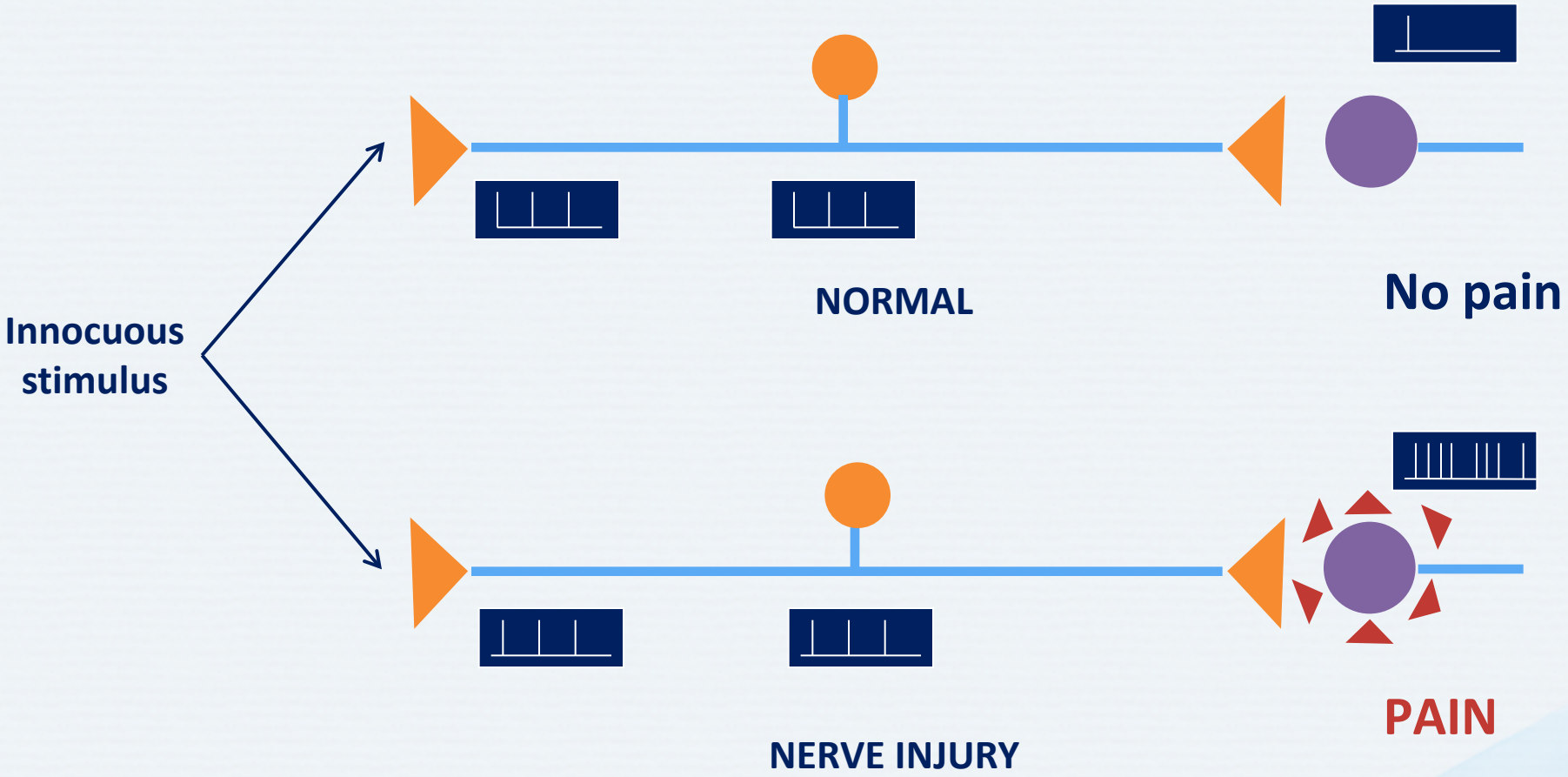


Believed to result from excessive release of 2 important neurotransmitters:

- **Substance P**
- **Glutamate**

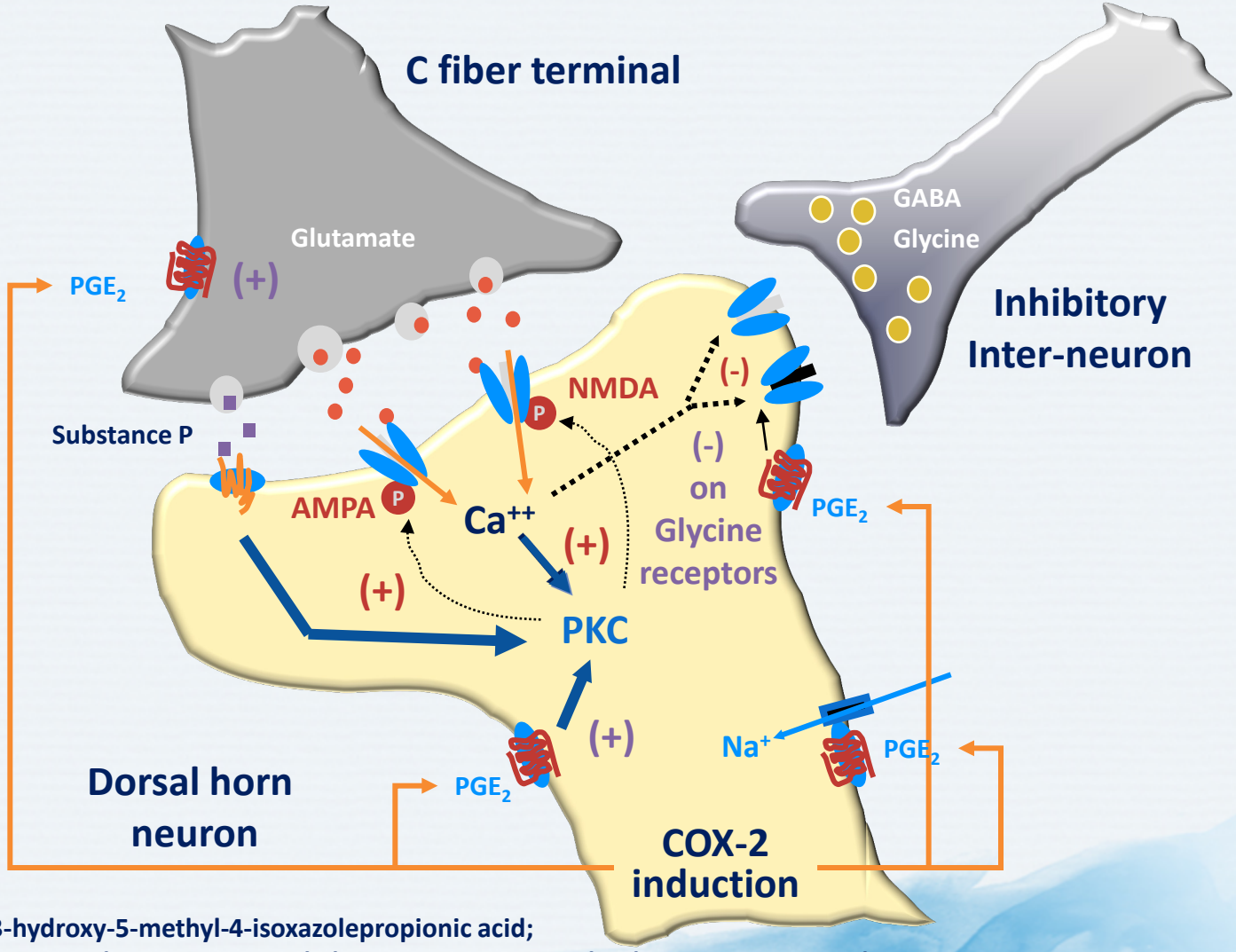
Costigan M *et al. Annu Rev Neurosci* 2009; 32:1-32; Costigan M *et al.* In: Siegel GJ *et al* (eds). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. 7th ed. Elsevier Academic Press; Burlington, MA: 2006; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14.

Central Sensitization after Nerve Injury



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

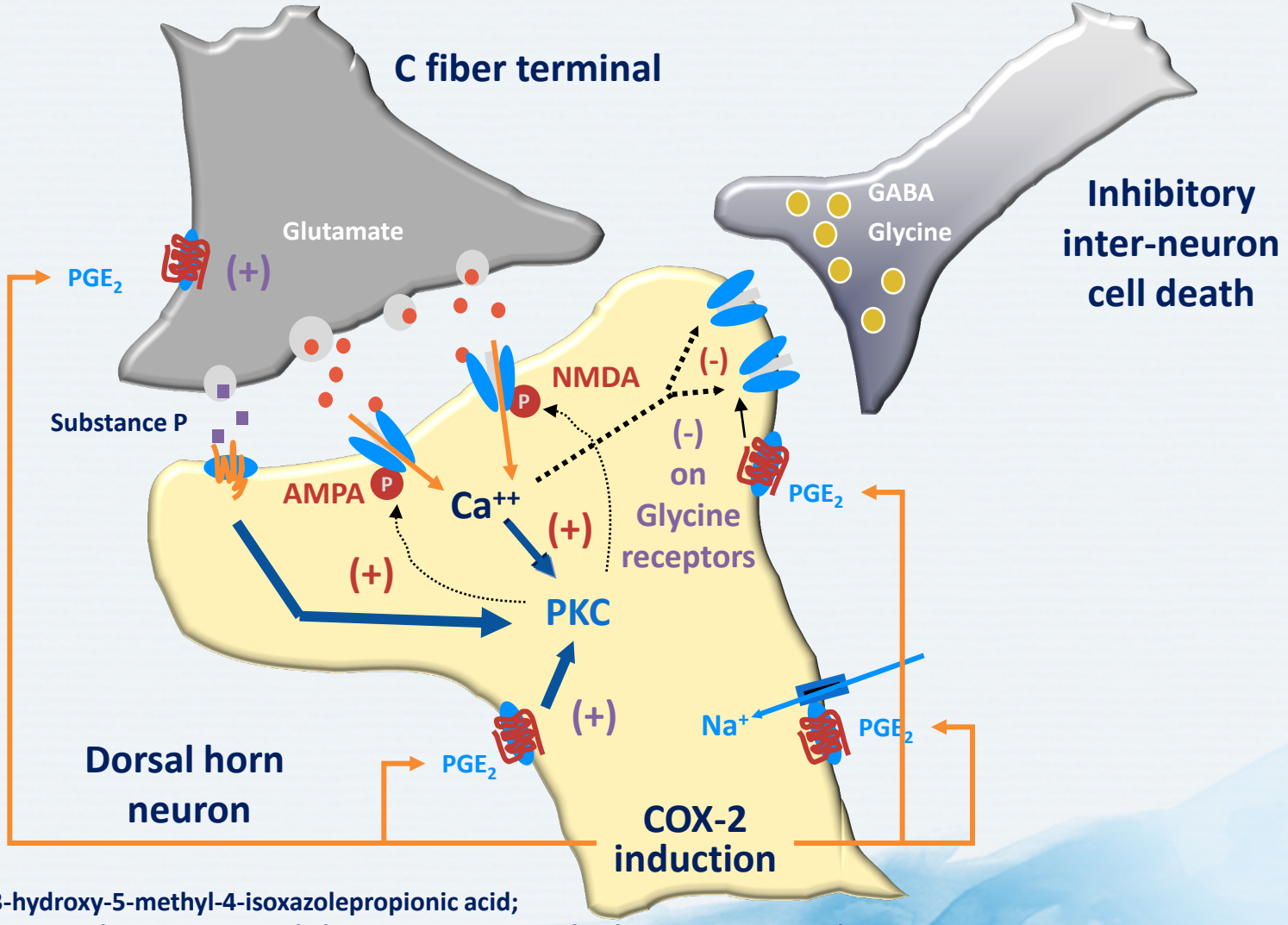
Central Sensitization



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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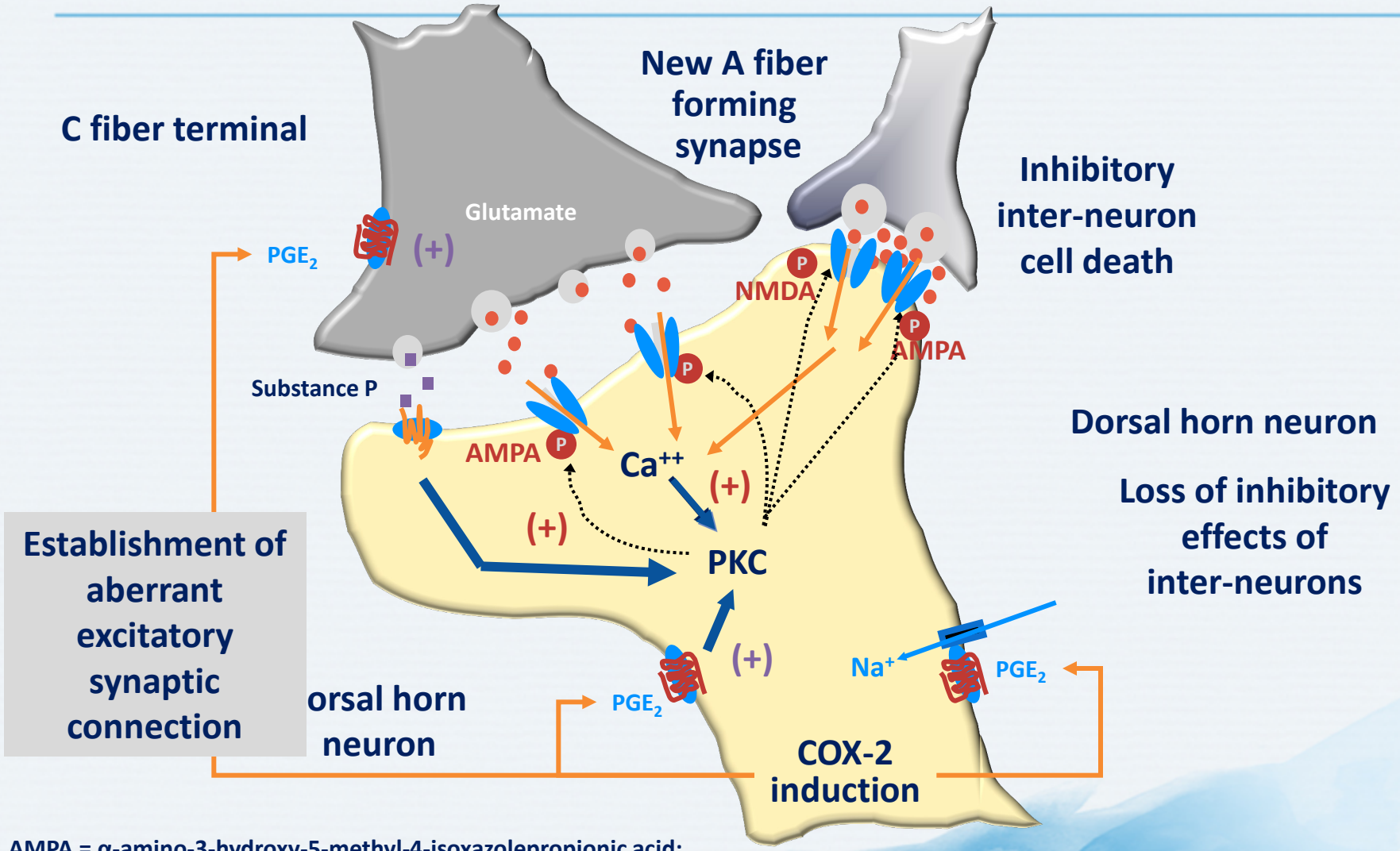
Central Sensitization



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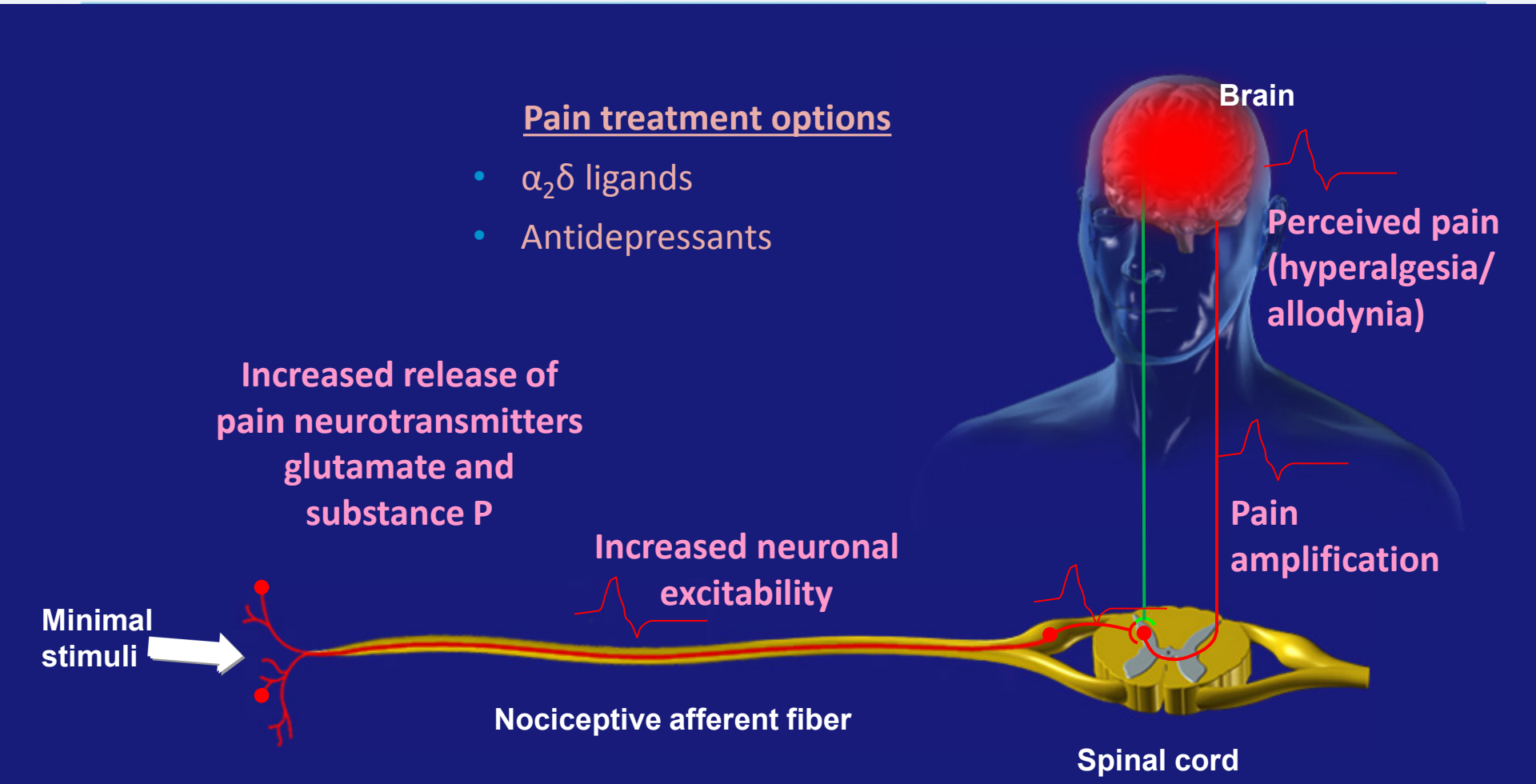
GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

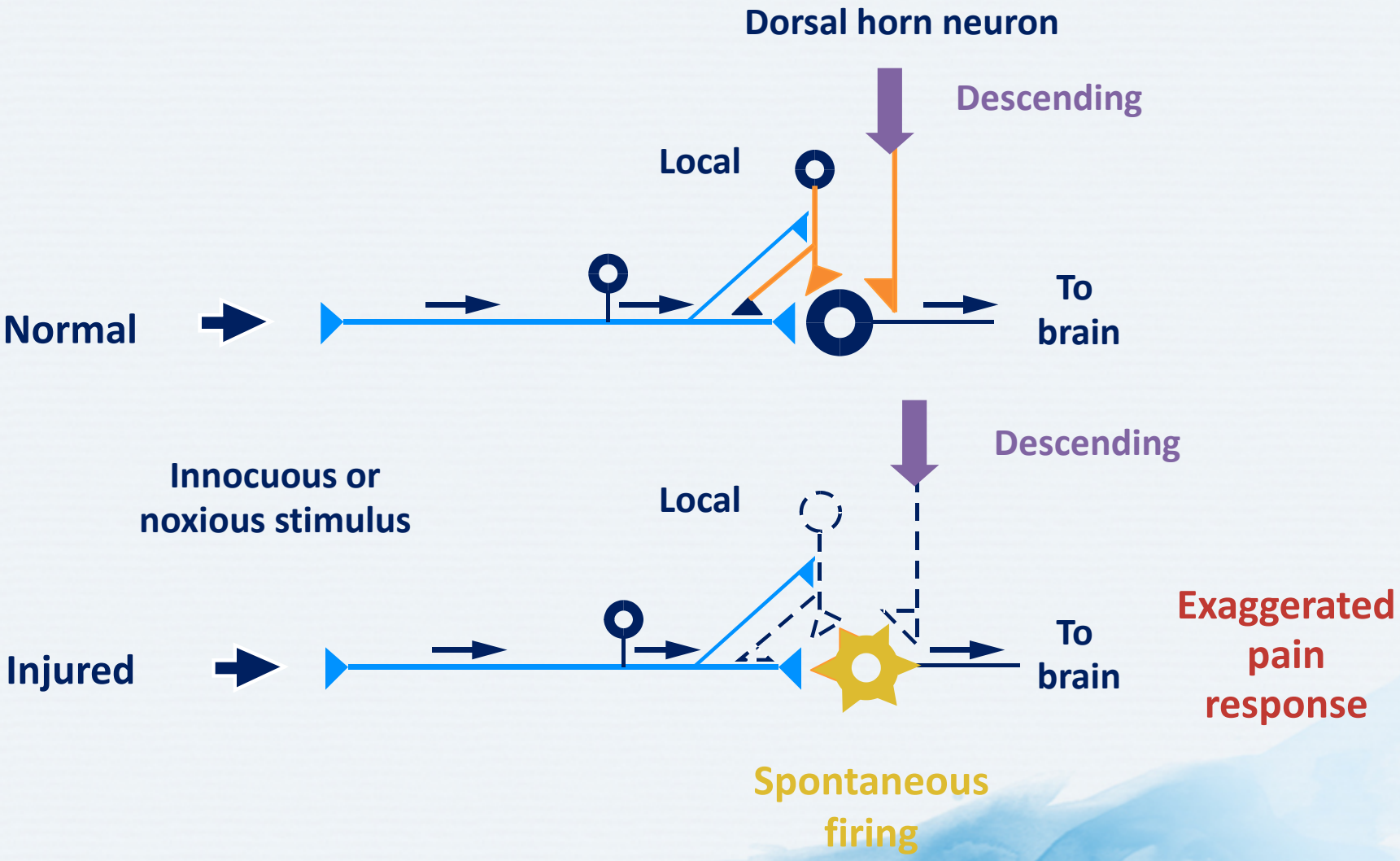
Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Central Sensitization Produces Abnormal Pain Signaling



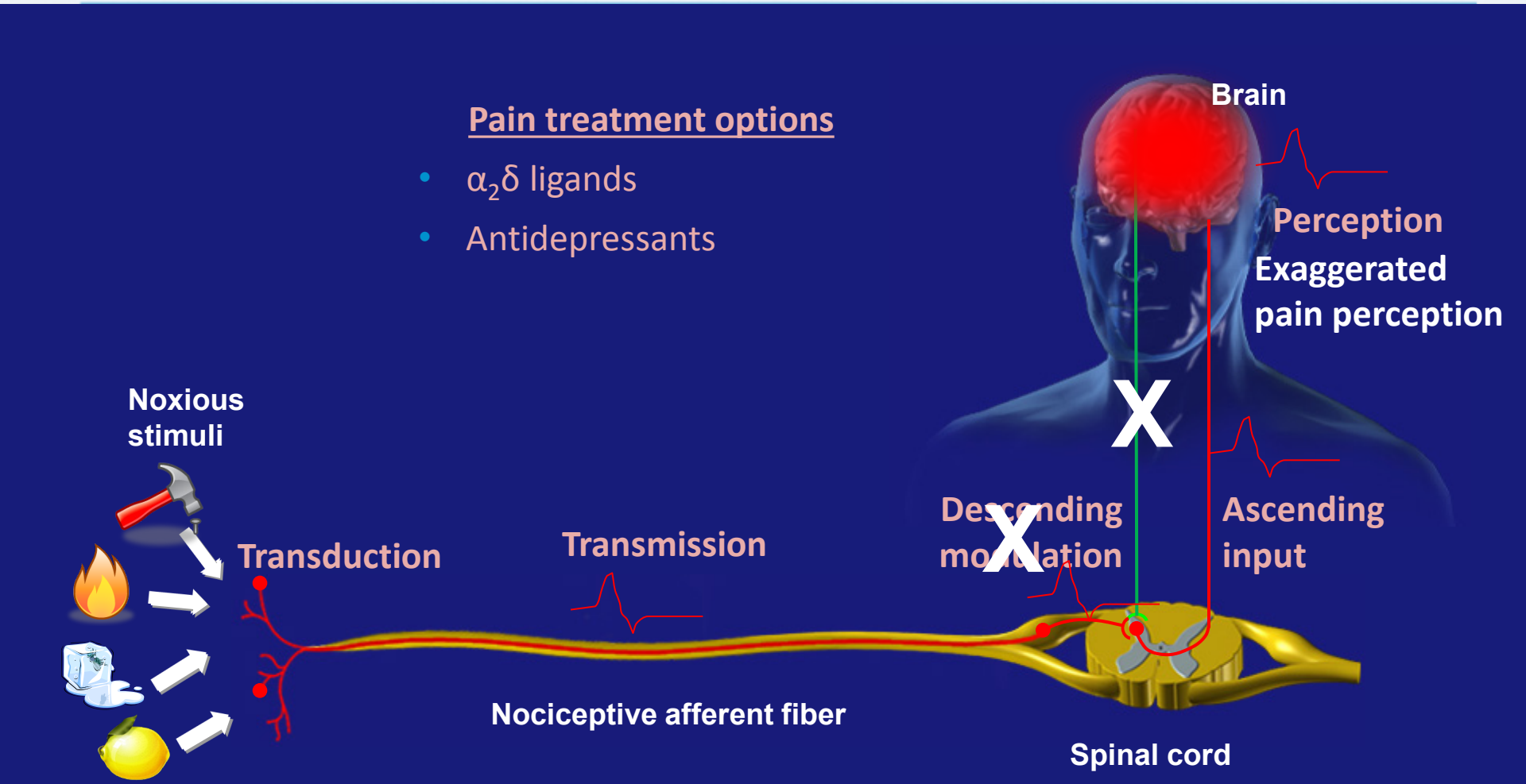
Adapted from: Campbell JN, Meyer RA. *Neuron* 2006; 52(1):77-92; Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10)1979-86; Henriksson KG. *J Rehabil Med* 2003; 41(Suppl):89-94; Larson AA *et al. Pain* 2000; 87(2):201-11; Marchand S. *Rheum Dis Clin North Am* 2008; 34(2):285-309; Rao SG. *Rheum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

Loss of Inhibitory Controls



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 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.

Summary

Pathophysiology: Summary

- Pain can be classified according to:
  - Duration
  - Location
  - Severity
  - Pathophysiology
- 3 underlying types of pain:
  - Nociceptive pain
    - Caused by nociceptors responding to noxious stimuli
  - Neuropathic pain
    - Caused by a lesion or disease of somatosensory system
  - Central sensitization/dysfunctional pain
    - May be caused by persistent neuronal dysregulation or dysfunction