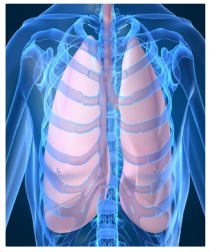
PATHOPHYSIOLOGY

Overview

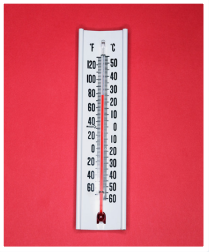
Pain Is the 5th Vital Sign



Respiration

Pulse

Blood pressure



Temperature

Pain

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

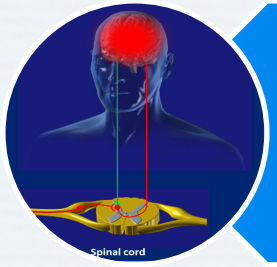
Overview of Pain

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.

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

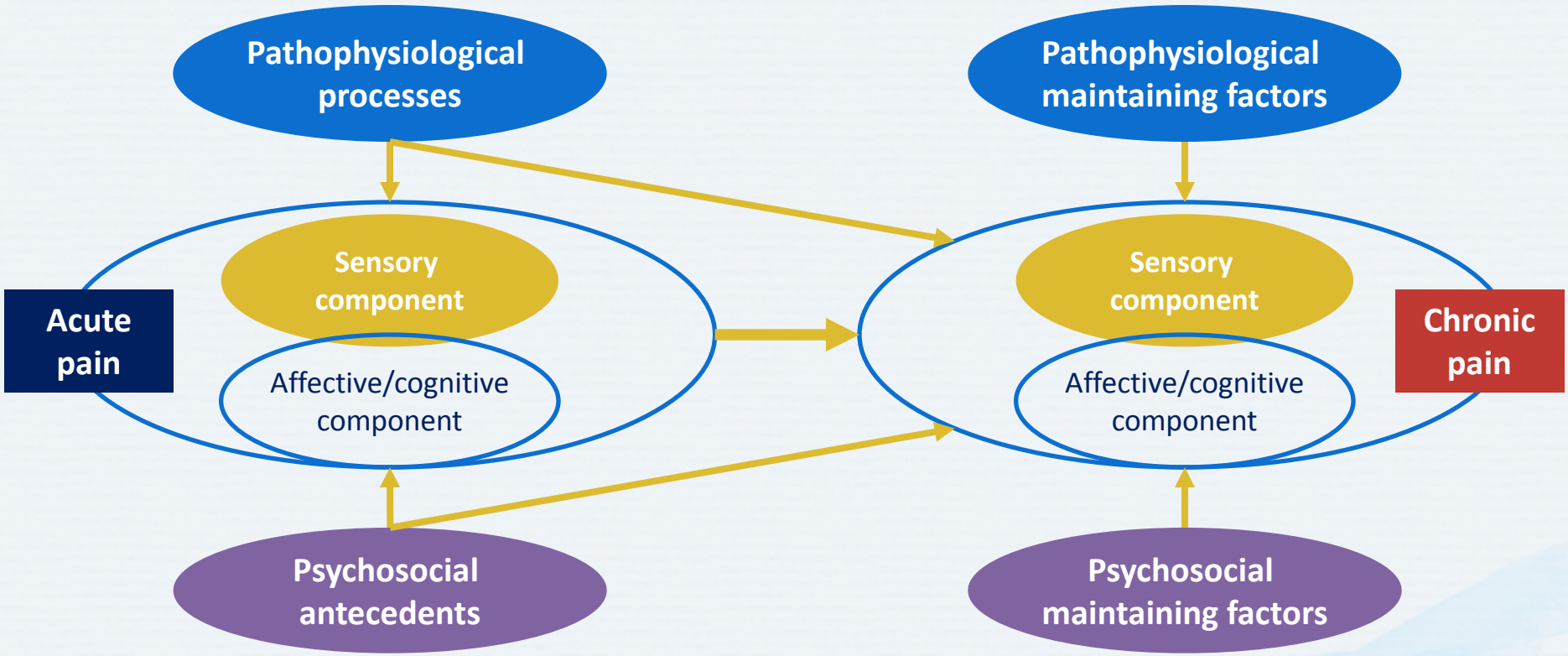
Chapman CR, Stillman M. In: Kruger L (ed). *Pain and Touch*. Academic Press; New York, NY: 1996; Cole BE. *Hosp Physician* 2002; 38(6):23-30;
International Association for the Study of Pain. *Unrelieved Pain Is a Major Global Healthcare Problem.*
Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Press_Release&Template=/CM/ContentDisplay.cfm&ContentID=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.

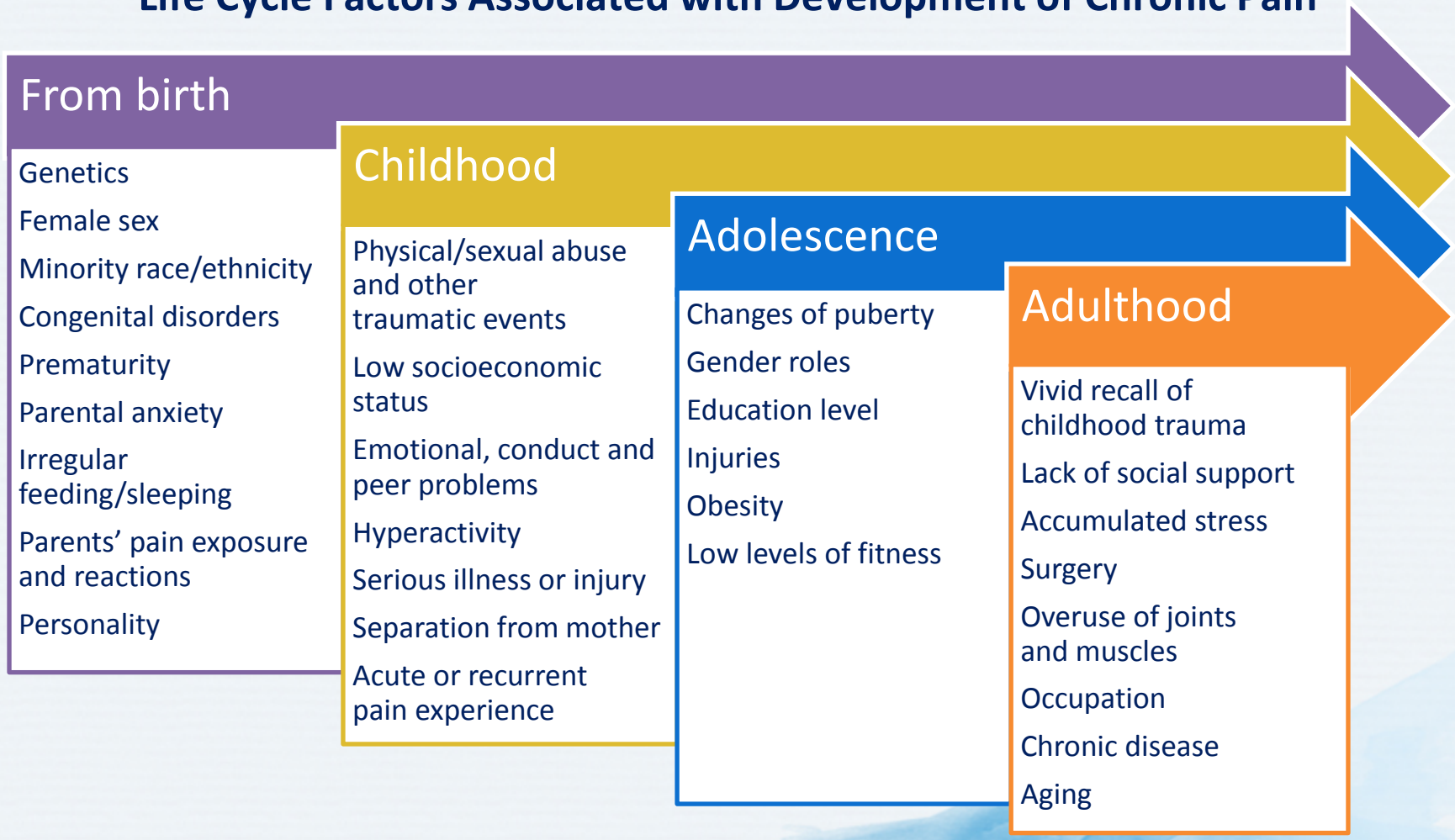
Acute Pain Can Become Chronic



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.

Risk Factors for Chronic Post-operative Pain

Pre-operative factors

- Moderate to severe pain, lasting >1 month
- Repeat surgery
- Psychologic vulnerability (e.g., catastrophizing)
- Pre-operative anxiety
- Female gender
- Younger age (adults)
- Workers' compensation
- Genetic predisposition
- Inefficient diffuse noxious inhibitory control

Intra-operative factors

- Surgical approach with risk of nerve damage

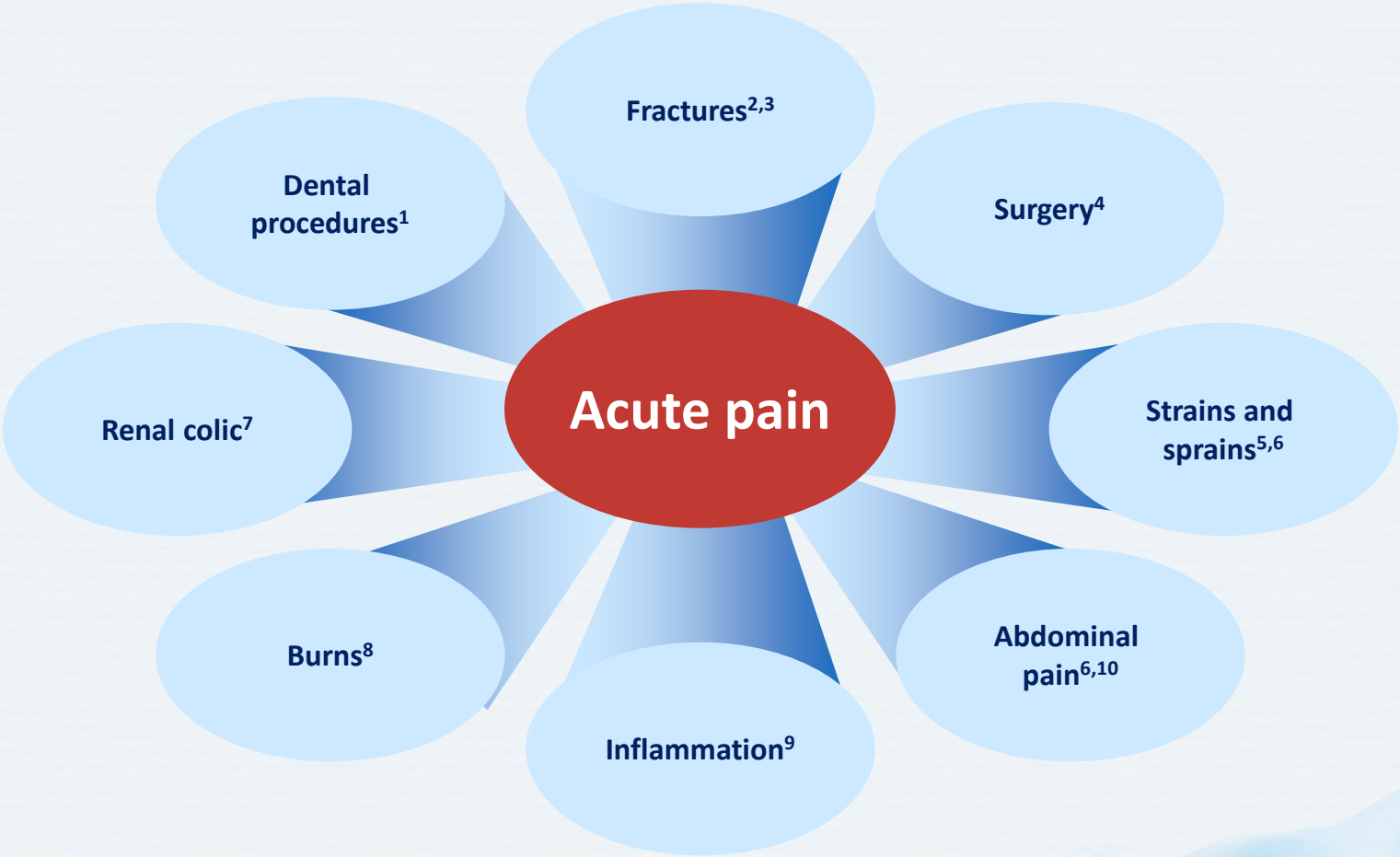
Post-operative factors

- Moderate to severe acute pain
- Radiation therapy to area
- Neurotoxic chemotherapy
- Depression
- Psychological vulnerability
- Neuroticism
- Anxiety

Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine.
Acute Pain Management: Scientific Evidence. 3rd ed. ANZCA & FPM; Melbourne, VIC: 2010.

Etiology

Common Causes of Acute Pain

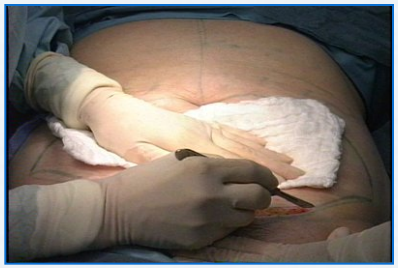


1. Pau AK *et al. Oral Health Prev Dent* 2003; 1(3):209-20; 2. Karmakar MK *et al. J Trauma* 2003; 54(3):615-25; 3. Brown JC *et al. Ann Emerg Med* 2003; 42(2):197-205; 4. Apfelbaum JL *et al. Anesth Analg* 2003; 97(2):534-40; 5. Wilson JJ *et al. Am Fam Physician* 2005; 72(5):811-8; 6. Nawar EW *et al. Adv Data* 2007; 29(386):1-32; 7. Heid F *et al. BJU Int* 2002; 90(5):481-8; 8. Pal SK *et al. Burns* 1997; 23(5):404-12.; 9. Lee Y *et al. Curr Pharm Des* 2005; 11(14):1737-55; 10. Cartwright SL *et al. Am Fam Physician* 2008; 77(7):971-8.

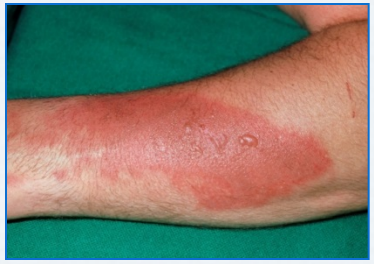
Nociceptive Pain

Musculoskeletal injury

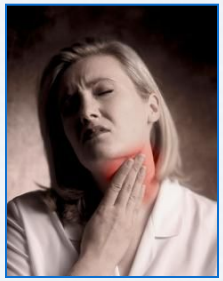
Trauma



Post-operative pain

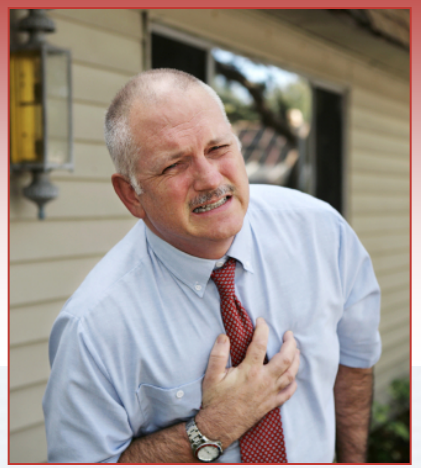


Burn pain



Infection, e.g., pharyngitis

Visceral



Ischemic, e.g., myocardial infarction

Abdominal colic

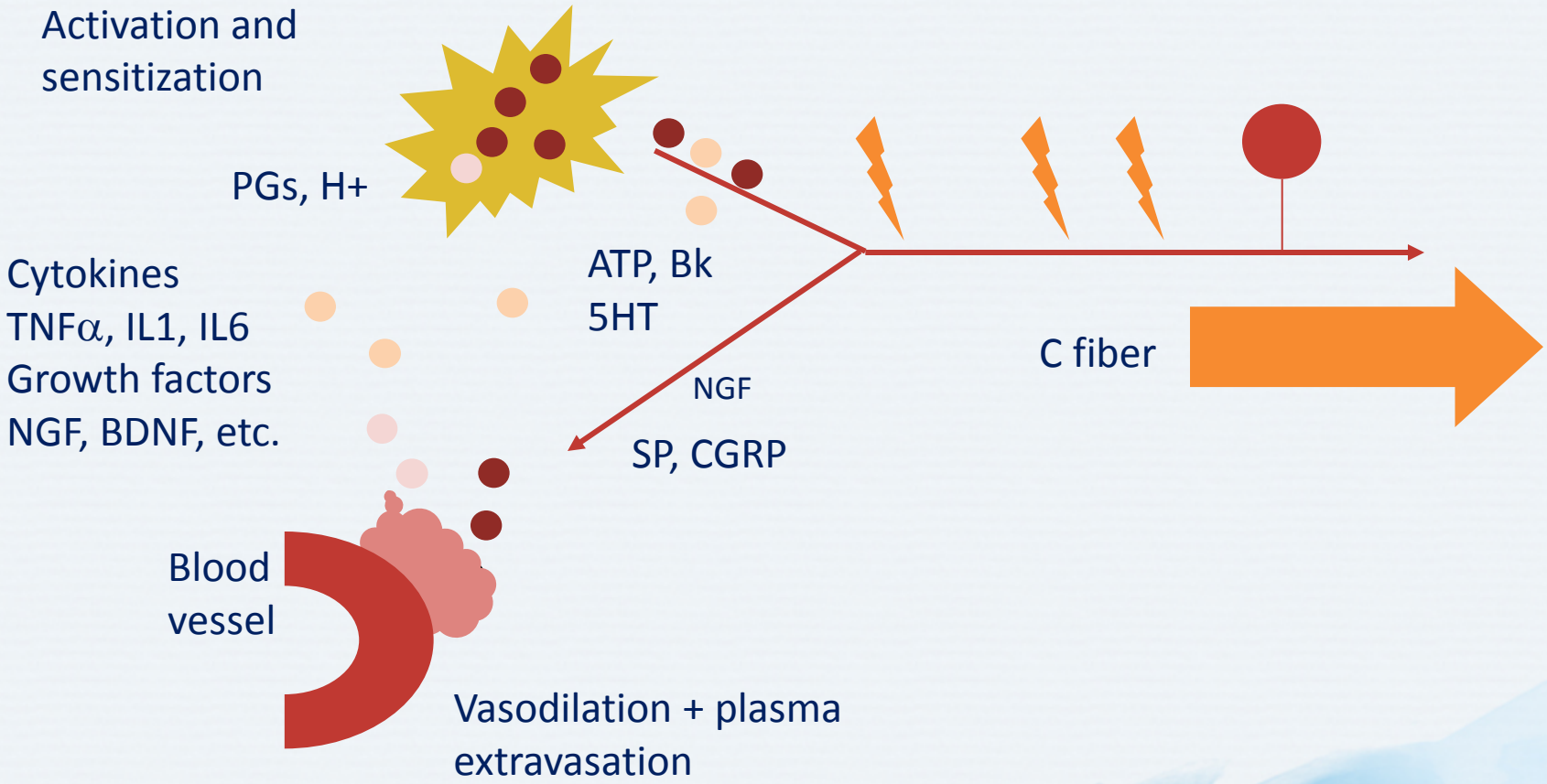
Dysmenorrhea

Fishman SM *et al* (eds). *Bonica's Management of Pain*. 4th ed. Lippincott, Williams and Wilkins; Philadelphia, PA: 2010.

Pathophysiology

Acute Pain: Normal Nociception Is Modified by Inflammation

Tissue damage zone



5HT = serotonin; ATP = adenosine triphosphate; BDNF = brain-derived neurotrophic factor; Bk = bradykinin; CGRP = calcitonin gene-related peptide ; IL = interleukin; PG = prostaglandin; NGF = nerve growth factor; SP = substance P; TNF = tumor necrosis factor

Kidd BL, Urban LA. *Br J Anaesth* 2001; 87(1):3-11; Oprée A, Kress M. *J Neurosci* 2000; 20(16):6289-93.

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.

Somatic vs. Visceral Pain

Somatic

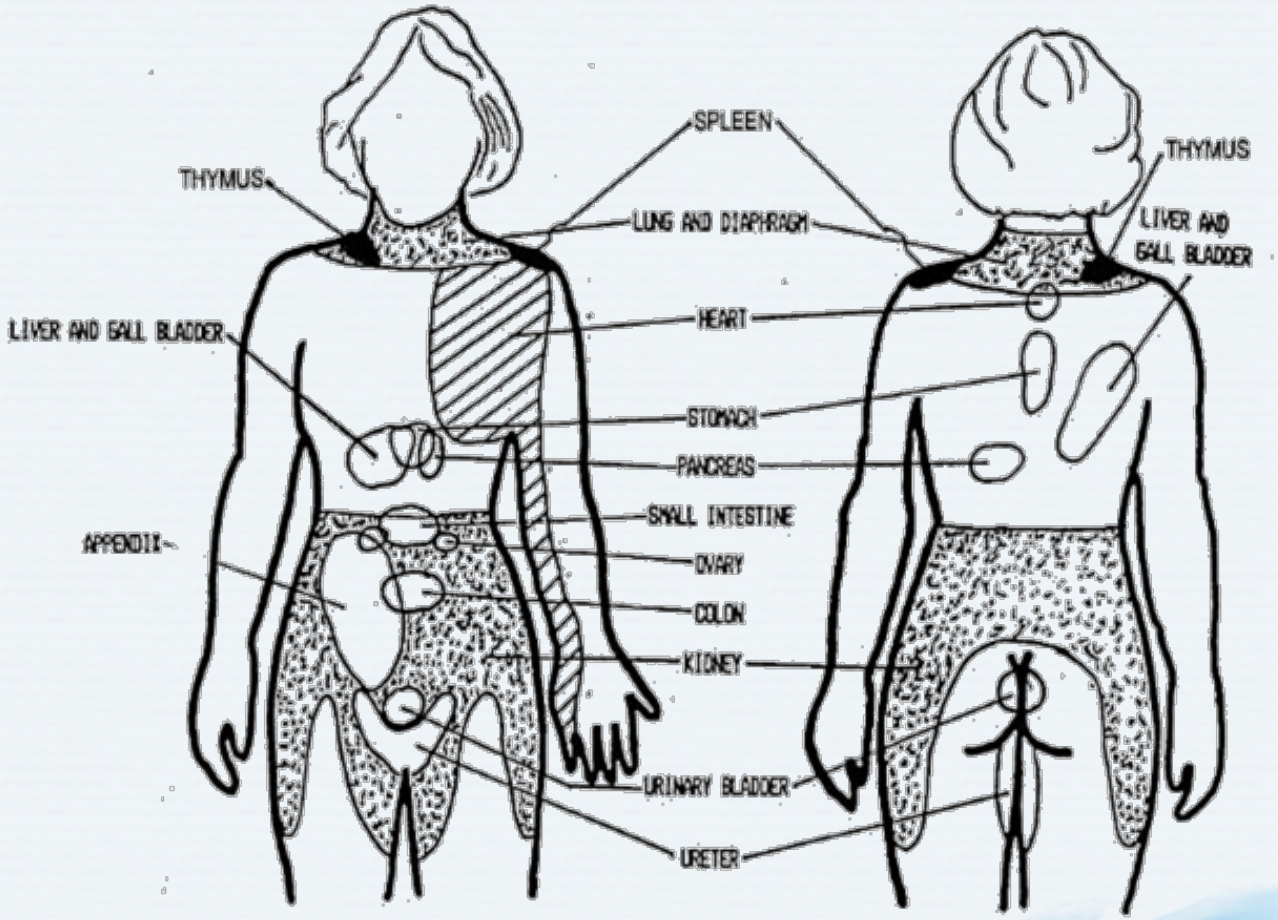
- Nociceptors are involved
- Often well localized
- Usually described as throbbing or aching
- Can be superficial (skin, muscle) or deep (joints, tendons, bones)

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)

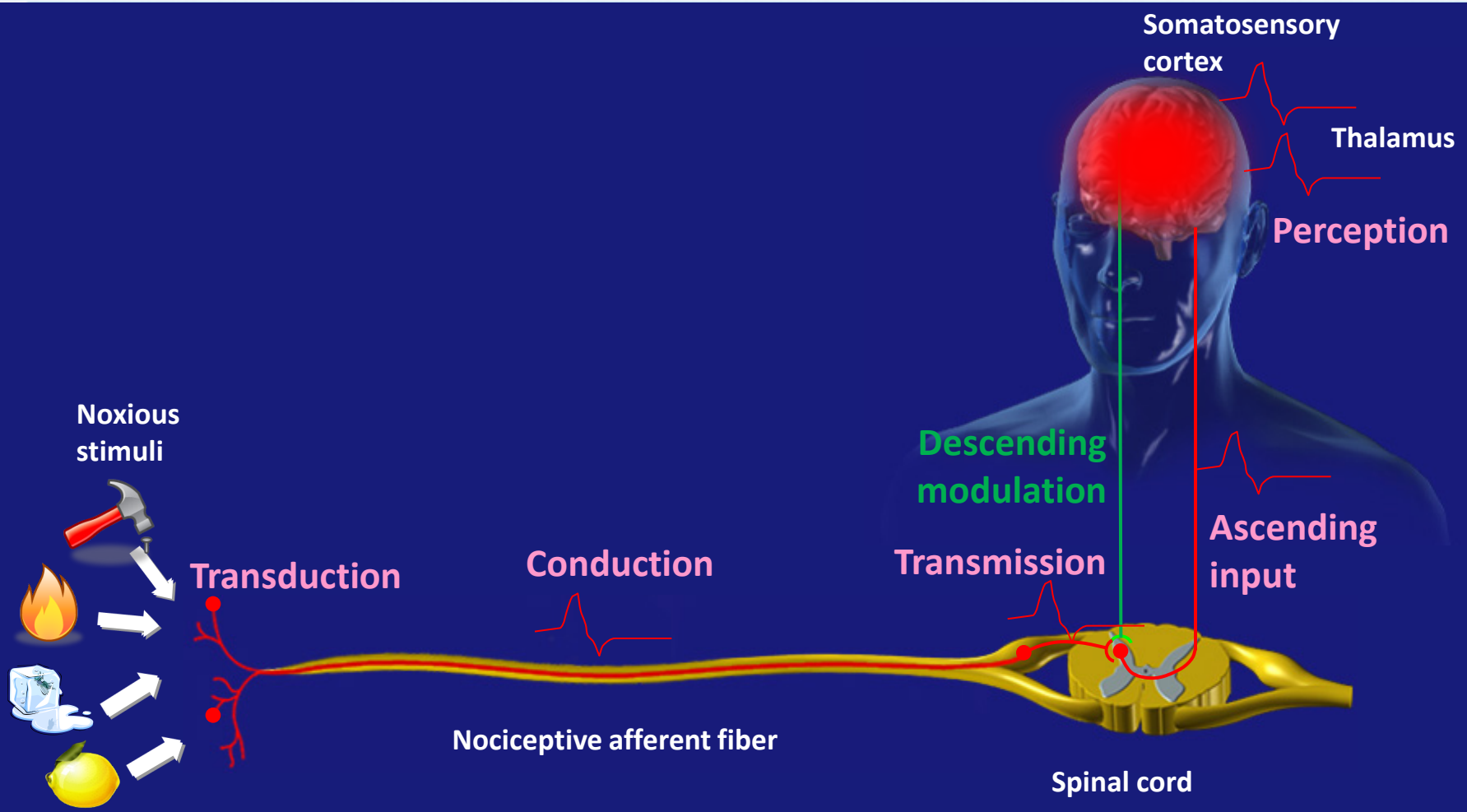
McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
Sikandar S, Dickenson AH. *Curr Opin Support Palliat Care* 2012; 6(1):17-26.

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.

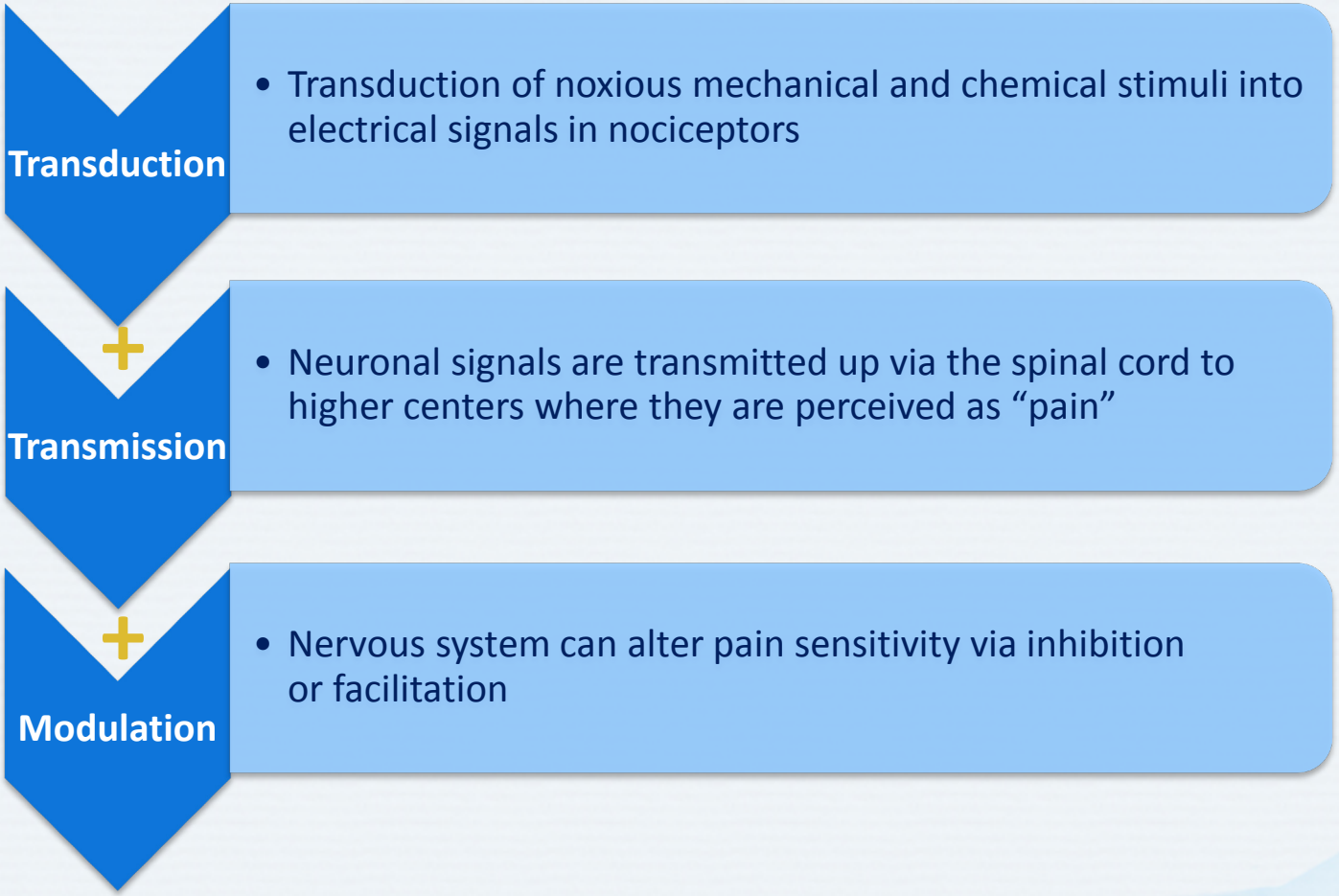
Nociception: Neural Process of Encoding Noxious Stimuli



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.

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

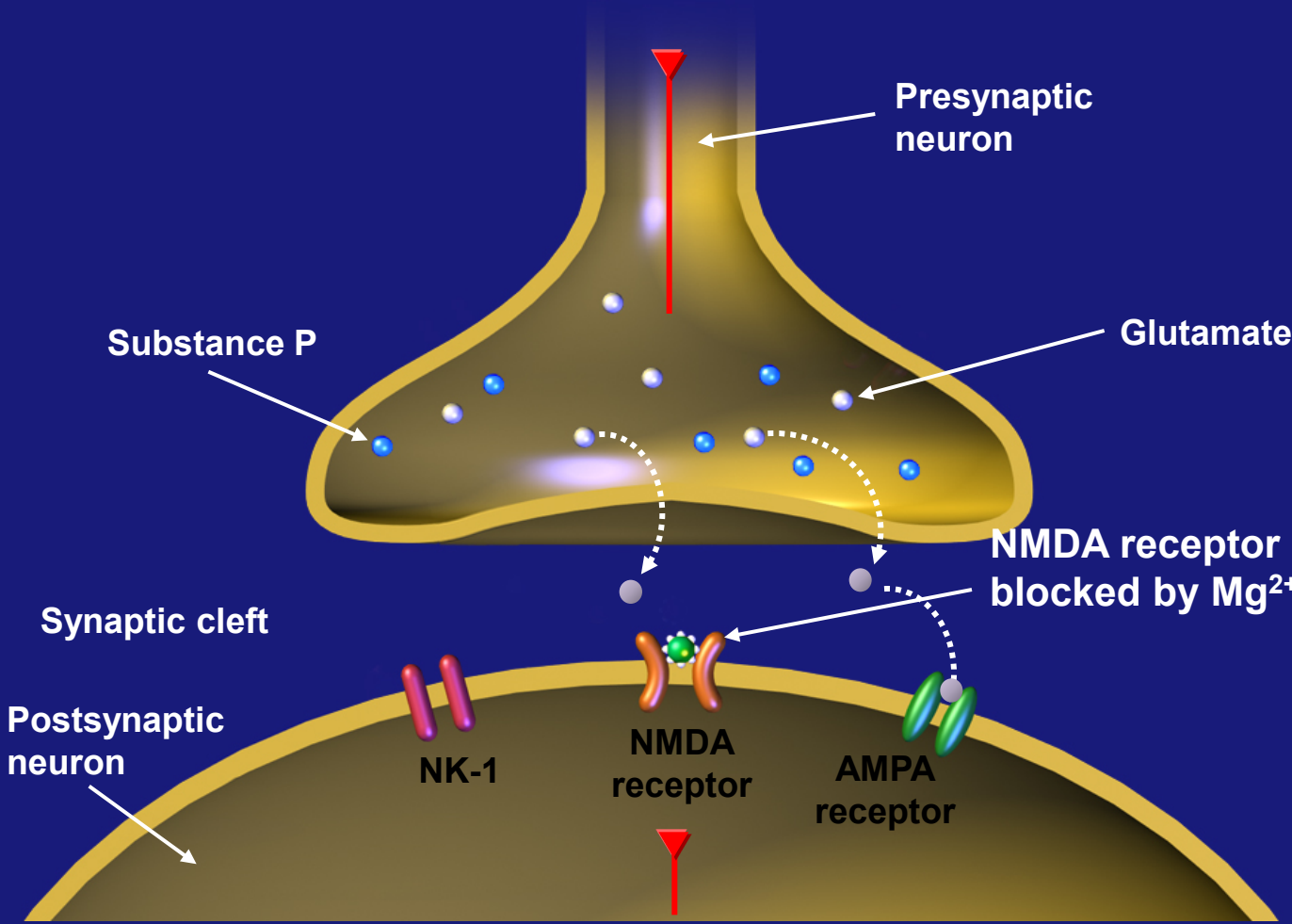
- Prostaglandins
- Leukotrienes
- Substance P
- Histamine
- Bradykinin
- Serotonin
- Hydroxyacids
- Reactive oxygen species
- Inflammatory cytokines and chemokines

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

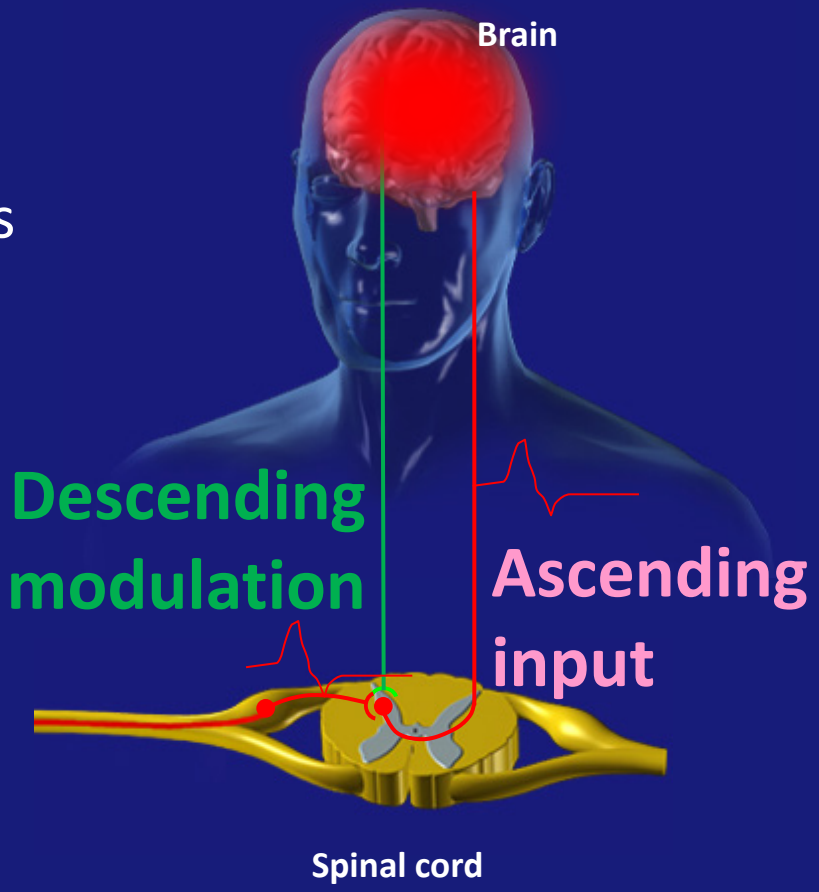
Fields HL *et al.* In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Julius D, Basbaum AI. *Nature* 2001; 413(6852):203-10; Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-68.

Pain Modulation

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

Ascending Nociceptive
C fibers Aδ fibers

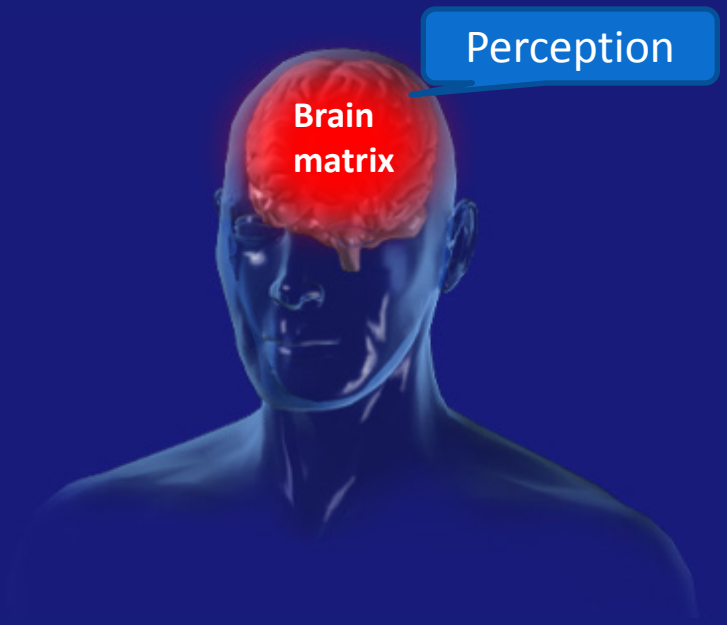
Descending Inhibitory/facilitatory
Serotonin Norepinephrine Dopamine



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.

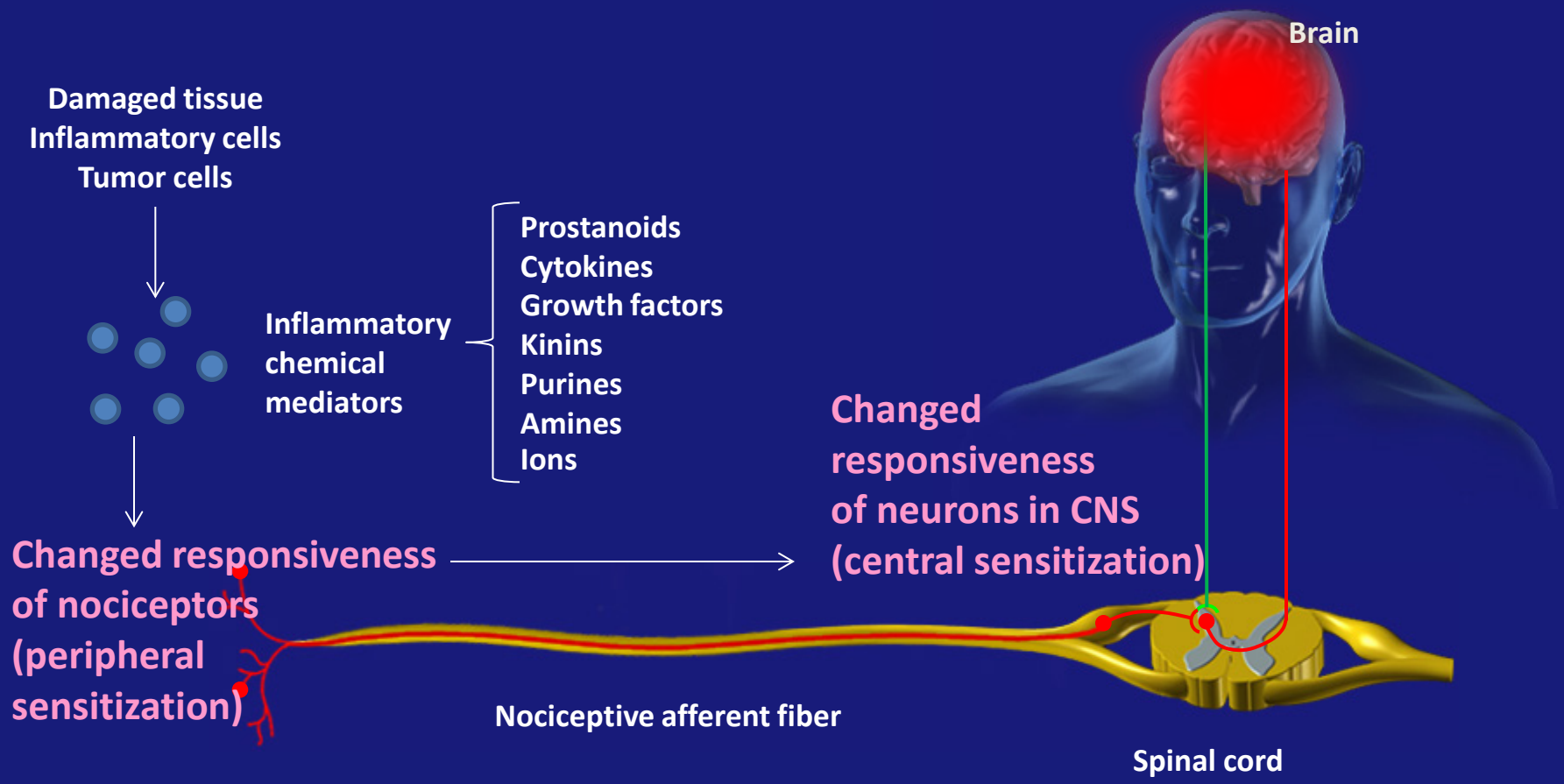
Pain Perception

- 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.

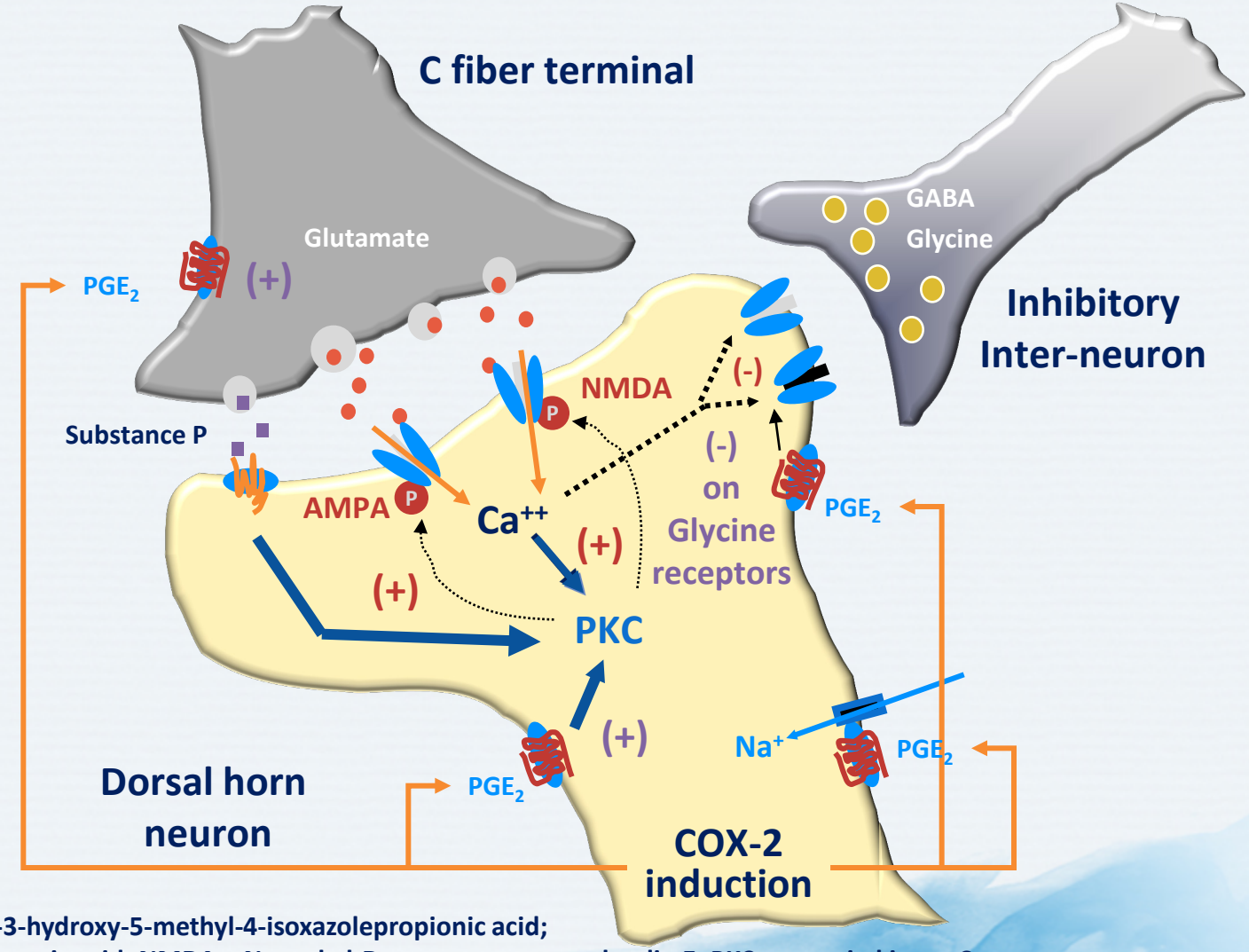
Inflammation



CNS = central nervous system

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

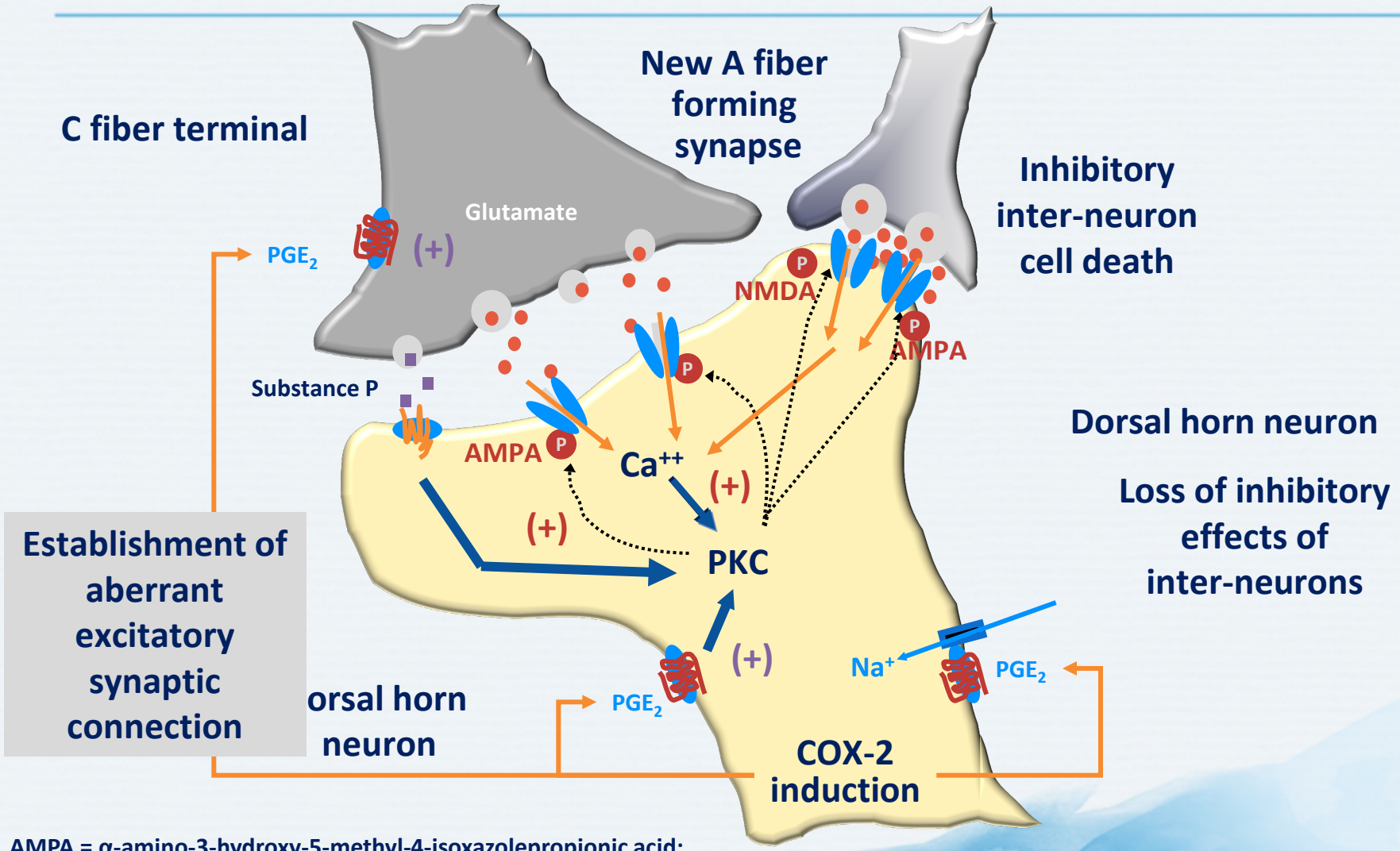
Central Sensitization



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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Summary

Pathophysiology of Acute Pain: Summary

- In acute pain, normal nociception is modified by inflammation
- Acute pain may develop into chronic pain through modulation of synaptic transmission
  - Repeated activation of C fiber nociceptors and peripheral inflammation can lead to increased expression of COX-2, iNOS and c-Fos in the secondary neuron and microglia
  - Peripheral injury can generate pain hypersensitivity in neighbouring, uninjured tissues (secondary hyperalgesia) via central sensitization

iNOS = inducible nitric oxide synthase