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
Pain Is the 5th Vital Sign

Respiration  Pulse  Blood pressure  Temperature

Pain

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

Biopsychosocial Model of Pain

Pain Classification


### Duration
- Acute
- Chronic

### Location
- Head
- Low back
- Etc.

### Severity
- Mild
- Moderate
- Severe

### Pathophysiology
- Nociceptive
- Neuropathic
- Central sensitization/dysfunctional
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

# Acute vs. Chronic Pain

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

Acute Pain Can Become Chronic

Pathophysiological processes

<table>
<thead>
<tr>
<th>Sensory component</th>
<th>Affective/cognitive component</th>
<th>Psychosocial antecedents</th>
</tr>
</thead>
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<td></td>
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</tbody>
</table>

Pathophysiological maintaining factors

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</tbody>
</table>

Acute Pain Can Become Chronic

Life Cycle Factors Associated with Development of Chronic Pain

From birth
- Genetics
- Female sex
- Minority race/ethnicity
- Congenital disorders
- Prematurity
- Parental anxiety
- Irregular feeding/sleeping
- Parents’ pain exposure and reactions
- Personality

Childhood
- Physical/sexual abuse and other traumatic events
- Low socioeconomic status
- Emotional, conduct and peer problems
- Hyperactivity
- Serious illness or injury
- Separation from mother
- Acute or recurrent pain experience

Adolescence
- Changes of puberty
- Gender roles
- Education level
- Injuries
- Obesity
- Low levels of fitness

Adulthood
- Vivid recall of childhood trauma
- Lack of social support
- Accumulated stress
- Surgery
- Overuse of joints and muscles
- Occupation
- Chronic disease
- Aging

Multiple pain mechanisms may coexist (mixed pain)

Nociceptive pain
- Somatic
- Visceral

Neuropathic pain
- Peripheral
- Central

Central sensitization/dysfunctional pain

Several Pathophysologies May Contribute to Chronic Pain

- Fibromyalgia
- 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
- 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
- Necrotizing fasciitis
- 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

Central sensitization/dysfunctional pain

Nociceptive pain

Neuropathic pain

Woolf CJ. Pain 2011; 152(3 Suppl):S2-S15.
Example of Coexisting Pain: Herniated Disc Causing Low Back Pain and Lumbar Radicular Pain

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
Pathophysiology
## What is nociceptive pain?

<table>
<thead>
<tr>
<th><strong>Definition</strong></th>
<th><strong>Pain Quality</strong></th>
</tr>
</thead>
</table>
| • 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 | • 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 |

# Characteristics of Nociceptive Pain

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

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

Examples of Nociceptive Pain

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

*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.

# Somatic vs. Visceral Pain

<table>
<thead>
<tr>
<th>Somatic</th>
<th>Visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nociceptors are involved</td>
<td>• Involves hollow organ and smooth muscle nociceptors that are sensitive to stretching, hypoxia and inflammation</td>
</tr>
<tr>
<td>• Often well localized</td>
<td>• Pain is usually referred, poorly localized, vague and diffuse</td>
</tr>
<tr>
<td>• Usually described as throbbing or aching</td>
<td>• May be associated with autonomic symptoms (e.g., pallor, sweating, nausea, blood pressure and heart rate changes)</td>
</tr>
<tr>
<td>• Can be superficial (skin, muscle) or deep (joints, tendons, bones)</td>
<td></td>
</tr>
</tbody>
</table>

Referred Pain

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.

Nociception

Dorsal root ganglion

Dorsal root

Spinothalamic tract

Corticospinal tract

Aδ and C fibers

Neurons

I

II

III

To brain

### Primary Nociception Is Accomplished through Peripheral Nociceptors: C Fibers and A\(\delta\) Fibers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A(\delta) fibers</th>
<th>C fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive fields</td>
<td>Small</td>
<td>Broad</td>
</tr>
<tr>
<td>Diameter</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Myelination</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Receptors</td>
<td>Nociceptors, Thermoreceptors, Mechanoreceptors</td>
<td>Nociceptors, High threshold mechanoreceptors</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>Rapid (10–30 m/s)</td>
<td>Slow (0.5–2.0 m/s)</td>
</tr>
<tr>
<td>Activation stimuli</td>
<td>Thermal, Mechanical</td>
<td>Polymodal</td>
</tr>
</tbody>
</table>

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 capsaicin.  
SNS/PN3 allows sodium to enter neuron, thus decreasing firing threshold.  
Nociceptive Pain

Transduction
- Transduction of noxious mechanical and chemical stimuli into electrical signals in nociceptors

Transmission
- Neuronal signals are transmitted up via the spinal cord to higher centers where they are perceived as “pain”

Modulation
- Nervous system can alter pain sensitivity via inhibition or facilitation

NOCICEPTIVE PAIN

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**
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

Pain Modulation

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

<table>
<thead>
<tr>
<th>Ascending Nociceptive</th>
<th>Descending Inhibitory/facilitatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>C fibers</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Aδ fibers</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
</tr>
</tbody>
</table>

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.)

Inflammation

Damaged tissue
Inflammatory cells
Tumor cells

Inflammatory chemical mediators

Prostanoids
Cytokines
Growth factors
Kinin
Purines
Amines
Ions

Changed responsiveness of nociceptors (peripheral sensitization)

Changed responsiveness of neurons in CNS (central sensitization)

Nociceptive afferent fiber
Spinal cord

Brain

CNS = central nervous system
What is neuropathic pain?

<table>
<thead>
<tr>
<th>Definition</th>
<th>Pain Quality</th>
</tr>
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<tbody>
<tr>
<td>• Pain caused by a lesion or disease of the somatosensory nervous system</td>
<td>• Burning</td>
</tr>
<tr>
<td>• Can be peripheral or central</td>
<td>• Lancinating</td>
</tr>
<tr>
<td></td>
<td>• Electric shock-like</td>
</tr>
<tr>
<td></td>
<td>• Often diffuse</td>
</tr>
<tr>
<td></td>
<td>• Frequently with allodynia</td>
</tr>
<tr>
<td></td>
<td>and/or hyperalgesia</td>
</tr>
</tbody>
</table>

Citing:
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

Common Descriptors of Neuropathic Pain

- Burning
- Tingling
- Pins and needles
- Electric shock-like
- Numbness

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

Pain intensity

Hyperalgesia
(increased response to a stimulus that is normally painful)

Stimulus intensity

Allodynia
(pain due to stimulus that does not normally provoke pain)

Normal
pain response

Response after injury

Development of Neuropathic Pain


Etiology

- Metabolic
- Traumatic
- Ischemic
- Toxic
- Hereditary
- Infectious
- Compression
- Immune-related

Pathophysiology

Mechanisms

- Spontaneous pain
- Stimulus-evoked pain

Symptoms

- Neuropathic pain

Symptoms

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

- Nerve lesion/disease
- Spinal cord
- Nociceptive afferent fiber
- Loss of inhibitory control
- Central sensitization
- Ectopic discharge
- Peripheral sensitization
- Descending modulation
- Spinal cord
- Brain
- Nerve lesion/disease

References:
Neuropathic Pain: $\alpha\beta$, $\alpha\delta$ and C Fibers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$\alpha\beta$ fibers</th>
<th>$\alpha\delta$ fibers</th>
<th>C fibers</th>
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<tbody>
<tr>
<td>Diameter</td>
<td>Large</td>
<td>Larger</td>
<td>Small</td>
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<td>Myelination</td>
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<td>No</td>
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<td>Conduction velocity</td>
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<td>Intermediate</td>
<td>Slow</td>
</tr>
<tr>
<td>Activation stimuli</td>
<td>Non-noxious mechanical</td>
<td>Noxious</td>
<td>Noxious</td>
</tr>
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### Sensory Processing and Neuropathic Pain

<table>
<thead>
<tr>
<th>Nerve function</th>
<th>Stimulus</th>
<th>Primary afferent</th>
<th>Sensation</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Innocuous Mechanical</td>
<td>Aβ</td>
<td>Normal touch</td>
<td>Normal function</td>
</tr>
<tr>
<td></td>
<td>Noxious Mechanical Thermal Chemical</td>
<td>Aδ nociceptor C nociceptor</td>
<td>Normal sharp pain</td>
<td>Normal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal burning pain</td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>Innocuous Mechanical</td>
<td>Aβ</td>
<td>Tactile hypoanesthesia</td>
<td>Decreased transmission of impulses</td>
</tr>
<tr>
<td></td>
<td>Noxious Mechanical Thermal Chemical</td>
<td>Aδ nociceptor C nociceptor</td>
<td>Mechanical Heat or cold hypoalgesia</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Innocuous Mechanical</td>
<td>Aβ</td>
<td>Dynamic mechanical allodynia</td>
<td>Many theories (e.g., sensitization)</td>
</tr>
<tr>
<td></td>
<td>Noxious Mechanical Thermal Chemical</td>
<td>Aδ nociceptor C nociceptor</td>
<td>Mechanical Heat or cold hyperalgesia</td>
<td>Many theories (e.g., wind-up, peripheral sensitization)</td>
</tr>
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What is central sensitization/dysfunctional pain?

<table>
<thead>
<tr>
<th>Definition</th>
<th>Examples</th>
<th>Pain Quality</th>
</tr>
</thead>
</table>
| • Amplification of neural signaling within the CNS that elicits pain hypersensitivity | • Fibromyalgia  
• Irritable bowel syndrome  
• Interstitial cystitis  
• Temporomandibular joint pain  
• May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis | • Burning  
• Lancinating  
• Electric shock-like  
• Often diffuse  
• Frequently with allodynia and/or hyperalgesia |

CNS = central nervous system  
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

Neuronal Plasticity

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

Neuronal Plasticity and Pain Pathogenesis

• Neuronal plasticity can cause pain\textsuperscript{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\textsuperscript{1,3}
  – Characterized by hyperalgesia and allodynia\textsuperscript{2}

\textit{CNS} = central nervous system

2. Woolf CJ. \textit{Ann Intern Med} 2004; 140(6):441-51;
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

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*
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”

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

Wind-Up

Stimulus

Primary afferent nerve fibers

Dorsal horn neurons

Ectopic Discharges

Sodium channel expression increased

Primary excitatory afferent nerve fiber

Conduction frequency amplified

Peripheral Sensitization

Innocuous stimulus

Primary afferent nerve fibers

Neuropeptide release

Dorsal horn neurons

NGF

PAIN

Central Sensitization

Believed to result from excessive release of 2 important neurotransmitters:
- Substance P
- Glutamate
Central Sensitization after Nerve Injury

- **Innocuous stimulus**
- **NORMAL**
- **NERVE INJURY**
- **No pain**
- **PAIN**

Central Sensitization

Dorsal horn neuron

C fiber terminal

GABA
Glycine

Substance P

Glutamate

AMPA
NMDA
Ca++

PKC(+)

PGE2

(-)

Na+
PGE2

(+)

PGE2

COX-2 induction

Inhibitory Inter-neuron

AMP A = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Central Sensitization

Dorsal horn neuron

C fiber terminal

Substance P

Glutamate

PKC (+)

AMP A

NMDA

Ca++

PGE2 (-)

PGE2 (+)

GABA

Glycine

Inhibitory inter-neuron cell death

COX-2 induction

AMP A = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;
GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Central Sensitization

C fiber terminal

New A fiber forming synapse

Inhibitory inter-neuron cell death

Dorsal horn neuron

Loss of inhibitory effects of inter-neurons

Establishment of aberrant excitatory synaptic connection

Dorsal horn neuron

COX-2 induction

AMP = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

Central Sensitization Produces Abnormal Pain Signaling

- Minimal stimuli
- Pain amplification
- Increased neuronal excitability
- Increased release of pain neurotransmitters glutamate and substance P
- Nociceptive afferent fiber
- Spinal cord
- Brain
- Perceived pain (hyperalgesia/allodynia)

Pain treatment options:
- $\alpha_2\delta$ ligands
- Antidepressants

Loss of Inhibitory Controls

Normal

Innocuous or noxious stimulus

Injured

Dorsal horn neuron

Descending

Local

Spontaneous firing

Exaggerated pain response

Loss of Inhibitory Control: Disinhibition

Pain treatment options
- $\alpha_2\delta$ ligands
- Antidepressants

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