PATHOPHYSIOLOGY
Overview
Multiple pain mechanisms may coexist (mixed pain)
What is central sensitization/dysfunctional pain?

<table>
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<th>Definition</th>
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| • Amplification of neural signaling within the CNS that elicits pain hypersensitivity | • Fibromyalgia  
• Tension-type headache  
• Irritable bowel syndrome  
• Interstitial cystitis  
• Temporomandibular joint pain  
• May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis | • Often diffuse  
• Frequently with allodynia and/or hyperalgesia  
• Rarely burning, lancinating or electric shock-like |

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

What is fibromyalgia?

Fibromyalgia is a common chronic widespread pain disorder, characterized by an amplification of pain signals, analogous to the “volume control setting” being turned up too high.

Fibromyalgia: An Amplified Pain Response


Pain amplification response

- **Normal pain response**
- **Pain in fibromyalgia**

**Subjective pain intensity**

- **Hyperalgesia**
  - (when a pinprick causes an intense stabbing sensation)

- **Allodynia**
  - (hugs that feel painful)

**Stimulus intensity**
Biopsychosocial Model of Pain

Etiology
Etiology of Central Sensitization Syndromes

- **Central sensitization syndromes** are a group of medically indistinct disorders for which no organic cause can be found
  
  - Examples include:
    - Fibromyalgia
    - Chronic fatigue syndrome
    - Irritable bowel syndrome
    - Temporomandibular joint disorder
    - Tension headache/migraine

- These disorders share many symptoms, including pain
- Central sensitization has been proposed as root etiology for these conditions

Etiology of Fibromyalgia

• Etiology and pathogenesis still not fully understood
• Several factors appear to be involved, including:
  – CNS and autonomic nervous system dysfunction
  – Neurotransmitters
  – Hormones
  – Immune system
  – External stressors
  – Psychiatric aspects

CNS = central nervous system
Etiology of Fibromyalgia

- **Central sensitization** is considered to be **main mechanism** involved
  - Defined by increased response to stimulation mediated by CNS signaling
  - Due to spontaneous nerve activity, enlarged receptive fields, and augmented stimulus responses transmitted by primary afferent fibers
  - Various neurotransmitters, especially serotonin, implicated

- **“Windup”** is important
  - Increased excitability of spinal cord neurons
  - After a painful stimulus, subsequent stimuli of the same intensity are perceived as stronger
  - Occurs normally in everyone but is excessive in patients with fibromyalgia

- **Impaired descending inhibitory pain pathways**
  - Modulate spinal cord responses to painful stimuli
  - Impairment in patients with fibromyalgia exacerbates central sensitization

*CNS* = central nervous system
What causes fibromyalgia?

- Pain-prone phenotype?
- Role of genetics (family members, relatives)?
- Environmental factors?
  - Infections
  - Motor vehicle trauma
  - Psychological stress
- Inflammation?
  - Approximately 10-30% of patients with osteoarthritis or inflammatory arthritis also meet criteria for fibromyalgia
- Small fiber neuropathy? Hyperexcitable small nerve fibers?
- Abnormal central pain processing?

Pathophysiology
Why do patients suffering from central sensitization experience dysfunctional pain?

- During central sensitization, the sensation of pain is enhanced as a result of:
  - Changes in nerve fibers and the environment
  - Modifications of the functional properties and the genetic programming of primary and secondary afferent neurons

Sensory Hypersensitivity

• Pain hypothesized to be a result of persistent neuronal dysregulation or dysfunction
• No identifiable nerve or tissue damage
• Fibromyalgia is the prototype condition
• May drive/contribute to the pain of irritable bowel syndrome, temporomandibular joint disorder, chronic fatigue and chronic low back pain, as well as osteoarthritis and rheumatoid arthritis

Pathogenesis of Fibromyalgia: Overview

- Fibromyalgia is a condition of global dysregulation of pain processing
- Central sensitization is one component
  - Mechanisms of central sensitization

Excitatory mechanisms

Inhibitory mechanisms

Overview of Pathophysiologival Observations in Fibromyalgia

• **Peripheral**
  – Peripheral sensitization
  – Temporal summation (wind-up) (short-term)

• **Spine and brain**
  – Central sensitization (long-term)
  – Change in gray matter volume

• **Descending inhibition**

• **Other factors**
  – Hypothalamic-pituitary-adrenal axis dysregulation
  – Sleep disturbance
  – Cognitive effects

Despite extensive research, the exact cause of pain in fibromyalgia is not clearly understood.

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

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

Inhibitory Inter-neuron

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

Central Sensitization

**Dorsal horn neuron**

- C fiber terminal

- AMPA
- NMDA
- Ca++
- Substance P
- Glutamate
- PKC (+)
- COX-2 induction
- PGE2
- Na+
- Inhibitory inter-neuron cell death

**GABA**

- Glycine

**AMPAR**

- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

**GABAA**

- γ-aminobutyric acid

**NMDAR**

- N-methyl-D-aspartate

**PKC**

- Protein kinase C

**PGE2**

- Prostaglandin E

**COX-2**

- Induction

Central Sensitization

C fiber terminal

Dorsal horn neuron

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

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

Pain treatment options
- α₂δ ligands
- Antidepressants

Increased release of pain neurotransmitters glutamate and substance P

Increased neuronal excitability

Minimal stimuli

Nociceptive afferent fiber

Spinal cord

Brain

Perceived pain (hyperalgesia/allodynia)

Pain amplification

Loss of Inhibitory Controls

Loss of Inhibitory Control: Disinhibition

- Noxious stimuli
- Transduction
- Transmission
- Nociceptive afferent fiber
- Spinal cord
- Descending modulation
- Ascending input
- Brain
- Perception
- Exaggerated pain perception

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

Pathophysiological Changes in Fibromyalgia

- **Gray matter atrophy**
- **Altered intrinsic connectivity**
- **Exaggerated pain perception**
- **fMRI studies show marked regional increase in cerebral blood flow following a painful stimulus in patients with fibromyalgia compared to controls**
- **Altered metabolite levels in pain-processing regions of brain**
- **Increased levels of pain neurotransmitter substance P (>3x)**
- **Deficit in endogenous pain inhibitory systems noted**
- **Impaired small fiber function**
- **Minimal stimuli**
- **Nociceptive afferent fiber**
- **Spinal cord**

fMRI = functional magnetic resonance imaging

Potential Small Fiber Pathology in Patients with Fibromyalgia

- Compared to healthy controls and controls suffering from depression (but free of pain), patients with fibromyalgia had:
  - Increased cold and warm detection thresholds in quantitative sensory testing
  - Reduced amplitudes of pain-related evoked potentials upon stimulation of face, hands and feet
  - Reduction in dermal unmyelinated nerve fibre bundles obtained through skin biopsies at the lower leg and upper thigh

Summary
Pathophysiology of Fibromyalgia: Summary

• Central sensitization/dysfunctional pain is hypothesized to be a result of persistent neuronal dysregulation or dysfunction
  – Fibromyalgia, a chronic, persistent and debilitating widespread pain disorder, is the most common syndrome associated with this type of pain

• Etiology and pathogenesis are still not fully understood

• Several factors appear to be involved
  – Central sensitization is considered to be main mechanism involved
  – “Wind-up” is important
  – Impaired descending inhibitory pain pathways also play a role