

Fibromyalgia

A Unifying Neuroendocrinologic Model

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What Is Fibromyalgia?

- a syndrome (*not a disease*)
- widespread tenderness in the extremities and trunk anteriorly and posteriorly
(*11/14 points definition per ACR criteria*)
- exclusion of other, measurable conditions
(*sed rate ↔ polymyalgia rheumatica, RF ↔ rheumatoid arthritis, ↑TSH ↔ hypothyroidism*)

Fibromyalgia “Fun Facts”

- 1904 Gowers coined term “fibrositis”
- reference to a condition “whole body impediment” with widespread pain and organ involvement in *Nei Jing* ~200 BC
- 1945 Kelly describes local and distant referred-pain caused by “fibrositis” nodules
- history of fibromyalgia (aka fibrositis, tension myalgia, etc) closely intertwined

Fibromyalgia “Fun Facts”

- widespread body pain is believed to affect approximately 3.6% of the adult population in the United States
- prevalence of fibromyalgia is estimated to be at least 2% (range 2-5%) of the population (>5 million individuals)
- similar prevalence in other countries

What Is The Difference
Between Fibromyalgia
and
Widespread Myofascial Pain?

Some Similarities

- widespread trigger points in the extremities and trunk
- impairments in function related to same (up to 26.5% of those with fibromyalgia receive disability)
- sleep disturbances

Big Differences!

- 7:1 female to male ratio fibromyalgia (some report 8-9:1 ratio)
- 1:1 female to male ratio in chronic myofascial pain
- **THE ASSOCIATED CONDITIONS**
- 4-25 times more prevalent in individuals with fibromyalgia than in those not diagnosed with that condition

<i>Clinical Condition</i>	<i>% Fibromyalgia Patients</i>	<i>% General Populaton</i>
Chronic headache	50%	5%
Dysmenorrhea	60%	15%
Endometriosis	15%	2%
Interstitial cystitis	25%	<1%
Irritable bladder/ urethra	15%	<1%
Irritable bowel syndrome	60%	10%
Mitral valve prolapse	75%	15%
Multiple chemical sensitivities	40%	5%
Restless legs syndrome	30%	2%
TMJ syndrome	25%	5%

Autonomic Nervous System and Fibromyalgia

The missing link?

Autonomic Nervous System Physiologic Functions

(as opposed to dysfunctions)

SANS Effects	PANS Effects
"fight or flight"	"rest and digest"
↑ alertness/vigilance	↓ alertness/vigilance
↑ heart rate and contractility	↓ heart rate and contractility
↑ breathing rate & bronchodilation	↓ breathing rate & bronchoconstriction
↑ cardiac/skeletal muscle blood flow	↓ cardiac/skeletal muscle blood flow
↓ gut blood flow	↑ gut blood flow
↓ cutaneous blood flow	↑ cutaneous blood flow
↑ blood sugar	↓ blood sugar
↑ temperature	↓ temperature
↓ gut contractility	↑ gut contractility
↓ bladder contractility	↑ bladder contractility
↓ salivation	↑ salivation
↓ lacrimation	↑ lacrimation
↓ digestion	↑ digestion

Autonomic Nervous System Physiologic Dysfunctions

(as opposed to functions)

Autonomic Nervous System Imbalance in Fibromyalgia (*relative degree of tonus*)

Clinical Condition	SANS	PANS
Migraine	↑ initial phase	↑ later phase
IBS (diarrhea predominant)	↓	↑
IBS (constipation predominant)	↑	↓
Interstitial Cystitis	↑	↑
Raynaud's-like phenomenon	↑	↓
Endometriosis	↑	↓
Aseptic Prostatitis	↑	↓
Idiopathic Urethritis	↑	↓
Skeletal Muscle Tone	↑	-

IBS= irritable bowel syndrome

SANS= sympathetic autonomic nervous system

PANS= parasympathetic autonomic nervous system

Literature Support

- Migraine (Petrouka, 2004)
- Irritable Bowel Syndrome (Mazur, 2007)
- Interstitial Cystitis (Pacak, 2001, in cat)
- Endometriosis (Possover, 2005)
- Idiopathic Urethritis (Husmann, 2006)
- TMJ Syndrome (Rodrigues, 2006)

Medications Demonstrating Efficacy for Fibromyalgia

Good Efficacy	Marginal Efficacy
Pregabalin	NSAID agents
Gabapentin	Opioids
Duloxetine	
Milnacipran	
Cyclobenzaprine	

NSAID= non-steroidal anti-inflammatory drugs

Neuroendocrine Model of Fibromyalgia

Brain

Hypothalamus = Controller

Hypothalamus

- SANS and PANS responses of the organism are opposite in their effects
- hypothalamus is the central nervous system site that controls the balance of these responses
- circadian rhythms of sleep as well as appetite regulation, mood, and temperature also are regulated at the hypothalamic level

Hypothalamus

- SANS output from its posterolateral nuclei → interomediolateral nuclei of spinal cord
- PANS output from its anteromedial nuclei → vagus nerve
- controls cortisol + norepinephrine release through the HPA axis (*SANS activation with slower onset and longer duration*)
- controls descending inhibition of pain at the spinal cord dorsal horn through descending pathways from the rostroventral medulla, periaqueductal gray, and locus ceruleus

Hypothalamic Dysfunction in Fibromyalgia

- systemic norepinephrine release via the HPA axis +
- ↑ hypothalamic SANS output to the interomediolateral cells of the spinal cord +
- ↓ descending pain inhibition at the spinal cord level =
- sensitization of primary nociceptors in fibromyalgia

Clinical Research Support

- plasma catecholamine concentrations are increased in patients with fibromyalgia

Torpy et al. Arthritis Rheum 2000;43(4):872-880

- elevated catecholamine levels are associated with hyperalgesia

Khasar et al. J Neurophysiol 1999;81(3):1104-1112

- ~8% of spinal nerve fibers are postganglionic sympathetic fibers
- these fibers also invest the arteries that accompany spinal nerves and their branches to the extremities

Paleocortex Input

- right insular cortex → sympathetic outflow to the hypothalamus
- left insular cortex → parasympathetic outflow
- orbitofrontal + medial prefrontal cortex areas → hypothalamus allows emotions to directly influence autonomic balance
- amygdala integrates behavioral and autonomic responses from the somatosensory cortex and limbic system structures (medial prefrontal cortex, orbitofrontal cortex, cingulate gyrus, hippocampus, anterior & medial thalamic nuclei)
- amygdala effect on hypothalamus inhibitory

Clinical Research Support

- abnormally high metabolic activity seen in the thalamus, amygdala, hippocampus, cingulate gyrus, and other limbic system structures in fibromyalgia patients

Williams et al. Arthritis Res Ther 2006; 8(6): 224

- psychological stress causes degranulation of mast cells (many estrogen receptor positive) → neurogenic inflammation

Alexacos et al. Urology 1999; 53(5):1035-40

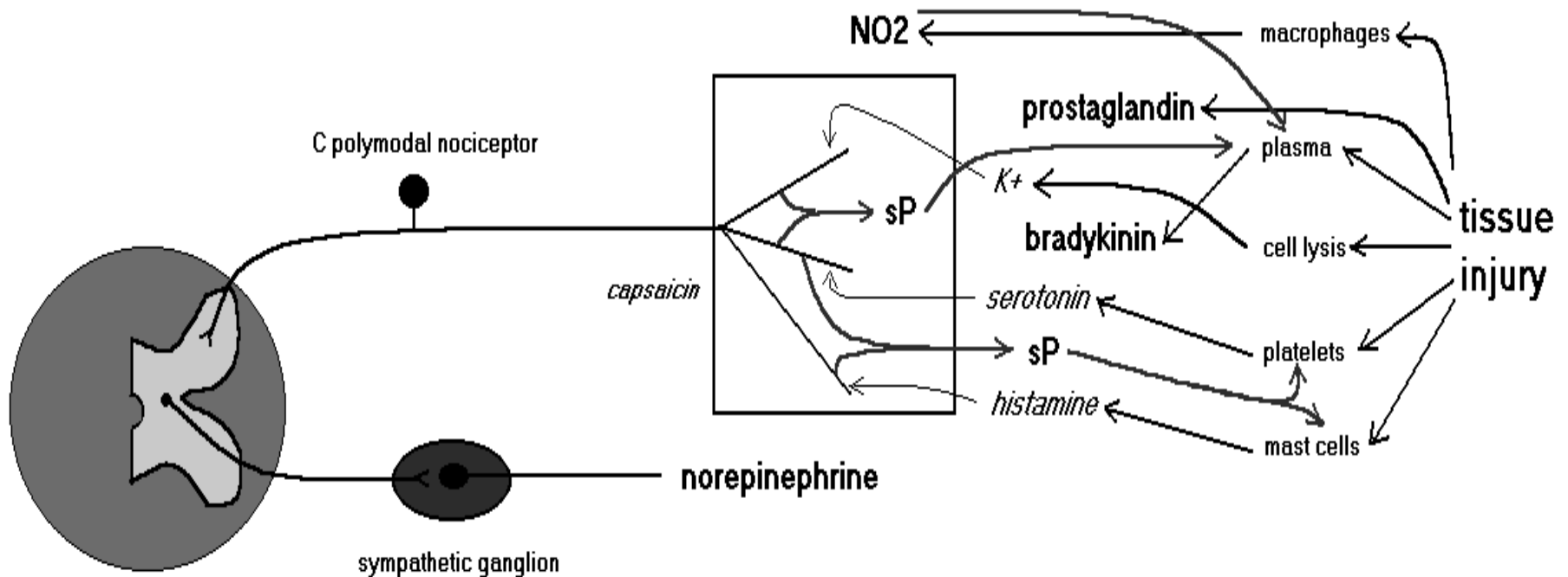
Eutamene et al. J Physiol 2003; 553(3) 959-966

Peripheral Mechanisms

Neurogenic Inflammation

- physiologic phenomenon that occurs in vivo
- efferent (antidromic) outflow from the spinal cord (dorsal root reflexes, or DRR) produces nociceptive C-fibers to release substance P (sP), calcitonin gene related peptide (cGRP), and somatostatin from their terminal axons
- their release → release of bradykinin, histamine, & serotonin from local vasculature (plasma), platelets, & macrophages
- → activate those nociceptive neurons
- local positive feedback loop is produced

Peripheral Sensitization & Neurogenic Inflammation



Neurogenic Inflammation Effects

- local edema → fibromyalgia nodules
- widespread neurogenic inflammation → widespread myofascial tenderness (fibromyalgia tender points) without overt presence of inflammatory cells
- neurogenic inflammation via dorsal root reflexes and propriospinal pathways → ascending and descending sensitization of nociceptors in adjacent spinal levels →, spread of pain & tenderness to wider areas of the body
- sensitization of primary nociceptors → sensitization of wide dynamic range neurons in the deeper spinal cord lamina, which have much wider cutaneous receptive fields as well as afferent sensory input from viscera

Research Evidence

- active trigger points have markedly increased concentrations of inflammatory mediators
- muscle sites (soleus) distant from those trigger points demonstrated lesser elevations of these inflammatory mediators (higher than normal)
- → central nervous system sensitization

Shah et al. Arch Phys Med Rehab 2008;89(1):16-23

Ascending Pathways

- primary nociceptors relay through the lateral spinothalamic tract to the lateral thalamus to the somatosensory cortex to localize painful stimuli
- wide dynamic range neurons send afferent signals through the paleospinothalamic tract to the anterior and medial thalamus relay to limbic system structures which subserve the emotional and behavioral reactions to the painful stimuli
- completes positive feedback loop

Simplified Neuroendocrinologic Model

