Fibromyalgia: A Unifying Neuroendocrinologic Model for Understanding Its Pathophysiology

Peter T. Dorsher, MS, MD

From the Department of Physical Medicine and Rehabilitation, Mayo Clinic, Jacksonville, Florida

Address reprint requests to Peter T. Dorsher, MD, Department of Physical Medicine and Rehabilitation, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224.
E-mail: dorsher.peter@mayo.edu. Phone 904-953-2823 Fax 904-953-0276

Text word count: 1682 (2956 with references, tables, and legends)
Abstract word count: 121
Introduction word count: 246
Discussion word count: 273
No. of tables: 3
No. of figures/parts: 3

Abstract

Fibromyalgia is believed to affect at least 2% of the population. Despite advances in the scientific understanding of the derangements of central and peripheral pain processing mechanisms in fibromyalgia, no current models of its pathophysiology account for the other clinical conditions associated with it such as fatigue, migraine headache, irritable bowel syndrome, and sleep cycle abnormalities. A neuroendocrinologic model of fibromyalgia is presented that accommodates both its known central and peripheral pain mechanisms as well as the myriad of hormonal, visceral, and psychological symptoms associated with that disorder. This model also provides a unifying pathophysiologic basis of fibromyalgia and chronic muscle pain, and offers the potential for developing new avenues of research and treatment for these enigmatic, frequently disabling medical conditions.

Introduction

In 1852, Virchow first described "muscular rheumatism" [1] and five decades later Gowers described persons with widespread pain symptoms he termed "fibrositis" [2]. The fibromyalgia and myofascial pain histories have overlapped, with Kelly [3] in 1945 discussing the concept of distant referred-pain produced by "fibrositis" nodules. The historical overlap of these conditions is not surprising, since both the myofascial pain and fibromyalgia syndromes are pain conditions characterized by tender soft tissue (especially muscle) sites that may generate referred-pain distant to those sites.

There are significant clinical differences between the fibromyalgia and myofascial pain syndromes, however. Fibromyalgia afflicts females seven times more frequently than males, while myofascial pain syndrome afflicts genders equally [4]. Myofascial pain syndrome often affects only one body region, though widespread myofascial pain has been described [5]. In contrast, the diagnosis of fibromyalgia requires the presence of widespread soft tissue tenderness in multiple body regions [6]. Both conditions may be associated with sleep disturbances, but fibromyalgia is also associated with other clinical conditions (Table 1) including irritable bowel syndrome, interstitial cystitis, and migraine headaches [7]. These conditions are 4-25 times more common in individuals diagnosed with fibromyalgia [7].

Widespread body pain affects approximately 3.6% of adults in the United States [8], with fibromyalgia diagnosed in 5 million (2%) of adults [4]. In terms of rheumatologic disorders, only osteoarthritis and gout [9] have higher prevalence than fibromyalgia; yet fibromyalgia is associated with the highest disability rate (up to 26.5%) of all rheumatologic disorders [10, 11].

A Neuroendocrinologic Model of Fibromyalgia and Chronic Muscle Pain

The sympathetic autonomic nervous system (SANS) subserves the body's "fight or flight" responses to dangerous or stressful stimuli, while the parasympathetic

autonomic nervous system (PANS) subserves its vegetative, "rest and digest" functions (S. Bakewell, http://www.nda.ox.ac.uk/wfsa/html/u05/u05_010.htm). Most body structures, including muscle, have dual sympathetic and parasympathetic innervation. As shown in Table 2, SANS and PANS responses have opposite physiologic effects, with the hypothalamus controlling the balance of those responses (D. Molavi, http://thalamus.wustl.edu/course/hypoANS.html). As an example relevant to musculoskeletal pain, SANS activation increases resting skeletal muscle tone while PANS activation reduces it [12].

The clinical conditions associated with fibromyalgia (Table 1) are postulated to result from imbalance or instability of the autonomic nervous system (Table 3). SANS abnormalities have been described for many of those conditions, including migraines [13], irritable bowel syndrome [14], interstitial cystitis [15], endometriosis [16], idiopathic urethritis [17], chronic prostatitis [18], and temporomandibular joint pain [19]. Thus, abnormal regulation of SANS/PANS outflow balance by the hypothalamus could result in these clinical conditions seen in fibromyalgia patients. The circadian rhythms of sleep [20], appetite regulation [21], mood [22], and temperature [23] also are regulated at the hypothalamic level; and the abnormalities of those physiologic functions often described by fibromyalgia patients are also consistent with hypothalamic dysfunction.

Though the insular cortex is believed to be mainly a viscerosensory structure, the right insular cortex is believed to provide sympathetic outflow to the hypothalamus and the left insular cortex its parasympathetic outflow [24]. The orbitofrontal and medial prefrontal cortex areas of the limbic system have direct anatomic input to the

hypothalamus, allowing emotions to directly influence autonomic balance there [25]. The amygdala serves to integrate behavioral and autonomic responses from the somatosensory cortex and limbic system structures including the medial prefrontal cortex, orbitofrontal cortex, cingulate gyrus, hippocampus, anterior thalamic nuclei, and medial thalamic nuclei [26]. The amygdala is thought to have inhibitory influence on the hypothalamus to attenuate SANS output [27]. These thalamic and cortical influences on the hypothalamus are demonstrated in Figure 1.

Hypothalamic SANS output arises from its posterolateral nuclei that ultimately innervate the interomediolateral nuclei of the spinal cord, while its PANS output arises from its anteromedial nuclei that ultimately course to peripheral structures via the vagus nerve (D. Molavi, http://thalamus.wustl.edu/course/hypoANS.html). The hypothalamus also regulates the release of cortisol and norepinephrine through the hypothalamic-pituitary-adrenal (HPA) axis, which provides systemic SANS activation with slower onset and longer duration (D. Molavi, http://thalamus.wustl.edu/course/hypoANS.html). Further, hypothalamic output regulates brainstem structures (rostroventral medulla, periaqueductal gray, and locus ceruleus) whose descending pathways to the dorsal horn of the spinal cord modulate pain transduction in nociceptive neurons there, as shown in Figure 1 [28].

The systemic norepinephrine release via the HPA axis, accentuated SANS tone through hypothalamic output to the interomediolateral cells of the spinal cord, and reduced descending pain inhibition at the spinal cord level are then postulated in this neuroendocrinologic model to produce sensitization of primary nociceptors in fibromyalgia patients. Clinical research supporting this includes documentation that

fibromyalgia patients have elevated plasma catecholamine levels, which are associated with hyperalgesia [29,30]. Approximately 8% of spinal nerve fibers are postganglionic sympathetic fibers [31], which also invest the arteries that accompany spinal nerves and their branches to the extremities [32] (H. Gray, http://www.bartleby.com/107/214.html).

Neurogenic inflammation is a physiologic phenomenon [33] in which efferent outflow from the spinal cord (dorsal root reflexes) causes nociceptive C-fibers to release substance P (sP), calcitonin gene related peptide (cGRP) and somatostatin from their terminal axons. These substances then cause local vasculature (plasma), platelets, and macrophages to release bradykinin, histamine, and serotonin, which serve to activate those nociceptive neurons [34], as illustrated in Figure 2. Thus, a local positive feedback loop is produced as neurogenic inflammation ultimately produces release of substances from the terminal axons that activate the primary nociceptors. Efferent or systemic SANS activation can further sensitize these nociceptive neurons (Figures 1 and 2). The abnormally high metabolic activity seen in the thalamus, amygdala, hippocampus, cingulate gyrus, and other limbic system structures in fibromyalgia patients [35] is consistent with abnormal central nervous system (CNS) autonomic efferent activity contributing to nociceptor sensitization and neurogenic inflammation peripherally. Psychological stress alone can cause degranulation of mast cells (many of which are estrogen receptor positive) to initiate neurogenic inflammation [36,37], which may help explain the predominance of fibromyalgia in females. Neurogenic inflammation causes local edema (fibromyalgia nodules) and tenderness without histological presence of inflammatory cells [38]. Continuing activation of dorsal root reflexes and propriospinal

pathways produces ascending and descending sensitization of nociceptors in adjacent spinal levels, providing a mechanism for the spread of tender regions to increasingly larger areas of the body [34]. This is consistent with Shah's findings [39] that trigger points have markedly increased concentrations of inflammatory mediators, but also that muscle sites distant from the trigger points in those subjects have lesser elevations of these inflammatory mediators (higher than normal), suggesting systemic nervous system sensitization as predicted by this neuroendocrinologic model. Efferent output of these sensitized primary nociceptors also leads to activation of wide dynamic range neurons in the deeper lamina of the spinal cord, which have wider cutaneous receptive fields and visceral sensory input.

Primary nociceptors relay information through the lateral spinothalamic tract to the lateral thalamus then on to the somatosensory cortex to localize painful stimuli, while wide dynamic range neurons send information through the paleospinothalamic tract to the anterior and medial thalamus then on to limbic system structures that subserve the emotional and behavioral reactions to painful stimuli [34]. These ascending pathways are largely anatomically independent of each other. As shown in Figure 1, abnormal activation of the neospinothalamic and paleospinothalamic pathways then forms the final link in a positive feedback loop to produce excessive activation of the thalamus, neocortex, and limbic system structures that regulate autonomic balance centrally. Abnormal activation of hypothalamic and limbic system structures provides an anatomic substrate that could account for the excessive behavioral reactions to noxious stimuli seen in chronic pain patients [40,41]. This may represent the central mechanism of the lowering

of pain perception threshold ("thermostat") in chronic pain patients, which in its extreme progresses from hyperpathia to allodynia.

There is also pharmacologic evidence that supports this neurogenic model of fibromyalgia. Drugs that demonstrate the most efficacy for treating fibromyalgia are in the anti-convulsant (e.g. pregabalin) and anti-depressant (e.g. duloxitene) classes, which act on the central and peripheral nervous systems. Fibromyalgia symptoms are relatively resistant to opioids and anti-inflammatory drugs, which are efficacious for treating musculoskeletal pain conditions.

Discussion

Functional MRI and neurophysiologic studies have demonstrated objective evidence of abnormal central nervous system pain sensitization in patients with fibromyalgia, even though its cause remains enigmatic. The recent work of Shah [39] demonstrates physiologic evidence of similar central nervous system sensitization in myofascial pain syndrome.

Though both fibromyalgia and myofascial pain syndrome share the phenomenon of tender muscular regions, only fibromyalgia is associated with other conditions such as chronic headaches, irritable bowel syndrome, interstitial cystitis, and temporomandibular joint pain syndrome. Clinical and experimental evidence of the role of neurogenic inflammation and autonomic nervous system dysfunction in those disorders continues to accumulate.

This neuroendocrinologic model of fibromyalgia provides an anatomically and physiologically based conceptualization of the central and peripheral physiologic

mechanisms that can produce the widespread muscular tenderness and visceral dysfunction seen clinically in fibromyalgia patients. The model integrates the known clinical and experimental findings of abnormal hypothalamic- pituitary- adrenal axis activation and abnormal and/or unstable autonomic nervous system balance that are associated with widespread pain and visceral dysfunction in fibromyalgia patients (Figure 3).

The clinical syndrome of fibromyalgia, then, can be initiated by excessive noxious input at any point along this loop by a wide variety of causes. Excessive psychological trauma or stress is postulated to initiate this positive feedback loop centrally at the level of the paleocortex (limbic system). Visceral injury or recurrent insult (myocardial infarct, "leaky gut syndrome" after antibiotic administration, recurrent prostatitis) then initiates this positive feedback loop through severe or recurrent abnormal visceral nociceptor activation. Similarly, severe and or recurrent musculoskeletal or peripheral nerve injuries can activate this positive feedback loop through A-delta and C-fiber activation with neurogenic inflammation.

Conclusion

The model of fibromyalgia presented herein as dysfunction of the autonomic nervous system with sensitization of central nervous system nociception can unify the multiple clinical findings noted in that disorder including cognitive impairment, depression, sleep disturbance, widespread pain, and organ dysfunction such as irritable bowel syndrome and interstitial cystitis. This model offers a novel view of the

pathogenesis of this enigmatic syndrome that causes substantial morbidity and not infrequently disability, and may lead to new avenues of treatment.

References

1) Virchow, R. Über parenchymatöse entzündung. *Arch. Pathol. Anat.* **4**, 261-279 (1852).
2) Gowers, W.R. Lumbago: its lessons and analogues. *Br. Med. J.* **1**, 117-121 (1904).
3) Kelly, M. The nature of fibrositis: 1. the myalgic lesion and its secondary effects: a reflex theory. *Ann. Rheum. Dis.* **5**, 1-7 (1945).
4) Wolfe, F., Ross, K., Anderson, J., Russell, I.J. & Hebert, L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* **38**, 19-28 (1995).
5) Bergman, S., Herrstrom, P., Jacobsson, L.T. & Petersson, I.F. Chronic widespread pain: a three year follow up of pain distribution and risk factors. *J. Rheumatol.* **29**, 818-825 (2002).
6) Wolfe, F. *et al*. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter committee. *Arthritis Rheum.* **133**, 160-172 (1990).
7) Clauw, D. Fibromyalgia: more than just a musculoskeletal disease. *Am. Fam. Physician.* **52**, 843-851 (1995).
8) Hardt, J., Jacobsen, C., Goldberg, J., Nickel, R. & Buchwald, D. Prevalence of chronic pain in a representative sample in the United States. *Pain Med.* **10**.1111/j.1526-4637.2008.00425.x [doi] (2008).

9) Lawrence, R.C. *et al*. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* **41**, 778-799 (1998).

10) Hoffman, D.L. & Dukes, E.M. The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. *Int. J. Clin. Pract.* **62**, 115-126 (2007).

11) Wolfe, F. *et al*. Work and disability status of persons with fibromyalgia. *J. Rheumatol.* **24**, 1171-8 (1997).

12) Roatta, S., Windhorst, U., Ljubisavljevic, M., Johansson, H. & Passatore, M. Sympathetic modulation of muscle spindle afferent sensitivity to stretch in rabbit jaw closing muscles. *J. Physiol.* **540**, 237–248 (2002).

13) Peroutka, S.J. Migraine: a chronic sympathetic nervous system disorder. *Headache.* **44**, 53-64 (2004).

14) Mazur, M. *et al*. Dysfunction of the autonomic nervous system activity is responsible for gastric myoelectric disturbances in the irritable bowel syndrome patients. *J. Physiol. Pharmacol.* **58** *Suppl.* 3:131-139 (2007).

15) Pacak, K. Increased plasma norepinephrine concentration in cats with interstitial cystitis. *J. Urol.* 165, 2051-2054 (2001).

16) Possover, M., Rheim, K. & Chiantera, V. The “neurologic hypothesis”: a new concept in the pathogenesis of the endometriosis? *Gynecol. Surg.* **2**, 107-111 (2005).

17) Husmann, D.A. Use of sympathetic alpha antagonists in the management of pediatric urologic disorders. *Curr. Opin. Urol.* **16**, 277-282 (2006).

18) Yilmaz, U., Liu, Y., Berger, R. & Yang, C. Autonomic nervous system changes in men with chronic pelvic pain syndrome. *J. Urol.* **177**, 2170 – 2174 (2003).

19) Appelgren, A. Neuropeptides in temporomandibular joint arthritis. Dissertations from Karolinska Institutet. kl. 9.00. Föreläsningssal 1, plan 4, Odontologiska Institutionen, Huddinge (1999).

20) Saper, C.B., Scammell, T.E. & Lu, J. Hypothalamic regulation of sleep and circadian rhythms. *Nature.* **437**, 1257-1263 (2005).

21) Neary, N.M., Goldstone, A.P., & Bloom, S.R. Appetite regulation: from the gut to the hypothalamus. *Clin. Endocrinol.* **60**, 153-160 (2004).

22) Müller, M.B., Uhr, M., Holsboer, F. & Keck, M.E. Hypothalamic-pituitary-adrenocortical system and mood disorders: highlights from mutant mice. *Neuroendocrinology.* **79**, 1-12 (2004).

23) Hammel, H.T., Jackson, D.C., Stolwijk, J.A., Hardy, J.D. & Stromme, S.B. Temperature regulation by hypothalamic proportional control with an adjustable set point. *J. Appl. Physiol.* **18**, 1146-1154 (1963).

24) Oppenheimer, S.M., Gelb, A., Girvin, J.P. & Hachinski, V.C. Cardiovascular effects of human insular cortex stimulation. *Neurology.* **42**, 1727–32 (1992).

25) Cechetto, D.R. & Saper, C.B. in Central Regulation of Autonomic Functions. (eds. Loewy, A.D. & Spyer, K.M.) 208–223 (Oxford University Press, Oxford, UK, 1990).

26) Cechetto, D.R. & Gelb, A.W. The amygdala and cardiovascular control. *J. Neurosurg. Anesthesiology.* **13**, 285-287 (2001).

27) Palkovits, M. Interconnections between the neuroendocrine hypothalamus and the central autonomic system. *Front. Neuroendocrinol.* **20**, 270-295 (1999).

28) Benarroch, E.E. Descending monoaminergic pain modulation: bidirectional control and clinical relevance. *Neurology.* **71**, 217-21 (2008).

29) Khasar, S.G., McCarter, G. & Levine, J.D. Epinephrine produces a beta adrenergic receptor-mediated mechanical hyperalgesia and in vitro sensitization of rat nociceptors. *J. Neurophysiol.* **81**, 1104-1112 (1999).

30) Torpy, D.J., *et al*. Responses of the sympathetic nervous system and the hypothalamic pituitary adrenal axis to interleukin-6: a pilot study in fibromyalgia. *Arthritis Rheum.* **43**, 872-880 (2000).

31) McCorry, L.K. Physiology of the autonomic nervous system. *Am. J. Pharmacol. Educ.* **71**, Article 78 (2007).

32) Birch, D.J., Turmaine, M., Boulos, P.B. & Burnstock, G. Sympathetic innervation of human mesenteric artery and vein. *J. Vasc. Res.* **45**, 323-332 (2008).

33) Lin, Q., Wu, J. & Willis, W.D. Dorsal root reflexes and cutaneous neurogenic inflammation after intradermal injection of capsaicin in rats. *J. Neurophysiol.* **82**, 2602–2611 (1999).

34) Fields, H.L. Pain. 1-354 (McGraw Hill, San Francisco, 1987).

35) Williams, D.A. & Gracely, R.H.. Biology and therapy of fibromyalgia: functional magnetic resonance imaging findings in fibromyalgia. *Arthritis Res. Ther.* **8**, 224 (2006).

36) Alexcaos, N. *et al*. Neurotensin mediates rat bladder mast cell degranulation triggered by acute psychological stress. *Urology.* **53**, 1035-40 (1999).

37) Eutamene, H., Theodorou, V., Fioramonti, J. & Bueno, L. Acute stress modulates the histamine content of mast cells in the gastrointestinal tract through interleukin-1 and corticotropin-releasing factor release in rats. *J. Physiol.* **553**, 959-966 (2003).

38) Huguenin, L.K. Myofascial trigger points: the current evidence. *Phys. Ther. Sports.* 5, 2-12 (2004).

39) Shah, J.P. *et al*. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. *Arch. Phys. Med. Rehabil.* **89**, 16-23 (2008).

40) Bradley, R.A. *et al*. Abnormal regional cerebral blood flow in the caudate nucleus among fibromyalgia patients and non-patients is associated with insidious symptom onset. *J Musculoskel. Pain.* **7**, 285-292 (1999).

41) Gracely, R.H., Petzke, F., Wolf, J.M. & Clauw, D.J. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum.* **46**, 1333-1343 (2002).

42) Lambert, G.W. *et al*. Internal jugular venous spillover of noradrenaline and metabolites and their association with sympathetic nervous activity. *Acta. Physiol. Scand.* **163**, 155-163 (1998).

43) Quintner J. & Cohen M. Referred pain of peripheral nerve origin: an alternative to the myofascial pain construct. *Clin. J. Pain.* **10**, 243–251 (1994).

Table 1. Clinical Conditions Associated with Fibromyalgia

Clinical Condition	*% fibromyalgia patients*	*% general populaton*
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%

Table 2. Autonomic Nervous System and Its Clinical Effects

SANS Effects	**PANS Effects**
"fight or flight"	"rest and digest"
↑ alertness/vigilance	↓ alertness/vigilance
↑ heart rate and contractility	↓ heart rate and contractility
↑ breathing rate with bronchodilitation	↓ breathing rate with bronchoconstriction
↑ cardiac and skeletal muscle blood flow	↓ cardiac and 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

SANS= sympathetic autonomic nervous system
PANS= parasympathetic autonomic nervous system

Table 3. 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

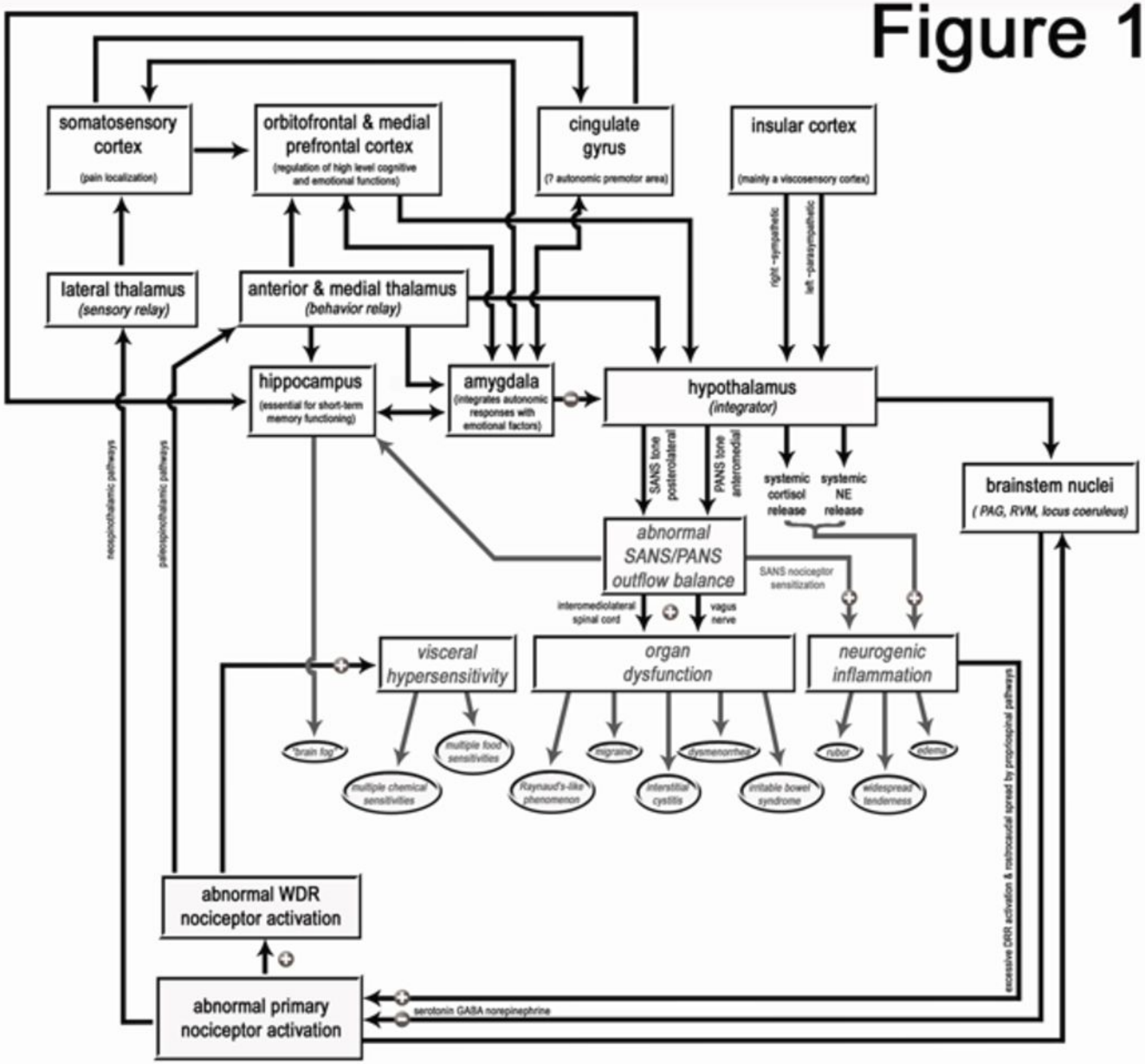
Legends

Figure 1. Detailed Neurophysiology of Positive Feedback Loop in Fibromyalgia

Figure 2. Peripheral Sensitization Mechanisms

Figure 3. Simplified Positive Feedback Loop in Fibromyalgia

Figure 1


somatosensory cortex
(pain localization)
orbitofrontal & medial prefrontal cortex
(regulation of high level cognitive and emotional functions)
cingulate gyrus
(? autonomic premotor area)
insular cortex
(mainly a viscosensory cortex)
right ~sympathetic
left ~parasympathetic
lateral thalamus
(sensory relay)
anterior & medial thalamus
(behavior relay)
hippocampus
(essential for short-term memory functioning)
amygdala
(integrates autonomic responses with emotional factors)
hypothalamus
(integrator)
SANS tone posterolateral
PANS tone anteromedial
systemic cortisol release
systemic NE release
brainstem nuclei
(PAG, RVM, locus coeruleus)
neospinothalamic pathways
paleospinothalamic pathways
abnormal SANS/PANS outflow balance
SANS nociceptor sensitization
interomediolateral spinal cord
vagus nerve
visceral hypersensitivity
organ dysfunction
neurogenic inflammation
"brain fog"
multiple chemical sensitivities
multiple food sensitivities
Raynaud's-like phenomenon
migraine
interstitial cystitis
dysmenorrhea
irritable bowel syndrome
rubor
edema
widespread tenderness
excessive DRR activation & rostrocaudal spread by propriospinal pathways
abnormal WDR nociceptor activation
abnormal primary nociceptor activation
serotonin GABA norepinephrine

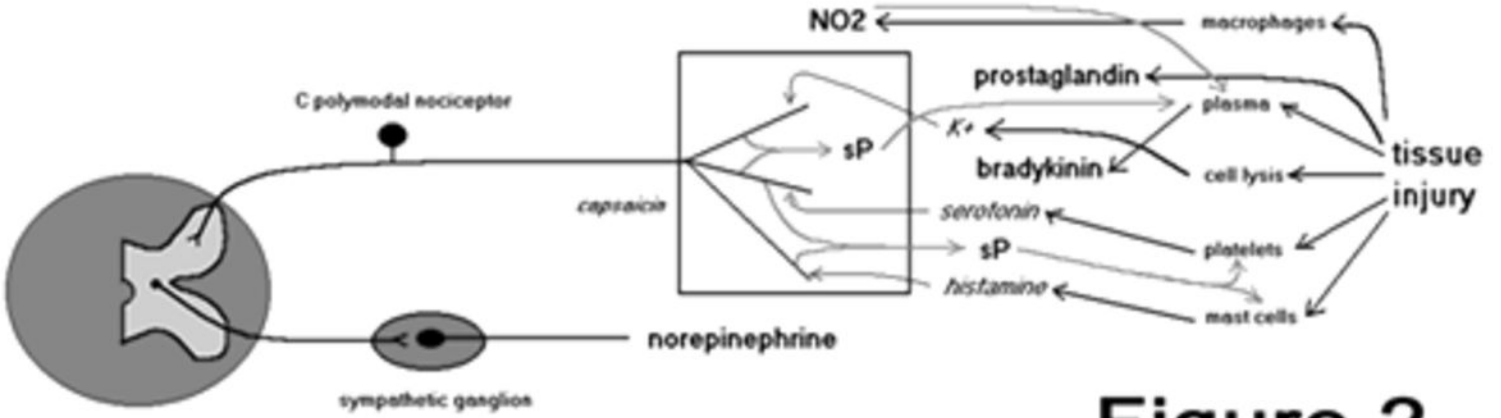

NO2
macrophages
prostaglandin
plasma
C polymodal nociceptor
sP
K+
bradykinin
cell lysis
tissue
injury
capsaicin
serotonin
sP
platelets
histamine
mast cells
norepinephrine
sympathetic ganglion

Figure 2

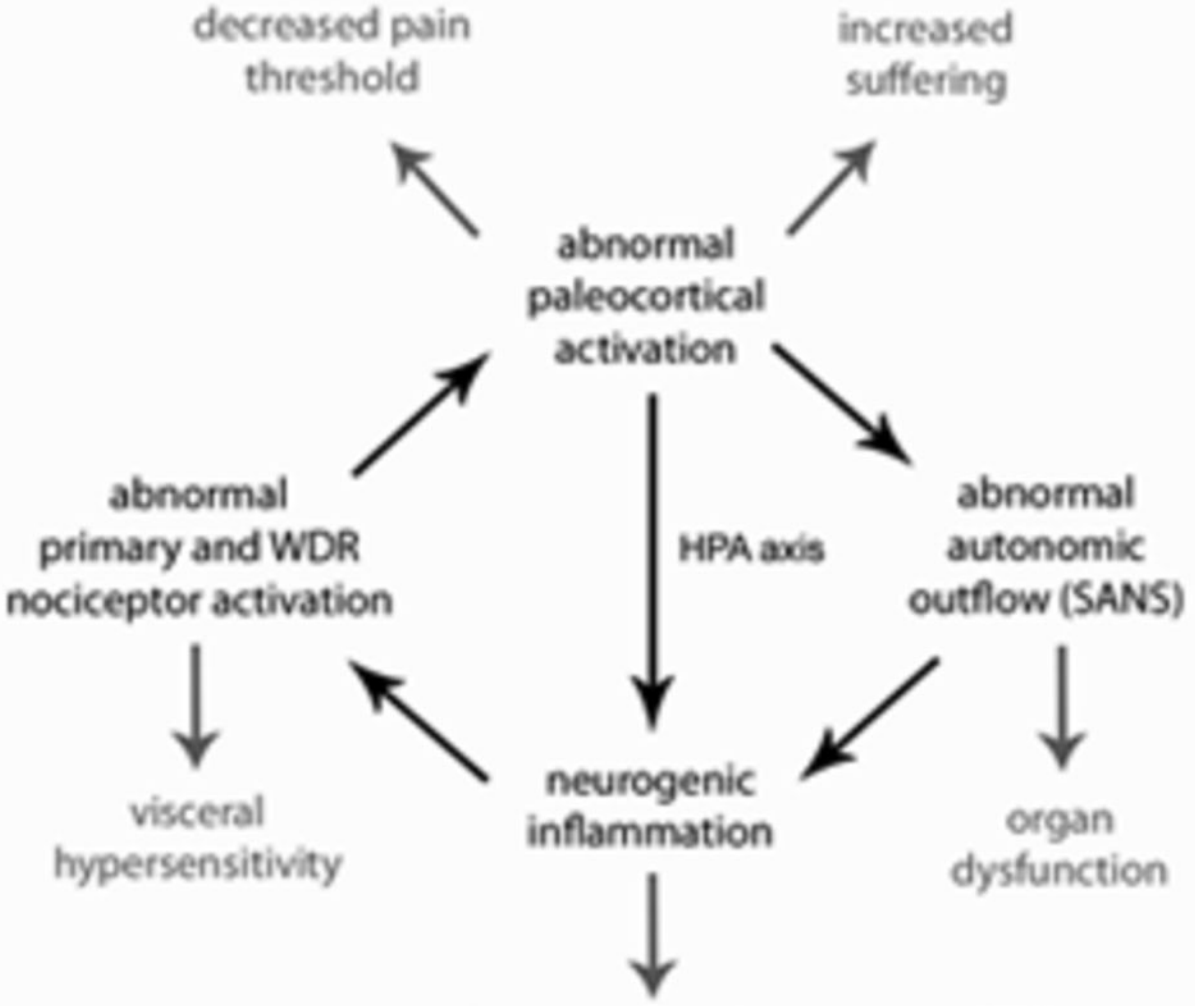

decreased pain threshold
increased suffering
abnormal paleocortical activation
abnormal primary and WDR nociceptor activation
HPA axis
abnormal autonomic outflow (SANS)
visceral hypersensitivity
neurogenic inflammation
organ dysfunction
widespread tenderness

Figure 3