Pathophysiologic Mechanisms of Fibromyalgia and Its Related Disorders

Laurence A. Bradley, Ph.D.

This article reviews current findings regarding the pathophysiologic abnormalities that contribute to the enhanced pain responses of individuals with fibromyalgia as well as the relationships between fibromyalgia and commonly co-occurring disorders. Risk factors for fibromyalgia or enhanced pain responses include genetic and family influences, environmental triggers, and abnormal neuroendocrine and autonomic nervous system function. These risk factors also are associated with several disorders that frequently co-occur with fibromyalgia, such as major depressive disorder, migraine, and irritable bowel syndrome. Indeed, fibromyalgia and these co-occurring conditions may be part of a group of affective spectrum disorders that share important common, and perhaps heritable, causal factors. Recent research strongly suggests that alterations in central processing of sensory input also contribute to the cardinal symptoms of fibromyalgia, persistent widespread pain and enhanced pain sensitivity. Exposure to psychosocial and environmental stressors, as well as altered autonomic nervous system and neuroendocrine responses, also may contribute to alterations in pain perception or pain inhibition. Understanding the pathophysiology of fibromyalgia and co-occurring disorders may help clinicians provide the most appropriate treatment to their patients.

(J Clin Psychiatry 2008;69[suppl 2]:6–13)

The pathophysiology of fibromyalgia involves multiple systems, including family and genetic factors, environmental triggers, and the neuroendocrine and autonomic nervous systems. These systems are often involved in disorders characterized by persistent or recurrent pain and affective distress that frequently co-occur with fibromyalgia, such as chronic fatigue syndrome, irritable bowel syndrome, and affective disorders (Table 1).[1,2] Fibromyalgia also may occur concurrently with hypothyroidism,[3] as well as with chronic autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus.[4] Fibromyalgia and the comorbid disorders shown in Table 1 may have common genetic or biological risk factors. Moreover, the co-occurrence of 1 or more of these comorbid conditions with fibromyalgia may complicate patient diagnosis and treatment.[1] Understanding the pathophysiology of fibromyalgia and co-occurring disorders may help clinicians provide the most appropriate treatment to their patients.

From the Division of Clinical Immunology and Rheumatology, Department of Medicine, and the Center for Education and Research on Therapeutics of Musculoskeletal Disorders, University of Alabama, Birmingham.

This article is derived from the planning teleconference series "Understanding Fibromyalgia and Its Related Disorders" that was held in October and November 2007 and supported by an educational grant from Eli Lilly and Company.

Dr. Bradley is a consultant for Eli Lilly, Pfizer, and Forest; has received grant/research support from the National Institutes of Health, the Agency for Healthcare Research and Quality, Eli Lilly, Pfizer, and the American Fibromyalgia Syndrome Association; has received honoraria from Eli Lilly, Pfizer, Forest, and the Society for Women's Health Research; is a member of the speakers/advisory board for Pfizer; and has received royalties from UpToDate Rheumatology.

Corresponding author and reprints: Laurence A. Bradley, Ph.D., Shelby Interdisciplinary Biomedical Research Bldg., Room 178A, 1825 University Blvd., Birmingham, AL 35294 (e-mail: larry.bradley@ccc.uab.edu).

BIOLOGICAL AND GENETIC INFLUENCES FOR FIBROMYALGIA

Fibromyalgia may be part of a group called affective spectrum disorders (ASD) that share 1 or more physiologic abnormalities important to their etiology. It has been proposed that this group includes, but may not be limited to, 10 psychiatric disorders and 4 medical disorders (Table 2).[5] Recent studies[5,6] of patients with fibromyalgia or rheumatoid arthritis (RA), as well as the first-degree relatives of these individuals, have provided support for the validity of this proposal known as the *ASD hypothesis*. It should be noted that the use of RA probands and their relatives ensured that any associations between fibromyalgia and other ASD conditions would be independent of the potential effects of treatment-seeking for chronic musculoskeletal pain. Arnold and colleagues[6] reported that the first-degree relatives of patients with fibromyalgia, compared with those of patients with RA, more frequently met diagnostic criteria for fibromyalgia or major depressive disorder (MDD) and exhibited a greater number of sensitive tender points (i.e., enhanced pain sen-

Table 1. Prevalence of Common Comorbid Conditions in Patients With Fibromyalgia[a]

Condition	Prevalence (%)
Chronic fatigue syndrome	21–80
Irritable bowel syndrome	32–80
Temporomandibular disorder	75
Headache (tension and migraine)	10–80
Major depressive disorder[b]	62
Multiple chemical sensitivities	33–55
Interstitial cystitis	13–21
Chronic pelvic pain	18

[a]Adapted with permission from Aaron and Buchwald.[1]
[b]Data from Arnold et al.[2]

Table 2. Affective Spectrum Disorders Hypothesized to Share Common Physiologic Abnormalities[a]

Psychiatric Conditions	Medical Conditions
Attention-deficit/hyperactivity disorder	Fibromyalgia
Bulimia nervosa	Irritable bowel syndrome
Dysthymic disorder	Migraine
Generalized anxiety disorder	Cataplexy
Major depressive disorder	
Obsessive-compulsive disorder	
Panic disorder	
Posttraumatic stress disorder	
Premenstrual dysphoric disorder	
Social phobia	

[a]Based on Hudson et al.[5]

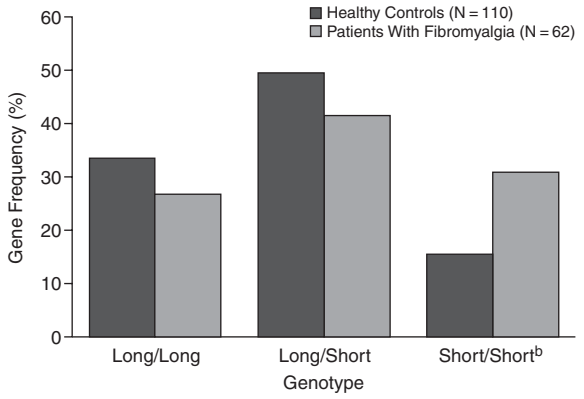
sitivity) as defined by the American College of Rheumatology classification criteria.[7] The frequency of fibromyalgia among the first-degree relatives of probands with fibromyalgia and those with RA was 6.4% and 1.1%, respectively; the frequency of lifetime (i.e., present or past) MDD diagnoses within these 2 groups of relatives was 29.5% and 18.3%.[6] After including both the bipolar disorders and MDD, the frequency of major mood disorders increased to 32.1% and 19.1% among the family members of the fibromyalgia and RA probands, respectively. With respect to pain sensitivity, the median number of tender points among the relatives of the fibromyalgia probands was 17 (maximum 18), whereas the median number was 12 among relatives of the RA probands. After controlling for the effects of familial aggregation of fibromyalgia, the co-aggregation of fibromyalgia and MDD remained statistically significant ($p = .013$).

Hudson et al.[5] further examined data from the family study by Arnold et al.[6] in order to determine whether fibromyalgia would co-aggregate with forms of ASD other than the mood disorders even after controlling for the latter. It was found that 38.6% of first-degree relatives of 90 probands with an ASD (78 of whom had fibromyalgia) met criteria for at least 1 form of ASD, compared with 31.2% of the first-degree relatives of 28 probands without an ASD ($p = .065$). This group difference probably failed to achieve statistical significance due to low power because an ASD was treated as a categorical variable (1 or 0) even when an individual met criteria for more than 1 ASD condition. When an ASD was measured as a continuous variable, a significant association was found between the number of lifetime forms of ASD among the relatives and their corresponding probands ($p = .002$). In addition, among relatives of the 78 probands with fibromyalgia, the lifetime frequency of non-fibromyalgia ASDs was 42.2%, compared with 26.5% among relatives of the 40 probands with RA. Even after excluding the mood disorders, the frequency of non-fibromyalgia ASD was 24.2% among the relatives of the probands with fibromyalgia and 13.6% among the relatives of probands with RA. Thus, fibromyalgia co-aggregated with 1 or more other forms of ASD including mood disorders ($p = .004$), as well as with 1 or more forms of ASD after eliminating the mood disorders ($p = .012$). The findings produced by these family studies[5,6] support the hypothesis that fibromyalgia co-aggregates with other forms of ASD and that these disorders may share heritable physiologic abnormalities.

My colleagues and I[8] recently assessed pain threshold levels evoked by 3 forms of stimulation as well as blood serum serotonin levels among the siblings of fibromyalgia probands and healthy controls. Preliminary data showed that the fibromyalgia probands and their siblings displayed significantly lower pain threshold levels in response to mechanical pressure, thermal heat, and ischemic stimulation compared to healthy controls and their siblings, respectively. These findings are especially noteworthy because none of the proband siblings reported persistent or recurrent musculoskeletal pain. These findings, in conjunction with those of Arnold et al.,[6] indicate that both fibromyalgia probands and their first-degree relatives display enhanced pain sensitivity to multiple nociceptive stimuli.

Positive evidence concerning the ASD hypothesis produced by Arnold, Hudson, and their colleagues,[2,5,6] as well as the findings of enhanced pain sensitivity among persons with fibromyalgia and their first-degree relatives, suggests that both environmental and heritable factors may contribute to family aggregation of pain sensitivity in fibromyalgia. One candidate gene that may contribute to enhanced pain sensitivity is the serotonin transporter (5-HTT) gene.[9] Offenbaecher et al.[10] were the first to report that a single nucleotide polymorphism (short/short allele) in the regulatory region of the 5-HTT gene occurs significantly more frequently in patients with fibromyalgia than in healthy controls (31% vs. 16%, $p = .046$; Figure 1). This finding was replicated by Cohen and colleagues in an independent sample.[11] Consistent with these findings, preliminary data from our family study[8] of pain sensitivity show that both the fibromyalgia probands and their siblings exhibit significantly lower blood serum levels of 5-HT than healthy controls and their siblings, respectively. The importance of this particular polymorphism is that not only is it found more frequently in patients with fibromyalgia,[10,11] but it is also found more frequently among patients with MDD

Figure 1. Distribution of the Serotonin Transporter (5-HTT) Promoter Region Polymorphism in Patients With Fibromyalgia and Healthy Controls[a]



[a]Data from Offenbaecher et al.[10]
[b]$\chi = 3.981$, df = 1, p = .046.

compared with healthy controls.[12] In addition, there are reports[13,14] that this polymorphism is also found more frequently in patients with diarrhea-predominant irritable bowel syndrome compared with healthy controls. However, some studies have failed to replicate this association.[15] Thus, a genetic risk factor for the development of fibromyalgia may exist, which may also be a risk factor for the development of MDD and irritable bowel syndrome. It has been concluded, then, that self-report, biological, and genetic data[5,6,9–12] provide support for the validity of the ASD hypothesis.

ENVIRONMENTAL TRIGGERS FOR FIBROMYALGIA

Environmental triggers may also be involved in the pathophysiology of fibromyalgia, especially in combination with other risk factors. These triggers include mechanical or physical trauma or injury and psychosocial stressors.[16–18] The effects of psychosocial stressors may be especially pervasive because these stressors are associated with both onset of chronic widespread pain (i.e., the first classification criterion for fibromyalgia) and enhanced pain responses.

Mechanical and Physical Trauma

Harkness et al.[19] reported that both physical and psychosocial stressors predict the development of chronic widespread body pain. In this study, 896 newly employed workers recruited from 12 diverse settings who were free of pain at baseline were followed for a 2-year period to determine the extent to which exposure to physical and psychosocial risk factors would predict onset of widespread pain. It was found that 15% and 12% of workers had new-onset widespread pain at 12 months and 24 months, respectively. Several variables involving manual work, such as heavy lifting, repetitive motions, or squatting for extended periods of time, were associated with the occurrence of widespread pain. Pulling more than 56 kg (odds ratio [OR] = 1.8, 95% CI = 0.98 to 3.2) and squatting for more than 15 minutes (OR = 2.0, 95% CI = 1.1 to 3.6) significantly increased the risk of symptom onset in workers.

Psychosocial Stress Factors

Harkness et al.[19] also found that psychosocial factors may trigger the development of widespread pain. For example, workers who reported dissatisfaction with the amount of psychosocial support they received at work and those who found their work monotonous were at a significantly higher risk for developing widespread pain (OR = 2.4, 95% CI = 0.96 to 6.0; OR = 2.4, 95% CI = 1.5 to 3.9, respectively). Additional environmental factors, such as working in hot conditions, also tended to increase the risk of developing widespread pain, although the magnitude of these associations was not statistically significant. Therefore, both physical and psychosocial factors contribute to the risk of onset of widespread pain in the workplace.

Nevertheless, it should be noted that additional analyses of risk factors for pain onset among the workers studied by Harkness and colleagues[19] have shown that similar physical and psychosocial factors predict the onset of knee pain,[20] shoulder pain,[21] and low back pain.[22] Examples of these factors include lifting heavy weights above shoulder level (shoulder and low back pain), lifting heavy weights with one or both hands (shoulder and low back pain), lifting or carrying heavy weights with one hand (knee pain), monotonous work (shoulder pain), stressful work (low back pain), and level of general psychological distress (knee pain). To summarize, exposures involving heavy weights, negative psychosocial factors involving the work environment, and psychological distress represent risk factors for new onset of several musculoskeletal pain conditions, including widespread pain.

Psychosocial stressors also may affect the severity or aversiveness of pain associated with fibromyalgia. It is widely recognized that patients with fibromyalgia frequently report that their pain is intensified by exposure to psychosocial stressors. Davis et al.[23] examined the effects of exposure to psychosocial stressors on reports of clinical pain among women with fibromyalgia or osteoarthritis of the knee. Prior to undergoing the experimental procedures, the women with fibromyalgia, compared with those with knee osteoarthritis, produced lower ratings of physical health, positive affect, and the quality of their social networks as well as higher ratings of emotional disturbance and greater use of maladaptive coping strategies. Both groups of women were randomly assigned to undergo a 3-minute procedure designed to induce either a negative mood (via reading sad text) or neutral mood (via relaxation). Following the mood induction procedure, the

women were asked to discuss for 30 minutes a stressful event that had occurred in their lives. It was found that prolonged discussion of stressful events did not alter the clinical pain ratings of women with fibromyalgia or knee osteoarthritis who had first undergone neutral mood induction. However, women with fibromyalgia who underwent negative mood induction prior to discussion of stressful events, compared with their counterparts with knee osteoarthritis, reported significantly greater increases in their clinical pain ($p < .05$). Furthermore, women with fibromyalgia who underwent neutral mood induction, compared to those who underwent negative mood induction, reported greater decreases in pain intensity ratings during recovery from stressor exposure. This suggests that negative mood states and exposure to personally relevant psychosocial stressors may produce a prolonged negative impact on both pain and pain inhibition among women with fibromyalgia.

My colleagues and I[24] recently reported preliminary findings indicating that negative mood and brief (4-minute) exposure to personally relevant, psychosocial stressors produce greater adverse changes on thermal heat ratings among women with fibromyalgia compared with those of healthy controls. Both groups of women were exposed twice to repetitive pulses of thermal heat stimuli (i.e., temporal summation) that were calibrated so that each woman would produce moderate ratings of thermal pain intensity after termination of stimulation (50 ± 5 on a 100-point scale). Prior to each thermal stimulation procedure, the women vividly imagined either a relatively neutral or highly stressful personal experience for a period of 4 minutes. We found that exposure to stressful versus neutral imagery did not influence thermal pain intensity ratings of either the patients or the healthy controls. However, women with fibromyalgia, compared to controls, produced significantly greater increases in their ratings of the aversiveness of the thermal stimuli as a function of stressful versus neutral imagery. Moreover, the group difference on change in pain aversiveness ratings was due primarily to the responses of the patients with elevated scores on a standardized measure of depressive symptoms. Together, the above studies[23,24] strongly suggest that the combination of negative mood and exposure to psychosocial stressors enhances the clinical and experimental pain responses of women with fibromyalgia. These stressor-induced changes in patients' pain reports may be due primarily to changes in perceived aversiveness of their subjective pain experiences.

PATHOPHYSIOLOGIC ABNORMALITIES IN FIBROMYALGIA

Neuroendocrine Abnormalities

Fibromyalgia is generally considered to be a stress-related disorder characterized by abnormal functioning in the hypothalamic-pituitary-adrenal (HPA) axis, such as the inability to suppress cortisol, a neuroendocrine abnormality that has also been found in patients with psychiatric disorders. McCain and Tilbe[25] assessed patients with fibromyalgia ($N = 20$) or RA ($N = 20$) for 3 days and found that those with fibromyalgia exhibited higher peak and trough levels of plasma cortisol compared with those with RA; patients with fibromyalgia also displayed significantly higher overall plasma cortisol levels than the RA patients ($p < .001$). Further, 35% of patients with fibromyalgia treated with dexamethasone were unable to suppress plasma cortisol levels compared with only 5% of patients with RA ($p < .001$). Crofford et al.[26] also found disturbances in the HPA axis among patients with fibromyalgia, including a decreased response to an ovine corticotropin-releasing hormone (CRH) used to stimulate a stress response in individuals. The data indicated elevated basal trough cortisol levels similar to those reported by McCain and Tible.[25] The results of these studies suggest that patients with fibromyalgia are characterized by perturbed HPA axis function.

McCain and Tilbe[25] noted that normal sleep is associated with diurnal variations of serum cortisol. Their data indicated that while serum prolactin, growth hormone, and thyroid-stimulating hormone levels were within normal ranges among patients with fibromyalgia, normal diurnal cortisol patterns were lost. The loss of normal variations in diurnal patterns may be associated with nonrestorative sleep that is often concurrent with fibromyalgia.

Autonomic Nervous System Abnormalities

Abnormalities are also present in the function of the autonomic nervous system among patients with fibromyalgia. These abnormalities include decreased microcirculatory vasoconstriction,[27] increased hypotension,[28,29] variations in heart rate,[30] and sleep disturbance.[31,32] Abnormal function of the autonomic nervous system may contribute to enhanced pain and other clinical problems associated with fibromyalgia through alterations of physiologic responses required for effective stress management (e.g., increases in blood pressure) and pain inhibition (e.g., availability of neurotransmitters such as norepinephrine and dopamine).

Vasoconstriction. Vaerøy and colleagues[27] found that patients with fibromyalgia exhibit altered sympathetic nervous system responses compared with those of healthy controls. Subjects' left hands were submerged in cold water for 1-minute intervals that were separated by recovery breaks (i.e., cold pressor task). The patients with fibromyalgia, compared with the control group, displayed blunted vasoconstriction responses to cold water ($p = .0001$). The patients also showed decreased microcirculatory responses to auditory stimulation relative to controls. These data suggest that altered function of the sympathetic nervous system arm of the autonomic nervous system may

Table 3. Quantitative Sensory Testing Tasks That Distinguish Patient Groups From Healthy Controls[a]

Patient Subgroup	Heat Pain	Cold Press Threshold	Cold Press Tolerance	von Frey Pressure Pain Threshold	Tourniquet Tolerance
Multiregional pain					✓
Multiregional pain associated with 11 tender points				✓	✓
Widespread pain			✓	✓	✓
Secondary-concomitant fibromyalgia syndrome		✓	✓	✓	✓
Fibromyalgia syndrome	✓	✓	✓	✓	✓

[a]Adapted with permission from Carli et al.[36]
✓ = Patients in subgroup more sensitive than control groups.

contribute to abnormal physiologic responses to environmental stressors in patients with fibromyalgia.

Hypotension and heart rate variability. Several studies[28–30,33,34] have examined altered autonomic responses with regard to hypotension and heart rate variability in patients with fibromyalgia. Bou-Holaigah et al.[28] reported that, during tilt-table testing, 60% of patients with fibromyalgia exhibited an abnormal drop in blood pressure ($p < .001$, versus controls), and all of the patients who tolerated the test for more than 10 minutes reported a worsening of pain symptoms, whereas controls were asymptomatic. Difficulty in maintaining blood pressure levels may directly produce unpleasant symptoms frequently associated with fibromyalgia such as fatigue and dizziness. In addition, blood pressure regulation also is necessary for maintaining effective physiologic responses to stressors.

Martínez-Lavín et al.[29] showed that patients with fibromyalgia are characterized by significantly lower heart rate variability at the 0.050 Hz to 0.150 Hz frequency domain compared with controls while in a standing position (–0.057 vs. 0.081, respectively, $p < .05$). Significant variability in heart rate during deep breathing has also been found relative to controls ($p < .001$).[34] Stein et al.[33] found similar results but reported that heart rate variability may also be sex dependent, suggesting that autonomic mechanisms associated with fibromyalgia may be different in men and women. Martínez-Lavín et al.[30] suggested that diminished heart rate variability in patients with fibromyalgia is due to an abnormal chronobiology that may also contribute to sleep disturbance and fatigue.

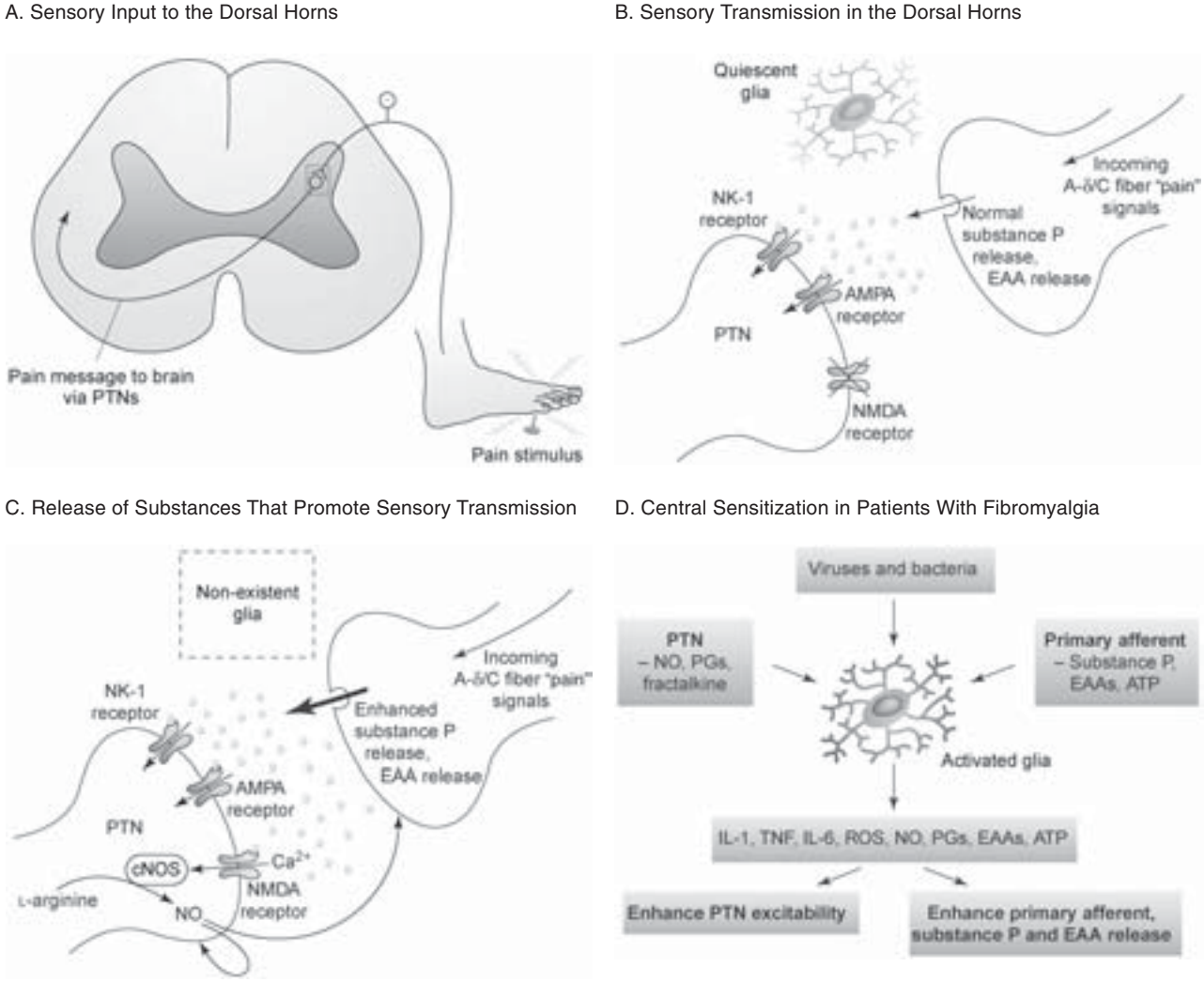
Sleep disturbances. Fibromyalgia is often associated with sleep disturbances, such as nonrestorative sleep, insomnia, early morning awakening, and poor quality of sleep.[31,32] Roizenblatt et al.[31] found that sleep quality was significantly lower in patients with fibromyalgia than in controls ($p = .04$), and patients with fibromyalgia reported worsening of pain symptoms after poor sleep. Alpha-delta sleep patterns associated with interrupted and nonrestorative sleep[32] are frequently observed in patients with fibromyalgia who undergo polysomnography. Sleep disturbance may contribute to reduced energy and fatigue among patients with fibromyalgia. It also may contribute to enhanced pain. That is, frequent alpha wave intrusions during delta wave sleep are associated with reductions in production of growth hormone (GH) and insulin-like growth factor (IGF-1). Given that GH and IGF-1 are necessary for repairing muscle microtrauma, sleep disturbance may increase the likelihood of inadequate healing of muscle tissue damage and prolonged transmission of afferent sensory transmission from muscle tissue to the spinal cord and brain that underlie the perception of muscle pain.[35] There also may be an interaction between sleep disturbance and pain in that enhanced pain may contribute to increases in sleep disturbance that help maintain fatigue and inadequate repair of muscle tissue.[32]

PATHOPHYSIOLOGY OF ENHANCED PAIN PERCEPTION

Patients with fibromyalgia show sensitivity to a wide array of stimuli. Table 3 demonstrates the variance in sensory testing tasks used to determine pain sensitivity in 5 patient groups.[36] Patients with primary fibromyalgia, compared with healthy controls, showed enhanced pain sensitivity to 5 forms of sensory stimuli, and those with secondary fibromyalgia syndrome displayed enhanced pain sensitivity to 4 of the 5 stimuli. In contrast, patients with multiregional or widespread pain showed enhanced pain sensitivity to between 1 and 3 stimulation sources. There is increasing evidence that persons with fibromyalgia are characterized by augmentation of sensory input that is mediated by central nervous system events similar to those associated with central sensitization. The following discussion reviews our current understanding of these events as well as evidence produced by imaging studies of neural responses of patients with fibromyalgia regarding central augmentation of sensory input and altered pain inhibitory function.

The traditional understanding of acute pain is that a stimulus is applied to tissue (e.g., skin or muscle) and the sensory input from nerve receptors in these tissues is transmitted along primary afferents (A-δ and C nerve fibers) to the dorsal horns of the spinal cord (Figure 2, quadrant A).[37] Sensory input is then transmitted along second-order, spinal neurons to the brain, although this input may be altered by physiologic processes that occur in the dorsal horns. Quadrants B and C show the events involved in sensory transmission (B) or augmentation of this

Figure 2. Pathophysiologic Mechanisms Involved in Enhanced Pain Perception[a]



[a]Reprinted with permission from Watkins et al.[37]
Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, ATP = adenosine triphosphate, EAA = excitatory amino acids, IL = interleukin, NK-1 = neurokinin-1, NMDA = *N*-methyl-D-aspartic acid, NO = nitrous oxide, NOS = nitrous oxide system, PG = prostaglandin, PTN = posterior tibial nerve, ROS = reactive oxygen species, TNF = tumor necrosis factor.

transmission (i.e., central sensitization) in the dorsal horns of the spinal cord (C). Quadrant B shows that A-δ and C nerve fibers transmit action potentials to their presynaptic terminals in the spinal dorsal horns. Substance P and excitatory amino acids are released that bind to and activate postsynaptic receptors (i.e., neurokinin [NK]-1, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) located on second-order pain transmission neurons that ascend to the brain carrying sensory input that may produce perceptions of pain. The *N*-methyl-D-aspartate (NMDA)–linked channels are inoperative as they are "plugged" by Mg^{2+}.

Quadrant C shows that intense or prolonged sensory input from A-δ and C afferents sufficiently depolarizes the dorsal horn neurons so that Mg^{2+} exits NMDA-linked ion channels. This is followed by an influx of extracellular Ca^{2+} and production of nitric oxide, which diffuses out of the dorsal horn neurons. Nitric oxide, in turn, promotes the exaggerated release of excitatory amino acids and substance P from presynaptic afferent terminals and causes the dorsal horn neurons to become hyperexcitable.

Until the 1990s, activation of glia cells (i.e., astrocytes and microglia) was not considered relevant to the function of dorsal horn neurons and pain signaling. However, quadrant D shows that dorsal horn glia cells are activated by release of nitric oxide, prostaglandins, fractalkine, substance P, adenosine triphosphate (ATP), and excitatory

amino acids from primary afferents and posterior tibial nerves. These glia cells, in turn, release pro-inflammatory cytokines, nitric oxide, prostaglandins, reactive oxygen species, and ATP as well as excitatory amino acids, such as glutamate, substance P, and calcitonin gene-related peptide. These substances (1) further increase the release of excitatory amino acids and substance P from the A-δ and C afferents that synapse in the dorsal horn as well as (2) enhance or prolong the hyper-excitability of the second-order, dorsal horn neurons that drive pain states. The enhanced or prolonged excitability of these neurons is considered to be largely responsible for the low pain thresholds and reports of high pain intensity displayed by persons with neuropathic pain syndromes.

Additional evidence for the role of spinal glia cells in central sensitization and enhanced pain sensitivity is found in studies of agents that modulate glia cell activity. For example, a recent preclinical study[38] has shown that a nonselective phosphodiesterase inhibitor, AV-411, suppresses spinal glia cell activity and attenuates pain sensitivity to mechanical pressure in an animal model of neuropathic pain.

The model of central sensitization described above also may underlie the enhanced sensitivity to low-intensity stimuli that is exhibited by patients with fibromyalgia. It should be noted, however, that in both animal and human models of central sensitization, the source of sensory input (e.g., nerve injury) is identified and pain sensitivity is reduced if the source of sensory input is eliminated. In contrast, the source of sensory input among patients with fibromyalgia remains unknown. For this reason, most investigators involved in fibromyalgia research refer to central augmentation of sensory input rather than central sensitization when they discuss the pathophysiology of fibromyalgia.[39]

Recent documentation of changes in brain activity using functional magnetic resonance imaging (fMRI) illustrates the phenomenon of central augmentation of sensory input among patients with fibromyalgia. Gracely and colleagues,[40] for example, reasoned that if central augmentation of sensory input is associated with fibromyalgia, one would expect that patients, compared with healthy controls, would report equivalent levels of perceived pain at lower stimulus intensity levels. Nevertheless, both patients and controls would show large increases in fMRI measured activity (i.e., regional cerebral blood flow [rCBF]) in the same brain structures involved in pain processing. To test this hypothesis, the investigators first measured the amount of repetitive mechanical pressure stimulation of the left thumbnail bed required by fibromyalgia patients and healthy controls to produce moderate ratings of pain intensity (i.e., 11 on a 20-point scale). It was found that patients produced these ratings at about one half the intensity of stimulation required by the controls ($p < .001$). Despite the group difference in stimulation intensity, both patients and controls showed significant increases in brain rCBF in the same 7 brain structures (e.g., somatosensory cortex, cerebellum). Moreover, when the healthy controls were exposed to the same stimulus intensity levels administered to the patients, they did not experience pain, and fMRI measures indicated little activation in brain structures involved in pain processing.

Investigators also are beginning to use neuroimaging procedures to document alterations in brain inhibitory function of patients with fibromyalgia. For example, Wood et al.[41] used ligand positron emission tomographic (PET) imaging to compare patients and healthy controls with respect to dopamine receptor availability in areas of the brain involved in processing pain during noxious stimulation. There is substantial evidence that dopamine is involved in pain inhibition in several brain regions within the basal ganglia (e.g., nucleus accumbens).[42] Thus, one would expect that, during exposure to noxious stimulation, ligand PET imaging will show reductions in dopamine binding potential at dopamine receptors in these areas (i.e., evidence of enhanced release of endogenous dopamine). However, Wood and colleagues[41] demonstrated that, after infusion of hypertonic saline in the anterior tibialis muscle of the right leg, patients with fibromyalgia reported higher levels of pain. Moreover, only the healthy controls were characterized by significant reductions in binding potential at dopamine receptors in basal ganglia structures including the nucleus accumbens, globus pallidus, and putamen. These findings suggest, then, that both central augmentation of sensory input and diminished central pain inhibitory functions contribute to the abnormal pain sensitivity and persistent pain experienced by patients with fibromyalgia.

CONCLUSION

Factors that contribute to the pathophysiology of fibromyalgia include biologic and genetic influences, environmental triggers including stressors, and abnormal function of the neuroendocrine and autonomic nervous systems. These factors are frequently shared by persons with disorders that co-occur with fibromyalgia, such as chronic fatigue syndrome, irritable bowel syndrome, and MDD. Enhanced pain sensitivity occurs not only in patients with fibromyalgia but also more frequently in their first-degree relatives compared with the relatives of both healthy people and persons with other painful illnesses. Both central augmentation of sensory input and deficits in central pain inhibitory mechanisms appear to contribute to enhanced pain sensitivity in persons with fibromyalgia.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Aaron LA, Buchwald D. Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. Best Pract Res Clin Rheumatol 2003;17:563–574
2. Arnold LM, Hudson JI, Keck PE, et al. Comorbidity of fibromyalgia and psychiatric disorders. J Clin Psychiatry 2006;67:1219–1225
3. Garrison RL, Breeding PC. A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. Med Hypotheses 2003;61:182–189
4. Weir PT, Harlan GA, Nkoy FL, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. J Clin Rheumatol 2006;12:124–128
5. Hudson JI, Arnold LM, Keck PE, et al. Family study of fibromyalgia and affective spectrum disorder. Biol Psychiatry 2004;56:884–891
6. Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. Arthritis Rheum 2004;50:944–952
7. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–172
8. Bradley L, Fillingim R, Sotolongo A, et al. Family aggregation of pain sensitivity in fibromyalgia. J Pain 2006;7(4, suppl 1):S1
9. Wolfe F, Russell IJ, Vipraio G, et al. Serotonin levels, pain threshold, and fibromyalgia symptoms in the general population. J Rheumatol 1997;24: 555–559
10. Offenbaecher M, Bondy B, de Jonge S, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis Rheum 1999;42:2482–2488
11. Cohen H, Buskila D, Neumann L, et al. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. Arthritis Rheum 2002;46:845–847
12. Hoefgen B, Schulze TG, Ohlraun S, et al. The power of sample size and homogenous sampling: association between the 5-HTTLPR serotonin transporter polymorphism and major depressive disorder. Biol Psychiatry 2005;57:247–251
13. Yeo A, Boyd P, Lumsden S, et al. Association between functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowl syndrome in women. Gut 2004;53:1452–1458
14. Park JM, Choi MG, Park JA, et al. Serotonin transporter gene polymorphism and irritable bowl syndrome. Neurogastroenterol Motil 2006;18: 995–1000
15. Camilleri M. Is there a SERT-ain association with IBS? Gut 2004;53: 1396–1399
16. Al-Allaf AW, Dunbar KL, Hallum NS, et al. A case-control study examining the role of physical trauma in the onset of fibromyalgia syndrome. Rheumatology (Oxford) 2002;41:450–453
17. Cruz BA, Catalan-Soares B, Proietti F. Higher prevalence of fibromyalgia in patients infected with human T cell lyphotropic virus type I. J Rhematol 2006;33:2300–2303
18. Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Ann N Y Acad Sci 1998;840: 684–697
19. Harkness EF, Macfarlane GJ, Nahit E, et al. Mechanical injury and psychosocial factors in the work place predict the onset of widespread body pain. Arthritis Rheum 2004;50:1655–1664
20. Jones GT, Harkness EF, Nahit ES, et al. Predicting the onset of knee pain: results from a 2-year prospective study of new workers. Ann Rheum Dis 2007;66:400–406
21. Harkness EF, Macfarlane GJ, Nahit ES, et al. Mechanical and psychosocial factors predict new onset shoulder pain: a prospective cohort study of newly employed workers. Occup Environ Med 2003;60:850–857
22. Harkness EF, Macfarlane GJ, Nahit ES, et al. Risk factors for new-onset low back pain amongst cohorts of newly employed workers. Rheumatology (Oxford) 2003;42:959–968
23. Davis MC, Zautra AJ, Reich JW. Vulnerability to stress among women in chronic pain from fibromyalgia and osteoarthritis. Ann Behav Med 2001;23:215–226
24. Okonkwo R, Bradley L, Sotolongo A, et al. Effect of stressful imagery on thermal pain ratings of patients with fibromyalgia: what mediates this relationship? J Pain 2007;8(4):S25
25. McCain GA, Tilbe KS. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. J Rheumatol Suppl 1989 Nov;19:154–157
26. Crofford LJ, Pillemer SR, Kalogeras KT, et al. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum 1994;37:1583–1592
27. Vaerøy H, Qiao ZG, Mørkrid L, et al. Altered sympathetic nervous system response in patients with fibromyalgia (fibrositis syndrome). J Rheumatol 1998;16:1460–1465
28. Bou-Holaigah I, Calkins H, Flynn JA, et al. Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. Clin Exp Rheumatol 1997;15:239–246
29. Martínez-Lavín M, Hermosillo AG, Mendoza C, et al. Orthostatic sympathetic derangement in subjects with fibromyalgia. J Rheumatol 1997;24: 714–718
30. Martínez-Lavín M, Hermosillo AG, Rosas M, et al. Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart rate variability analysis. Arthritis Rheum 1998;41:1966–1971
31. Roizenblatt S, Moldofsky H, Benedito-Silva AA, et al. Alpha sleep characteristics in fibromyalgia. Arthritis Rheum 2001;44:222–230
32. Harding SM. Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci 1998;315:367–376
33. Stein PK, Domitrovich PP, Ambrose K, et al. Sex effects on heart rate variability in fibromyalgia and gulf war illness. Arthritis Rheum 2004;51:700–708
34. Ulas UH, Unlu E, Hamamcioglu K, et al. Dysautonomia in fibromyalgia syndrome: sympathetic skin responses and RR interval analysis. Rhematol Int 2006;26:383–387
35. Bennett RM, Clark SR, Campbell SM, et al. Low levels of somatomedin C in patients with the fibromyalgia syndrome: a possible link between sleep and muscle pain. Arthritis Rheum 1992;35:1113–1116
36. Carli G, Suman AL, Biasi G, et al. Reactivity to superficial and deep stimuli in patients with chronic musculoskeletal pain. Pain 2002;100: 259–269
37. Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. Trends Neurosci 2001;24:450–455
38. Ledeboer A, Liu T, Shumilla JA, et al. The glial modulatory drug AV411 attenuates mechanical allodynia in rat models of neuropathic pain. Neuron Glia Biol 2007;2:279–291
39. Watkins LR, Milligan ED, Maier SF. Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. Adv Exp Med Biol 2003;521:1–21
40. Gracely RH, Petzke F, Wold JM, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002;46:1333–1343
41. Wood PB, Schweinhardt P, Jaeger E, et al. Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci 2007;25:3576–3582
42. Altier N, Stewart J. The role of dopamine in the nucleus accumbens in analgesia. Life Sci 1999;65:2269–2287