Fibromyalgia: The Nerve of That Disease

JON D. LEVINE and DAVID B. REICHLING

ABSTRACT. Fibromyalgia syndrome (FM) is a common, often debilitating and intractable, chronic, generalized pain condition. The development of effective therapies to treat FM has been hindered by a lack of understanding of fundamental mechanisms in the etiology of FM. In view of prominent characteristics that FM shares with other generalized pain conditions, we suggest that a key mechanism in such disorders may be that of altered activity in the subdiaphragmatic vagus nerve. Specifically, we propose that activity in vagal afferents, arising from the gastrointestinal tract, and sympathoadrenal function mediate a contribution of stress to FM and its strong association with irritable bowel syndrome. An important prediction of the proposed mechanism is that interventions that selectively modulate activity in specific populations of subdiaphragmatic afferents might be used to treat the symptoms of FM and other generalized pain syndromes. (J Rheumatol 2005;32 Suppl 75:29-37)

Key Indexing Terms:
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A GENERALIZED PAIN SYNDROME

Fibromyalgia syndrome (FM) is a common pain condition, estimated to occur in 2.4% of the general population[1-3]. The syndrome is characterized by widespread musculoskeletal pain, sleep disturbance[4], psychological distress, and comorbidity with other pain syndromes [e.g., irritable bowel syndrome (IBS), interstitial cystitis[5], and the female urethral syndrome[6]], which have considerable impact on the everyday life of patients[7-13]. FM occurs predominantly in women[14] and demonstrates familial aggregation[1].

Since 1990, the diagnosis of FM has been based on criteria of the American College of Rheumatology (ACR)[15]. A key dimension of the ACR criteria is the concept of tender points, 18 specific points on the body surface at which digital palpation elicits pain. By giving a sense of objectivity to the diagnosis of FM, the criteria helped diminish social stigma associated with FM, which lacks a diagnostic laboratory test or sign on physical examination. This has facilitated not only treatment, but also aided in the development of research programs and clinical trials.

Although the concept of tender points has been very useful in establishing FM as a medical entity that can be diagnosed, treated, and researched, the emphasis on ten-

der points has also caused some confusion concerning the characteristics of pain in FM. A common misconception is that patients with FM experience points of tenderness (sometimes confused with "trigger points"[16]), whereas, in fact, tender points are designated sites at which patients are tested for tenderness. This has been a distraction from the fundamental nature of FM as a generalized pain syndrome. Indeed, the first component of the ACR criteria for diagnosis of FM is that patients must have generalized chronic pain (longer than 3 months, present axially, bilaterally, and in both upper and lower body segments[15]).

Studies during the decade since introduction of the ACR criteria have demonstrated that most patients with FM have a diffuse reduction in pain threshold not localized to tender points[17-19]. Reduced threshold (sensitization) was observed in respone to thermal, chemical, and mechanical stimuli[20-23]. Moreover, lack of correlation between tender point scores and self-reported pain is consistent with the idea that the production of pain in FM is related to the generalized hypersensitivity to a variety of stimuli[24].

The recognition of FM as a syndrome of generalized pain is important because attempts to mechanistically explain FM based on the phenomenon of focal tender points have been unsuccessful. This review addresses our current understanding of FM as a generalized pain syndrome, and from that perspective, discusses potential neuroendocrine mechanisms of the syndrome.

COMORBIDITY

One of the most intriguing features of FM as a generalized pain syndrome is its comorbidity with several other pain syndromes that also have no known diagnostic laboratory abnormalities or signs on physical examination[25]. These comorbid clinical entities include: chronic fatigue syndrome[26-28], myofascial pain[28-30], multiple chemical

J.D. Levine, MD, PhD; D.B. Reichling, PhD.

Address reprint requests to Dr. J.D. Levine, Division of Rheumatology, Department of Medicine, University of California at San Francisco, C-522/Box 0440, 521 Parnassus Ave., San Francisco, CA 94143-0440. E-mail: Levine@itsa.ucsf.edu

sensitivities[31,32], and perhaps the best-established comorbid condition, IBS, which occurs in up to 70% of patients with FM[26,33-38]. Interestingly, FM and IBS are more likely to co-occur in individuals in whom severity of either diagnosis alone is greater[39,40]. While this comorbidity has, to date, remained a phenomenological observation, it presents a significant opportunity to explore FM mechanisms based on symptoms and response to treatment of these other pain syndromes.

In addition to the comorbidities discussed above, it is intriguing that in some medical conditions (e.g., arthritis and colitis) patients manifest symptom complexes indistinguishable from that of FM[41-43]. In fact, the similarity is so pronounced that this phenomenon has been termed "secondary" FM[44]. In addition, patients recovering from surgery following radiotherapy for cancer[45,46] or patients experiencing a variety of infectious diseases[47,48] can experience diffuse musculoskeletal pain, tenderness, and fatigue that is difficult to distinguish from FM. FM-like symptoms can also be induced by drugs, including cytokines[49-52] and antineoplastic agents[53], interferon in particular.

Taken together, the existence of comorbidity, secondary FM, FM-like symptom complexes associated with infections, and FM-like symptoms as side effects of drugs provides a compelling rationale for considering common mechanisms that may be shared among these diverse diseases. Further, this avenue of investigation may not only illuminate the etiology of FM, but also have much broader implications for our understanding of widespread pain as it occurs in a variety of illnesses.

EFFECTS OF STRESS
Symptoms in FM can be exacerbated after a stressful event; indeed, daily stresses commonly have a significant negative influence on the FM patient[15,54-57]. Symptoms of FM can be aggravated by noise, bright lights, and other acute stresses[58]. Poor sleep also appears to increase the painful symptoms of FM, via either sleep deprivation-induced stress or some specific mechanism[58]. Stress may be an etiological as well as a perpetuating factor in some patients with FM. For example, FM has been reported to occur at increased frequency in patients who have post-traumatic stress disorder[59]. It has been noted that following a stressful event, there is a delay in the development of the symptoms of FM, suggesting that it is necessary for subacute or chronic changes to develop for clinical FM to evolve[60,61]. One precipitating factor that has been proposed to contribute to the effect of stress is a significant decrease in physical activity, which often occurs after stress and especially after a physically traumatic event[62-64]. Nevertheless, while a decrease in exercise may predispose to FM, and aerobic exercise and stress management programs are reported to provide salutary effects[65], acute activity may actually exacerbate symptoms. Some authors have suggested that it is the stress itself, rather than an injury to specific muscle sites, that provides the etiologic basis for FM (reviewed in Pillemer, et al[4]); others believe stress leads to muscle tension abnormalities and biochemical changes that underlie the development of both specific tender points and the development of diffuse muscular pain[66-69]. Of interest, stress aggravates and possibly may contribute to the etiology of other related disorders, such as rheumatoid arthritis and IBS[26,70,71].

A better understanding of these opposing effects of stress will require mechanistic analysis. Numerous studies have already documented complex abnormalities in the stress response of patients with FM. These patients exhibit a hyperactive pituitary-adrenal corticotrophic hormone (ACTH) release in response to corticotrophin releasing hormone (CRH) and to insulin-induced hypoglycemia; they were also found to have mild hypocortisolemia[68,69,72-74]. The role of peripheral sympathetic activity and activity of the sympathoadrenal axis have also been investigated. It has been reported that patients with FM exhibit alterations in the peripheral autonomic nervous system[75], including dysregulation of the sympathetic nervous system[28,76-78]. For example, plasma levels of neuropeptide Y, which colocalizes with norepinephrine in cells of the sympathetic nervous system, have been reported to be low in patients with FM[55]. A similar change was seen with orthostatic stress[79] and other stresses[75]. Of note, there are also well described cooperative interactions between the adrenal cortex and the adrenal medulla[80-83] that might account for the coincidence of changes in both the hypothalamic-pituitary-adrenal and sympathoadrenal axes. It has been postulated that many clinical features of FM, such as widespread pain and fatigue, are related to some of these neuroendocrine perturbations[4]. The fact that some successful therapies such as exercise programs and tricyclic antidepressants affect the function of these neuroendocrine axes provides further support for the importance of neuroendocrine mechanisms in FM[84-92].

The degree to which stress can precipitate, chronically maintain, or exacerbate the symptoms of FM remains to be elucidated. However, the expression of FM is greatly affected by integrative activity in multiple neuroendocrine axes involved in stress, as well as (based on the known characteristics of FM) peripheral nociceptive circuits, musculoskeletal and gastrointestinal (GI) sites, and higher central nervous system (CNS) centers, including those affecting sleep.

THERAPY
Most current therapies, both pharmacological and nonpharmacological, are usually only partially efficacious against the symptoms of FM in only a subset of patients. Since our understanding of the underlying mechanism of FM is still very preliminary, these therapies have been

derived from empirical observations[93,94]. Classes of pharmacological agents that have shown some efficacy in clinical studies include tri- and tetracyclic agents and other antidepressants, sedatives, anxiolytics, serotonergic agents, and analgesics[94-97], while nonpharmacological therapies have included aerobic exercise and high-fiber vegetarian diet[65,98-101]. Although pain constitutes the major diagnostic criterion for FM, there has been a paucity of studies of the effect of analgesics to control pain in patients with FM[93-95,102,103] — this in spite of the now well accepted use of opioids in the treatment of chronic pain unrelated to malignancy[102,104,105]. Finally, it has been suggested that poor or suboptimal response to therapeutic regimens may be due to heterogeneity in the underlying mechanisms of FM in different patients[103]. Therapeutic optimization is further complicated by the possibility that combination therapies may be more effective than single agents[93-95,106] and that dose-response relationships for many agents prescribed in FM are nonlinear[107,108].

An initial approach to the rational design of treatment for FM may come from studies of the comorbid pain condition IBS. Selective and potent antagonists for the $5HT_3$ receptor (e.g., alosetron, which normalizes visceral sensation), thought to contribute to sensitization of nociceptors in patients with IBS and found efficacious for women (90% of IBS patients) with the diarrhea-predominant form of IBS (75% of IBS patients), may also be efficacious for some FM patients[109-112]. Whether $5HT_4$ agonists (e.g., tegaserod or prucalopride, prokinetics that help normalize GI function by increasing small bowel and colonic motility), which work for patients with constipation-predominant IBS, might be effective for patients with FM unresponsive to $5HT_3$ antagonists remains an intriguing possibility.

MECHANISMS OF GENERALIZED PAIN SYNDROMES
Several mechanisms have been postulated to underlie the diffuse lowering of nociceptive threshold seen in FM. Both central nervous system and peripheral nervous system mechanisms have been proposed[113-116]. The presence in FM of other centrally-associated phenomena such as sleep disturbance and blunted stress response, as well as the diffuse nature of pain, suggests that a central mechanism may be involved[22,68], and it appears that centrally-mediated secondary hyperalgesia plays a role[20,117,118]. Finally, a deficiency in endogenous pain modulators may be another CNS mechanism contributing to pain in FM[119].

We propose that abnormalities in normal physiological interactions between the sympathoadrenal axis, vagal afferent activity from the GI tract, and central nociceptive mechanisms underlie both the contribution of stress to FM and the association of FM with IBS; further, abnormalities in vagal afferent activity from the GI tract, pro-

posed as a cause of IBS, may be an etiologic factor in FM.

We have found that a well defined, discrete disruption in the peripheral nervous system (i.e., of subdiaphragmatic vagal afferents) can produce long-lasting sensory abnormalities resembling the generalized pain that occurs in syndromes such as FM, chronic fatigue, and IBS. Specifically, we found that interruption of vagal afferent activity caused a widespread decrease in mechanical nociceptive thresholds, as well as a heightened sensitivity for the hyperalgesic response to an inflammatory mediator, bradykinin, in the rat[120,121]. This observation suggested to us that this vagotomy-induced condition might serve as an experimentally tractable model of generalized pain.

In experiments with vagotomized animals, and in animals intermittently exposed to noise stress, there is a state of diffuse, heightened nociceptive response that resembles generalized pain in FM. Animals that receive a subdiaphragmatic vagotomy demonstrate a slowly developing decrease in mechanical nociceptive threshold, constituting a 40% decrease at 2 weeks[120,121]. Similar effects were observed with chronic noise stress (unpublished observation). In addition, vagotomized animals exhibit an enhanced nociceptive response to bradykinin, which may be relevant to the symptomatology of FM. For example, it is known that physical activity can release bradykinin[122-124]. A heightened sensitivity to bradykinin in FM may explain why exercise, often recommended as a therapy, can acutely aggravate symptoms. Also, a heightened sensitivity to bradykinin could explain the presence of inflammatory-type hyperalgesic pain without signs of cellular inflammation. The decrease in mechanical nociceptive threshold and increase in nociceptive sensitivity to bradykinin after vagotomy is reversed by adrenal denervation, suggesting that activity in vagal afferents, in conjunction with stress-induced activity in a neuroendocrine axis, may be important in the pain symptomatology of FM.

Physiological or pathophysiological stimuli that alter activity in the subdiaphragmatic vagal afferents to enhance nociceptive sensitivity and central sensitization in FM remain to be elucidated; however, it is known that stress that alters GI motility, and therefore vagal afferent activity, can exacerbate FM symptoms; moreover, toxins or dietary factors, which also affect GI motility, may also be important.

During the 1960s, surgical subdiaphragmatic vagotomy was used in attempts to treat severe peptic ulcer disease complicated by recurrent GI hemorrhage. While the literature does not mention FM-like syndrome in these patients, it should be kept in mind that diagnostic criteria for FM were not to be established until decades later, and that these patients suffered from a variety of other severe symptoms related to changes in their GI tract (e.g., fullness after meals, heartburn, dumping, bilious vomiting, hypoglycemia, and diarrhea); moreover, what was referred to as fibrositis at that time was often considered a

functional disorder. Thus, both surgeons and gastroenterologists may have lacked the clear criteria to diagnosis the syndrome and may have been distracted by other complications of this procedure that ultimately led to the discontinuation of this therapeutic modality.

Several studies suggest that peripheral neural mechanisms, in particular sensitization of primary afferent nociceptors, contribute to FM. Sensitization changes have been found in polymodal nociceptors[125,126], including a lowered thermal threshold[20] and increased response to mechanical painful stimuli[21,23]. Some of the strongest evidence for peripheral mechanisms underlying the symptoms of FM is the demonstration of decreased pain and decreased tender point count after topical application of capsaicin[127]. Patients with FM also exhibit an increased flare response (i.e., axon reflex) to capsaicin, with a diminished threshold dose and increased size of flare[128,129], as well as increased dermatographia[20]. Further, there is a correlation between size of the peripheral flare response and degree of mechanical and thermal sensitivity in patients with FM[128]. In addition, injection of local anesthetic into a tender area[113] as well as administration of a regional sympathetic block[130,131] have both been reported to result in clinical improvement.

The neuropathic-like characteristics of pain symptoms in FM[132-135] further suggest a role for peripheral mechanisms. The high comorbidity with IBS, for which there is evidence of peripherally-sensitized nociceptors in the GI tract[136-142], also supports this view. As discussed below, there is also evidence in the FM literature for a role of peripheral components of the hypothalamic-pituitary-adrenal and sympathoadrenal neuroendocrine stress circuits. Our animal model of generalized pain syndromes also appears to have a strong peripheral component involving both primary afferent nociceptors and adrenal medulla-derived factors[120,121].

That neuroendocrine systems play an important role in FM is suggested by the finding that chronic stress may be an etiological as well as exacerbating factor[15,54,59,61,69-71,143-145]. The adrenal medulla plays a central role in mediating physiological effects of stress[146]: we found that surgical removal of the adrenal medulla can reverse vagotomy-induced generalized hyperalgesia in rats. Thus, it seems likely that a thorough understanding of generalized pain induced by changes in activity in subdiaphragmatic vagal afferents will provide important insights into the mechanisms of FM: conceivably, altered vagal activity may prove to be a contributing factor in FM and other generalized pain syndromes.

A striking characteristic of FM is its predominant occurrence in women. It is clear from the altered nociceptor processing in FM that a gender effect for nociception would be relevant to the disease. Similarly, a gender influence on stress is also relevant, as are differences in prevalence and type of stresses in men and women. From studies by us[120,121] and others[147,148] indicating an influence of vagal function on nociception, gender differences in this physiological function would also be important in FM. The literature demonstrates that nociception, stress, and vagal function are affected by gender.

Sexual dimorphism in vagal function may also partly explain sexual dimorphism in FM and other generalized pain syndromes. Sex-dependent differences in the levels of afferent and efferent vagal activity have been reported[149,150]. Further, specifically with regard to generalized hyperalgesia, we found that vagotomy in female rats causes a greater generalized enhancement of bradykinin-induced hyperalgesia than it does in males[151,152]. This sex-dependence of vagotomy-induced generalized pain may shed light on mechanisms of the marked female preponderance of FM.

Stress responses have also been shown to vary with sex. Observations on sympathetic response, by measurement of norepinephrine and neuropeptide Y, suggest possible stress-induced downregulation of adrenergic receptors in women due to elevated circulating catecholamines, in contrast to upregulation of neuropeptide Y and adrenergic receptors in men[153]. Female rats exhibit higher basal[154] and stimulated[155,156] plasma epinephrine and norepinephrine levels; similarly, in women, muscle sympathetic nerve activity (burst frequency and burst incidence) is higher[157]. Stress-induced increases in plasma norepinephrine in men are enhanced by estradiol[158]. Sex steroids also influence the hypothalamic-pituitary-adrenal axis. Short-term elevation of estradiol in men by cutaneous patch resulted in a statistically significantly increased response to psychosocial stresses[158]; these included increased peak adrenocorticotrophic hormone and cortisol response, as well as increased total norepinephrine output. These observations indicate that sex has a significant influence on all 3 axes that mediate stress response and suggest that this influence may substantially contribute to sex predominance in FM. An effect of gender on adrenal medullary function would be expected to influence our model of vagotomy-induced generalized hyperalgesia since the adrenal medulla is required for maintenance of the syndrome.

A CNS component to FM pain has also been suggested[159-161]. In our animal model of generalized pain, changing activity in the subdiaphragmatic vagal afferents modulates the function of descending antinociceptive controls, and could thereby alter sensory processing in the spinal cord dorsal horn of input from the whole body. Similarly, the sympathoadrenal axis, which is upregulated following subdiaphragmatic vagotomy, could cause widespread sensitization of primary afferent nociceptors throughout the body via release of catecholamines[120,162].

Afferent activity in subdiaphragmatic vagal afferents may have broader implications for the clinical features of FM because such activity affects other systems that could

influence its major symptoms. Specifically, the vagus is well known to control physiological processes that are disrupted in FM (and in other generalized pain syndromes), including GI motility and pain in IBS[163-165] and sleep[148,166-170]. Additionally, plasma extravasation, which can lead to local swelling, as reported subjectively by patients with FM[13,96,171,172], is also modulated by subdiaphragmatic vagal function[173]. Consistent with our hypothesis that decreased vagal afferent activity contributes to the pathophysiology of FM are data suggest-

ing decreased parasympathetic tone in FM patients[28,78,174,175].

Of note with regard to the comorbidity of FM and IBS, selective lesioning of the celiac branch of the subdiaphragmatic vagus, which mainly provides innervation of the GI tract, mimics the pronociceptive effects of subdiaphragmatic vagotomy[120,121]. Finally, even if these mechanisms were not the direct cause of FM, they would be expected to have a significant influence on FM symptoms, since fluctuations in vagal afferent or sympathoadrenal activity likely alter nociceptive response in these patients.
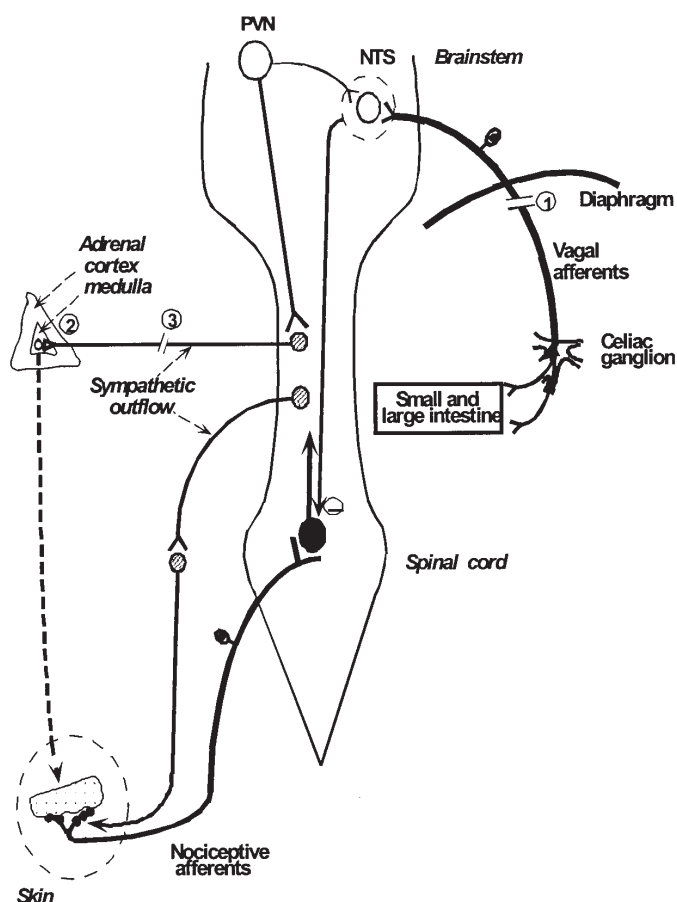
FUTURE DIRECTIONS

A number of generalized pain syndromes lack diagnostic laboratory tests or objective physical findings (e.g., FM, IBS, and chronic fatigue), despite researchers' attempts to elucidate underlying mechanisms. We draw attention to shared properties among these chronic pain conditions and suggest how they might support common mechanisms for generalized pain syndromes. A key element of this hypothesis, with respect to pathophysiology and potential therapy, is altered activity in subdiaphragmatic vagal afferents (Figure 1 illustrates a proposed neuroendocrine circuit mediating enhanced pain in FM and other generalized pain syndromes). A prediction of the proposed mechanism is the potential of highly specific interventions that pharmacologically or nonpharmacologically modulate activity in specific populations of subdiaphragmatic vagal afferents from the GI tract, which could be used to treat the symptoms of FM. An example of a potential treatment is $5HT_3$ receptor antagonist[109]. Such therapy could be targeted to the GI tract, potentially producing fewer side effects than current FM therapies.

A challenge in developing a hypothesis of a common pathophysiology for generalized pain syndromes will be to explain the symptomatic predominance of different organ systems in the various syndromes (e.g., the musculoskeletal system in FM vs the GI system in IBS). Finally, identification of the specific stimuli producing activity in the relevant subdiaphragmatic vagal afferents and the specific population of afferents that are activated will be critical issues.

Figure 1. Proposed circuit for vagal-adrenal medullary modulation of nociception. Subdiaphragmatic vagal afferents terminate in the nucleus of the solitary tract (NTS), which in turn projects to the paraventricular nucleus (PVN), and preganglionic sympathetic nerves from the PVN innervate the adrenal medulla. Decreased activity in a population of subdiaphragmatic vagal afferents (1) produces increased adrenal medullary tone and plasma epinephrine levels. Stressful stimuli from higher centers activate the PVN, stimulating the production of corticotrophin releasing factor (CRF), a coordinator of the stress response. Activation of the locus coeruleus by CRF is transmitted to the adrenal medulla via sympathetic fibers in the splanchnic nerve, leading to the release of epinephrine, which sensitizes primary afferent nociceptors, which can be reversed by removal of the adrenal medulla (2) or by denervation of adrenal medulla (3). It is also possible that the proposed CNS mechanisms also contribute to central sensitization, which has been implicated in FM. From Khasar SG, *et al. Eur J Neurosci 2003*;17:909-15[162]. With permission.

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