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Minireviews

Fibromyalgia Syndrome in Need of Effective Treatments

Theoharis C. Theoharides, Irene Tsilioni, Lauren Arbetman, Smaro Panagiotidou, Julia M. Stewart, Rae M. Gleason, and Irwin J. Russell

Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, Massachusetts (T.C.T., I.T., L.A., S.P., J.M.S.); Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts (T.C.T.); Department of Psychiatry, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts (T.C.T.); Sackler School of Graduate Biomedical Sciences, Tufts University, Boston, Massachusetts (T.C.T.); National Fibromyalgia and Chronic Pain Association, Logan, Utah (R.M.G.); Fibromyalgia Research and Consulting, Arthritis and Osteoporosis Center of South Texas, San Antonio, Texas (I.J.R.)

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ABSTRACT

Fibromyalgia syndrome (FMS) is a chronic, idiopathic condition of widespread musculoskeletal pain, affecting primarily women. It is clinically characterized by chronic, nonarticular pain and a heightened response to pressure along with sleep disturbances, fatigue, bowel and bladder abnormalities, and cognitive dysfunction. The diagnostic criteria have changed repeatedly, and there is neither a definitive pathogenesis nor reliable diagnostic or prognostic biomarkers. Clinical and laboratory studies have provided evidence of altered central pain pathways. Recent evidence suggests the involvement of neuroinflammation with stress peptides triggering the release of neurosenzitizing mediators. The management of FMS requires a multidimensional approach including patient education, behavioral therapy, exercise, and pain management. Here we review recent data on the pathogenesis and propose new directions for research and treatment.

Introduction

Fibromyalgia syndrome (FMS) is a chronic, idiopathic condition of widespread musculoskeletal pain that is clinically characterized by aches, soft tissue tenderness, stiffness, general fatigue, and sleep disturbances (Clauw et al., 2011; Schmidt-Wilcke and Clauw, 2011; Clauw, 2014) as well as cognitive dysfunction (Theoharides et al., 2015b). FMS is estimated to affect 2%–8% of the adult population and is considered to be the most common cause of generalized, musculoskeletal pain in women between the ages of 20 and 55 years (Branco et al., 2010). Diagnosis of FMS has changed over the last 10 years, but there are still no objective criteria (McBeth and Mulvey, 2012; Wolfe and Walitt, 2013). FMS belongs to a family of overlapping conditions that involve diffuse pain; they are called central sensitivity syndromes and may occur concomitantly (Table 1). These include chronic fatigue syndrome, irritable bowel syndrome, functional dyspepsia, myogenic temporomandibular disorder, tension headache, myofacial pain syndrome, restless leg syndrome, interstitial cystitis/bladder pain syndrome, posttraumatic stress disorder (PTSD), and Gulf War syndrome (Table 1) (Yunus, 2007; Theoharides, 2013a).

Here we review recent data on the pathogenesis of FMS, especially with respect to the involvement of stress peptides triggering the release of inflammatory and neurosenzitizing mediators. We also propose new directions for research and treatment.

Diagnosis

In the absence of any objective biomarker, the diagnosis of FMS is based on the chief complaint of pain and associated symptoms of fatigue, sleep disturbance, cognitive decline, and mood changes. In the past, diagnosis was principally based on the presence of widespread pain for ≥3 months in at least 11 of

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Current affiliation: Lauren Arbetman is currently at School of Medicine, George Washington University, Washington, D.C.

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ABBREVIATIONS: ACR, American College of Rheumatology; COMT, catecholamine methyltransferase; CoQ_{10}, coenzyme Q_{10}; CSF, cerebrospinal fluid; CRH, corticotropin-releasing hormone; CXCL8, proinflammatory chemokine IL-8; FMS, fibromyalgia syndrome; IL, interleukin; MC, mast cell; MCP-1/CCL2, monocyte chemoattractant protein-1; mtDNA, mitochondrial DNA; NSAID, nonsteroidal anti-inflammatory drug; PBMCs, peripheral blood mononuclear cells; PGB, pregabalin; SP, substance P; TCA, tricyclic antidepressant; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

TABLE 1
Central sensitivity syndromes often comorbid with FMS

Chronic fatigue syndrome (CFS)
Functional dyspepsia
Gulf War syndrome
Interstitial cystitis/bladder pain syndrome (IC/BPS)
Irritable bowel syndrome (IBS)
Myogenic temporomandibular disorder (TMD)
Myofacial pain syndrome
Posttraumatic stress disorder (PTSD)
Restless leg syndrome
Tension headache

18 "tender points." In 2010, the American College of Rheumatology (ACR) proposed preliminary diagnostic criteria for FMS that placed increased emphasis on patient symptoms (Wolfe et al., 2011). A later modification of the ACR 2010 criteria used a self-report questionnaire (the Fibromyalgia Survey Questionnaire) to assess patient symptoms (Ferrari and Russell, 2013) with a score of $\geq$12 having 93.1% sensitivity and 91.7% specificity, as compared with 90.2% and 89.5%, respectively, of the modified ACR criteria (Clauw, 2014).

A stepwise diagnostic work-up of patients with chronic widespread pain in primary care is recommended, with referral to specialists in cases of mental disorders (Clauw, 2014). The absence of distinct pathogenesis and objective markers hinders the development of effective treatment (Boomershine and Crofford, 2009; Clauw, 2010).

Pathogenesis

Investigations on the possible mechanisms involved in the etiology and pathogenesis of FMS have focused on dysfunction of the autonomic and central nervous systems, abnormalities in brain functional and neuroimaging studies, as well as genetic and environmental factors (Table 2). These include physical trauma (McLean et al., 2011), viral infections (hepatitis C, Epstein-Barr, human papillomavirus, human immunodeficiency virus, parvovirus, coxsackie B), and Lyme disease (Buskila et al., 2008).

A number of studies have linked FMS to early sexual abuse (Paras et al., 2009). In addition, emotional or psychologic stress, especially associated with deployment to war, may also trigger FMS (Eisen et al., 2005) (Figure 1).

Genetic Factors. About one-third of patients with FMS have a close relative, usually a female, who is similarly affected (Russell and Larson, 2009). One study performed genomewide linkage analysis in members of 116 families from the Fibromyalgia Family Study with 341 microsatellite markers and showed an estimated sibling recurrence risk ratio for FMS of 13.6 (95% confidence interval, 10.0–18.5), based on a reported population prevalence of 2% (Arnold et al., 2013). This was also one of the first reports of genomewide suggestive linkage of FMS to the chromosome 17p11.2-q11.2 region (Arnold et al., 2013).

Functional polymorphisms have linked FMS to serotonin receptor 2A region of chromosome 13 and the HLA region of chromosome 6 (Dudek et al., 2003). A significantly higher frequency of a polymorphism of the serotonin transporter (5-HTT) gene regulatory region was found in FMS patients (31%) compared with healthy controls (16%) (Offenbaecher et al., 1999). The serotonin transporter (5-HTT) gene was also found to be more frequent in patients affected by FMS who also had anxiety traits (Cohen et al., 2002).

TABLE 2
Pathogenetic mechanisms in FMS

Genetic factors
Linkage to the chromosome 17p11.2-q11.2 region
Linkage to serotonin receptor 2A region of chromosome 13
Linkage to HLA region of chromosome 6
Polymorphisms associated with the serotonin transporter (5-HTT) gene regulatory region
Linkage to catecholamine methyltransferase (COMT) genes
Negative association with the COMT val158met polymorphism
Association with dopamine-D-3 receptor (DRD3) Ser9Gly polymorphism
Single nucleotide polymorphisms (SNPs) involving gamma-aminobutyric acid receptor subunit beta 3 (GABRB3), trace amine receptors (TAAR1), and guanylate binding protein 1 (GBP1)
Neural processes
Altered heat and cold thresholds
Reduced tolerance for pain and nociceptive reflex threshold
Smaller than normal brain gray matter volumes
Less connectivity within the brain's pain inhibitory network
Chiari malformation
Neuroinflammation
High serum IL-6
High serum TNF
High plasma monocyte chemoattractant protein-1 (MCP-1/CCL2) and eotaxin (CCL)
High serum and CSF levels of IL-8 (CXCL8)
Increased plasma levels of IL-17A
Increased CSF levels of SP and nerve growth factor
Increased skin mast cells
Oxidative stress
Lower total nitrite levels
Higher serum prolidase activity,
Higher total oxidative status (TOS)
Reduced level of coenzyme Q10 (CoQ10)
High level of reactive oxygen species (ROS)

Other genetic factors may also account for the decrease of pain thresholds in FMS patients (Buskila et al., 2007). Catecholamine methyltransferase (COMT) genes that have been implicated in predisposition to both pain and depression have also been invoked in FMS. There was an association between FMS and the COMT val^{158}met polymorphism, with the COMT met allele appearing to confer "protection" to nonaffected relatives from developing full-blown FMS symptomatology (Cohen et al., 2009). There is also increased evidence that COMT is associated with increased psychologic vulnerability (Finan et al., 2011). Another study reported that a dopamine-D-3 receptor Ser9Gly polymorphism influenced diffuse noxious inhibitory control efficacy and pain tolerance in FMS patients (Potvin et al., 2009). There has also been evidence for the association of FMS with various adrenergic receptor gene polymorphisms (Vargas-Alarcon et al., 2009).

A large candidate gene association study examined over 350 genes in 496 FMS patients and 348 chronic-pain-free controls; three unsuspected genes [gamma-aminobutyric acid receptor subunit-β3 (GABRB3), trace amine receptors (TAAR1) and guanylate binding protein 1 (GBP1)] harbored single-nucleotide polymorphisms that differed in frequency between FMS patients and healthy controls (Smith et al., 2012).

Neural Processes. Nociception is composed of two opposed components: pronociception and antinociception. FMS patients exhibit increased pronociception and decreased antinociception, resulting in chronic allodynia (Russell and Larson, 2009). Central sensitization is the main mechanism involved in

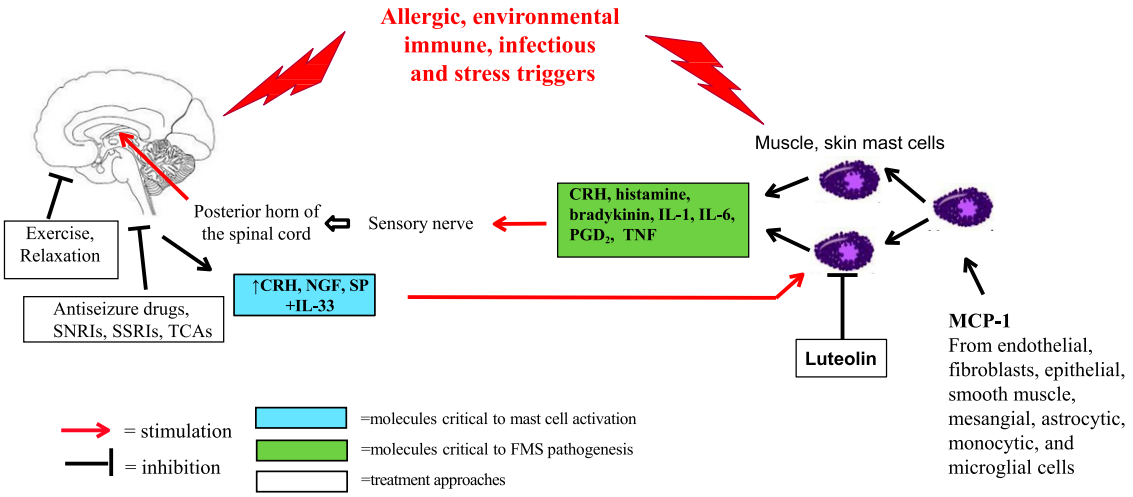

Fig. 1. Diagram representation of the proposed steps involved in the pathogenesis of FMS and targets for treatment. Stress peptides (CRH, nerve growth factor, neurotensin, SP) are released from the spinal cord in peripheral tissues (blood vessels, muscles, skin) in response to allergic, environmental, immune, infectious, and stress triggers (blue box). There, they act synergistically with IL-33 to stimulate mast cells, which secrete inflammatory and neurosensitizing molecules such asCRH, histamine, bradykinin, IL-1, IL-6, prostaglandin D2, and TNF (green box). These molecules can either activate peripheral sensory nerves directly or reach the brain through the systemic circulation, thus creating a self-sustaining pain circuit. Treatment approaches (white box) include exercise and relaxation to reduce stress (specific norepinephrine reuptake inhibitors (SNRIs); specific serotonin reuptake inhibitors (SSRIs); tricyclic antidepressants (TCAs) to reduce anxiety and depression; as well as TCAs and antiseizure medications to provide analgesia. Finally, luteolin and related compounds can inhibit the release of MC mediators.

the development and maintenance of chronic pain (Woodman, 2013), and it is characterized by allodynia and hyperalgesia (Staud et al., 2001). Allodynia is defined as the perception of pain resulting from a stimulus that would not normally be painful, whereas hyperalgesia occurs when an actual painful stimulus is perceived as more painful than it should be (Woolf, 2011). In FMS, allodynia is evidenced by pain at "tender points" with a stimulus (pressure $\leq$4 kg) that is not normally painful to healthy normal controls (Russell and Larson, 2009).

A quantitative sensory testing study in 85 FMS patients and 40 matched controls found that FMS patients had altered heat and cold thresholds; these patients also exhibited a reduced tolerance for pain as well as a reduced nociceptive reflex threshold, a measure of central excitability (Desmeules et al., 2003).

Functional brain imaging studies have provided compelling evidence for abnormal pain processing in FMS, including brain activity that correlated with patients' pain sensitivity (hyperalgesia/allodynia), temporal summation of pain, and prolonged pain after noxious sensations (Staud, 2011). Voxel morphometric examination of brain MRI images of FMS patients showed significantly smaller than normal brain gray matter volumes, with this loss rapidly progressing with time compared with healthy controls (Kuchinad et al., 2007).

A number of studies have provided further evidence of dysfunctional connectivity of the pain network in FMS (Jensen et al., 2012; Flodin et al., 2014). One study found that FMS patients exhibited higher sensitivity to pain provocation than controls and that they required less pressure to evoke equal pain, but they failed to respond to pain provocation in the primary link in the descending pain-regulating system (the rostral anterior cingulate cortex) (Flodin et al., 2014). Another study comparing the functional connectivity of the descending pain inhibitory network in age-matched FMS patients and healthy controls found that patients displayed less connectivity within the brain's pain inhibitory network during calibrated pressure pain compared with healthy controls (Jensen et al., 2012).

Some studies have suggested that FMS patients may suffer from compressive cervical myelopathy (Holman, 2012), possibly secondary to Chiari malformation (Heffez et al., 2004), which may be correctable surgically.

Psychologic Stress and Trauma. Stress seems to increase the risk of developing FMS (Geenen et al., 2002). Psychologic factors have been shown to influence pain severity in FMS, and they may modulate the severity of perceived distress (Bote et al., 2012, 2013). The normal circadian rhythm for plasma cortisol level is disrupted in FMS patients as evidenced by elevated plasma concentrations in the evening (Crofford et al., 2004). Corticotropin-releasing hormone (CRH), the principal central nervous system mediator of the stress response, was elevated in the cerebrospinal fluid (CSF) of FMS patients and was associated with pain but not fatigue symptoms (McLean et al., 2006).

FMS is quite common in patients with systemic mastocytosis (Theoharides et al., 2015b), a disorder characterized by a higher number and reactivity of mast cells (MCs) (Theoharides et al., 2015c). Emotional stress is the most common trigger of symptoms in mastocytosis patients and is correlated with elevated serum levels of CRH, a receptor of which was expressed on bone marrow MCs (Theoharides et al., 2014). In fact, CRH can trigger *selective* release of vascular endothelial growth factor (VEGF) from human MCs (Cao et al., 2005) and also acts synergistically with the neuropeptide neurotensin to augment VEGF release, increasing vascular permeability (Donelan et al., 2006). CRH also leads to blood-brain barrier disruption (Theoharides and Konstantinidou, 2007) through brain MC activation (Esposito et al., 2002).

Recent studies have reported that estradiol augments immune (Kovats, 2015) and allergic (Hox et al., 2015) reactions. We showed that MCs express estrogen receptors (Pang et al., 1995) and that 17β-estradiol augmented substance P (SP)-induced MC activation (Theoharides et al., 1993). These findings may explain the higher prevalence of FMS in women. Levels of SP are increased in the CSF of FMS patients

(Russell, 1998), and SP can stimulate MCs (Theoharides et al., 2010, 2012a). In fact, SP-induced MCs express CRH receptor-1 (Scholzen et al., 2001), and the SP receptor neurokinin-1 has been implicated in the pathophysiology of pain (Greenwood-Van Meerveld et al., 2014).

Nerve growth factor is elevated in the CSF of patients with FMS (Giovengo et al., 1999) and has been considered as a target for analgesic therapy (Lewin et al., 2014). Serum, plasma, and CSF levels of brain-derived neurotrophic factor are elevated in FMS (Nugraha et al., 2012), but it is not clear whether this is secondary to dysfunction of its receptor.

Neuroinflammation. It has been suggested that MCs may be involved in FMS (Lucas et al., 2006; Pollack, 2015) as well as other comorbid conditions (Theoharides, 2013a). MCs have been increasingly associated with inflammation (Galli et al., 2008; Theoharides et al., 2012a) and pain (Heron and Dubayle, 2013; Chatterjea and Martinov, 2015). The number of MCs was significantly increased in the papillary dermis of FMS patients (Blanco et al., 2010). Moreover, chronic urticaria, which involves MCs, is more common in FMS (Torresani et al., 2009).

Monocyte chemoattractant protein-1 (MCP-1/CCL2) and eotaxin (CCL) have both been reported to be elevated in plasma of FMS patients (Zhang et al., 2008). MCP-1 also plays a pivotal role in inflammatory myopathies; myoblasts treated with MCP-1 or eotaxin secrete significant amounts of interleukin-1β (IL-1β) (Zhang et al., 2008). In addition, a study using a rat model to evaluate the involvement of MCP-1 in stress-induced chronic pain showed that MCP-1 induces long-lasting muscle hyperalgesia and a state of latent chronic sensitization to other allogenic substances through activation of its high-affinity receptor, CCR2, located on the peripheral terminals of IB4+ nociceptors (Alvarez et al., 2014). MCP-1 is a strong MC chemoattractant (Conti et al., 1998) and also triggers MCs (Conti and Theoharides, 1994).

MCs develop from bone marrow progenitors in response to stem cell factor, the ligand of the transmembrane tyrosine kinase Kit receptor, which regulates growth, migration, survival, and effector functions of MCs (Galli et al., 2011). These progenitors migrate from the blood into all tissues, including the brain, lung, mucosal interfaces, muscles, and skin where they mature in close proximity to blood vessels and nerve endings (Theoharides et al., 2015c).

MCs are major effector cells stimulated by allergens cross-linking specific IgE bound to their high-affinity surface receptors (Rivera et al., 2008). MCs also express Toll-like receptors, which can be activated by bacterial and viral antigens (Abraham and St John, 2010). Once stimulated, MCs secrete numerous vasoactive and proinflammatory mediators, leading to multiple symptoms (Theoharides et al., 2012a). MC activation can be enhanced by IL-33 (Fux et al., 2014), which synergizes with SP to induce VEGF release (Theoharides et al., 2010), acting as a "sensor of cell injury" (Enoksson et al., 2011; Theoharides et al., 2015a).

Preformed molecules stored in MC secretory granules include histamine, serotonin, bradykinin, proteases (chymase, carboxypeptidase, tryptase), and tumor necrosis factor (TNF) (Olszewski et al., 2007), which also participates in T-cell activation (Nakae et al., 2005; Kempuraj et al., 2008). MCs also release other proinflammatory and neurosensitizing molecules such as newly synthesized leukotrienes, prostaglandins, and platelet-activating factor as well as many cytokines (IL-6, IL-9, IL-13, TNF) and chemokines (CXCL8, CCL2, CCL5) (Theoharides et al., 2015c). MCs can release various cytokines, such as IL-6, selectively, without degranulation (Theoharides et al., 2007), which permits them to participate in many diverse functions. In addition, MCs secrete mitochondrial DNA (mtDNA), which has autocrine and paracrine stimulatory actions (Zhang et al., 2012), as well as exosomes that could deliver regulatory molecules such as microRNAs (Tsilioni et al., 2014; Kawikova and Askenase, 2015). MCs are now considered important in innate immunity (Galli et al., 2011), autoimmunity (Rottem and Mekori, 2005), and neuroinflammation (Theoharides et al., 2012a).

Chemokines act as modulators of nociception, enhancing sensitivity to pain by direct action on chemokine receptors throughout the pain pathway (Abbadie, 2005; Charo and Ransohoff, 2006). Several studies have shown elevated levels of the proinflammatory chemokine IL-8 (CXCL8) in both serum and CSF of patients with FMS (Ross et al., 2010; Kadetoff et al., 2012; Rodriguez-Pintó et al., 2014). However, exercise induced a *decrease* in the systemic concentration of IL-8 as compared with an exercise-induced increase in healthy women (Bote et al., 2012); this finding may explain the beneficial effect of mild exercise in FMS.

Sudden changes in the inflammatory cytokine profile may influence the severity of symptoms (Carvalho et al., 2008; Nugraha et al., 2013) and an imbalance between pro- and anti-inflammatory cytokine levels could explain, at least in part, the induction and maintenance of symptoms in FMS patients (Bazzichi et al., 2007). There appears to be an increase in cytokines early in the course of the disease that may sensitize peripheral and central nociceptors.

A number of studies have reported disturbances in cytokine levels in the blood and CSF of FMS patients, but the results vary considerably depending on whether they were measured in the plasma, serum, or from activated peripheral blood mononuclear cells (PBMCs), as well as the type of assay used. Moreover, measuring many of these mediators in biologic fluids may be tricky as they may be released episodically and are broken down quickly; so they may be best measured in 24-hour urine collected and stored cold as done for methylhistamine and prostaglandin $F_{2\alpha}$ (Branco et al., 2010).

For instance, in one study, IL-6 was increased in the serum of FMS patients (Behm et al., 2012) and correlated with FMS severity (Uceyler et al., 2011). A recent study of plasma cytokines/chemokines in patients with chronic fatigue syndrome reported slightly elevated IL-1RA, IL-4, IL-13, but only during the short and *not* the long duration of the disease (Hornig et al., 2015). It is of interest that acute restraint stress of mice led to increased serum IL-6 that was entirely MC dependent (Geiss et al., 2012).

Other mediator levels were uniformly *low*, but were characterized by bursts of secretion with an increased ratio of IL-10 to that of IL-1β, IL-8, and TNF (Togo et al., 2009). A recent study using a Multiplex assay reported that the cytokine/chemokine release (IL-6, IL-8, MIP-1α and MIP-1β) from PBMCs in FMS patients was lower than in controls, as well as lower than in rheumatoid arthritis and systemic lupus erythematosus patients (Wallace et al., 2015). IFN-γ, IL-5, IL-6, IL-8, IL-10, MIP-1β, MCP-1, and MIP-1α released from stimulated PBMCs were also reported to be lower in FMS patients compared with healthy controls, and there was no difference in plasma levels (Behm et al., 2012).

One study showed increased plasma levels of IL-17A in patients with FMS and correlated their levels with increased levels of TNF (Pernambuco et al., 2013). CSF and serum IL-17 also positively correlated with indices of pain (Meng et al., 2013), depression, and anxiety (Liu et al., 2012), which are symptoms frequently reported by patients with FMS. TNF and IL-17 seem to act together in perpetuating the inflammatory process (Romero-Sanchez et al., 2011; Griffin et al., 2012). MC-derived IL-6 and transforming growth factor-β induce the development of T_H17 cells through dendritic cell maturation (Dudeck et al., 2011); moreover, MCs themselves can secrete IL-17 (Kenna and Brown, 2013).

Increased levels of IL-4 and IL-10 may suggest a possible attempt to regulate the overproduction of IL-17 and other inflammatory cytokines (Wang et al., 1995). Both IL-4 and IL-10 seem to be necessary for regulatory T-cell–mediated suppression of the Tr17 response (McGeachy et al., 2007).

Oxidative Stress. FMS patients have higher oxidative stress index and lower total nitrite levels than healthy controls (Neyal et al., 2013). In particular, patients with FMS demonstrated higher serum prolidase activity, total oxidative status, and oxidative stress index than healthy controls, and serum prolidase activity positively correlated with pain and fatigue scores (Bozkurt et al., 2014). Moreover, PBMCs from FMS patients showed reduced levels of coenzyme Q_{10} (CoQ_{10}) and mtDNA contents, but high levels of mt reactive oxygen species and serum TNF (Cordero et al., 2013). Oxidative stress is present during tissue inflammation and also triggers MCs (Frossi et al., 2003). These findings may be relevant to our reports that MCs secrete extracellularly mtDNA, which has proinflammatory actions (Zhang et al., 2012), and that the mt uncoupling protein 2 (UCP2) inhibits MC secretion (Tagen et al., 2009).

Coenzyme Q_{10} (CoQ_{10}) is an essential electron carrier in the mt respiratory chain and a strong antioxidant. Low CoQ_{10} levels have been detected in patients with FMS (Iqbal et al., 2011). One study showed decreased CoQ_{10}, catalase, and ATP levels with increased level of lactoperoxidase in blood mononuclear cells from FMS patients as compared with normal controls; there was a significant negative correlation between these levels and headaches in FMS (Cordero et al., 2012a). Interestingly, CoQ_{10} deficiency has also been detected in depression and chronic fatigue, two common symptoms found in FMS patients, and both symptoms were markedly improved after CoQ_{10} supplementation (Maes et al., 2009).

Treatment

Unfortunately, there are no effective treatments of FMS presently available, but a number of drugs have been shown to reduce pain to variable extents. Management of FMS patients should integrate pharmacologic and nonpharmacologic approaches, while engaging patients as active participants in the process (Table 3) (Russell, 2008). However, a recent meta-analysis showed that multicomponent treatment is effective in the short term for improving key symptoms of FMS including pain, fatigue, depression, and quality of life, but disappointingly there is no evidence for a continued effect other than maintenance of physical fitness (Hauser et al., 2009a) (Figure 1).

TABLE 3
Treatment options

Nonpharmacologic
Cognitive behavioral therapy
Exercise
Qigong, tai-chi, yoga
Education
Pharmacologic
Amitriptyline
Cyclobenzaprine
Duloxetine
Gabapentin
Pregabalin
Complementary
CoQ10
l-carnitine
Luteolin

Nonpharmacologic Treatment. One study found that patients receiving educational intervention had significantly more improvement than controls and that the beneficial effects continued for 3 to 12 months after the sessions had ended (Goldenberg et al., 2004). A meta-analysis of randomized clinical trials using cognitive behavioral therapy showed it could reduce fear of pain and fear of activity (Bernardy et al., 2010); however, it provided little benefit as single modality except possibly in juvenile FMS (Bennett and Nelson, 2006). Comprehensive reviews of Chinese stress reduction exercise programs, such as tai-chi and qigong, reported improvement of symptoms in FMS patients but with little difference when compared with controls (Mist et al., 2013; Sawynok and Lynch, 2014).

Pharmacologic Treatment. The anticonvulsant drug pregabalin (PGB) has been approved by the U.S. Food and Drug Administration for the treatment of FMS (Hauser et al., 2011). PGB hyperpolarizes neurons and thus possibly lowers the firing threshold of sensory neurons, leading to reduced pain sensation. PGB is believed to reduce the magnitude of the enhanced pronociception process in FMS (Crofford et al., 2005; Arnold et al., 2008; Mease et al., 2008). Imaging studies using fMRI confirmed that PGB connects neuronal connectivity and biochemical aspects of pain in FMS (Harris et al., 2013; Kim et al., 2013).

A meta-analysis of five placebo-controlled randomized trials (four with PGB and one with gabapentin) consisting of 2918 patients with FMS showed that they significantly reduced pain and improved sleep and quality of life compared with placebo (Hauser et al., 2009c). However, a 2014 Cochrane review concluded that gabapentin (1200 mg or more per day) reduced pain intensity by 50% in only 37% of patients as compared with 21% on placebo (Moore et al., 2014).

A 2009 meta-analysis of 18 randomized trials using a variety of agents reported that antidepressants significantly improved pain, fatigue, depressed mood, sleep disturbance, and health-related quality of life (Hauser et al., 2009b). A 2014 systematic meta-analysis of six randomized trials involving 2249 patients using duloxetine (60 mg daily), a serotonin-norepinephrine reuptake inhibitor (SNRI), concluded that it was significantly more likely than placebo to reduce pain by at least 50% at 12 and 28 weeks (Lunn et al., 2014). The efficacy of duloxetine in patients with FMS was initially demonstrated in two multicenter trials of 12-week duration. In one trial, pain was reduced by at least 30% in a significantly greater proportion of patients receiving duloxetine (60 mg once or twice daily) compared with those taking placebo (Arnold et al., 2005). A longer-term benefit was demonstrated in a subsequent

6-month, multicenter, randomized, double-blind, placebo-controlled trial of 520 patients who were assigned to a single daily dose of either 60 mg or 120 mg of duloxetine or to placebo; duloxetine significantly reduced pain severity and improved mental fatigue in patients receiving duloxetine at 3 and 6 months (Russell et al., 2008).

Cyclobenzaprine is a muscle relaxant used to relieve skeletal muscle spasms and associated pain in acute musculoskeletal conditions. A randomized 8-week trial conducted with 36 patients showed that use of very low-dose cyclobenzaprine (1 to 4 mg at bedtime) significantly improved the symptoms of FMS, including pain, fatigue, and depression, compared with symptoms at baseline and with use of placebo (Moldofsky et al., 2011).

Amitriptyline (25–50 mg/day), a tricyclic antidepressant (TCA), was compared with duloxetine and milnacipran and was shown to be effective in reducing pain, sleep disturbance, and fatigue (Hauser et al., 2011). The apparent beneficial action of amitriptyline may be related to its ability to inhibit MC activation (Clemons et al., 2011).

Oxycodone was not found to be useful in patients with FMS (Gaskell et al., 2014). Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a synergistic beneficial effect on pain when combined with antidepressants or anticonvulsants (Abrams et al., 2002). However, NSAIDs decrease the antidepressant action of specific serotonin reuptake inhibitors (SSRIs), but not TCAs (Theoharides et al., 2011).

Complementary and Emerging Treatments. Nutritional supplementation is often used in FMS (Porter et al., 2010; Arranz et al., 2012), but the objective findings are limited. CoQ_{10} supplementation improved clinical symptoms in some FMS patients (Cordero et al., 2012a,b). One multicenter, double-blind, trial investigated the effect of 1000 mg oral and 500 mg of L-carnitine for 20 days and showed statistically significant benefits up to 10 weeks (Rossini et al., 2007).

Nutraceutical formulations containing the natural flavonoids quercetin and luteolin hold promise because they have anti-inflammatory, antioxidant, antiallergic, and antimicrobial actions (Middleton et al., 2000; Cazarolli et al., 2008). Flavonoids may exert anti-inflammatory actions via their ability to inhibit reactive oxygen or nitrogen compounds (Izzi et al., 2012), inhibiting MC activation (Kimata et al., 2000). The flavone luteolin can inhibit MCs (Asadi and Theoharides, 2012) and keratinocytes (Weng et al., 2014b). The luteolin structural analog tetramethoxyluteolin is more potent than luteolin (Weng et al., 2014a).

Flavonoids are safe (Kawanishi et al., 2005; Harwood et al., 2007). A recent clinical trial reported statistically significant benefits of a luteolin-containing dietary supplement in children with autism (Taliou et al., 2013), many of whom have "allergic-like" symptoms (Theoharides, 2013b), which implicates MC activation (Theoharides et al., 2012b). In fact, flavonoids have recently been discussed as a possible treatment of central nervous system disorders (Jager and Saaby, 2011; Grosso et al., 2013).

Conclusions and Future Directions

FMS is a complex disorder that is difficult to diagnose, and it needs a multimodal treatment approach (Garcia-Campayo et al., 2008). Many patients can achieve moderate symptom control, but pharmacologic treatments should be initiated in low doses with gradual titration upward to minimize side effects.

(Figure 1) Research should focus on the potential synergistic pathogenetic effect of neuropeptides such as CRH, nerve growth factor, and SP, and the possible role of episodic release of neurosensitizing molecules such as histamine, prostaglandin D2, IL-6, MCP-1, and TNF. Other potentially useful target molecules include IL-33, which has been considered an "alarmin" of tissue damage (Chan et al., 2012; Bessa et al., 2014). Available biologics, such as the TNF blockers etanercept and adalimumab, which are currently approved by the Food and Drug Administration for rheumatoid and psoriatic arthritis, should also be considered for FMS. CRH receptor-1, neurokinin-1, and TrKA antagonists should be considered, and luteolin and related flavonoids should be explored further (Figure 1).

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Theoharides, Tsilioni, Arbetman, Panagiotidou, Stewart, Gleason, Russell.

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Address correspondence to: Dr. Theoharis C. Theoharides, Ph.D., M.D, Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 136 Harrison Avenue, Suite J304, Boston, MA 02111. E-mail: theoharis.theoharides@tufts.edu