

REVIEW ARTICLE

FIBROMYALGIA - NEW CONCEPTS OF PATHOGENESIS AND TREATMENT

H.J. LUCAS, C.M. BRAUCH¹, L. SETTAS² and T.C. THEOHARIDES³

Special Clinic for FMS and CFS, Trier, Germany; ¹The Feller Pharmacy, Fell, Germany; ²Department of Rheumatology, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece; ³Departments of Pharmacology and Experimental Therapeutics, Internal Medicine and Biochemistry, Tufts University School of Medicine, Tufts-New England Medical Center, USA

Received November 29, 2005 – Accepted January 11, 2006

Fibromyalgia (FMS) is a debilitating disorder characterized by chronic diffuse muscle pain, fatigue, sleep disturbance, depression and skin sensitivity. There are no genetic or biochemical markers and patients often present with other comorbid diseases, such as migraines, interstitial cystitis and irritable bowel syndrome. Diagnosis includes the presence of 11/18 trigger points, but many patients with early symptoms might not fit this definition. Pathogenesis is still unknown, but there has been evidence of increased corticotropin-releasing hormone (CRH) and substance P (SP) in the CSF of FMS patients, as well as increased SP, IL-6 and IL-8 in their serum. Increased numbers of activated mast cells were also noted in skin biopsies. The hypothesis is put forward that FMS is a neuro-immunoendocrine disorder where increased release of CRH and SP from neurons in specific muscle sites triggers local mast cells to release proinflammatory and neurosensitizing molecules. There is no curative treatment although low doses of tricyclic antidepressants and the serotonin-3 receptor antagonist tropisetron, are helpful. Recent nutraceutical formulations containing the natural anti-inflammatory and mast cell inhibitory flavonoid quercetin hold promise since they can be used together with other treatment modalities

Fibromyalgia (FMS) is a disorder characterized by chronic diffuse muscle pain all over the body. Other associated symptoms include fatigue, as well as sleep, cognitive and emotional disturbances, leading to high disability and poor quality of life. Fibromyalgia occurs in about 3-13% of the population depending on the definition used and the population studied; it is more common in middle-age, especially in females (8:2). Other comorbid diseases include allergic reactions, chronic fatigue syndrome, migraines, interstitial cystitis (IC) and irritable bowel syndrome (IBS). About 30% of patients suffer also from depression or anxiety.

The most common presenting symptom is generalized muscle pain of gradual onset, often following illness or an operation. FMS may also present with chronic fatigue and it is mostly a diagnosis of exclusion (1). FMS can be confirmed in about 80% of patients. The Fibromyalgia Impact Questionnaire (FIQ) was developed at Oregon University (www.myalgia.com/FIQ/FIQ) (2). The “FibroFatigue” scale was developed to monitor symptoms during treatment (3). The criteria established by the American College of Rheumatology in 1990 require that widespread pain

Key words: corticotropin-releasing hormone, IL-6, IL-8, mast cells, quercetin

Mailing address:

T. C. Theoharides, Ph.D., M.D.
Department of Pharmacology and Experimental Therapeutics
Tufts University School of Medicine - 136 Harrison Avenue
Boston, MA 02111, USA
Tel: (617) 636-6866 - Fax: (617) 636-2456
E-mail: theoharis.theoharides@tufts.edu

0394-6320 (2006)

Copyright © by BIOLIFE, s.a.s.

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties

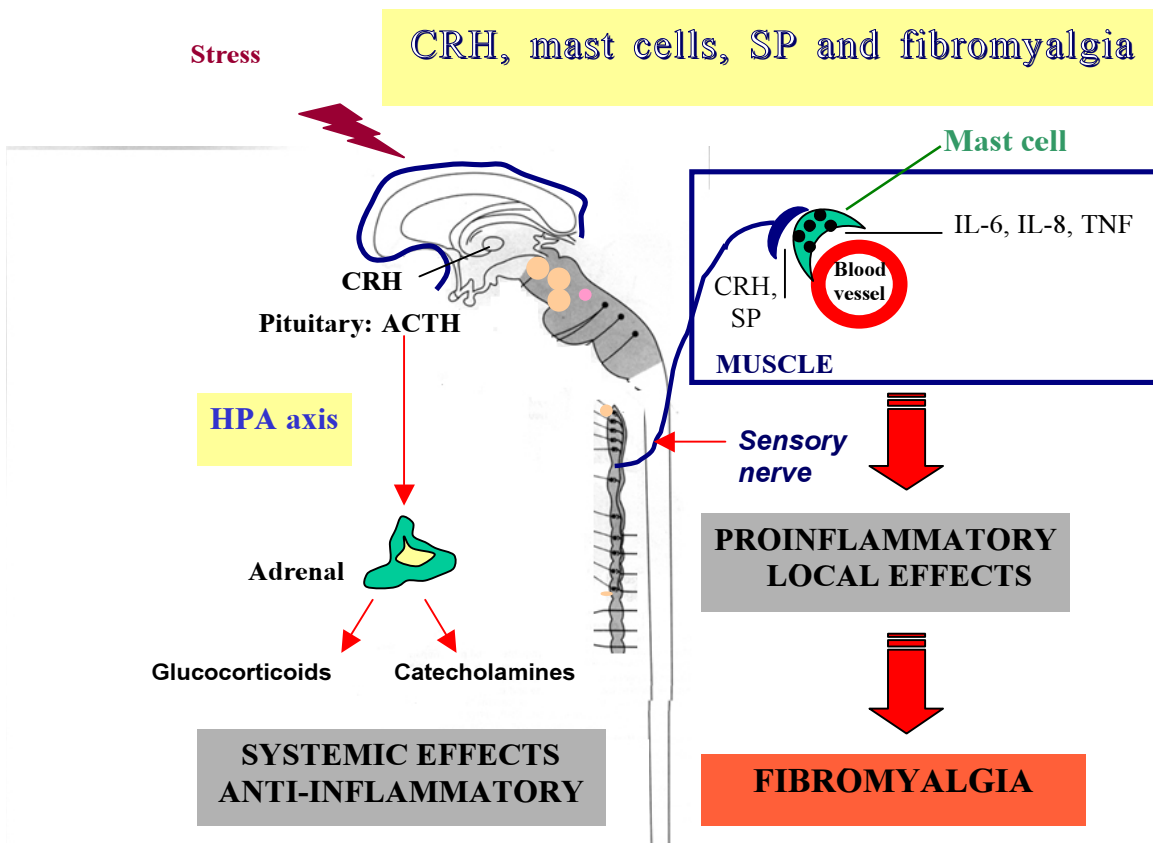


Fig. 1. The role of CRH, mast cells and SP in the pathogenesis of fibromyalgia. Local release of CRH and SP from nerve endings activates mast cells to release proinflammatory and neurosensitizing molecules, such as IL-6, IL-8 and TNF. These molecules could then further stimulate CRH release.

must be present in all four quadrants of the body, as well as the axial skeleton, together with 11/18 tender points (4). Recent studies have challenged the need for 11/18 tender points, especially in newly diagnosed patients, who may constitute as many as 60% of FMS patients. There may also be a continuum of tender point presentation, as the symptoms worsen over time in untreated patients. “Tender” points have to be differentiated from “trigger” points characterizing myofascial pain syndrome (5). FMS patients appear to have a generalized low pain threshold to a variety of stimuli. It is interesting that many FMS patients also complain of skin “sensitivity” without any evidence of skin erythema or the indication of atopic dermatitis.

It is quite intriguing that many FMS patients describe symptom onset after some psychological or inflammatory stressor (4). FMS is may not a distinct clinical entity (6); there may be at least one subgroup of patients in which stress factors were the most predictive indicator of pain (7). A recent FM

workshop tried to identify outcome measures and research objectives (8). Nevertheless, it is beneficial for patients to identify with a specific medical entity because it allows them to feel accepted and empowers them to seek treatment. Whether FMS is a distinct entity or not, it represents a significant burden for the health care system and requires better information for both physicians and patients.

Pathogenesis

Family proband studies have not produced any evidence of genetic factors (9). There is no precise pathogenesis at present. Some evidence indicates that there are common risk factors between FMS and psychiatric disorders. Most recent publications indicate that there is some abnormality with the hypothalamic-pituitary-adrenal (HPA) axis, with elevated activity of corticotropin-releasing-hormone (CRH) and substance P (SP) (10) that may not only affect the PHA axis, but other endocrine and immune processes (11).

In view of this finding and the observation that FMS symptoms commonly occur after a psychological or inflammatory stressor, FMS may be another inflammatory disorder exacerbated by stress (12). For instance, pain perception appeared to be enhanced by the concurrent presence of stressful events (13), and repeated sound stress was shown to increase inflammatory hyperalgesia in rats (14). One study showed an inverse relationship between serum levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and low pain scores, as well as with serum SP and sleep disturbances (15).

Other recent publications have reported elevated levels of cytokines in the serum of FMS patients (16). In one study, serum IL-1 and IL-6 levels were not different from controls but IL-8 was significantly elevated (17). Nevertheless, IL-6 was elevated in the supernatants from peripheral blood mononuclear cells from FMS patients (18). Moreover, injection of IL-6 produced excessive heart rate responses in FMS patients (19). Interestingly, young FMS patients with milder symptoms had significantly increased serum IL-8 levels (20).

These findings are of particular interest as mast cells have been proposed as the target of CRH outside the brain, leading to enhanced inflammatory processes that could contribute to pain (21). In fact, it was recently shown that human mast cells express functional CRH receptors, and CRH can induce selective release of vascular endothelial growth factor (VEGF), which could enhance inflammation (22). Once inflammation occurs, IL-1 could then stimulate mast cells to release IL-6 selectively (23). In other words, mast cells do not have to degranulate as is customarily seen in allergic reactions and their activation could, therefore, be missed in routine pathology of biopsies from FMS patients. Increased activated mast cells have been reported in association with IgG deposits in skin biopsies from FMS patients (24).

This hypothesis (Fig. 1) could also explain the skin sensitivity present in many FMS patients. For instance, skin biopsies from FMS patients had high IL-6 expression by RT-PCR (25) and trapezius muscle biopsies had more SP immunoreactivity (26). CRH content (27) and vascular permeability (28) increased in the skin or rats in response to stress, a process mimicked by

intradermal administration of CRH (29). CRH could be acting together with SP or other neurokinin-1 receptor agonists (30).

Treatment

There is neither effective nor standardized treatment for FMS (31). Low doses of tricyclic antidepressants, along with nonsteroidal anti-inflammatory drugs or tramadol, constitute the main therapeutic approach (32). Sublingual administration of interferon-alpha is reported to have considerable benefit (33). Recent studies indicate that local injection of the serotonin-3 receptor antagonist tropisetron could have analgesic effects in FMS (34). However, intravenous tropisetron appeared to help only 50% of FMS patient "responders" and in these treatments, significantly reduced serum SP (35). In general, the results are inconsistent and a number of adverse effects have been reported (36). The best approach would be a combination of pharmacologic treatment with behavioral and physical therapy (37).

Recent evidence indicates that a formulation containing the naturally occurring flavonoid quercetin could have considerable benefit in neuro-inflammatory conditions, such as FMS (38). Flavonoids have strong anti-inflammatory and cytoprotective actions (39) and are particularly potent inhibitors of cytokine release from human mast cells (40). One particular formulation (www.algonot.com, www.algonot.de) (Algonot-plus®) contains quercetin with chondroitin sulfate that was shown to also inhibit mast cell secretion (41) in a formulation with olive kernel extract that increases absorption of the active ingredients (42).

Future research should focus on CRH-mast cell interactions and CRH receptor expression in skin or muscle biopsies from FMS patients. Clinical studies could use CRH receptor antagonists (21) or mast cell activation inhibitors, such as Algonot-plus®.

ACKNOWLEDGEMENTS

Aspects of this work were supported by Theta Biomedical Consulting and Development Co., Inc. (Brookline, MA). We thank Ms. Jessica Christian for her word processing skills.

REFERENCES

1. **Bates D.W., W. Schmitt, D. Buchwald, N.C. Ware, J. Lee, E. Thoyer, R.J. Kornish and A.L. Komaroff.** 1993. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. *Arch. Intern. Med.* 153:2759.
2. **Bennett R.** 2005. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. *Clin. Exp. Rheumatol.* 23:(S):154.
3. **Zachrisson O., B. Regland, M. Jahreskog, M. Kron and C.G. Gottfries.** 2002. A rating scale for fibromyalgia and chronic fatigue syndrome (the FibroFatigue scale). *J. Psychosom. Res.* 52:501.
4. **Bennett R.** 2004. Fibromyalgia: present to future. *Curr. Pain Headache Rep.* 8:379.
5. **Pongratz D.E. and M. Sievers.** 2000. Fibromyalgia-symptom or diagnosis: a definition of the position. *Scand. J. Rheumatol.* 113(S):3.
6. **Rau C.L. and I.J. Russell.** 2000. Is fibromyalgia a distinct clinical syndrome? *Curr. Rev. Pain* 4:287.
7. **Thieme K., C. Spies, P. Sinha, D.C. Turk and H. Flor.** 2005. Predictors of pain behaviors in fibromyalgia syndrome. *Arthritis Rheum.* 53:343.
8. **Mease P.J., D.J. Clauw, L.M. Arnold, D.L. Goldenberg, J. Witter, D.A. Williams, L.S. Simon, C.V. Strand, C. Bramson, S. Martin, T.M. Wright, B. Littman, J.F. Wernicke, R.M. Gendreau and L.J. Crofford.** 2005. Fibromyalgia syndrome. *J. Rheumatol.* 32:2270.
9. **Arnold L.M., J.I. Hudson, E.V. Hess, A.E. Ware, D.A. Fritz, M.B. Auchenbach, L.O. Starck and P.E. Keck, Jr.** 2004. Family study of fibromyalgia. *Arthritis Rheum.* 50:944.
10. **Mease P.** 2005. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *J. Rheumatol.* 75(S):6.
11. **Neeck G.** 2002. Pathogenic mechanisms of fibromyalgia. *Ageing Res. Rev.* 1:243.
12. **Theoharides T.C. and D.E. Cochrane.** 2004. Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J. Neuroimmunol.* 146:1.
13. **Van H.B. and U.T. Egle.** 2004. Fibromyalgia: a stress disorder? Piecing the biopsychosocial puzzle together. *Psychother. Psychosom.* 73:267.
14. **Khasar S.G., P.G. Green and J.D. Levine.** 2005. Repeated sound stress enhances inflammatory pain in the rat. *Pain* 116:79.
15. **Schwarz M.J., M. Spath, H. Muller-Bardorff, D.E. Pongratz, B. Bondy and M. Ackenheil.** 1999. Relationship of substance P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients. *Neurosci. Lett.* 259:196.
16. **Mullington J.M., D. Hinze-Selch and T. Pollmacher.** 2001. Mediators of inflammation and their interaction with sleep: relevance for chronic fatigue syndrome and related conditions. *Ann. N.Y. Acad. Sci.* 933:201.
17. **Gur A., M. Karakoc, S. Erdogan, K. Nas, R. Cevik and A.J. Sarac.** 2002. Regional cerebral blood flow and cytokines in young females with fibromyalgia. *Clin. Exp. Rheumatol.* 20:753.
18. **Wallace D.J., M. Linker-Israeli, D. Hallegua, S. Silverman, D. Silver and M.H. Weisman.** 2001. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. *Rheumatology* 40:743.
19. **Torpy D.J., D.A. Papanicolaou, A.J. Lotsikas, R.L. Wilder, G.P. Chrousos and S.R. Pillemer.** 2000. Responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to interleukin-6: a pilot study in fibromyalgia. *Arthritis Rheum.* 43:872.
20. **Gur A., M. Karakoc, K. Nas, Remzi, Cevik, A. Denli and J. Sarac.** 2002. Cytokines and depression in cases with fibromyalgia. *J. Rheumatol.* 29:358.
21. **Theoharides T.C., J.M. Donelan, N. Papadopoulou, J. Cao, D. Kempuraj and P. Conti.** 2004. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol. Sci.* 25:563.
22. **Cao J., N. Papadopoulou, D. Kempuraj, W.S. Boucher, K. Sugimoto, C.L. Cetrulo and T.C. Theoharides.** 2005. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor (VEGF). *J. Immunol.* 174:7665.
23. **Kandere-Grzybowska K., R. Letourneau, W. Boucher, J. Bery, D. Kempuraj, S. Poplawski, A. Athanassiou and T.C. Theoharides.** 2003. IL-1 induces vesicular secretion of IL-6 without degranulation

- from human mast cells. *J. Immunol.* 171:4830.
24. **Enestrom S., A. Bengtsson and T. Frodin.** 1997. Dermal IgG deposits and increase of mast cells in patients with fibromyalgia-relevant findings or epiphenomena? *Scand. J. Rheumat.* 26:308.
 25. **Salemi S., J. Rethage, U. Wollina, B.A. Michel, R.E. Gay, S. Gay and H. Sprott.** 2003. Detection of interleukin 1beta (IL-1beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. *J. Rheumatol.* 30:146.
 26. **De Stefano R., E. Selvi, M. Villanova, E. Frati, S. Manganeli, E. Franceschini, G. Biasi and R. Marcolongo.** 2000. Image analysis quantification of substance P immunoreactivity in the trapezius muscle of patients with fibromyalgia and myofascial pain syndrome. *J. Rheumatol.* 27:2906.
 27. **Lytinas M., D. Kempuraj, M. Huang, W. Boucher, P. Esposito and T.C. Theoharides.** 2003. Acute stress results in skin corticotropin-releasing hormone secretion, mast cell activation and vascular permeability, an effect mimicked by intradermal corticotropin-releasing hormone and inhibited by histamine-1 receptor antagonists. *Int. Arch. Allergy Immunol.* 130:224.
 28. **Singh L.K., X. Pang, N. Alexacos, R. Letourneau and T.C. Theoharides.** 1999. Acute immobilization stress triggers skin mast cell degranulation via corticotropin releasing hormone, neurotensin and substance P: A link to neurogenic skin disorders. *Brain Behav. Immunity* 13:225.
 29. **Theoharides T.C., L.K. Singh, W. Boucher, X. Pang, R. Letourneau, E. Webster and G. Chrousos.** 1998. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its pro-inflammatory effects. *Endocrinology* 139:403.
 30. **Kandere-Grzybowska K., D. Gheorghe, J. Priller, P. Esposito, M. Huang, N. Gerard and T.C. Theoharides.** 2003. Stress-induced dura vascular permeability does not develop in mast cell-deficient and neurokinin-1 receptor knockout mice. *Brain Res.* 980:213.
 31. **Millea P.J. and R.L. Holloway.** 2000. Treating fibromyalgia. *Am. Fam. Physician* 62:1575.
 32. **Dadabhoj D. and D.J. Clauw.** 2005. Fibromyalgia: progress in diagnosis and treatment. *Curr. Pain Headache Rep.* 9:399.
 33. **Russell I.J., G.A. Vipraio, J.E. Michalek, F.E. Craig, Y.K. Kang and A.B. Richards.** 1999. Lymphocyte markers and natural killer cell activity in fibromyalgia syndrome: effects of low-dose, sublingual use of human interferon-alpha. *J. Interferon Cytokine Res.* 19:969.
 34. **Muller W. and T. Stratz.** 2004. Local treatment of tendinopathies and myofascial pain syndromes with the 5-HT3 receptor antagonist tropisetron. *Scand. J. Rheumatol.* 119(S):44.
 35. **Stratz T., B. Fiebich, U. Haus and W. Muller.** 2004. Influence of tropisetron on the serum substance P levels in fibromyalgia patients. *Scand. J. Rheumatol.* 119(S):41.
 36. **Spath M.** 2002. Current experience with 5-HT3 receptor antagonists in fibromyalgia. *Rheum. Dis. Clin. North Am.* 28:319.
 37. **Baker K. and A. Barkhuizen.** 2005. Pharmacologic treatment of fibromyalgia. *Curr. Pain Headache Rep.* 9:301.
 38. **Theoharides T.C. and L. Bielory.** 2004. Mast cells and mast cell mediators as targets of dietary supplements. *Ann. Allergy Asthma Immunol.* 93:S24.
 39. **Middleton E. Jr., C. Kandaswami and T.C. Theoharides.** 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. *Pharmacol. Rev.* 52:673.
 40. **Kempuraj D., B. Madhappan, S. Christodoulou, W. Boucher, J. Cao, N. Papadopoulou, CL. Cetrulo and T.C. Theoharides.** 2005. Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. *Br. J. Pharmacol.* 145:934.
 41. **Theoharides T.C., P. Patra, W. Boucher, R. Letourneau, D. Kempuraj, G. Chiang, S. Jeudy, L. Hesse and A. Athanasiou.** 2000. Chondroitin sulfate inhibits connective tissue mast cells. *Br. J. Pharmacol.* 131:1039.
 42. **Theoharides T.C.** 2003. Dietary supplements for arthritis and other inflammatory conditions: key role of mast cells and benefit of combining anti-inflammatory and proteoglycan products. *Eur. J. Inflamm.* 1:1.