Mod Rheumatol (2007) 17:179–184
DOI 10.1007/s10165-007-0563-1

REVIEW ARTICLE

Kayo Masuko · Hiroshi Nakamura

Functional somatic syndrome: how it could be relevant to rheumatologists

Received: December 18, 2006 / Accepted: March 19, 2007

Abstract Functional somatic syndrome (FSS) is defined as a group of related syndromes characterized more by symptoms, suffering, and disability than by structural or functional abnormality. The diagnostic criteria and/or symptoms of FSS often overlap, and co-morbidity is commonly found among the diseases of FSS. For example, patients with irritable bowel syndrome often suffer from chronic pain, and a high percentage of co-morbidity can be found with fibromyalgia. Accumulating evidence indicates the presence of visceral and somatic hyperalgesia in FSS as a common feature, and the central sensitization mechanism has been suggested to play an important role in the pathophysiology of FSS. In the present article, the authors introduce the concept of FSS focusing on its possible relevance to rheumatology in terms of pain perception. A possible implication of mast cells and proteinase-activated receptor-2 (PAR-2) in FSS is also reviewed.

Key words Functional somatic syndrome · Mast cells · Pain

Introduction

As rheumatologists, each of us often comes across patients with intractable chronic pain. It may be caused by systemic or local inflammation which can be manifested, e.g. by redness, swelling, fever, elevated levels of erythrocyte sedimentation rate, and/or C-reactive protein levels. On the other hand, there is a group of "painful" situations which *cannot* be, or has not been proved to be, attributed to any detectable "inflammation" with biochemical, roentgenological, or immunological abnormalities. Such "chronic pain" may accompany an array of autonomic symptoms, and more importantly, it seems to be enhanced if the patient is exposed to "stressful" conditions.

Such a symptom that is exacerbated upon stress, but cannot be attributable to known structural disorders, is not only limited to musculoskeletal pain but may also embrace abdominal pain, chronic fatigue, etc.. In this regard, a relatively new concept of "functional somatic syndrome" (FSS) has arisen.

K. Masuko (✉)
Department of Bioregulation and Proteomics, Institute of Medical Science. St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki 216-8512, Japan
Tel. +81-44-977-8111; Fax +81-44-976-9319
e-mail: kmarianna@mac.com

H. Nakamura
Department of Joint Disease and Rheumatism, Nippon Medical School, Tokyo, Japan

Functional somatic syndrome

The term "functional somatic syndrome" has been defined as one that, after appropriate medical assessment, cannot be explained in terms of a conventionally defined medical disease,[1] or refers to several related syndromes that are characterized more by symptoms, suffering, and disability than by disease-specific, demonstrable abnormalities of structure or function.[2] FSS is generally supposed to be categorized into disease entities in which psychological or emotional distress elicits at least a part of the physical manifestation or the complaint.

According to the concept, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic fatigue syndrome (CFS), and fibromyalgia (FMS) are generally included as representative diseases of FSS. Moreover, there are several clinical conditions or diseases with so-called medically unexplained symptoms (Table 1). In fact, Sharpe[3] described each medical specialty as having at least one of these medically unexplained or functional syndromes"

Wessely et al.[1] hypothesized and reviewed the features of FSS as follows:

1. There is substantial overlap in the case definitions of specific FSS.
2. Patients with one FSS frequently meet criteria for others.

Table 1. Functional somatic syndromes by speciality[1]

Gastroenterology[a]	Irritable bowel syndrome, non-ulcer dyspepsia
Gynecology	Premenstrual syndrome, chronic pelvic pain
Rheumatology	Fibromyalgia
Cardiology	Atypical or non-cardiac chest pain
Respiratory medicine	Hyperventilation syndrome
Infectious diseases	Chronic (postviral) fatigue syndrome
Neurology	Tension headache
Dentistry	Temporomandibular joint dysfunction, atypical facial pain
Ear, nose, and throat	Globus syndrome
Allergy	Multiple chemical sensitivity

[a]Should review more recent updates on Rome III diagnostic criteria for functional bowel disorders and functional abdominal pain[24]

3. Patients with different FSS share non-symptom characteristics.
4. All FSS respond to the same therapies.

Thus, it is suggested that the diseases included in FSS have much in common. Indeed, the different diseases or conditions often coexist in the same patient, and the diagnostic criteria and/or symptoms frequently overlap.[3–5] For example, patients with non-cardiac chest pain were found more likely to have IBS than patients with cardiac chest pain.[6] Another example is that symptom worsening during menses in IBS can falsely suggest a gynecologic explanation for "chronic pelvic pain".[4] In addition, it is widely recognized that patients with CFS often have accompanying chronic musculoskeletal pain, as well as FMS (reviewed in Meeus et al.[7]),because the presence of muscle pain and noninflammatory multi-joint pain are included in the diagnostic criteria of CFS.[8]

The hypothalamic–pituitary–adrenal axis in FSS

As symptoms of FSS often deteriorate or are even triggered by various physical or psychological/emotional stresses, the possible implication or stress response in FSS has been widely investigated.

In this regard, it has been widely accepted that stress response in vivo is essentially regulated via the hypothalamic–pituitary–adrenal (HPA) axis using an array of hormonal responses. Briefly, a stressor is first recognized by the hypothalamus, followed by the activation of neurons that produce corticotropin-releasing hormone (CRH). This leads to the release of adrenocorticotropic hormone (ACTH) from the pituitary and cortisol from the adrenal cortex. This is followed by the release of an array of catecholamines and neurotransmitters; then the secondary mediators are also activated.

Considerable evidence has demonstrated that a dysregulation of the HPA axis plays an essential role in the pathophysiology of diseases of FSS.[9–11] For example, dysregulation of HPA axis activity is reported in CFS, which is believed to be caused by impaired drive by the central nervous system.[10] Specifically, Gaab et al.[12] reported that patients with CFS show reduced baseline levels of ACTH and significantly lower ACTH response after psychosocial stress tests, exercise tests, and insulin tolerance tests, despite a lack of significant difference of cortisol response. In other studies, low CRH/cortisol level and upregulation of the serotonergic system have been reported in CFS.[13,14]

However, abnormalities of the HPA axis or central nervous system alone are not sufficient to explain the symptoms in CFS,[14,15] and it is unclear whether the changes of the HPA axis are primary or secondary phenomena to the behavioral changes in FSS.[15–18] A recent report by Bomholt et al.[19] reported that an animal model of neuropathic pain, which exerts marked mechanical allodynia and hyperalgesia (that might be an animal model of FMS), also showed normal function of the basal HPA axis.

Pain perception in FSS

Irritable bowel syndrome: co-morbidity with FMS

Among the FSS, it is well recognized that symptoms of IBS and FMS often coexist. Co-morbidity between IBS and FMS has been assumed: for example, that 70% of patients with primary FMS had IBS, and 65% of IBS patients had FMS in a study by Veale et al.[20] on four patient groups with 20 patients in each group.[20] In a large population study in the United States, Cole et al.[21] estimated that the prevalence odds ratio (OR) for FMS in IBS patients was 1.8 times greater in the IBS cohort relative to the comparison cohort. As per Sperber et al.,[22] 25 of the 79 IBS patients studied (31.6%) had FMS, whereas only 4.2% of matched controls had FMS. The prevalence of IBS among the FMS patients in their study was 32%. In addition, they showed that IBS patients had significantly more tender points than the controls. A more recent report by Whitehead et al.[23] showed that FMS had the best-documented association with IBS (median of 49% of FMS patients had IBS), followed by CFS (51%): the strong co-morbidity suggested a common important feature to the disease expression, a part of which is likely to be psychological.

It has been assumed that IBS shows altered visceral perception,[24] whereas FMS is a syndrome of altered somatic perception.[25] However, evidence indicates that the alteration of pain perception in IBS is not gastrointestinal specific. In a report by Verne et al.,[26] IBS patients demonstrated

cutaneous allodynia/hyperalgesia to thermal pain applied to the hand and foot. The finding suggested coexistence of visceral and cutaneous hyperalgesia, i.e., a central hyperalgesic state in the IBS patients.[26,27] The cutaneous hypersensitivity in IBS patients was also supported by other studies.[26,28,29] Price et al.[29] suggested that IBS patients might develop widely distributed hyperalgesia, possibly related to chronic nociceptive input from the rectum and colon.[29]

Chang et al.,[30] using positron emission tomography, reported that IBS + FMS patients had a higher response to somatic stimuli significantly higher than IBS patients without FMS. The finding was supported by a greater increase of regional cerebral blood flow (rCBF) to somatic stimuli in IBS + FMS patients, whereas IBS patients showed greater rCBF response to visceral stimuli.[30]

Nevertheless, in contrast, there are reports that suggest somatic hypoalgesia in IBS.[31–33] Recently, Iovino et al.,[32] using transcutaneous electrical nerve stimulation (TENS), reported that IBS patients had altered sensitivity to electrical stimuli compared with higher thresholds (somatic hypoalgesia). However, they also showed that the co-morbidity of FMS in the IBS patients influenced the perception of somatic stimuli, with increased perception of the stimuli (lower threshold). Thus, the physiological significance of pain perception in IBS and FSS needs to be further clarified, comparing the experimental protocols, and also referring the co-morbidity among FSS diseases in each patient. In fact, somatic hypersensitivity has also been reported in another FSS, i.e., interstitial cystitis.[34]

Central sensitization

As discussed earlier, several reports suggest the "central sensitization" mechanism as a dominant pathology in the chronic widespread pain in FSS.[27,35–37] Central sensitization is defined as "an augmentation of responsiveness of central pain-signaling neurons to input from low-threshold mechanoreceptors," and it has been suggested to result in somatization and activity avoidance, e.g., in CFS.[38] Of note, central sensitization is also important in itch processing in addition to pain control.[39]

Petrenko et al.[40,41] defined central sensitization as "the state where dorsal horn excitability is increased and, as a consequence, its response to sensory input is facilitated," which would lead to hyperalgesia, and suggested a role of the ionotropic membrane receptor *N*-methyl-D-aspartate (NMDA) in central sensitization. In this context, a low dose of NMDA antagonist was applied in a subgroup of FMS;[42] however, the significance of NMDA receptors in the pathogenesis of FMS is still controversial.[43]

Pain, FSS, and depression?

It has been often recognized that patients with depression frequently report pain and fatigue. In fact, studies indicated that the percentages of patients with psychiatric disorders who complained of aches and pains were high.[44]

Conversely, it has been reported that FSS often co-morbids with psychiatric disorders such as depression and anxiety. For example, as for FMS, a recent report by Arnold et al.[45] calculated the co-occurrence OR (the odds of a lifetime co-morbid DSM-IV disorder in an individual with FMS divided by the odds of a lifetime co-morbid disorder in an individual without FMS) and showed that there was a substantial lifetime psychiatric co-morbidity in FMS patients, for example to bipolar disorder (OR = 153) or with anxiety (OR = 6.7), suggesting an underlying pathophysiologic link with FMS and psychiatric disorders. On the other hand, a population-based study in Sweden enrolling 44 897 individuals also revealed co-occurrence in cases with chronic widespread pain for depressive symptoms, suggesting an involvement of familial factors.[46]

In this regard, serotonergic (5-HT) and noradrenergic (NE) pathways have been suggested to play important roles. Specifically, 5-HT and NE pathways ascending from the brain stem into the brain would mediate emotional and physical functions, whereas descending 5-HT and NE pathways down the spinal cord regulate painful symptoms of depression by suppressing painful input.[44,47] Thus, the possible therapeutic efficacy of antidepressants to the painful condition via the 5-HT and NE systems has been suggested.[44,48]

Gormsen et al.[49] applied electroconvulsive therapy (ECT) to patients with severe depression and compared pain thresholds during and after ECT. The results demonstrated significant improvement of Hamilton depression scores without significant change of pain thresholds after ECT in the patients, suggesting that depression and pain processing might not be directly mediated by a simple common pathway. On the other hand, a recent article by Usui et al.[50] applied the therapy to FMS patients and reported that ECT improved severe pain in FMS. In the latter study,[50] pain was assessed using tender point examination and the visual analogue scale in FMS patients, most of whom were taking antidepressants, whereas the study by Gormsen tested pressure pain detection threshold and pressure pain tolerance threshold with a pressure algometer and also performed the cold pressor test for the assessment of pain tolerance in patients with depression when compared with controls. Thus, the essential effect on pain perception of ECT and its clinical indication in FSS should be further discussed comparing the protocols utilized in the studies.

Giesecke et al.[51] analyzed quantitative sensory testing and neural responses to painful stimuli in FMS patients using functional magnetic resonance imaging (fMRI). The results showed that the level of symptoms of depression or the presence of major depressive disorders did not associate with either subjective pain sensitivity or neuronal activations in regions of the brain that process the sensory-discriminative dimension of pain; however, they were associated with neuronal activation in brain regions implicated in processing the motivational-affective dimension of pain (i.e., amygdalae and anterior insula). Thus, it is suggested that the pain in FMS might be regulated by at least two dimensions and that the effects of antidepressants on pain may be independent of mood.[51]

Hypothesis: involvement of mast cells/PAR2-pathway in hyperalgesia of FSS?

In addition to the previously discussed mechanisms, we hypothesize that mast cells play an important role in the hyperalgesic state in FSS, at least in part, through the proteinase-activated receptor-2 (PAR-2) pathway.

The possible relationship between mast cells and hyperalgesia has been documented, and some of the reports focused on its potent implication in the pathophysiology of diseases in the entity of FSS. For example, the levels of mast cell-derived serine protease tryptase in 24-h urine samples were elevated in patients with IBS and interstitial cystitis.[52,53] In a report by Barbara et al.,[54] colonic mucosa of IBS patients were found to be occupied by mast cells; there was a 150% increase in the number of degranulating mast cells, with increased mucosal content of tryptase, in IBS patients compared with controls. The increase in mast cell numbers was also noted in the jejunum of diarrhea-prone IBS patients.[55] In addition to tryptase, an increase of histamine release in IBS has been also reported.[56] Further, using a rat model of IBS, La et al.[57] reported that pretreatment of a mast cell stabilizer doxantrazole reduced not only the degradation rate of mucosal mast cells but also visceral hypersensitivity to rectal distention. Zuo et al.[58] showed that stabilization of mast cells with sodium cromoglycate reduced cellular recruitment to the injured nerve and suppressed the development of hyperalgesia, proposing the importance of mast cells and their mediators in neuropathic pain.[58]

PAR-2 is a G-protein coupled receptor to which proteases including trypsin and mast cell tryptase would bind followed by activation.[59] PAR-2 is known to be widely expressed in various cells and tissues, including intestinal tract, airway, cardiovascular system, pancreas, and epidermis; and has been shown to exert a variety of bioactivity (reviewed by Macfarlane et al.[60]). In 2001, interesting reports on the role of PAR-2 in hyperalgesia were presented.[61,62] Kawabata et al.[61] utilized intraplanter injection of PAR-2 agonist peptide in rats, and demonstrated that the PAR-2 activation by exogenously added agonist elicited thermal hyperalgesia and nociceptive behavior. In the study of Vergnolle et al.,[62] the authors also demonstrated upregulation of spinal Fos expression by the PAR-2 agonists. In addition, they showed that the thermal and mechanical hyperalgesia in PAR-2-deficient mice which were injected with a mast cell activator compound 48/80 were markedly reduced relative to wild-type controls, suggesting a PAR-2-mediated pathway of hyperalgesia.

The distinct role of mast cell–tryptase–PAR-2 interaction in IBS has been postulated,[63–65] focusing on its role in colonic hypersensitivity. In fact, expression of PAR-2 in the gastrointestinal tract has been reported.[59] More specifically, Coelho et al.[63] demonstrated that intracolonic injection of the PAR-2 agonist peptide (SLIGRL-NH2 for rat) increased rectal hyperalgesia and also caused increased intestinal permeability but did not cause inflammation. Kawao et al.[66] also reported that the intracolonic administration of SLIGRL-NH2 facilitated the capsaicin-evoked visceral nociception and augmented the capsaicin-evoked referred hyperalgesia, suggesting the role of PAR-2 expressed in the colonic luminal surface in the sensitization.[66] More recently, Cenac et al.[67] demonstrated that colonic biopsy samples from IBS patients released increased levels of proteolytic activity compared with asymptomatic controls, and more interestingly, that the biopsy supernatants elicited thermal and mechanical hyperalgesia and allodynia in PAR-$2^{+/+}$ mice, but not in PAR-$2^{-/-}$ mice, establishing the role of PAR-2 activation in visceral pain in IBS.[67]

On the other hand, PAR-2 is also suggested to play a role in cutaneous nociception: the PAR-2 agonistic peptide was reported to excite a part of C-fiber nociceptors in experiments using rat skin-saphenous nerve preparation.[68] In addition, Moorman et al.[69] reported that human cutaneous mast cells express PAR-2, which was functional because PAR-2 agonists induced histamine release; and that PAR-2 co-localized with tryptase in the majority of human skin mast cells. In this regard, it has been shown that skin biopsy samples from FMS patients had a higher mean number of mast cells compared with control samples.[70] Because positive signals of inflammatory cytokines such as of IL-1 or TNF-α were also detected in skin tissues of a subset of FMS patients,[71] it is conceivable that PAR-2 expressed in skin of FMS would be activated by local inflammatory factors including mast cell-derived mediators, leading to cutaneous inflammation and hyperalgesia. Although it may be very difficult to obtain enough skin samples from FSS patients, further investigation on the expression of PAR-2 in hyperalgesic skin would help more detailed understanding.

Considering the findings altogether, it would be hypothesized that a part of the pathophysiology of visceral and/or somatic hyperalgesia in FSS are derived by signaling through PAR-2, and activated by mast cell mediators such as tryptase. In addition, mast cell mediators other than tryptase (e.g. histamine, serotonin, and substance P) themselves would also contribute to the pathophysiology of FSS more directly.[53,55,72] As Theoharides[73] recently reviewed, a subset of FSS diseases may be set as "neuroinflammatory syndromes," in which activated mast cells might be playing an essential role. As Vergnolle et al.[62] suggested, proteinase inhibitors and PAR-2 antagonists might be anti-nociceptive drugs, e.g., a new analgesic; however, as they also mentioned in the same article, the clinical efficacy remains to be determined because the pain is regulated by multiple factors and PAR-2 is widely expressed in many tissues exerting a variety of bioactivity. The clinical application of PAR-2-targeted strategy should therefore be further investigated.

Concluding remarks

Although the concept of FSS might not have been completely established, studies from FSS lead us to understand that there would be a failure of pain processing in FSS patients involving, e.g., 5-HT and NE systems. In particular, a possible involvement of mast cells in FSS has been

speculated. There has been, nevertheless, no established biomarker(s) to make a definite diagnosis of FSS including FMS to date; therefore it might be over- or under-diagnosed if the diagnosis is derived solely from patient complaints without examination and assessment.

Thus, rheumatologists should, at first, recognize the current concept of FSS along with other "inflammatory" pain, and next, confront the painful situation exploring possible immunological, biochemical, physiological as well as psychological, or social factors, which are altogether giving birth to the long-standing pain within the individual patient. In addition, it might be helpful to establish a concept of "functional pain" syndrome on rheumatologic bases as Rome III diagnostic criteria help gastroenterologists to diagnose the functional abdominal symptoms. The diagnosis must be made after detailed clinical surveillance, and rheumatologists should consult psychiatrists or specialists of the respective field if psychological and/or co-morbid problems underlie the complaint of pain. Substantial pain should not be treated with prejudice either by the patients or by the doctors in charge.

References

1. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354(9182):936–9.
2. Barsky A, Borus J. Functional somatic syndrome. Ann Intern Med 1999;130:910–21.
3. Sharpe M, Carson A. "Unexplained" somatic symptoms, functional syndromes, and somatization: do we need a paradigm shift? Ann Intern Med 2001;134(9 Pt 2):926–30.
4. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut 1999;45 Suppl 2:II43–7.
5. Van Houdenhove B, Egle UT. Fibromyalgia: a stress disorder? Piecing the biopsychosocial puzzle together. Psychother Psychosom 2004;73(5):267–75.
6. Scott A, Mihailidou A, Smith R, Kellow J, Jones M, Lorang C, et al. Functional gastrointestinal disorders in unselected patients with non-cardiac chest pain. Scand J Gastroenterol 1993;28(7):585–90.
7. Meeus M, Nijs J, Meirleir KD. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. Eur J Pain 2006;11:377–386.
8. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121(12):953–9.
9. Crofford LJ. The hypothalamic-pituitary-adrenal stress axis in fibromyalgia and chronic fatigue syndrome. Z Rheumatol 1998;57 Suppl 2:67–71.
10. 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;840:684–97.
11. Neeck G, Crofford LJ. Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome. Rheum Dis Clin North Am 2000;26(4):989–1002.
12. Gaab J, Huster D, Peisen R, Engert V, Heitz V, Schad T, et al. Hypothalamic-pituitary-adrenal axis reactivity in chronic fatigue syndrome and health under psychological, physiological, and pharmacological stimulation. Psychosom Med 2002;64(6):951–62.
13. Bradley LA, McKendree-Smith NL, Alarcon GS. Pain complaints in patients with fibromyalgia versus chronic fatigue syndrome. Curr Rev Pain 2000;4(2):148–57.
14. Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006;367(9507):346–55.
15. Cho HJ, Skowera A, Cleare A, Wessely S. Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. Curr Opin Psychiatry 2006;19(1):67–73.
16. Parker AJ, Wessely S, Cleare AJ. The neuroendocrinology of chronic fatigue syndrome and fibromyalgia. Psychol Med 2001;31(8):1331–45.
17. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. Endocr Rev 2003;24(2):236–52.
18. Inder WJ, Prickett TC, Mulder RT. Normal opioid tone and hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome despite marked functional impairment. Clin Endocrinol (Oxf) 2005;62(3):343–8.
19. Bomholt SF, Mikkelsen JD, Blackburn-Munro G. Normal hypothalamo-pituitary-adrenal axis function in a rat model of peripheral neuropathic pain. Brain Res 2005;1044(2):216–26.
20. Veale D, Kavanagh G, Fielding JF, Fitzgerald O. Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process. Br J Rheumatol 1991;30(3):220–2.
21. Cole JA, Rothman KJ, Cabral HJ, Zhang Y, Farraye FA. Migraine, fibromyalgia, and depression among people with IBS: a prevalence study. BMC Gastroenterol 2006;6:26.
22. Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M, et al. Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. Am J Gastroenterol 1999;94(12):3541–6.
23. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology 2002;122(4):1140–56.
24. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006;130(5):1377–90.
25. Lubrano E, Iovino P, Tremolaterra F, Parsons WJ, Ciacci C, Mazzacca G. Fibromyalgia in patients with irritable bowel syndrome: an association with the severity of the intestinal disorder. Int J Colorectal Dis 2001;16(4):211–5.
26. Verne GN, Robinson ME, Price DD. Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. Pain 2001;93(1):7–14.
27. Verne GN, Price DD. Irritable bowel syndrome as a common precipitant of central sensitization. Curr Rheumatol Rep 2002;4(4):322–8.
28. Verne GN, Himes NC, Robinson ME, Gopinath KS, Briggs RW, Crosson B, et al. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. Pain 2003;103(1, 2):99–110.
29. Price DD, Zhou Q, Moshiree B, Robinson ME, Nicholas Verne G. Peripheral and central contributions to hyperalgesia in irritable bowel syndrome. J Pain 2006;7(8):529–35.
30. Chang L, Berman S, Mayer EA, Suyenobu B, Derbyshire S, Naliboff B, et al. Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia. Am J Gastroenterol 2003;98(6):1354–61.
31. Cook IJ, van Eeden A, Collins SM. Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. Gastroenterology 1987;93(4):727–33.
32. Iovino P, Tremolaterra F, Consalvo D, Sabbatini F, Mazzacca G, Ciacci C. Perception of electrocutaneous stimuli in irritable bowel syndrome. Am J Gastroenterol 2006;101(3):596–603.
33. Whitehead WE, Holtkotter B, Enck P, Hoelzl R, Holmes KD, Anthony J, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 1990;98(5 Pt 1):1187–92.
34. Ness TJ, Powell-Boone T, Cannon R, Lloyd LK, Fillingim RB. Psychophysical evidence of hypersensitivity in subjects with interstitial cystitis. J Urol 2005;173(6):1983–7.
35. Staud R. Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome. Arthritis Res Ther 2006;8(3):208.
36. Staud R, Rodriguez ME. Mechanisms of disease: pain in fibromyalgia syndrome. Nat Clin Pract Rheumatol 2006;2(2):90–8.
37. Bell IR, Baldwin CM, Schwartz GE. Sensitization studies in chemically intolerant individuals: implications for individual difference research. Ann N Y Acad Sci 2001;933:38–47.
38. Nijs J, Meeus M, De Meirleir K. Chronic musculoskeletal pain in chronic fatigue syndrome: recent developments and therapeutic implications. Man Ther 2006;11(3):187–91.

39. Stander S, Schmelz M. Chronic itch and pain: similarities and differences. Eur J Pain 2006;10(5):473–8.
40. Schaible HG, Ebersberger A, Von Banchet GS. Mechanisms of pain in arthritis. Ann N Y Acad Sci 2002;966:343–54.
41. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg 2003;97(4):1108–16.
42. Henriksson KG, Sorensen J. The promise of *N*-methyl-D-aspartate receptor antagonists in fibromyalgia. Rheum Dis Clin North Am 2002;28(2):343–51.
43. Wood PB. A reconsideration of the relevance of systemic low-dose ketamine to the pathophysiology of fibromyalgia. J Pain 2006;7(9): 611–4.
44. Delgado PL. Common pathways of depression and pain. J Clin Psychiatry 2004;65 Suppl 12:16–9.
45. Arnold LM, Hudson JI, Keck PE, Auchenbach MB, Javaras KN, Hess EV. Comorbidity of fibromyalgia and psychiatric disorders. J Clin Psychiatry 2006;67(8):1219–25.
46. Kato K, Sullivan PF, Evengard B, Pedersen NL. Chronic widespread pain and its comorbidities: a population-based study. Arch Intern Med 2006;166(15):1649–54.
47. Stahl SM. Does depression hurt? J Clin Psychiatry 2002;63(4): 273–4.
48. Gendreau RM, Thorn MD, Gendreau JF, Kranzler JD, Ribeiro S, Gracely RH, et al. Efficacy of milnacipran in patients with fibromyalgia. J Rheumatol 2005;32(10):1975–85.
49. Gormsen L, Ribe AR, Raun P, Rosenberg R, Videbech P, Vestergaard P, et al. Pain thresholds during and after treatment of severe depression with electroconvulsive therapy. Eur J Pain 2004;8(5): 487–93.
50. Usui C, Doi N, Nishioka M, Komatsu H, Yamamoto R, Ohkubo T, et al. Electroconvulsive therapy improves severe pain associated with fibromyalgia. Pain 2006;121(3):276–80
51. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 2005;52(5):1577–84.
52. Boucher W, el-Mansoury M, Pang X, Sant GR, Theoharides TC. Elevated mast cell tryptase in the urine of patients with interstitial cystitis. Br J Urol 1995;76(1):94–100.
53. Pang X, Boucher W, Triadafilopoulos G, Sant GR, Theoharides TC. Mast cell and substance P-positive nerve involvement in a patient with both irritable bowel syndrome and interstitial cystitis. Urology 1996;47(3):436–8.
54. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126(3):693–702.
55. Guilarte M, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. Gut 2006;56:203–209.
56. Wood J. Histamine, mast cells, and the enteric nervous system in the irritable bowel syndrome, enteritis, and food allergies. Gut 2006;55:445–447.
57. La JH, Kim TW, Sung TS, Kim HJ, Kim JY, Yang IS. Role of mucosal mast cells in visceral hypersensitivity in a rat model of irritable bowel syndrome. J Vet Sci 2004;5(4):319–24.
58. Zuo Y, Perkins NM, Tracey DJ, Geczy CL. Inflammation and hyperalgesia induced by nerve injury in the rat: a key role of mast cells. Pain 2003;105(3):467–79.
59. Bohm SK, Kong W, Bromme D, Smeekens SP, Anderson DC, Connolly A, et al. Molecular cloning, expression and potential functions of the human proteinase-activated receptor-2. Biochem J 1996;314 (Pt 3):1009–16.
60. Macfarlane SR, Seatter MJ, Kanke T, Hunter GD, Plevin R. Proteinase-activated receptors. Pharmacol Rev 2001;53(2):245–82.
61. Kawabata A, Kawao N, Kuroda R, Tanaka A, Itoh H, Nishikawa H. Peripheral PAR-2 triggers thermal hyperalgesia and nociceptive responses in rats. Neuroreport 2001;12(4):715–9.
62. Vergnolle N, Bunnett NW, Sharkey KA, Brussee V, Compton SJ, Grady EF, et al. Proteinase-activated receptor-2 and hyperalgesia: a novel pain pathway. Nat Med 2001;7(7):821–6.
63. Coelho AM, Vergnolle N, Guiard B, Fioramonti J, Bueno L. Proteinases and proteinase-activated receptor 2: a possible role to promote visceral hyperalgesia in rats. Gastroenterology 2002;122(4): 1035–47.
64. Bueno L. Gastrointestinal pharmacology: irritable bowel syndrome. Curr Opin Pharmacol 2005;5(6):583–8.
65. Barbara G, Stanghellini V, De Giorgio R, Corinaldesi R. Functional gastrointestinal disorders and mast cells: implications for therapy. Neurogastroenterol Motil 2006;18(1):6–17.
66. Kawao N, Ikeda H, Kitano T, Kuroda R, Sekiguchi F, Kataoka K, et al. Modulation of capsaicin-evoked visceral pain and referred hyperalgesia by protease-activated receptors 1 and 2. J Pharmacol Sci 2004;94(3):277–85.
67 Cenac N, Andrews CN, Holzhausen M, Chapman K, Cottrell G, Andrade-Gordon P, et al. Role for protease activity in visceral pain in irritable bowel syndrome. J Clin Invest 2007. Feb 15 [Epub ahead of print].
68. Ding-Pfennigdorff D, Averbeck B, Michaelis M. Stimulation of PAR-2 excites and sensitizes rat cutaneous C-nociceptors to heat. Neuroreport 2004;15(13):2071–5.
69. Moormann C, Artuc M, Pohl E, Varga G, Buddenkotte J, Vergnolle N, et al. Functional characterization and expression analysis of the proteinase-activated receptor-2 in human cutaneous mast cells. J Invest Dermatol 2006;126(4):746–55.
70. Enestrom S, Bengtsson A, Frodin T. Dermal IgG deposits and increase of mast cells in patients with fibromyalgia-relevant findings or epiphenomena? Scand J Rheumatol 1997;26(4):308–13.
71. Salemi S, Rethage J, Wollina U, Michel BA, Gay RE, Gay S, et al. Detection of interleukin 1beta (IL-1beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. J Rheumatol 2003;30(1):146–50.
72. Santos J, Saperas E, Nogueiras C, Mourelle M, Antolin M, Cadahia A, et al. Release of mast cell mediators into the jejunum by cold pain stress in humans. Gastroenterology 1998;114(4): 640–8.
73. Theoharides TC, Papaliodis D, Tagen M, Konstantinidou A, Kempuraj D, Clemons A. Chronic fatigue syndrome, mast cells, and tricyclic antidepressants. J Clin Psychopharmacol 2005;25(6): 515–20.