Neuroendocrine Dysfunction in Fibromyalgia and Migraine

Marcelo Moraes Valença, MD, PhD, Fabíola Lys Medeiros, MD, PhD, Hugo A. Martins, MD, Rodrigo Meirelles Massaud, MD, and Mario F. P. Peres, MD, PhD

Corresponding author
Mario F. P. Peres, MD, PhD
Instituto Israelita deEnsino e Pesquisa Hospital Albert Einstein, Al Joaquim Eugenio de Lima, 881 cj 708, 01403-001, Sao Paulo, Brazil..
E-mail: marioperes@yahoo.com

Current Pain & Headache Reports 2009, **13:**358–364
Current Medicine Group LLC ISSN 1531-3433

Fibromyalgia (FM) and migraine are common chronic disorders that predominantly affect women. The prevalence of headache in patients with FM is high (35%–88%), with migraine being the most frequent type. A particular subgroup of patients with FM (approximately half) presents with a combined clinical form of these two painful disorders, which may exhibit a different manner of progression regarding symptomatology and impact on daily activities. This article reviews several common aspects of the pathophysiology regarding pain control mechanisms and neuroendocrine dysfunction occurring in FM and migraine, particularly in the chronic form of the latter. We also discuss the participation of hypothalamic and brainstem centers of pain control, the putative role played by neurotransmitters or neuromodulators on central sensitization, and changes in their levels in the cerebrospinal fluid. Understanding their mechanisms will help to establish new treatment strategies for treating these disabling brain disorders.

Introduction

Fibromyalgia (FM) and migraine—frequent painful central nervous system (CNS) conditions—have a number of common signs and symptoms with similar pathophysiologic aspects, particularly regarding pain control mechanisms and neuroendocrine dysfunction. This article reviews a selection of the most recent advances in medical research on the neuroendocrinal pathophysiology involved in the onset and progression of these two brain disorders.

FM is a relatively common chronic disorder present in up to 4% of the general population [1,2]. A strong gender predilection is observed in this disorder, which disproportionately affects women (4–9:1). FM, as a syndrome with subjective physical signs, is usually characterized by prevalent musculoskeletal pain and stiffness associated with fatigue, sleep disturbances, emotional distress, depression, panic disorders, anxiety, decreased motivation, and memory/concentration problems. The pathophysiology of FM remains unknown, although we know that it is marked by the influence of genetic and environmental triggers. Migraine, depressive disorders, and irritable bowel syndrome are comorbidities commonly present in the course of FM, all of which may share the same hereditary or other causal factors as FM [3].

Fibromyalgia and Migraine

The prevalence of headache in patients with FM is estimated to be 35% to 88% [4•]. Migraine is the most frequent type, with a rate ranging from 45% to 80% [4•]. On the other hand, FM is present in about one third of primary headache patients [5••]. Therefore, a particular subgroup of patients with FM (approximately half) presents with a combined clinical form of these two painful disorders, which may exhibit a different manner of progression or intensity regarding the symptomatology and impact on daily activities. Patients suffering from both migraine and FM had lower quality-of-life scores and higher levels of mental distress [6].

Neuroendocrine and autonomic nervous system dysfunction is also commonly encountered in patients with FM. Alterations in the central processing of sensory input may play a role in the mechanism of both FM and migraine, resulting in persistent widespread pain and enhanced pain sensitivity. Anxiety and insufficient sleep were notably associated with FM [5••]. Thus, a mechanism of facilitation of central sensitization phenomena may also be favored by anxiety and sleep disturbances.

Abnormal concentrations of CNS neuropeptides and biogenic amines, alterations in the hypothalamo-pituitary axis, and brain gray matter changes have been described in FM, indicating that FM is a primary disorder of the brain [7–10,11••,12–14] (Table 1). CNS pain modulatory systems seem to be impaired in FM, causing an imbalance in the

Table 1. Neuropeptide, neurotransmitter, or neuromodulator changes found in cerebrospinal fluid of patients with fibromyalgia

GDNF	↓
Somatostatin	↓
NGF	↑
BDNF	↑
Glutamate	↑
β-Endorphin	↔
Anandamide	↓
Palmitoylethanolamide	↑
Norepinephrine (MHPG)	↓
Serotonin (5-HIAA)	↓
Hypocretin-1	↔
Corticotropin-releasing factor	↑
Substance P	↑
Met-enkephalin-Arg(6)-Phe(7)	↑
Nitric oxide	↑
Homocysteine	↑
Dynorphin A	↑

↓—decrease; ↑—increase; ↔—no changes when compared with control group; 5-HIAA—5-hydroxyindoleacetic acid; BDNF—brain-derived neurotrophic factor; GDNF—glial cell line–derived neurotrophic factor; MHPG—3-methoxy-4-hydroxyphenylglycol; NGF—nerve growth factor.

excitatory versus inhibitory pain control mechanisms. The inadequate processing of environmental stimuli and those that arise from within the body may lead to a heightened perception of pain and other unpleasant stimuli [15••].

The diagnosis of FM is based on the subjective report by the patient of widespread pain and sensitivity to palpation [16]. Pain is an unpleasant sensory and emotional experience exerting a major protective function. It is a warning sign indicating the existence of imminent or actual tissue injury that needs to be avoided or treated. Occasionally a headache can signal a serious condition requiring prompt medical attention. As with other internal organs, a pain system that signals tissue injury is functioning in the brain, causing headache to help safeguard the intracranial structure against insults such as hemorrhage, ischemia, toxins, and intrinsic diseases. In the case of secondary headaches, the pain component of the syndrome indicates a potential danger to the individual's life. In the context of primary headaches, its role as a warning sign is still unclear. Stressful situations, in which the individual feels that something may be hazardous, habitually cause headache. Farias da Silva et al. [17] stated that emotional stress was the principal triggering factor of migraine attacks. In their series of 844 patients, 43% reported that emotional problems precipitated migraine attacks. The other trigger factors were olfactory (17%) and visual (glaring lights, 12%) stimuli, lack of sleep (16%), and food deprivation/hunger (9%).

Along these lines, patients with migraine are more vulnerable to sensory overload (sensory dysmodulation) during and between attacks [18], probably due to widespread neural "dysexcitability" [19]. This highlights the fact that in migraine and FM there is an enhanced sensibility to various stimuli, some of which are common to both conditions.

A decreased tolerance to noise (phonophobia) and altered olfactory perception are also observed in FM patients [20]. In one study, FM patients perceived unpleasant odors, but not pleasant ones, as more intense, with a tendency to rate the positive odors as less pleasant and the negative odors as more unpleasant [20]. Likewise, some of the migraineurs stated that olfactory stimuli sometimes initiated a migraine attack. Moreover, aversion to strong smells (osmophobia) during a migraine attack is another relatively common feature encountered in migraineurs. This enhanced perception of unpleasant stimuli suggests that the neural responses to afferent signals are amplified in FM. Significantly more activity in response to pressure and thermal stimuli in several of the brain regions is also observed in both migraine and FM patients, particularly in those structures involved in sensory-discriminative processing [20–22].

It seems that a primary headache attack or a change in its frequency/intensity may be a warning that something abnormal is happening either inside the body or in the living environment. In the case of patients with FM or chronic daily headache, the evidence clearly suggests a dysfunction in the endogenous protective alarm system. Thus, these individuals are highly sensitive to normally painless stimuli, including touch, heat, cold, chemicals, light, sounds, and smells.

Exposure to psychosocial and environmental stressors may contribute to alterations in pain perception or pain inhibition, and as a result may trigger the subsequent progression of FM in susceptible subjects (Fig. 1). Because many FM patients report that the onset of their symptoms occurred after physiologic or psychological stress, FM is frequently regarded as a stress-related disorder [23]. This symptomatology may be exacerbated in stressful situations, reinforcing the role of stress in FM pathophysiology [22,23].

In view of this, women with FM reported higher rates of childhood and adolescent negative life events [24]. Somatic symptoms, negative life events, increased focus on bodily symptoms, psychological distress, and passive pain coping mechanisms are some of the psychological risk factors encountered in FM patients. More than half of 77 patients with FM studied by Cohen et al. [25] had clinically significant levels of posttraumatic stress disorder symptoms. Amital et al. [26] studied 55 patients with posttraumatic stress disorder precipitated because they had experienced, witnessed, or had been confronted with an event that involved actual or threatened death, serious injury, or a threat to the physical integrity of self or others during military combat. FM was diagnosed in 49% of these patients compared with 5% of major

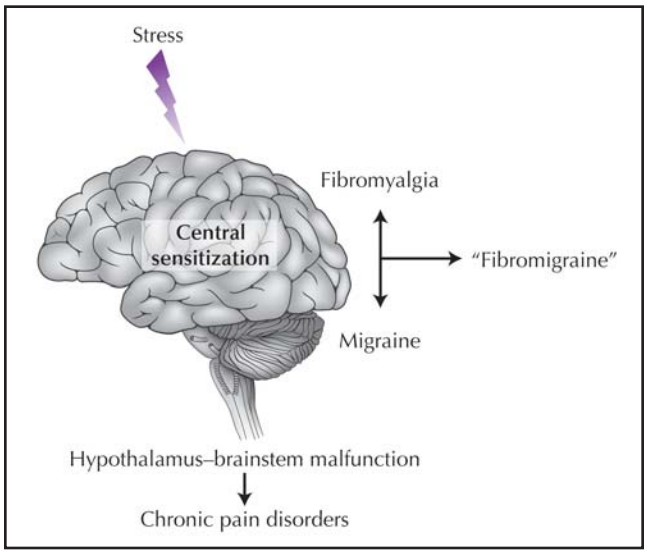

Figure 1. Psychosocial and environmental stressors may contribute to alterations in pain perception or pain inhibition and trigger FM or CM in susceptible subjects. Alterations in the central processing of sensory input may play a role in the mechanism of both FM and CM. The inadequate processing of environmental stimuli and those that arise from within the body may lead to a heightened perception of pain and other unpleasant stimuli. Abnormal concentrations of CNS neuropeptides and biogenic amines, as well as alterations in the hypothalamo-pituitary axis, occur in both migraine and FM patients, indicating that they are primary disorders of the brain. CNS pain modulatory systems seem to be impaired, causing an imbalance in the facilitatory and inhibitory pain control mechanisms. The patient may then progress to clinical states described as migraine, FM, or a combination of both ("fibromigraine"). CM—chronic migraine; CNS—central nervous system; FM—fibromyalgia.

depressive disorder patients and none of the controls, reinforcing the concept that FM is a dysfunctional biologic response to stress.

Hypothalamus–Brainstem Axis and Neuroendocrine Dysfunction

In normal circumstances the autonomic nervous system and the neuroendocrine system are activated to prepare the body and optimize a reaction of fighting or fleeing during a condition that is different from the day-to-day routine, particularly in those that generate stress. In such situations, the hypothalamus immediately initiates a series of events to increase blood levels in the adrenocorticotropic hormone, β-endorphin, cortisol, oxytocin, and adrenaline [27,28]. Some of these stress hormones, as well as stress situations, may cause acute pain relief under certain circumstances. According to this line of reasoning, the presence of pain could be a way in which the CNS signals an alarm whenever the organism is exposed to a potentially harmful environment during various stress types. Migraine comorbidity (ie, psychiatric disorders, epilepsy, sleep disturbance, asthma/allergies, FM) or some undesirable associated condition (obesity, hypertension) may also trigger or exacerbate headache. A significant clinical association between obesity and FM was recently postulated [29].

Significant evidence indicates that a hypothalamic dysfunction occurs in FM, particularly involving the hypothalamic-pituitary-adrenal axis [30] and the hypothalamic-pituitary-growth hormone axis [10]. However, routine endocrine tests usually are normal in FM patients. Abnormalities of the hypothalamo-pituitary axis responses to stressors, increased levels of neuropeptides, excitatory amino acids, and neurotrophins in the cerebrospinal fluid (CSF) were observed in FM [7–10,12,13], suggesting again that this disorder, like migraine, is of central origin.

The hypothalamus is wired to the brainstem periaqueductal gray substance, the locus coeruleus, and the median raphe nuclei, which are all involved in autonomic regulation, sleep, and the descending control of pain perception mechanisms. The hypothalamus also exerts a major influence on the mechanism of headache triggers [31]. Therefore, the presence of pain and concomitant changes in the hormonal secretory pattern is to be expected during a headache attack when hypothalamic structures are involved [32]. In the case of hypothalamic injury or dysfunction, headache may be the result of such damage. Thus, the hypothalamus and the adjacent brainstem both represent a complex interconnected neural region responsible for the chronobiological and autonomic features and lateralization of some headache disorders [33]. A disruption in the normal function of the hypothalamus is implicated in the genesis of some prodromal symptoms and signs of migraine, such as mood changes, drowsiness, thirst, craving for food, and yawning. In 72% of 97 patients studied by Giffin et al. [34], premonitory symptoms predicted migraine headaches. The most regular premonitory symptoms were the following: feeling tired and weary (72% of attacks with warning features); having difficulty concentrating (51%); and a stiff neck (50%). These signs and symptoms may occur for several hours, or as long as 2 days, before the onset of the headache, or may persist for the entire duration of the headache attacks. Furthermore, not every premonitory phase progresses to a migraine. In addition, premonitory symptoms may cause a significant impact on the individual's life [35]. The most common premonitory symptoms encountered in a series of 893 migraine patients were tiredness, mood change, and gastrointestinal symptoms [36]. Thus, fatigue, mood changes, cognitive dysfunction, and muscle pain are reported by patients with FM and those with migraine. Do these complaints, observed in both diseases, originate from the same brain area?

Significant evidence indicates that in the peripheral and central nervous systems, there are both nociceptive and non-nociceptive pathways that modulate the perception of pain. During some stress situations the individual normally adapts to an excessive environmental demand, and the sensation of pain may be an additional reason for failure. Thus, stress is an adaptive response of the organism to stressors to maintain homeostasis, also defined as a general reaction of the

CNS, which plays a vital role in the way an organism monitors internal conditions, as well as conditions in the world around it in its attempt to survive.

Under stressful circumstances the endogenous analgesic system is activated to suppress pain. Several endogenous substances are involved in the regulatory mechanisms of pain modulation, either facilitating pain or leading to an analgesic state or pain inhibition. Among these substances, endogenous opioid peptides exert a major influence on this pain-alleviating system. In this regard, the mean CSF level of β-endorphin in patients with FM was 20.7 ± 0.7 fmol/mL and 20.5 ± 2.0 fmol/mL in healthy controls (*P* = not significant) [37]. We would expect an increase in the CSF concentration of this opioid peptide in this chronic condition of continuous pain in order to suppress pain. Does this absence of response (ie, equal levels of β-endorphin) indicate a deficiency in the endogenous analgesic neuronal system in patients with FM? If so, we may postulate an impairment of the hypothalamic pain control over brainstem centers in FM patients.

Recently, there has been accumulating evidence that chronic pain is associated with changes in brain anatomy, particularly related to a decrease in the gray matter in chronic pain patients [11••]. The longer the patients had FM, the greater the gray matter loss, particularly in regions associated with pain modulation or stress, such as the cingulate, insular, and medial frontal cortices, parahippocampal gyri, and thalamus, thus reinforcing the concept that FM is a stress-related disorder related to the sensitization of CNS pain pathways.

FM and migraine may share hereditary pathophysiologic features. It would seem that polymorphisms of genes in the serotoninergic, dopaminergic, and catecholaminergic systems occur in FM and related conditions [38]. In this connection, serotonin, dopamine, and noradrenaline metabolites in CSF are decreased in patients with FM [7].

During migraine episodes, cephalic and extracephalic allodynia may occur as a sign of sensory sensitization. Body pain and allodynia associated with migraine attacks (migrainous corpalgia) are intriguing phenomena reported in a few patients. Cuadrado et al. [39•] recently reported the cases of three patients presenting with spontaneous body pain in association with migraine attacks, usually ipsilateral to the head pain, that persisted for minutes to days. Allodynia to mechanical stimuli over the painful areas was also present. Recently, we identified a painful disorder in a 54-year-old man characterized by a "hemifibromyalgia," because his left hemibody, as described by him, was painful, with pain occurring at all nine tender points located on the left side (also associated with allodynia). A left cervicogenic headache was also diagnosed. This left "half-body" FM, associated with a cervicogenic headache, appeared 4 months previously—a few days after a stressful situation during a hospitalization for a gastrointestinal disorder. This patient also complained of sleep difficulties and depression. A total control of the cervicogenic headache was achieved immediately after a suboccipital injection of lidocaine/dexamethasone. This indicates that the occurrence of a lateralized central sensibilization is possible, considering that the symptomatology was restricted to only one side of the body.

A continuum of an increasing number of tender points with several painful body segments seems to occur. Some authors have hypothesized that FM represents one end of a spectrum of pain and tender points, and that both traits are probably continuous in the general population. Thus, a myofascial syndrome may progress to a severe FM [40].

The probable mechanisms of allodynia and hyperalgesia are still unknown, although evidence suggests that several levels of the nociceptive system, from the nociceptors in the muscle to the cortex, are involved. The central sensitization of nociceptive neurons in the dorsal horn because of the activation of N-methyl-D-aspartic (NMDA) acid receptors and the resultant triggering of pain, due to an imbalance between inhibitory and facilitatory impulses in the descending tracts from the brainstem to the dorsal horn, appears to be the cause of hypersensitivity to pain [15••].

Glutamate seems to be related to migraine chronification and is implicated in cortical spreading depression, trigeminovascular activation, and central sensitization. As the development of central sensitization has an impact on the effectiveness of triptan (serotonin [5-HT]1B/1D/1F receptor agonists) therapy, Vieira et al. [41] hypothesized that glutamate might be related to triptan response mechanisms. To substantiate this concept they studied patients diagnosed with chronic migraine (CM). Patients were divided into those overusing analgesics, those without overuse, and those overusing triptans. Patients overusing triptans had CSF glutamate levels significantly lower than those observed in non-overusers, and significantly higher than controls. Thus, CM patients overusing triptans presented lower glutamate levels in CSF, suggesting that glutamate may be implicated in triptan response mechanisms (ie, triptans may work in part by reducing extracellular glutamate levels in the brain). This may afford an insight into the possibility of using serotonin agonists to treat chronic pain syndromes, particularly when central sensitization occurs.

Significantly lower levels of somatostatin and glial cell line–derived neurotrophic factor were found in the CSF of FM patients, with and without analgesic abuse [13]. Identical findings were also encountered in CM patients, suggesting a similar neurochemistry dysfunction occurring in these two clinically related diseases [13].

In addition, significantly higher levels of two neurotrophins (brain-derived neurotrophic factor and nerve growth factor) and glutamate were detected in the CSF of patients with CM and FM [42]. This would play a role in the mechanism of a sustained central sensitization observed in both chronic pain states.

There is experimental evidence of the antinociceptive action of endocannabinoids. Some authorities have claimed a clinical endocannabinoid deficiency in the pathophysiology of migraine and FM [43]. Anandamide

is an endogenous cannabinoid neurotransmitter that potentiates 5-HT1A and inhibits 5-HT2A receptors. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. Anandamide is tonically active in the periaqueductal gray matter and may modulate glutamatergic neurotransmission via NMDA receptors. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral, and gastrointestinal mechanisms that promote pain in headache, FM, and related disorders [43]. CSF concentrations of anandamide were significantly lower and those of palmitoylethanolamide higher in patients with CM. A negative correlation was found between anandamide and calcitonin gene–related peptide levels in CM. A similar trend was observed between this endocannabinoid and nitrite levels [43]. This may reflect an impairment of the endocannabinoid system in these patients, which may facilitate a chronic pain status.

Some patients developed FM-like symptomatology after brainstem damage, indicating that brainstem malfunction may play a role in the onset of FM. Symptomatic migraine related to a pontine vascular malformation was also reported, suggesting that a brainstem lesion may trigger the onset of chronic pain [44]. In this regard, a case was reported in which migraine and FM occurred concurrently after a pontine hemorrhage [45]. Accordingly, in patients with FM or migraine, a dysfunction at the brainstem level is also postulated, because the mechanisms related to contralateral suppression of transiently evoked otoacoustic emissions seem equally impaired in both syndromes [46]. FM secondary to cervical spinal cord or caudal brainstem compression also has been reported [47]. Because neurological signs of cervical myelopathy may be mistaken for those of FM, some authors recommend a detailed neurological and neuroradiological evaluation of patients with FM symptomatology to exclude compressive cervical myelopathy [47]. The surgical treatment of cervical myelopathy in a series of 40 patients with an initial diagnosis of FM resulted in a significant improvement in a wide range of symptoms usually attributed to FM. This reinforces the assumption that FM may be the result of brainstem/spinal cord damage or dysfunction.

Thus, triggers such as stress, glare, noise, or other factors may activate specific centers in the brainstem. The concept of a central sensitization and a peripheral sensitization as part of migraine pathogenesis is a recent theory that supports the concept of a temporal progression and the symptomatic expression of migraine attacks [48]. This theory tries to explain the symptom of cutaneous allodynia and the development of CM.

Melatonin

The CNS has evolved over the millennia to meet the demands of environmental conditions, including the light–dark cycle, to ensure the survival and reproduction of living organisms. A synchronization system to adapt the internal to the external environment is one of the key elements of the CNS in maintaining life. The main elements for synchronization between the internal biological events and the environment are the pineal gland and its main secretory product, melatonin. Melatonin is absent during the daytime, and its nocturnal secretion is the main biological event signaling what is night for the organism. In modern-day life, individuals are light-exposed for a much longer time, namely from about 6 AM to 11 PM, because of the constant use of televisions and computers, as well as work-related activities. Furthermore, the time used for sleep is less than with people living without an electrical power supply, as in the case of our ancestors. Thus, circadian rhythm disorders and other related diseases may occur.

Peres [49] studied the plasma melatonin nocturnal profile, observing lowered melatonin levels in patients with insomnia, which is suggestive of a chronobiological dysfunction in CM patients.

Studies comparing melatonin concentrations in FM patients with healthy controls have reported conflicting results, namely normal, decreased, and increased melatonin levels; however, studies of patients with FM showed that they reported a significant improvement after the nightly use of melatonin [50]. The experts note the following possible explanations for the way in which melatonin attenuates FM symptomatology: 1) by synchronizing circadian rhythms and improving the quality of sleep; 2) by combating the excessive free-radical damage observed in individuals with FM, given that melatonin and its metabolites are potent free-radical scavengers and indirect antioxidants; 3) by inhibiting the rate-limiting enzyme in nitric oxide production; 4) by acting as an antidepressant agent; and 5) by exerting an antiepileptic action.

Conclusions

FM and migraine share similar demographic and clinical characteristics, which suggest a common pathophysiological mechanism such as a CNS dysfunction. Current hypotheses highlight an abnormal CNS sensory processing (particularly by the hypothalamus–brainstem axis) and dysfunction in the skeletal muscle nociception. Based on the idea of a dysregulation in the neuroendocrine control over hormonal, sleep, autonomic, behavioral, and pain control mechanisms, the ideal pharmacologic treatment for FM would presently be the use of selective serotonin and norepinephrine reuptake inhibitors, which enhance neurotransmission in the descending pain pathways. We should now start to consider whether the combined form of these two painful diseases—migraine and FM ("fibromigraine")—is in fact an individualized clinical condition that merits consideration as a disorder distinct from those found in patients with migraine or FM alone.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wolfe F, Ross K, Anderson J, et al.: **The prevalence and characteristics of fibromyalgia in the general population.** *Arthritis Rheum* 1995, **38:**19–28.
2. Thompson D, Lettich L, Takeshita J: **Fibromyalgia: an overview.** *Curr Psychiatry Rep* 2003, **5:**211–217.
3. Bradley LA: **Pathophysiologic mechanisms of fibromyalgia and its related disorders.** *J Clin Psychiatry* 2008, **69(Suppl 2):**6–13.
4.• Stuginski-Barbosa J, Dach F, Speciali JG: **Relationship between primary headache and fibromyalgia: literature review (in Portuguese).** *Rev Bras Reumatol* 2007, **47:**114–120.

This comprehensive review discusses the evidence regarding the association of fibromyalgia and headache.

5.•• Tommaso M, Sardaro M, Serpino C, et al.: **Fibromyalgia comorbidity in primary headaches.** *Cephalalgia* 2009, **29:**453–464.

This article includes promising research detailing the prevalence and clinical features of fibromyalgia in the different forms of primary headaches at a tertiary headache center.

6. Ifergane G, Buskila D, Simiseshvely N, et al.: **Prevalence of fibromyalgia syndrome in migraine patients.** *Cephalalgia* 2006, **26:**451–456.
7. Russell IJ, Vaeroy H, Javors M, Nyberg F: **Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis.** *Arthritis Rheum* 1992, **35:**550–556.
8. Schweinhardt P, Sauro KM, Bushnell MC: **Fibromyalgia: a disorder of the brain?** *Neuroscientist* 2008, **14:**415–421.
9. Gur A, Oktayoglu P: **Central nervous system abnormalities in fibromyalgia and chronic fatigue syndrome: new concepts in treatment.** *Curr Pharm Des* 2008, **14:**1274–1294.
10. Jones KD, Deodhar P, Lorentzen A, et al.: **Growth hormone perturbations in fibromyalgia: a review.** *Semin Arthritis Rheum* 2007, **36:**357–379.
11.•• Kuchinad A, Schweinhardt P, Seminowicz DA, et al.: **Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain?** *J Neurosci* 2007, **27:**4004–4007.

This article describes relevant issues about anatomical changes in the brain associated with fibromyalgia.

12. Vaerøy H, Sakurada T, Førre O, et al.: **Modulation of pain in fibromyalgia (fibrositis syndrome): cerebrospinal fluid (CSF) investigation of pain related neuropeptides with special reference to calcitonin gene related peptide (CGRP).** *J Rheumatol Suppl* 1989, **19:**94–97.
13. Sarchielli P, Alberti A, Candeliere A, et al.: **Glial cell line-derived neurotrophic factor and somatostatin levels in cerebrospinal fluid of patients affected by chronic migraine and fibromyalgia.** *Cephalalgia* 2006, **26:**409–415.
14. Neeck G, Crofford LJ: **Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome.** *Rheum Dis Clin North Am* 2000, **26:**989–1002.
15.•• Nielsen LA, Henriksson KG. **Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition.** *Best Pract Res Clin Rheumatol* 2007, **21:**465–480.

This comprehensive review on fibromyalgia may be the far end of a continuum that starts with chronic localized or regional musculoskeletal pain and ends with widespread chronic disabling pain, with a longstanding or permanent change in the function of the nociceptive nervous system.

16. Wolfe F, Smythe H, Yunus M, et al.: **The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee.** *Arthritis Rheum* 1990, **33:**160–172.
17. Farias da Silva W, Sampaio M, Costa Neto J, et al.: *Migrânea*. Rio de Janeiro: Sociedade Brasileira de Cefaléia; 2005.
18. Goadsby PJ: **Recent advances in understanding migraine mechanisms, molecules and therapeutics.** *Trends Mol Med* 2007, **13:**39–44.
19. Ambrosini A, Schoenen J: **Electrophysiological response patterns of primary sensory cortices in migraine.** *J Headache Pain* 2006, **7:**377–388.
20. McDermid AJ, Rollman GB, McCain GA: **Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification.** *Pain* 1996, **66:**133–144.
21. Gracely RH, Petzke F, Wolf JM, et al.: **Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.** *Arthritis Rheum* 2002, **46:**1333–1343.
22. Staud R: **Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome.** *Arthritis Res Ther* 2006, **8:**208.
23. Bradley LA: **Pathophysiologic mechanisms of fibromyalgia and its related disorders.** *Clin Psychiatry* 2008, **69(Suppl 2):**6–13.
24. Anderberg UM, Marteinsdottir I, Theorell T, et al.: **The impact of life events in female patients with fibromyalgia and in female healthy controls.** *Eur Psychiatry* 2000, **15:**295–301.
25. Cohen H, Neumann L, Haiman Y, et al.: **Prevalence of post-traumatic stress disorder in fibromyalgia patients: overlapping syndromes or post-traumatic fibromyalgia syndrome?** *Semin Arthritis Rheum* 2002, **32:**38–50.
26. Amital D, Fostick L, Polliack ML, et al.: **Posttraumatic stress disorder, tenderness, and fibromyalgia syndrome: are they different entities?** *J Psychosom Res* 2006, **61:**663–669.
27. López-Jiménez M, Valença MM, Moreira AC, Antunes-Rodrigues J: **Ether and immobilization stress effects on pituitary adrenal function in hemidecorticate rats.** *Braz J Med Biol Res* 1989, **22:**779–782.
28. Negro-Vilar A, Johnston C, Spinedi E, et al.: **Physiological role of peptides and amines on the regulation of ACTH secretion.** *Ann N Y Acad Sci* 1987, **512:**218–236.
29. Okifuji A, Bradshaw DH, Olson C: **Evaluating obesity in fibromyalgia: neuroendocrine biomarkers, symptoms, and functions.** *Clin Rheumatol* 2009, **28:**475–478.
30. Macedo JA, Hesse J, Turner JD, et al.: **Glucocorticoid sensitivity in fibromyalgia patients: decreased expression of corticosteroid receptors and glucocorticoid-induced leucine zipper.** *Psychoneuroendocrinology* 2008, **33:**799–809.
31. Cortelli P, Pierangeli G: **Hypothalamus and headaches.** *Neurol Sci* 2007, **28:**S198–S202.
32. Peres MF, Sanchez del Rio M, Seabra ML, et al.: **Hypothalamic involvement in chronic migraine.** *J Neurol Neurosurg Psychiatry* 2001, **71:**747–751.
33. Valença MM, Andrade-Valença LP, da Silva WF, Dodick DW: **Hemicrania continua secondary to an ipsilateral brainstem lesion.** *Headache* 2007, **47:**438–441.
34. Giffin NJ, Ruggiero L, Lipton RB, et al.: **Premonitory symptoms in migraine: an electronic diary study.** *Neurology* 2003, **60:**935–940.
35. Lipton RB, Bigal ME: *Migraine and Other Headache Disorders,* edn 1. New York: Informa Healthcare; 2006:529.
36. Kelman L: **The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs.** *Headache* 2004, **44:**865–872.
37. Vaeroy H, Helle R, Førre O, et al.: **Cerebrospinal fluid levels of beta-endorphin in patients with fibromyalgia (fibrositis syndrome).** *J Rheumatol* 1988, **15:**1804–1806.
38. Buskila D, Sarzi-Puttini P, Ablin JN: **The genetics of fibromyalgia syndrome.** *Pharmacogenomics* 2007, **8:**67–74.
39.• Cuadrado ML, Young WB, Fernández-de-las-Peñas C, et al.: **Migrainous corpalgia: body pain and allodynia associated with migraine attacks.** *Cephalalgia* 2008, **28:**87–91.

This article reports that cephalic and extracephalic allodynia are recognized as common signs of central sensory sensitization during migraine episodes.

40. Papageorgiou AC, Silman AJ, Macfarlane GJ: **Chronic widespread pain in the population: a seven year follow up study.** *Ann Rheum Dis* 2002, **61:**1071–1074.

41. Vieira DS, Naffah-Mazzacoratti G, Zukerman E, et al.: **Glutamate levels in cerebrospinal fluid and triptans overuse in chronic migraine.** *Headache* 2007, **47:**842–847.
42. Sarchielli P, Mancini ML, Floridi A, et al.: **Increased levels of neurotrophins are not specific for chronic migraine: evidence from primary fibromyalgia syndrome.** *J Pain* 2007, **8:**737–745.
43. Russo EB: **Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?** *Neuro Endocrinol Lett* 2004, **25:**31–39.
44. Obermann M, Gizewski ER, Limmroth V, et al.: **Symptomatic migraine and pontine vascular malformation: evidence for a key role of the brainstem in the pathophysiology of chronic migraine.** *Cephalalgia* 2006, **26:**763–766.
45. Ifergane G, Shelef I, Buskila D: **Migraine and fibromyalgia developing after a pontine haemorrhage.** *Cephalalgia* 2007, **27:**191.
46. Gunduz B, Bayazit YA, Celenk F, et al.: **Absence of contralateral suppression of transiently evoked otoacoustic emissions in fibromyalgia syndrome.** *J Laryngol Otol* 2008, **122:**1047–1051.
47. Heffez DS, Ross RE, Shade-Zeldow Y, et al.: **Treatment of cervical myelopathy in patients with the fibromyalgia syndrome: outcomes and implications.** *Eur Spine J* 2007, **16:**1423–1433.
48. Dodick D, Silberstein S: **Central sensitization theory of migraine: clinical implications.** *Headache* 2006, **46:** S182–S191.
49. Peres MF: **Melatonin, the pineal gland and their implications for headache disorders.** *Cephalalgia* 2005, **25:**403–411.
50. Reiter RJ, Acuna-Castroviejo D, Tan DX: **Melatonin therapy in fibromyalgia.** *Curr Pain Headache Rep* 2007, **11:**339–342.