

A Quest for Better Understanding of Biochemical Changes in Fibromyalgia Syndrome

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Fibromyalgia Syndrome (FMS) is one of the least understood pain syndrome in medicine today, which is a chronic disorder characterized by persistent and widespread pain, with an estimated prevalence of 2–4 % in the adult general population (3.4 % for women and 0.5 % for men). The defining symptoms of FMS are chronic widespread pain and fatigue. Other symptoms include tingling of the skin, prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching and chronic sleep disturbances. Many patients of FMS also experience cognitive dysfunction. The initial FMS criteria included tenderness on pressure (tender points) in at least 11 of 18 defined anatomic sites with the presence of widespread pain.

However, in the recent criteria it is clear that apart from the pain other seminal features of the disorder such as cognitive dysfunction, unrefreshing sleep, fatigue and mood disorders also play an important role in the diagnosis. FMS is also considered to be a disorder of central pain processing that produces heightened responses to painful stimuli (hyperalgesia) and painful responses to non-painful stimuli (allodynia). Therefore, the heightened state of pain transmission may be due to increase in pronociceptive neurotransmitters, such as substance P and glutamate. Thus, the pain of FMS is often accompanied by one or more manifestations, such as affective moods, cognitive insecurity, autonomic dysfunction, or irritable bowel syndrome. The etiology and pathogenesis of FMS are still not fully understood. Several novel factors such as dysfunction of neurotransmitters, cytokines, sleep disturbances, perturbed circadian rhythm of cortisol and melatonin, free radical mediated oxidative damage and toxic metals seem to be involved.

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Neurotransmitters in FMS

There are data suggesting the involvement of dopamine, substance P and serotonin (5-HT) in the pathogenesis of FMS. Many studies have linked 5-HT, to sleep, pain perception, headaches, and mood disorders. 5-HT is a metabolic precursor to melatonin, a nocturnal hormone postulated to function in sleep. Specifically, 5-HT is metabolized by the melatonin synthetic enzyme *N*-acetyltransferase (NAT) to form *N*-acetylserotonin (NAS). Indeed, strong evidence has accumulated to support the hypothesis that deficiency in serotonergic neuronal functioning might be related to the pathophysiology of FMS. The neurotransmitter 5-HT plays diverse roles in a number of central and peripheral processes [1].

Cytokines

Cytokines induce symptoms, such as fatigue, fever, disturbed sleep, pain, and myalgia all of which develop in FMS patients. Reports have noted alterations in proinflammatory cytokine levels in serum of FMS patients [2], which might also be associated with disease symptoms. Taken together, the profile of pro- and anti-inflammatory cytokines in FMS patients has recently attracted considerable attention.

Sleep Disturbances

Patients with FMS often complain of sleep disorders and these are probably involved in its pathogenesis. Sleep dysfunction is integral feature of FMS. Several studies have linked abnormal sleep with symptoms of FMS, stage 4 sleep (the deepest sleep) is markedly deficient in FMS

patients, repeated nights of nonrestorative sleep causes extreme fatigue and exacerbate pain [3].

Circadian Rhythm of Cortisol

FMS patients have disturbed sleep patterns which may lead to altered circadian rhythm in serum cortisol secretion. The circadian rhythm in serum cortisol levels is very robust, and peak concentrations occur in the early morning hours, falling progressively to a nadir around the early to midpoint of sleep. Furthermore, studies have shown blunting of normal diurnal cortisol rhythm, with elevated evening serum cortisol level in patients with FMS [4]. Therefore, circadian pattern of cortisol abnormalities in FMS patients may help in better understanding the role of variation in symptoms of FMS.

Circadian Rhythm of Melatonin

Melatonin is a hormone normally secreted from the pineal gland at night. Synthesis of melatonin and its release from the pineal gland into the blood-stream undergoes a circadian rhythm with highest levels during the darkness and the lowest concentrations during the day. The increase of melatonin levels provides a convenient signal to all body cells about the onset of night which is a signal for sleep. FMS patients have lower melatonin secretion during the hours of darkness than the healthy subjects. This may contribute to impaired sleep at night, fatigue during the day and changed pain perception [5].

Free Radical Mediated Oxidative Damage in FMS

The role of free radical-mediated oxidative damage was reported in the etiopathogenesis of FMS where tender points result from local hypoxia in muscles [6]. Furthermore, total antioxidant capacity such as superoxide dismutase (SOD) and catalase were found decreased in FMS patients, lipid peroxidation (LP) and carbonylated proteins, the end products of membrane damage which is induced by ROS, are increased in the plasma of patients with FMS [7]. These results confirm the oxidative stress background of FMS, probably due to a defect in the antioxidant system and high production of ROS. Our understanding of oxidative stress/antioxidant system could help us to better

figure out the pathophysiology of FMS, and to offer new therapeutic strategies for this disease.

Toxic Metals and FMS

Toxic metals trigger the production of free radicals, leading to oxidative stress and depletion of antioxidant as well as influencing the metabolism of metallothioneins (small metal binding proteins high in sulphur). Toxic metals are also known to stimulate the production of inflammatory messengers known as cytokines in the immune system causing immense pain. Heavy metals toxicity is a growing threat to health and development. Research has suggested that serum magnesium and zinc levels may play an important role in the pathophysiology of FMS [8].

This article on FMS is therefore, intended to the standard approach of understanding the causes of disease, and also to encourage the researchers and clinicians to bolster the search for advance treatment of disease and improved prevention.

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