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COMMENTARY

Melatonin therapy in fibromyalgia

The fibromyalgia syndrome (FMS) is a chronic, widespread pain disorder of unknown etiology, mainly accompanied by fatigue, disturbed sleep and depression. The American College of Rheumatology (ACR) criteria for FMS requires that a patient has both a history of chronic widespread pain for at least 3 months and the finding of pain in 11 of 18 possible tender points on examination [1]. Using the ACR criteria, the prevalence of FMS in industrialized countries ranges from 0.5% to 4% in the population, being 11 times more frequent in women.

Factors that may contribute to the development of FMS include [2, 3]: (i) familial component, suggestive of a genetic factor; (ii) environmental factors, including stressors such as physical trauma, infections, psychological stress, endocrine disorders, and autoimmune diseases. Cytokines such as interleukin (IL)-1α, IL-6, and tumor necrosis factor-alpha have been shown to be related to neuropathic pain, and they are released by activated immune cells during inflammation; (iii) endocrine alterations including those of the hypothalamo-pituitary axis (HPA) and changes in the sympathetic nervous system; (iv) neurotransmitter alterations including increased substance P and decreased norepinephrine and serotonin levels; and (v) psychological factors.

Fibromyalgia syndrome is, at present, an incurable disease, and it should be consider a chronic illness. Current pharmacological treatment of FMS depends on the severity of the symptoms and include antidepressants, anti-inflammatory drugs, anti-epileptic drugs, sedative hypnotics, muscle relaxants, and opiates [3].

In an atempt to ameliorate some of the FMS symptoms including insomnia and thus improve chronic stress in these individuals, melatonin was given orally to four FMS patients. One patient was a 22-yr-old male, and the other three were females between the ages of 47–55 yr. All patients were receiving medication including chronic analgesics, antidepressants, sedative hypnotics, and in one case opioids. Melatonin was given at doses of 6 mg/day at night, 60 min before the expected sleeping time. After 15 days of treatment with melatonin, all patients developed a sleep/wake cycle that was considered normal. They also mentioned a significant reduction of pain. At this time, the patients were taken off hypnotics. Thirty days after the initiation of melatonin, other medications were withdrawn and thereafter they only took melatonin. They currently report feeling very well, have a normal sleep/wake cycle, normal diurnal activity, lack of pain and fatigue and claim significant improvement of the behavioral symptoms including lack of depression. At this time, none of them take any drug other than melatonin. These four patients have been on melatonin therapy for 3–15 months.

A previous study revealed that 3 mg melatonin daily for 30 days significantly improved the tender point count, severity of pain, global physician assessments and sleep [4]. Our experience, with 6 mg melatonin daily and more than 1 yr of treatment in some cases, suggests that chronic melatonin therapy may be highly beneficial in relieving the overall symptoms in FMS patients.

How is melatonin benefiting FMS patients? Melatonin has multiple actions including modulation of the sleep/wake cycle and benzodiazepine-like effects [5]. Thus, melatonin administration improves sleep and rest, and decreases anxiety derived from sleeplessness. Additionally, melatonin also synchronizes neurotransmitter circadian rhythms including those of γ-aminobutyric acid, benzodiazepine, dopamine, and glutamate [5, 6]. Data from the literature are inconsistent regarding melatonin levels and its circadian rhythm in FMS patients. Although it is unknown whether there is an alteration in the neurotransmitter and/or melatonin rhythms in FMS patients, we have reported that when the latter is altered, providing melatonin therapy reduces abnormal brain physiology [7]. Thus, one effect of melatonin in FMS may be the normalization of the neurotransmitter rhythms and the sleep/wake cycle. Also, melatonin has anti-stress properties and influences the HPA axis, which may account for some of its effects in FMS. Furthermore, new data regarding the anti-inflammatory role of melatonin [8], as well as its inhibition of the macrophage/monocyte activation including the reduction of both inducible nitric oxide synthase and proinflammatory cytokines may be of benefit in FMS. Finally, as altered muscle physiology may participate in the pathophysiology of FMS, the actions of melatonin in terms of its ability to enhance mitochondrial bioenergetics [9–11] may be pertinent to its beneficial effects in these patients. While reduced levels of melatonin have been reported in FMS women [12], alterations in its circadian rhythm seem to be not a primary cause of FMS.

Taken together, the observed effects in these patients along with the minimal side effects of melatonin, and the fact that melatonin reduces the toxicity and increases the efficacy of many drugs [13], suggest that melatonin alone or in combination with other therapies may be of significant benefit in the pharmacological management of FMS.

References

1. Wolfe F, Smythe HA, Yunus MB et al. The American College of Rheumathology Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990; **33**:160–172.
2. Staud R. Fibromyalgia pain: do we know the source? Curr Opin Rheumatol 2004; **16**:157–163.

3. Kranzler JD, Gendreau JF, Rao SG. The psychopharmacology of fibromyalgia: a drug development perspective. Psychopharmacology Bull. 2002; **36**: 165–213.
4. Citera G, Arias A, Maldonado-Cocco JA et al. The effect of melatonin in patients with fibromyalgia: a pilot study. Clin Rheumatol 2000; **19**:9–13.
5. Acuña-Castroviejo D, Escames G, Macias M et al. Cell protective role of melatonin in the brain. J Pineal Res 1995; **19**:57–63.
6. Khaldy H, Leòn J, Escames G et al. Circadian rhythm of dopamine and their metabolites in mouse striatum: effects of pinealectomy and melatonin replacement. Neuroendocrinology 2002; **75**:201–208.
7. Molina-Carballo A, Muñoz-Hoyos A, Reiter RJ et al. Utility of high doses of melatonin as adjunctive anticonvulsant therapy in a child with severe myoclonic seizures: two years' experience. J Pineal Res 1997; **23**:97–105.
8. Mayo JC, Sainz RM, Tan DX et al. Anti-inflammatory actions of melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), in macrophages. J Neuroimmunol 2005; **165**:139–149.
9. León J, Acuña-Castroviejo D, Escames G et al. Melatonin mitigates mitochondrial malfunction. J Pineal Res 2005; **38**:1–9.
10. Acuña-Castroviejo D, Escames G, León J et al. Melatonin and nitric oxide: two required antagonists for mitochondrial homeostasis. Endocrine 2005, in press.
11. Escames G, León J, Macias M et al. Melatonin counteracts lipopolysaccharide-induced expression and activity of mitochondrial nitric oxide synthase in rats. FASEB J 2003; **17**:932–934.
12. Almay BG, Von Knorring L, Wetterberg L. Melatonin in serum and urine in patients with idiopathic pain syndromes. Psychiatr Res 1987; **22**:179–191.
13. Reiter RJ, Tan DX, Sainz RM et al. Melatonin: reducing the toxicity and increasing the efficacy of drugs. J Pharm Pharmacol 2002; **54**:1299–1321.

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