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SEROTONIN ROLE IN FIBROMYALGIA

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ABSTRACT

Fibromyalgia (FM) is a musculo-skeletal disorder and tiredness which results in diffuse myalgia, localized pain, weakness, lower pain thresholds and non-restorative sleep. Multiple sources of evidence supporting the view of decreased flux via the serotonin pathway in FM patients. Supplementation with serotonin substrates, through L-tryptophan or 5-Hydroxytryptophan (5-HTP) significantly improves depression symptoms, anxiety, fatigue and poor sleep in FM patients. Advances in fibromyalgia recognition have helped to increase the therapy choices for FM patients. New medications, nutritional supplements, and nutritional / pharmacological improvement of deep-stage sleep are all being studied by researchers that emphasizes awareness, exercise, and serotonin substrate / receptor regulation.

KEYWORDS: Fibromyalgia; Tryptophan; Serotonin; nutritional supplementation.

INTRODUCTION

FM causes widespread pain in the skeleton and muscle that usually affects the women. Although, FM etiology has not been fully understood, multiple neuroendocrine disorders and abnormalities of autonomic function, have been related to its pathogenesis. This disorder most commonly affects persons between the ages of 30 and 50, but it can affect anyone of any age, including youngsters and the elderly (1). It is estimated that FM affects 2–4 percent of the people, the incidence ratio is female to male is about 9:1 (2). Diagnostically, rheumatological criteria (2016) requires widespread pain during a physical examination (3). Supplementation of serotonin substrates through L-tryptophan or 5-HTP significantly improves depression symptoms, anxiety, fatigue and poor sleep in FM patients. Identifying low level of tryptophan and serotonin can be an easy way of identifying individuals, who will react well to this assessment (4).

SEROTONIN PATHWAY

Serotonin influences sleep, muscular strength, vascular constrict and expansion, hunger/insulin response, and hormone level dynamics. It also plays an important part in fatigue, anxiety, sleep problem, depression and obsessive-compulsive disorders. Depression, anxiety, and personality disorders are treated with selective serotonin reuptake inhibitors (SSRIs). These medicines block reuptake of serotonin and increase the amount of serotonin that is available to bind with the post-synaptic receptor. Prozac block serotonin re-uptake while increasing serotonin level in the brain (5,6).

SEROTONIN BIOSYNTHESIS AND STORAGE: The serotonin pathway shown in the figure 1. Dietary tryptophan is a precursor in serotonin synthesis. Tryptophan is the least important of the eight necessary amino acids, accounting for only 1% of total protein. Once absorbed into the circulation, tryptophan is carried to peripheral locations by free-form protein, where 90% is utilized to build proteins and just 1% is converted to serotonin (5,8). Plasma tryptophan enter in the brain by an active absorption and is hydroxylated to 5-HTT by tryptophan hydroxylase. A vitamin B6-dependent decarboxylase aromatic amino-acid convert 5-HTP to serotonin. A monoamine vesicular transporter actively transports serotonin to vesicles, where it is stored until it is released (7,8).

SEROTONIN REUPTAKE: The reuptake pathways remove serotonin from the synaptic cleft once it is released. Serotonin is reabsorbed into neuronal terminals by serotonin transporter proteins (SERT) that pass through the plasma membrane. MAO (monoamine oxidase) deaminates serotonin to 5-hydroxyindoleacetaldehyde is subsequently oxidized by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid throughout metabolism. Urine is used to eliminate the latter (9). Depressive symptoms, anxiety, personality disorders, and a variety of personality disorders are treated with SSRIs. These medicines block serotonin reuptake into the presynaptic terminal, allowing more serotonin to reach the extracellular

level where it can bind to the post-synaptic receptor. Prozac increases serotonin levels in the brain by inhibiting serotonin reuptake specifically. It can help people with mental illnesses by increasing the transmission of 5-HT1A receptors. Sumatriptan constricts intracranial arteries and has shown to be helpful in treating migraines. It has been shown that THE 5-HT1B 5-HT1D receptors present in the muscle and endothelium of the cerebral artery are responsible for the constriction of these arteries triggered by sumatriptan (5,6).

anxiety, pain intensity, sleep quality, depression, appetite, and tender points were observed (14).

FM and migraine are generally found together, and it is thought that they have the same cause. 200 FM patients with migraines were given 5-HTP for a one year. Without the adverse effects of these antidepressants, 5-HTP was shown to be effective as tricyclic or monoamine oxidase inhibitor (MAOIs). In FM patients, a combination of 5-HTP and MAOIs has been reported to be more effective (15).

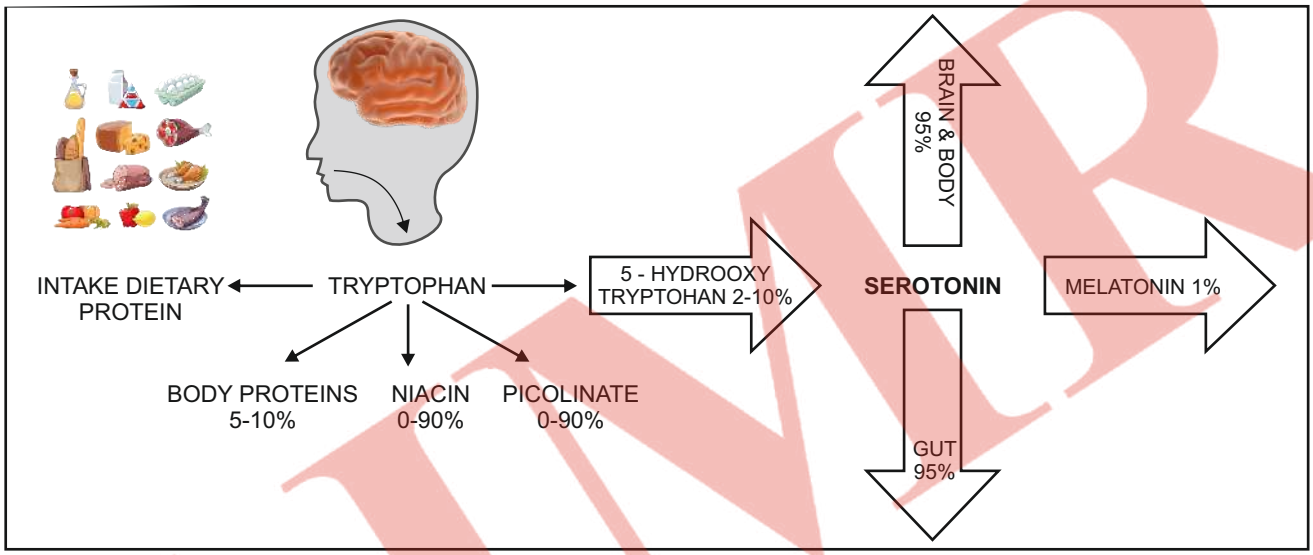

Fig. 1. Metabolism of Tryptophan

5-HYDROXYTRYPTOPHAN (5-HTP) CONNECTION WITH FMS

In 1981, L-tryptophan was found to be beneficial in treating depressed symptoms in FM patients (10). 5-HTP is metabolized into serotonin in the body. 5-HTP was found to be of therapeutic value in the treatment of depression with a daily dosage, notably in the depression subgroup with serotonin deficiency (11). Results were found improvement in the depressive mood, anxiety, poor sleep, and pain in a study of comparative multicenter trial of sixty depressed patients taking either fluvoxamine (SSRI) or 5-HTP thrice a day for six weeks. Negative effects were more common in the Fluvoxamine group (12).

Serotonin level were shown to be low in FMS patients, and 5-HTP was used in FMS therapy in two published trials. 50 FM patients were given 5-HTP (100 mg three times day) for thirty days in a double-blind, placebo-controlled study. All clinical indicators, including tender point examination, pain intensity, and poor-sleep were found to be improved (13). Later, in primary FMS patients, the same study group recommended (100 mg three times day) for 90 days. Significant changes in

Food	Amount (gm/100gm)
Turmeric powder	2.03
Sweet potato	1.90
Hilsa	1.88
Grapes	1.83
Chicken	1.80
Pumpkin	1.77
Amaranth	1.69
Soya bean	1.68
Egg	1.59
Milk	1.48

Tab. 1. Foods That Contain High Amount of Tryptophan

INVOLVEMENT OF SEROTONIN IN FIBROMYALGIA

The evaluation of serum serotonin level in FM patients resulted in conflicting data. I.J. Russell reported low level of serum serotonin in FM patients (16). Further research conducted by Russell et al. also found that lower serotonin metabolites were present in cerebrospinal fluid (CSF) of FMS patients (17). The 5-HT2A receptor and serotonin transporter (5-HTT) are responsible for the regulation of the serotonin pathway (18). 5-HT2A is a neurotransmitter which is found in the CNS and represented by the gene 5-hydroxytryptamine receptor 2A. (HTR2A). The SLC6A4 gene has been proposed to be a candidate gene for FM based on a single linkage study (19). Serotonin transport from synaptic spaces to presynaptic neurons is regulated by 5-HTT, which plays an important role in serotonergic neurotransmission (20). In terms of FM pathophysiology, genetic variations effect both 5-HTT gene and serotonin receptors, which have gained consideration as possible susceptibility genes.

In a group of patients with fibromyalgia, Offenbaecher and his colleagues found S/S genotype have increased frequency compared with that of healthy control participants. The S/S genotype has linked with the extreme depressive symptoms and other types of psychological distress (21). Specifically, the S/S subgroup had higher depressive symptoms. Cohen and his colleagues genotyped 5-HTT in FM patients and control group and observed a statistically significantly higher S/S genotype expression in FM patients (22). As in the research by Offenbaecher and colleagues, some patients have reported higher psychological distress level (23). The T102C polymorphism was also suggested to be a potential genetic contributing factor FM (24).

Gursoy also observed that neither the 5-HTT promoter region polymorphism nor the variable number of tandem repeats (VNTR) variation was linked with FM (25). Furthermore, In a meta-analysis, Lee YH et al. found no link between 5-HTT promoter regions polymorphism and FM (26). Taken together, these findings no difference between FM patients and control subjects found. But they indicated the difference between FM patients with anxiety trait and the control groups. Clinical findings in understanding of FM has provided patients more treatment choices. If both tryptophan and serum level are low in FMS patients, the following supplements should be included for the treating plan: Increased protein consumption, vitamin B6 and niacinamide. Compounds that raise serotonin levels while also increasing dopamine have found to be useful in treating FM and associated disorders (27-28). Tricyclic antidepressants (TCAs) increase serotonin level by inhibiting the reuptake of the serotonin (29). SSRIs have better effect compared with TCAs in FM patients (30). Dual serotonin and norepinephrine re-uptake inhibitors therapeutically analogous to TCAs, they also block serotonin and norepinephrine reuptake, but they differ in that they typically do not interfere with specific receptor systems. This specificity helps to reduce adverse effects and increase tolerance. Venlafaxine, the first drug of this kind to be approved for clinical use, has been shown to benefit in neuropathic disorders and migraines (31).

CONCLUSIONS

FM is a musculoskeletal disorder that results in depression, fatigue, anxiety, poor sleep, and headache. A significant subset of FMS patients has lower level of serotonin but a number of other chronic pain syndromes are also having low serotonin levels. There are several potential etiologies for the FMS are under research. Substrate's supplementation in a FM patient improves depression symptoms, anxiety, fatigue and poor sleep in FM patients. Identifying low level of tryptophan and serotonin can be an easy way of identifying individuals, those who will respond well to this examination. Dietary therapy, pharmacological improvement in deep-stage sleep, orthopedic, therapy in somatic dysfunction, exercising, and serotonin substrates are all complimentary approaches to FM treatment.

REFERENCES

1. Buskila Y, Buskila D, Jacob G, et al. High prevalence of fibromyalgia among Israeli school teachers. Clin Exp Rheumatol. 2019;37(116): 21-26.
2. Wolfe F, Walitt B, Perrot S, et al. Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. PloS one. 2018;13(9).
3. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016; 46(3) 319-329.
4. Hernandez-Leon A, Fernández-Guasti A, Martínez A, et al. Sleep architecture is altered in the reserpine-induced fibromyalgia model in ovariectomized rats. Behav Brain Res. 2019;364: 383-392.
5. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytryptamine. Br J Anaesth1994; 73:395-407.
6. Juhl JH. Fibromyalgia and the serotonin pathway. Alternative Medicine Review. 1998; 3: 367-75.
7. Turner EH, Loftis JM, Blackwell AD. Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. Pharmacology & Therapeutics. 2006;109(3): 325-338.
8. Birdsall TC. 5-Hydroxytryptophan: A clinically-effective serotonin precursor. Altern Med Rev. 1998;3: 271-280.
9. Fon EA, Edwards RH. Molecular mechanisms of neurotransmitter release. Muscle Nerve: 2001;

24(5):581-601.

10. Nichkova MI, Huisman H, Wynveen PM, et al. Evaluation of a novel ELISA for serotonin: urinary serotonin as a potential biomarker for depression. Analytical and bioanalytical chemistry. 2012 ;402(4):1593-600.
11. Popova NK, Kulikov AV. Targeting tryptophan hydroxylase 2 in affective disorder. Expert opinion on therapeutic targets. 2010;14(11):1259-71.
12. Jangid P, Malik P, Singh P, et al. Comparative study of efficacy of l-5-hydroxytryptophan and fluoxetine in patients presenting with first depressive episode. Asian journal of psychiatry. 2013;6(1):29-34.
13. Porter NS, Jason LA, Boulton A, et al. Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis /chronic fatigue syndrome and fibromyalgia. The Journal of Alternative and complementary medicine. 2010;16(3): 235-49.
14. Rus A, Molina F, Del Moral ML, et al. Catecholamine and Indolamine Pathway: A Case–Control Study in Fibromyalgia. Biological research for nursing. 2018;20(5):577-86.
15. Russo EB. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. Cannabis and cannabinoid research. 2016;1(1): 154-65.
16. Russell IJ. Neurohormonal aspects of fibromyalgia syndrome. Rheum Dis Clinics North Am 1989;15:149-168.
17. Russell IJ, Vaeroy H, Javors M, et al. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum 1992;35: 550-556.
18. Eison AS, Mullins UL. Regulation of central 5-HT2A receptors: a review of in vivo studies. Behav Brain Res 1996;73: 177-181
19. Arnold LM, Fan J, Russell IJ, et al. The fibromyalgia family study: a genome-wide linkage scan study. Arthritis Rheum 2013;65: 1122-1128.
20. Kuzelova H, Ptacek R, Macek M. The serotonin transporter gene (5-HTT) variant andpsychiatric disorders: review of current literature. Neuro Endocrinol Lett 2010;31:4-10.
21. Offenbaecher M, Bondy B, Jonge SD, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1999;42(11):2482-8.
22. Cohen H, Buskila D, Neumann L, et al. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. Arthritis & Rheumatism. 2002;46(3):845-7.
23. Bondy B, Spaeth M, Offenbaecher M, et al. The T102C polymorphism of the 5-HT2A-receptor gene in fibromyalgia. Neurobiol Dis 1999;6:433-439.
24. Mergener M, Becker RM, dos Santos AF, et al. Influence of the interaction between environmental quality and T102C SNP in the HTR2A gene on fibromyalgia susceptibility. Rev Bras Reumatol2011;51:594-602.
25. Gursoy S. Absence of association of the serotonin transporter gene polymorphism with the mentally healthy subset of fibromyalgia patients. Clin Rheumatol2002;21:194-197.
26. Lee YH, Choi SJ, Ji JD, et al. Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. Rheumatol Int 2012;32:417-426
27. Clauw D.J., Mease P., Palmer R.H., et al. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clinical therapeutics. 2008;30(11):1988-2004.
28. Mease PJ., Clauw DJ., Gendreau RM., et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. J Rheumatol. 2009; 36(2): 398-409.
29. Arnold L.M., Keck P.E.J., Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics. 2000;41:104- 113.
30. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain. 1995;61: 445-449
31. Adelman LC, Adelman JU, Von Seggern R, et al. Venlafaxine extended release (XR) for the prophylaxis of migraine and tensiontype headache: a retrospective study in a clinical setting. Headache. 2000;40: 572-580.

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