Review
Fibromyalgia syndrome and serotonin

M.N.Y. Alnigenis, P. Barland

Division of Rheumatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA.
M. Nergis Yanmaz Alnigenis, MD, Research Associate; Peter Barland, MD, Professor of Medicine, Director.

Please address correspondence to:
M. Nergis Yanmaz Alnigenis, MD, Gundogdu Sok, Inan Apt. B 1/2 Kat 4, Merter Istanbul, Turkey 34010.
E-mail: Muyessera@hotmail.com

Please address reprint requests to:
Dr. Peter Barland, MD, Montefiore Medical Center, 111 East 210th Street, Bronx, New York 10467, USA.

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ABSTRACT

Although disturbances in the musculoskeletal system, in the neuroendocrine system and in the central nervous system (CNS) have been implicated in the pathophysiology of fibromyalgia syndrome (FMS), the primary mechanisms underlying the etiopathogenesis of FMS remain elusive. It has been postulated that disturbances in serotonin metabolism and transmission, along with disturbances in several other chemical pain mediators, are present in patients with FMS. In this article we review published studies on the pathophysiological role of serotonin in FMS. Although studies that indirectly measured the function of serotonin in the CNS in FMS revealed some abnormalities in the metabolism and transmission of serotonin, the role of serotonin in the pathophysiology of syndrome remains inconclusive and warrants more studies.

Introduction

Fibromyalgia syndrome (FMS) is a commonly encountered "pain syndrome" which affects predominantly women (1-5). It is characterized by chronic widespread musculoskeletal pain, stiffness, tenderness, sleep disturbance, easy fatigability and psychological distress. There has been an ongoing debate over the existence of FMS as a distinct clinical entity (1, 6-10). Understanding the pathophysiology of the syndrome could help to settle this dispute. Although disturbances in the musculoskeletal system, in the neuroendocrine system and in the central nervous system (CNS) have been implicated in the pathophysiology of FMS, the primary mechanisms underlying the etiopathogenesis of FMS remain elusive (11-15).

"Nociception" refers to the physiologic process of transmitting a painful stimulus from the periphery, through afferent nociceptive neurons, the spinal cord, and the thalamus, to the cerebral cortex, where mental awareness of the pain and the body location of the stimulus are consciously perceived (16). Altered nociception is a persistent characteristic of FMS and serotonergic neurotransmission plays a significant role in nociception. It has been postulated that disturbances in serotonin metabolism and transmission, along with disturbances in several other chemical pain mediators [such as substance P (SP), nerve growth factor, and dynorphin], are present in patients with FMS (16). In this article, we will review studies on the pathophysiological role of serotonin in FMS.

Serotonin

Serotonin (5-hydroxytryptamine/5HT) is a neurotransmitter that is synthesized from its precursor L-tryptophan, an essential amino acid that cannot be synthesized by the human body (16-18). Serotonin is found in platelets, mast cells, enterochromaffin cells of the gastrointestinal tract, and in brain cells. The actual amount in the brain represents only 1% to 2% of the total amount in the body, but serotonin is widely distributed in the brain (17).

Dietary proteins are digested in the gut and released tryptophan is absorbed through the intestine. Some of the trytophan circulates as free plasma tryptophan and some is reversibly bound to albumin. Free plasma tryptophan is actively transferred across the blood-brain barrier by a carrier mechanism that also transports other amino acids. Dietary amounts of tryptophan and competition for the uptake of other amino acids influence the level of tryptophan and the synthesis of serotonin in the brain (19, 20).

The "raphe neurons"(serotonergic neurons) oxidatively decarboxylate tryptophan to serotonin through a process that involves trytophan hydroxylase, a rate-limiting enzyme which is not satu-

rated under normal conditions, and a decarboxylase enzyme. Serotonin is stored in dense-core vesicles at synapses in brain and spinal cord locations. The major pathways to degrade serotonin are re-uptake into the nerve and degradation by monoamine oxidase (MAO) to 5-hydroxyindolacetic acid (5-HIAA). Many of the tricyclic antidepressants inhibit serotonin re-uptake and all of the MAO inhibitors inhibit serotonin degradation.

The serotonergic pathways originate in the "raphe nucleus" (several groups of cells in a midline area of the pons and upper brain stem). The posterior cell group projects to the medulla and the spinal cord, and the anterior group to diffusely innervate the cortex, thalamus, and limbic systems.

Serotonergic neurons have been implicated in pain perception through inhibitory effects on pain pathways in the spinal cord, in temperature regulation, and in feeding behavior. Serotonin probably has a centrally-mediated influence on the cardiovascular system and may be involved in levels of wakefulness and sleep. Pharmacological observations implicate the serotonergic system in higher cognitive function, schizophrenia, anxiety, depression, and hallucinations. In the spinal cord, serotonin is known to inhibit the release of SP by afferent neurons responding to peripheral stimuli (21). SP is an 11-amino acid neuropeptide which is released by activated, small, thinly myelinated A-delta and C-fiber afferent neurons into the laminae of the spinal cord dorsal horn, and acts to sensitize the dorsal horn cells and lower nociception threshold (16). Increased SP in the brain increases serotonin levels in the spinal cord, which in turn decreases the release of SP into the spinal cord (22). Diverse serotonin receptors are important in modulating the functions of serotonin. A decrease in serotonin production in specific sites in the CNS and the peripheral nervous system can lead to increased nociception.

The role of serotonin in the pathogenesis of FMS has been studied in several ways: by focusing on tryptophan metabolism in the peripheral blood or CNS; by measuring serotonin or its metabolites and receptors in the peripheral blood and in the platelets as an indirect reflection of the situation in the CNS; and by studying serotonin metabolites in the cerebral spinal fluid (CSF). Recently, the existence of antibodies against serotonin and its receptors in patients with FMS and gene polymorphisms related to serotonin metabolism and transmission in FMS have also been studied. These studies provide indirect evidence for the abnormalities in serotonin metabolism in FMS patients.

Tryptophan levels in the peripheral blood of patients with FMS

Moldofsky *et al.*, from The Clarke Institute of Psychiatry in Toronto, first suggested abnormalities of brain serotonin in the pathogenesis of FMS based on animal studies and studies on pain perception and serotonin showing mostly an inverse relationship between brain serotonergic activity and pain perception or thresholds (23).

Presuming that the positive relationships among free tryptophan in the plasma, brain tryptophan, and brain serotonin shown in studies in rats are applicable to man, they studied plasma-free and bound trytophan in patients with fibrositis. In one study of 8 patients with fibrositis syndrome (6 females and 2 males) (24), selected using their predesignated criteria for fibrositis syndrome which included emotional stress-depression, anxiety, and irritability, both total and free tryptophan levels in plasma were not significantly different from the baseline values of normal controls or from patients with a diagnosis of primary affective disorders. Morning fasting plasma-free tryptophan was found to be inversely related to the subjective morning pain reported by fibrositis patients (24). The dolorimeter or threshold muscle tenderness scores and mood ratings were not significantly related to biochemical measurements.

In another double blind study by Moldofsky *et al*., 15 patients with fibrositis syndrome (10 females and 5 males, using the same criteria as above) were given 5 g L-tryptophan for 3 weeks, which increased somewhat their duration of sleep, but their subjective pain scores did not change and the dolorimeter or tenderness scores actually seemed to worsen (25). The small number of patients enrolled in the two studies makes it difficult to draw definite conclusions, however.

In another study utilizing tryptophan levels in the peripheral blood as a surrogate for CNS serotonin, Russell *et al.* from The University of Texas Health Science Center at San Antonio measured the levels of several serum amino acids (using automated analysis) in 20 female patients with fibromyositis syndrome, defined using the authors' own criteria, and matched healthy controls (26). Only 8 patients had scores above 13 on the Hamilton Depression Scale, suggesting possible depression. Six patients had mild, 8 had moderate and 4 had severe anxiety scores according to the Hamilton Anxiety Scales. Patients with FMS showed significantly lower levels of tryptophan ($p = 0.02$). However, the levels of 6 other typical amino acids (alanine, histidine, lysine, proline, serine, threonine) were also significantly lower in the FMS patients ($p < 0.05$). There was no correlation between the trytophan concentration and the severity of the patients' pain level as assessed by the Tenderness Point Index and by the dolorimeter tenderness scale.

Yunus *et al.* have measured plasma tryptophan levels and 21 other amino acids (including isoleucine, leucine, methionine, phenylalanine, tyrosine and valine) in 29 patients with primary FMS (defined according to the authors' own criteria) and in 30 matched healthy controls without significant pain by using the Waters PicoTag Amino Acid Analysis System (27). Since free plasma tryptophan is transferred across the blood-brain barrier by a carrier mechanism that also transports other large, branched chain, neutral amino acids, they calculated the transport ratios of these amino acids. It has been suggested that the transport ratio provides a better index of their entry into the brain than the plasma concentration of any one of these amino acids. Transport ratios of the amino acids were calculated as the molar concentration of a particular amino acid in plasma / sum of the molar concentrations of the other

large neutral amino acids.

Trytophan levels were found to be lower in patients with FMS, showing a tendency to significance ($p = 0.09$) and plasma histidine and serine were significantly lower than in control patients ($p < 0.01$). The transport ratio of tryptophan was significantly lower in FMS patients than in the control group ($p < 0.01$). There was a negative correlation between severity of pain and plasma tryptophan with a trend to significance ($p < 0.05$). Plasma tryptophan also showed a significant ($p < 0.01$) negative correlation with the scores on the Hassles scale for daily stress in the FMS group. Significant negative correlations between the transport ratio of plasma tryptophan and age, total sites of subjective pain,poor sleep, paresthesia, headaches and the Hassles score were found among the combined populations of patients with FMS and healthy controls, but none was found among the FMS group alone.

Russell *et al.* again measured serum trpytophan and kynurenine levels using assays developed in their laboratories in 40 patients with FMS, in 35 patients with rheumatoid arthritis (RA), in 33 patients with osteoarthritis (OA), and in 31 healthy controls (28). Tryptophan is metabolized via the serotonin or the kynurenine pathways in the body. Tryptophan levels were found to be lower in all 3 disease groups compared to normal controls, but only in RA was this difference significant ($p = 0.008$). No significant difference was observed between the groups for the kynurenine levels. Among patients with FMS kynurenine correlated directly with age and with the perception of pain, and inversely with serum serotonin.

In our opinion, studies of tryptophan metabolism in the blood in FMS have not shown a consistent abnormality in the level of tryptophan when compared to other chronic pain syndromes. In addition, blood tryptophan levels generally did not correlate with tenderness scores. Interestingly, observed deficiencies in other amino acids may suggest more generalized abnormalities in amino acid metabolism in FMS and warrant further studies.

Serotonin or its metabolites and receptors in the peripheral blood

Platelet ^{3}H-imipramine binding is considered a method for indirectly measuring serotonin re-uptake receptor density in the brain and reflects serotonergic function and activity. Low or normal values of platelet imipramine binding were found in depression. Russell *et al*. have measured ^{3}H-imipramine receptor density on the platelet membranes of 22 patients with primary FMS (author's own criteria and Yunus *et al*.'s) and serotonin concentrations in the blood (using a method by Yuwiler *et al*.) in 9 patients and compared with matched controls (29). Less than 20% of FMS patients were suffering from depression as measured using the Hamilton Depression Scale and CED-S, and only 18% scored more than 18 on the mean Hamilton Anxiety Scale. The mean serum concentration of serotonin was significantly lower ($p = 0.01$) in FMS patients than in controls. Binding of ^{3}H-imipramine showed significantly higher levels ($p = 0.035$) and these levels were normalized after therapy with alprazolam and ibuprofen. In another study by Kravitz *et al.*, however, the ^{3}H-imipramine binding levels in women with FMS or in men with depression were not significantly different from 10 normal controls of either sex (30). These two studies are conflicting and do not give definite proof for the connection between FMS and serotonin dysfunction.

Serum serotonin levels have been found to be consistently low in patients with FMS in a number of studies from different centers. In one study Russell *et al*. measured serum serotonin by high performance liquid chromatography (HPLC) coupled to an electrochemical detector (31). Serotonin levels were significantly lower in both FMS (39 cases) ($p= 0.002$) and OA (38 cases) ($p= 0.0002$) than in normal controls (39 cases). However, there was no significant difference in serotonin levels between FMS and OA.

In another report, the same group studied serotonin by HPLC in serum and platelets in 30 patients with FMS [American College of Rheumatology (ACR) criteria] and in matched 30 healthy controls. In both groups, the serum serotonin level correlated with platelet serotonin ($p = 0.007$). The serum and platelet serotonin in patients with FMS was significantly lower than in normal controls ($p < 0.03$ and 0.03 respectively) (32).

Hrycaj measured serum serotonin levels in 31 patients with primary FMS (28 women and 3 men; criteria by Muller and Lautenschlager), in 21 patients with RA (16 women and 5 men, 15 of whom had secondary FMS) and in 20 healthy volunteers using a commercially available ELISA kit (33). Both patients with FMS and those with RA had low serum serotonin levels when compared with healthy controls ($p < 0.0001$ and $p < 0.001$, respectively). Moreover, the serum concentration of serotonin was significantly lower in patients with FMS when compared with arthritis patients ($p < 0.01$). There was a significant negative correlation between serum serotonin levels and the number of painful tender points ($p < 0.05$) and a positive correlation between serotonin concentrations and the mean values for pressure tenderness, obtained by averaging the dolorimetry values for all tender points ($p < 0.05$). Such correlations were not found in the RA patients with or without secondary FMS.

Dessein *et al*. from South Africa measured serum serotonin in 57 female patients who met the ACR criteria (34). The mean level of serotonin was 69 ng/ml (SD = 44). In 23 patients (40%) it was below the reference range (using a double antibody radioimmunoassay; reference range 68-205 ng/ml). However, serotonin levels did not correlate with the health status of the patients evaluated using the Fibromyalgia Impact Scale.

The association of serum serotonin with FMS was also studied during the course of a population survey in 151 subjects with widespread pain (31 with FMS according to the ACR criteria), and compared with 63 patients without pain and 87 patients with regional pain (35). Serum serotonin levels were determined by HPLC coupled to an electrochemical detector. There was no significant difference in the levels of sero-

tonin between FMS patients and pain-free subjects or between FMS patients and patients with regional pain (35). Furthermore, there was no significant association between clinical variables [tender point count, dolorimetry scores, the Symptom Check List-90-Revised (SCL-90-R) Depression scale, the Arthritis Impact Measurement Scales' anxiety and depression scales, visual analog scales for pain, sleep disturbances, the Stanford Health Assessment Questionnaire Disability Index, health satisfaction] and serotonin levels in the whole group studied.

In summary, the majority of studies on serotonin levels in the peripheral blood, in contrast to studies on tryptophan, suggest a role for serotonin in FMS. Not all investigators found a correlation between FMS and low serum serotonin levels nor a correlation between the severity of FMS and serotonin levels. These discrepancies may be explained by methodological differences in measuring serotonin and by the fact that serum serotonin levels do not not exactly reflect the situation in the CNS. Moreover, as Russell noted, low serum levels could result from fewer platelets per volume of blood, lower serotonin stores within a given number of peripheral platelets, or the impaired release of platelet serotonin in FMS blood samples (33).

Tryptophan and serotonin metabolites in CSF

We found only three studies on tryptophan and serotonin metabolites in the cerebral spinal fluid of patients with FMS. Russell *et al.* studied abnormalities in the CNS metabolism of tryptophan to 3-kynurenine in FMS (36). CSF from 33 patients with FMS (using ACR criteria) and 24 unmatched normal controls were studied for tryptophan and kynurenine metabolites by HPLC coupled to a Coulochem Electrode Array System. Tryptophan levels were lower in fibromyalgia patients and kynurenine levels were significantly higher.

Russell *et al.* also studied CSF metabolites of serotonin, norepinephrine, and dopamine (37). Seventeen female patients with FMS [using different criteria from the ACR 1990 criteria for the classification of FMS, but it was likely that the patients would have met these criteria] and 12 unmatched controls (5 with RA, 7 healthy controls; 1 male). 5-HIAA (serotonin), 3-methoxy-4-hydroxyphenethylene glycol (MHPG) (norepinephrine), and homovanilic acid (HVA) (dopamine) were measured in CSF using high performance liquid chromatography with coulometric detection. The mean CSF MHPG level ($p = 0.028$) and HVA level ($p = 0.005$) were significantly lower in patients with FMS when compared to unmatched controls, whereas 5-HIAA levels were not significantly different but reached the significance level ($p = 0.057$). The mean concentration of 5-HIAA in the RA subgroup was more than 2-fold higher than the mean in the FMS patients, but the mean from the healthy subjects was only 18% higher than that in the FMS group.

Houvenagel *et al.*, however, observed more definite findings when they studied 5-HIAA in CSF in 22 patients with FMS, in 128 with lower back pain, and in 17 subjects without pain (38). FMS patients showed significantly lower levels of 5-HIAA in the CSF than patients with lower back pain ($p = 0.004$) and pain-free controls ($p = 0.006$).

Based on the published material so far, it seems fair to conclude that FMS is associated with low CSF serotonin levels. The specificity and the correlation of this phenomenon with the clinical severity of FMS needs additional studies.

Antibodies to serotonin in FMS

In a study by Klein *et al*. (39) from Germany, 50 patients with FMS (criteria of Yunus *et al.*) were studied for the presence of antiserotonin and antiganglioside (a portion of the serotonin receptor) antibodies by ELISA. They reported finding high titers of antiserotonin and antiganglioside antibodies (IgG and IgM which cross-reacted with pure tryptophan) in the serum of FMS patients relative to normal controls and in controls with rheumatic conditions (74%, 15%, and 2-4%, respectively). Their data raise the possibility that an autoimmune process might be responsible for the low levels of serotonin in FMS sera and platelets.

Russell *et al.* re-examined this question using solid-phase radioimmunoassays for both IgG and IgM antibodies to serotonin in 90 subjects, 30 with FMS, 30 with RA, and 30 healthy normal controls (16). Each serum sample was tested for IgG and IgM antibodies to serotonin or to neurophysiologically important gangliosides. They were unable to demonstrate consistently higher titers of antiserotonin antibodies from either immunoglobulin class in FMS compared with either of the control groups. In fact, the concentrations IgM antibodies to serotonin were significantly lower ($p = 0.03$) in FMS than in the normal control group. Similarly, they found no elevation of antibodies from either class against the gangliosides. Using a different methodology, Dr. Bennet's laboratory at Oregon Health Sciences University could not find any increase in serum antibodies to serotonin receptors (40).

In a recent study, Eich *et al.* used the same methodology as Klein *et al.* and found antibodies against serotonin in 20.2% of FMS patients, compared to 4.7% in controls ($p < 0.003$) (41). A similar distribution was found for antibodies against thromboplastin (23.6% versus 3.1% $p < 0.001$). There was no difference between groups for antibodies against the ganglioside. The clinical and pathogenetic significance of these antibodies remains inconclusive and warrants further exploration.

Gene polymorphisms of serotonin metabolism in FMS

Offenbaecher *et al.* analyzed the genotypes of the promoter region of the serotonin transporter gene in patients with FMS (42). Uptake of serotonin from the synaptic cleft by serotonin transporter into the presynaptic neuron plays a critical role in the termination of serotonergic transmission. A genetically impaired ability to rapidly clear serotonin from the synaptic cleft may lead to negative feedback, causing an overall decrease in serotonin neurotransmission in individuals. A polymorphism in the transcription region, composed of a 44-base pair insertion

("long allele", L) or deletion ("short allele", S), has been described. The long variant is associated with a 3-fold increase in transcriptional activity.

Genomic DNA from 62 FMS patients (ACR criteria) and 110 healthy controls was analyzed by a polymerase chain reaction. The psychopathologic state of 52 of the FMS patients was evaluated using the Beck Depression Inventory (BDI) and the SCL-90-R. The serotonin transporter gene promoter region's genotypes in FMS patients versus controls were distributed as follows: L/L 27% versus 34%, L/S 42% versus 50%, and S/S 31% versus 16% ($p = 0.046$). The frequency of the S allele, however, seemed to be increased, but the difference was not significant. FMS patients with the S/S genotype had higher mean scores on the BDI and the SCL-90-R compared with those in the LL and LS groups, although the difference was not significant. The authors suggested that serotonin metabolism may be genetically altered in at least a subgroup of patients with FMS and that this could contribute to the clinical severity of the condition.

Bondy *et al*. investigated a silent polymorphism of the 5-HT2A-receptor gene, which is defined by a T to C transition at position 102, in 168 FMS patients (ACR criteria) and 115 healthy controls (43). Their results showed a significantly different genotype distribution in FMS patients, with a decrease in T/T homozygotes and an increase in both the T/C and C/C genotypes as compared to the control population ($p = 0.008$), although the overall differences in allele frequency failed to reach significance ($p = 0.07$). Correlation of the genotypes to clinical parameters revealed no influence on age at onset, duration of disease or psychopathological symptoms, measured using the BDI and SCL-90-R. In contrast, the self-reported pain score was significantly higher in patients of the T/T genotype ($p = 0.028$). This suggested involvement of the T102-allele in nociception. T102C polymorphism may not be directly involved in the etiology of FMS, but could be in linkage disequilibrium with the true functional variant.

Conclusion

Serotonin is an important modulator of pain perception,sleep and mood in normal subjects. Since altered pain perception, sleep and mood disturbances are the hallmarks of FMS, abnormalities in the metabolism and transmission of serotonin could be important in the pathogenesis of FMS. Several indirect methods have been used to evaluate serotonin function in the CNS in human subjects. Studies on serotonin precursor tryptophan in the peripheral blood and CNS in FMS do not show consistent abnormalities in the level of tryptophan. Although serum serotonin levels have consistently been found to be significantly low in studies from different centers using different methodologies, this finding may not reflect the situation in the brain. At present, two genetic polymorphism studies on serotonin metabolism-related proteins suggest that these may contribute to the pathogenesis in some patients with FMS, but this will also require further exploration.

In conclusion, although studies on the function of serotonin in the CNS in FMS have yielded some positive findings, the role of serotonin in the pathophysiology of the syndrome remains inconclusive and warrants more studies. Studying serotonin synthesis in the brain using positron emission tomography would be a more direct way of measuring serotonin dysfunction and carries a potential for future research in FMS patients.

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