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REVIEW

Possible Molecular Mediators Involved and Mechanistic Insight into Fibromyalgia and Associated Co-morbidities

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Abstract

Fibromyalgia is a chronic complex syndrome of non-articulate origin characterized by musculoskeletal pain, painful tender points, sleep problems and co-morbidities including depression, migraine. The etiopathogenesis of fibromyalgia is complex, variable and remains inconclusive. The etiological factors that have been defined include stress, genetic predisposition and environmental components. As per the reports of the American College of Rheumatology (ACR) the prevalence of fibromyalgia varies from 2 to 22% among the general population with poor diagnostic features primarily pain. Fibromyalgia encompasses a spectrum of co-morbid conditions with multifarious pathogenesis. The highly prevalent manifestations of fibromyalgia include heterogeneous pain and aches. Biochemical and neurobiological elements of fibromyalgia include neurotransmitters, hypothalamic pituitary adrenal axis (HPA axis), inflammatory cytokines, monoaminergic pathway, opioid peptides, sex hormones, nerve growth factor (NGF) and local free radical insult. An imbalance in the serotonergic system is the major underlying etiological factor that has been explored most widely. Owing to complex interplay of diverse pathophysiological pathways, overlapping co-morbidities such as depression have been clinically observed. Therapeutic management of fibromyalgia involves both non pharmacological and pharmacological measures. The current review presents various dysregulations and their association with symptoms of fibromyalgia along with their underlying neurobiological aspects.

Keywords Chronic hepatitis C virus · Cytokines · Depression · Fibromyalgia · Inflammatory bowel disease · Migraine · Pain · Serotonin · Sleep

Introduction

Fibromyalgia is a chronic debilitating syndrome of non-articulate origin characterized by abnormal musculoskeletal pain, muscular fatigue, poor sleep, and hyperesthesia with or without co-morbidities such as depression, anxiety and migraine that compromise quality of life [1–3]. Patients diagnosed with fibromyalgia have also been documented to suffer from irritable bowel syndrome, sleep disorders and painful tender points [4–6]. Various dysregulations that have been reported to be involved in the pathophysiology of fibromyalgia include reduction in the levels of biogenic amines, alterations in the HPA axis, sex hormones, opioid peptides, increased oxidative stress and nerve growth factors [7–11]. The etiopathogenesis of fibromyalgia is complicated. The risk factors include familial predisposition, stress and genetic polymorphism [12]. Pain is the primary symptom presented by fibromyalgia patients followed by fatigue, sleep problems and cognitive dysfunction [13]. Studies on epidemiology estimated the prevalence of fibromyalgia to be approximately 2–6% in the general population with higher frequency among females in the age group of 40–60 years [14]. The diagnostic criterion for fibromyalgia categorizes the patients as fibromyalgia patients if they possess widespread pain index of 7or more and symptom scale severity of 5 or more. Pain must be present in 4 out of 5 areas apart from abdominal, chest and jaw and symptoms should persist for at least 3 months [15, 16]. Another review has documented a 30–60% co-occurrence of pain and depressive episodes in the patients that determines the course of treatment [17]. This is possibly due to the overlapping pathophysiologies.

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Currently, there is no specific treatment for fibromyalgia. However, some regulatory bodies recommended some drugs on the basis of meta-analysis or literature survey reports. The association of the Scientific Medical Societies (AWMF) guidelines recommended daily use of amitriptyline (10–50 mg), pregabalin (150–450 mg/day) and gabapentin in fibromyalgia patients [18]. In fibromyalgia patients with or without anxiety, the use of duloxetine (60 mg/day), fluoxetine (20–40 mg/day) and paroxetine (20–40 mg/day) has also been reported [18]. EULAR guidelines also recommended the use of milnacipran [18]. The existing therapies present a lot of problems while tackling the various co-morbidities of fibromyalgia due to their side-effects. The limitations of duloxetine and gabapentin include somnolence, weight increase, peripheral edema, dizziness and negative neurocognitive effects [19]. Amitriptyline presents with mouth dryness, dizziness, constipation and blood circulation related problems [20]. However, the cardiovascular adverse effects were not evident when amitryptiline was used in low doses in fibromyalgia [21].

Pathophysiology of fibromyalgia is very composite and multifactorial. The biochemical studies assert neurochemical disparity in the brain and peripheral tissue along with some autonomic, neuroendocrine and immune dysregulations in the body of fibromyalgia patients [8, 22–25]. Although there are many co-morbidities that are associated with fibromyalgia, the current review has been focused mainly on depression, migraine, chronic hepatitis C virus and inflammatory bowel disease which have been widely explored. Keeping these co-morbidities and variegated dysregulations in view, text has been divided into ten areas for better emphasis and insights into these pathways.

Dysregulation of Biogenic Amine Signaling in Fibromyalgia

As reported in several studies, the etiopathogenesis of fibromyalgia involves depletion of brain levels of biogenic amines which is principally responsible for the major clinically observed symptoms. Reduced level of various aminergic neurotransmitters particularly serotonin, dopamine, norepinephrine has been observed in the cerebrospinal fluid (CSF) of fibromyalgia patients [7]. All these neurotransmitters play a vital role in maintaining neuronal activity in the brain and peripheral tissues. Depletion of 5HT in the descending pain pathways in dorsal horn is essentially responsible for pain perception in fibromyalgia. It has been documented that there is a reduction in circulating tryptophan (precursor of serotonin), reduced serotonin transport ratio and metabolites particularly 5-hyroxyindole, in patients suffering from fibromyalgia as compared to healthy controls [7, 26, 27]. Arnold et al. and Mease et al. have postulated that effective clinical management of fibromyalgia has been achieved with selective nor-epinephrine reuptake inhibitors [28, 29]. In double blind, placebo trials, it was reported that doluxetine and milnacipran are effective in abrogating depression and pain in fibromyalgia patients, leading to the contention that depletion of 5HT is responsible for the depressive episodes in fibromyalgia [28, 29]. However, treatment with duloxetine and milnacipran has been documented to be effective in alleviating the symptoms of fibromyalgia in patients without depression as well [28]. Reduced levels of neurotransmitters have been postulated to be due to transcriptional changes in MAO-A encoding enzyme gene [30]. Gürsoy et al. analyzed monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B) gene alleles of fibromyalgia patients and normal subjects by polymerase chain reaction. The authors 'allele 3', with 251 base pairs of MAO-A had a significant increase in transcriptional activity in comparison to other alleles of MAO-A of fibromyalgia patients. Furthermore, these patients presented with the more severe form of fibromyalgia syndrome, suggesting that highly active 'allele 3' of MAO-A might be responsible for fibromyalgia syndrome [30]. Tort et al. reviewed the effectiveness of pirlindole and moclobemide (MAO-A inhibitors) in fibromyalgia patients. The patients on pirlindole treatment had significant improvement as indicated by reduction in pain and tender points with pain score1.45 points lower on 0–10 visual analog scale (VAS) in comparison to patients on placebo [31]. However, moclobemide had no significant effect on tender points and pain, indicating the limiting role of MAO inhibitors [31]. In the thalamic region, NMDA receptors are key modulators of pain perception [32]. Glutamate mediated NMDA receptor activation has also been implicated in peripheral as well as central pain processes [33].

The microdialysis experiment in a reserpine-induced animal model of fibromyalgia also reported the reduced levels of serotonin along with reduced muscle pressure threshold [34]. Systemic administration of lorcaserin, vabicaserin and YM348 (5-HT_{2C} receptor agonists) abrogated the reserpine induced muscular hyperalgesia dose-dependently, suggesting the role 5-HT_{2C} receptors in inverse modulation of pain in fibromyalgia syndrome [34]. Reduced serotonin levels may precipitate the symptoms of fibromyalgia as evidenced by the musculoskeletal derangements, sleep disturbances [35] and co-morbid depression [28, 29]. It has been documented that not only reduced serotonin level, but also the generation of antibodies against serotonin receptors might be responsible precipitation of fibromyalgia syndrome [36]. Klein et al. reported that 73% fibromyalgia patients in the study trial had antibodies against serotonin [37]. Another independent investigation reported a higher incidence of anti-serotonin and anti-ganglioside antibodies in fibromyalgia patients in comparison to control group [38]. In randomized, double-blind 16-week study, Olin et al. reported that 55%

of fibromyalgia patients recruited in the study had at least one antibody against serotonin, ganglioside and phospholipids [39]. Therefore, from the above investigations, it may be suggested that down regulation of 5-HT receptors and reduced 5-HT availability due to reduced level of tryptophan and targeted antibodies against these receptors might be responsible for the precipitation of symptoms and comorbidities associated with fibromyalgia. In a case control study on fibromyalgia patients with systemic lupus erythematosus (SLE), researchers observed anti-GluN2B antibodies (anti-NMDA 2B receptor subunit antibody) in the sera of fibromyalgia patients with SLS with a positive correlation of these antibodies was observed with tender points and pain index, suggesting the role of anti-GluN2B antibodies in pathogenesis of concomitant fibromyalgia [40].

The metabolite analysis revealed a reduced cerebrospinal level of homovanillic acid (metabolite of dopamine) in fibromyalgia patients in comparison to healthy subjects, suggesting the involvement of dopamine in fibromyalgia syndrome [41]. The urinary catecholamine estimation study of Riva et al. reported a decrease in adrenaline and dopamine levels in fibromyalgia patients during the relaxing period [42]. A negative correlation has been documented between D_2/D_3 receptor availability and pain threshold on right and left caudate of patients with and without co-morbid depression in fibromyalgia respectively [43]. Treatment of female patients of fibromyalgia with buspirone (5-$HT1_A$ receptor agonist and dopamine D_2 receptor antagonist) significantly increased the prolactin release (D_2 receptor mediated response), whereas no change was observed in 5-HT_{1A} responses (growth hormone and hypothermic response), depicting an increased sensitivity of dopaminergic D_2 autoreceptors, rather than the enhanced serotonergic 5-HT_{1A} sensitivity in fibromyalgia patients [44]. Wood et al. in their findings stated that alteration in dopaminergic metabolism is associated with reduced gray matter density within the bilateral parahippocampal gyri, right posterior cingulate cortex and left anterior cingulate cortex of fibromyalgia female patients, demonstrating that the behavioral symptoms in fibromyalgia might be associated with change in gray matter density [45]. Holman postulated a significant decrease in tender point score on increasing the dose of ropinirole (D_3 receptor agonist) from 0.25 mg/day to 24 mg/day with a window of 2.25 to 1 mg/day. However, 9 out of 19 patients on discontinuation of therapy suffered from depression, nausea, nightmares and agitation in a random manner [46]. Furthermore, treatment with pramipexole (D_3 receptor agonist) for a period of 14 days was found to be effective in a double-blind placebo trial in comparison to placebo controls evidenced by measure of pain, fatigue and global scale readings by the pramipexole treated group. However, the results of the study also revealed a decrease in body weight and an increase in the anxiety level of the patients. Therefore, the role of dopaminergic system needs to a more exhaustive exploration and to establish D_3 receptors as a target of fibromyalgia [47]. The above studies present a layout for future investigators to develop effective therapeutic options in managing fibromyalgia.

NGF and BDNF/Trk-B Downstream Pathway in Pain Modulation and Future Insight on Depression Associated with Fibromyalgia

Brain-derived neurotropic factor (BDNF) is one of the nerve growth factors that play a key role in neuronal survival [48], maintenance and repair [49] in the CNS. Various studies have documented the role of BDNF in fibromyalgia syndrome. A high serum level of BDNF has been reported in fibromyalgia patients [11, 50]. Sarchielli et al. had also observed an increase in cerebrospinal fluid concentration of BDNF along with an increase in nerve growth factor (NGF) in patients with primary fibromyalgia syndrome [23]. A significant increase in serum BDNF concentration was observed in fibromyalgia patients suffering from depression in comparison to non-depressed fibromyalgia patients, suggesting the involvement of BDNF in modulation of comorbid depression [23]. However, a few studies did not observe a correlation in serum BDNF concentrations with depression in fibromyalgia [11, 51–53]. Therefore, future studies exploring the role of BDNF in fibromyalgia induced depression may benefit in establishing the role of BDNF in fibromyalgia.

BDNF and NGF may be the potential mediators that are proposed to be involved in pain modulation [54, 55]. An enhanced glutamatergic transmission in fibromyalgia might also be a downstream mediator of BDNF-induced pain in fibromyalgia. Studies have revealed that the enhanced pain perception in fibromyalgia is associated with increased glutamatergic transmission [6, 56–58]. Functional magnetic resonance imaging has detected an increased level of glutamate in the right posterior insula of fibromyalgia patients as compared to controls and this enhanced glutamate level co-related with increased pain severity [6]. This analysis was further strengthened by a report suggesting that pregabalin induces reduction in glutamate and glutamine level within the posterior insula of fibromyalgia patients suffering from chronic pain [56]. The functional connectivity, magnetic resonance imaging study reported a decrease in functional connectivity within the posterior insula with reduction in glutamatergic activity [56]. Cohen et al. has postulated that some patients responded positively to ketamine and dextromethorphan (NMDA receptor antagonists) therapy in eliminating pain, thereby delineating that NMDA receptors might be involved in the regulation of pain in fibromyalgia [57]. Furthermore, a reduction in pain was noticed on

100 mm visual analog scale at the end of ketamine injection (0.3 mg/kg) in comparison to placebo controls [59].

Du et al. and Rogalski et al. have independently reported that BDNF interacts with tyrosine receptor kinase-B (Trk-B) on the neuronal surface that phosphorylate Trk-B residue on the receptor surface [60, 61]. The blockade of Trk-B receptor by anti-Trk-B-IgG significantly abrogated BDNF-induced hyperalgesia in rats through phosphorylation of Trk-B [62], thereby suggesting the role of phosphorylated Trk-B in downstream pain progression. Furthermore, BDNF and NGF are involved in enhancing the expression of NMDA receptors that further increase the glutamatergic sensitization [62–64]. Treatment with DL-2-amino-5-phosphonic acid (NMDA receptor antagonist) significantly reversed the NGF-induced mechanical sensitization in males [64]. Guo et al. also demonstrated that pretreatment with AP-5 (NMDA receptor antagonist) and dizocilpine maleate (NMDA channel blocker) abrogated the BDNF-induced increased paw withdrawal response to heat stimuli in rats [62]. The above investigations indicate that BDNF interacts with Trk-B receptors on neuronal membrane that leads to phosphorylation of Trk-B residue on the receptor surface, which further stimulates the release of glutamate via opening of NMDA channel and receptor modulation.

Furthermore, Nugraha et al. also reported a positive correlation between serum BDNF concentration and the age of fibromyalgia patients. The decreased level of BDNF was observed with an increase in age in healthy controls. Moreover, an increase in serum BDNF concentration was observed with an increase in depression level in fibromyalgia patients. Whereas, no significant correlation was observed between serum BDNF concentration and anxiety level in fibromyalgia patients, delineating that BDNF might be modulating depression but not anxiety in fibromyalgia patients [50]. The involvement of NMDA receptors needs to be explored in detail since clinical studies suggest that currently available NMDA antagonists offered no difference in reduction of temporal summation of pain observed in fibromyalgia patients and healthy controls [65].

Inflammatory Mediators in Fibromyalgia

Cytokines are proteins secreted by cells such as T- cells, macrophages and have a particular effect on the interaction between cells. On the basis of their activity these are of two types, inflammatory and anti-inflammatory [66, 67]. Studies have suggested a role of cytokines in pathogenesis of fibromyalgia. Wallace et al. demonstrated the role of IL-6 and IL-8 in fibromyalgia. The serum and peripheral blood mononuclear cells (BMC) were observed for the levels of cytokine (IL-2, IL-4, IL-6, IL-8, IL-10, IL-1β, IFN-γ and TNF-α) in control and fibromyalgia patients. An increased level of both IL-6 and IL-8 was observed in sera and peripheral BMC respectively, along with an increase in IL-1R antibody in fibromyalgia patients in comparison to healthy controls. Additionally, no change was observed in other cytokines except IL-6, IL-8 and IL-1R antibody [24]. This contention was further verified by the study of Mendieta et al. showing that IL-6 and IL-8 play an inflammatory role in fibromyalgia [68], who observed an increased level of IL-6 and IL-8 in the serum of fibromyalgia patients. However, no significant difference in IL-2, IL-4 and IL-10 levels were observed in control and fibromyalgia patients [69]. Meas et al. also reported an increased level of IL-1R antibody in fibromyalgia patients with more than 2 years of symptomatic history [68]. Furthermore, another independent study revealed an increased level of IL-6, IL-1ß and TNF-α in RT-PCR of the skin of fibromyalgia patients, whereas, no change was observed in healthy adult skin [70].

However, there have been studies suggesting that their data does not comply with the aforementioned studies. Hader et al. has previously reported a reduced level of IL-2 in fibromyalgia patients [71]. Further, the study of Ranzolin et al. delineated an increased serum level of IL-10 in fibromyalgia patients without a significant difference in IL-6 and IL-8 in fibromyalgia patients and the control group [51]. Some other investigations bolster the above contention of Ranzolin et al. to some extent. Maes et al. and Salemi et al. have reported that there was no significant difference in plasma levels of IL-6 in fibromyalgia sufferers and healthy subjects [72, 73]. However, increased plasma TNF-α [73], IL-10 [73, 74] and IL-8 [72, 73] were observed in fibromyalgia patients. Another study has revealed a reduced level of anti-inflammatory cytokine IL-5 in the fibromyalgia patient, but a normal level in IL-10 [75, 76].

The inflammatory cytokines are postulated to play an important role in the progression of depression [77, 78]. IL-6 and IL-8 potentiate the pain perception, whereas IL-6 also promotes fatigue and cognitive impairment that can lead to depression [22, 79], delineating that increased levels of these cytokines might be associated with these complications of fibromyalgia. IL-8 stimulates the sympathetic nervous system [22], which might be the major pathway of pain progression in fibromyalgia. The increased levels of IL-1R antibody and IL-10 in FMS might suggest the involvement of compensatory anti-inflammatory pathway along with inflammatory cascade. The IL-1R antibody has been found to inhibit the IL-1 induced hyperalgesia produced by vagal afferents [80] as well as block the expression of IL-8 [81]. IL-10 reduces the pain perception by decreasing the level of IL-6 and TNF-α production by monocytes [82]. Furthermore, there have been direct as well as indirect evidences delineating the presence of cardiovscular dysfunction attributable to endothelial derangements in patients with fibromyalgia [83–86]. An enhanced level of endothelin-1 has been

reported in fibromyalgia patients [85, 86]. Endothelins are 21 amino acid peptides, secreted by vascular endothelial cells through the action of endothelin converting enzyme and are of four types, ET-1, ET-2, ET-3 and ET-4. The isoform ET-1 is a predominant and potent vasoconstrictor that regulates blood pressure [87]. Pache et al. compared the levels of ET-1 in fibromyalgia patients and control subjects and the radio-immunoassay analysis revealed that the plasma ET-1 level was higher in fibromyalgia patients in comparison to healthy control subjects [85]. Nah et al. also reported an enhanced plasma level of ET-1 in fibromyalgia patients. Furthermore, the authors also studied the single nucleotide polymorphism of the ET-1 gene through PCR and reported that patients with 'TG' genotype/'T' allele, the endothelial cells secreted an increased amount of ET-1 in comparison to control subjects. The patients with 'TG' genotype and 'G' allele may be at a higher risk [86]. Furthermore, an increased serum level of asymmetric dimethylarginine (ADMA) and TNF-α has been observed in fibromyalgia patients [84]. The increased level of ADMA is associated with endothelial dysfunction [88, 89] and an enhanced level of TNF-α is responsible for the accumulation of ADMA and depletion of dimethyl-aminohydrolase (DDAH) which metabolizes ADMA [90], thereby suggesting that TNF-α might be responsible for endothelial dysfunction in FMS.

Several studies have reported that migraine and fibromyalgia are co-existing problems [91–93]. A survey conducted on 1730 patients revealed that 55.8% of fibromyalgia patients fulfilled the criteria established for migraine headaches [92]. Another cross-sectional study of chronic migraine (CM) and chronic tension type headache (CTTH) patients independently suggested that 66.9% of CM patients were suffering from co-morbid fibromyalgia [93]. Increased level of IL-4 and IL-5 has been documented in migraine patients [94]. Furthermore, an enhanced level of IL-6, IL-10 and TNF-α was also observed in migraine patients during acute attack [95, 96]. As discussed above enhanced level of cytokines is also reported in fibromyalgia thereby suggesting a possibility for the role of cytokines in modulating co-morbid migraine in fibromyalgia.

Anomalous Hypothalamic–Pituitary–Adrenal Axis (HPA-Axis) and Sympathetic Nervous System (SNS)

HPA axis is the core endocrine stress management system, while corticotropin-releasing hormone (CRH) is the major secretagogue peptide of this system [97] and it is a key regulator of HPA-axis responsible for the release of glucocorticoids from the adrenal gland [98]. There are various studies delineating the hypo as well as hyper-responsiveness of HPA axis in fibromyalgia patients. Crofford et al. reported a low level 24 h urinary free cortisol level in response to exogenous ovine corticotropin releasing hormone (oCRH) in fibromyalgia patients, suggesting the hypo-responsiveness of adrenal gland [99]. Women with fibromyalgia reported the hypo-responsiveness of the hypothalamic-pituitary part of HPA axis and a significant reduction in ACTH response to hypoglycemia [100]. It has been proposed that the administration of IL-6 (CRH stimulant) to fibromyalgia as well as to healthy subjects resulted in a delayed release of ACTH in fibromyalgia patients, also suggesting the reduced functioning of CRH in FMS. An abrupt increased basal level of norepinephrine (NE) has also been observed in fibromyalgia patients while no change was observed in healthy controls. On injecting IL-6, the basal NE significantly raised, while insignificant increase was observed in healthy controls, suggesting that an enhanced inflammatory response can lead to the hyperactivity of SNS in fibromyalgia patients [25].

However, the direct serum analysis studies have reported an enhanced level of CRH in fibromyalgia patients in comparison to healthy controls [101, 102]. McLean in another study reported that only pain related symptoms were amalgamated with corticotropin releasing factor (CRF) in CSF of fibromyalgia patients, whereas no correlation of CRF with fatigue and co-morbid depression was observed [103]. Moreover, it has been reported that stress affects the HPA axis functioning [103] and the temperamenting factors (stress, mood) may control the pain symptoms [104]. Enhanced stress is associated with an amplified release of CRH [105]. The above findings corroborate to the hypothesis that HPA axis abnormalities might regulate pain sensitivity in fibromyalgia.

Oxidative Stress in Fibromyalgia

An increase in oxidative stress results from dysregulation between products of oxidation and antioxidants. Various studies have demonstrated the role of oxidative stress in the pathoetiology of fibromyalgia. Neyal et al. reported an increased conversion of ferrous ion-*o*-dianisidine to ferric ion by oxidants in serum samples of fibromyalgia patients [9]. Furthermore, reduced levels of antioxidants (catalase, glutathione peroxidases and glutathione reductase) and increased levels of oxidant markers (lipid peroxides, nitric oxide and protein carbonyl) was observed in fibromyalgia patients [106]. Cordero and co-workers have observed a decreased level of coenzyme Q10 (CoE-Q10) (antioxidant) in BMC of fibromyalgia patients. The authors have also reported an increased production of reactive oxygen species (ROS) in BMC of fibromyalgia patients, suggesting that increased oxidative stress might be associated with a defective metabolism of CoE-Q10 [107]. Lister along with his co-workers observed an oxidative stress relieving impact

of CoE-Q10 supplements in patients suffering from fibromyalgia [108]. These reports were further consolidated by the reports suggesting an increased protein and lipid peroxidation in fibromyalgia patients. Begis et al. reported an increased level of the malondialdehyde (MDA), an indicator of lipid peroxidation and decreased levels of superoxide dismutase in female fibromyalgia patients [109]. However, Ranzolin et al. found no significant difference in biomarkers of oxidative stress (thiobarbituric acid reactive substances and protein carbonyl) in fibromyalgia patients and healthy controls [51]. Despite a few contradictory reports, the majority of the studies are suggestive of the involvement of oxidative stress in the pathoetiology of fibromyalgia.

It has been further reported in the literature that there is an increasing evidence for the role of oxidative stress, pain, muscle fatigue symptoms and co-morbid depression associated with fibromyalgia. Meta-analysis studies have reported that depression is associated with decreased antioxidants and increased oxidative stress markers [110, 111]. Pharmacological treatment with fluoxetine significantly reduced the oxidative stress, in addition to its antidepressant effect. Fluoxetine indirectly affects the electron transport chain (ETC) and FIFo-ATPase complex activity, that is reported to decrease the oxidative phosphorylation in rat brain [112]. Further, long term treatment with antidepressants such as desipramine, maprotyline, mirtazapine has been reported to increase the levels of superoxide dismustase and catalase significantly [113]. Burning pain, touch-evoked allodynia is documented to be present with the same frequency in neuropathy and fibromyalgia [114]. An increased level of MDA, nitric oxide, protein carbonyl and reduced levels of glutathione, catalase, and glutathione-s-transferease were observed in the chronic constriction injury (CCI) induced neuropathic pain in rats at spinal, sciatic and prefrontal cortex level, suggesting that oxidative stress is a key modulator of pain [115].Topal et al. reported an increased level of serum 8-iso-PGF2αin patients with FMS [84]. 8-iso-PGF2αis an oxidative stress and lipid peroxidation biomarker [116]. NADPH oxidase (NOX-4) is a major source of reactive oxygen species [117]. The dominant expression of NOX-4resulted in an increased level of ROS and nitrotyrosine (oxidative stress markers) in CCI-induced neuropathic pain model [118]. Furthermore, Naik et al. reported an increased and reduced level of MDA and glutathione respectively in CCI. However, the authors also observed increased levels of superoxide dismutase in CCI-induced neuropathic rats [119]. On the whole, these reports are suggestive of a comprehensive correlation between oxidative stress, neuropathic pain and fibromyalgia pain.

Role of Sex Hormones in Fibromyalgia

Gonadotrophins have varied roles in maintaining the homeostatic mechanisms. Non reproductive functions of sex hormones include vascular smooth muscle and skeletal mass buildup [120, 121]. The study of Hernandez-Leon et al. demonstrated the role of estrogens in reverting the reserpine-induced muscle hyperalgesia and tactile allodynia. Post reserpine treated ovariectomized rats showed reduced muscle pressure threshold in comparison to control. In consistent with these findings that pretreatment with 17ß-estradiol completely abrogated reserpine induced muscle hyperalgesia and tactile allodynia, suggesting the role of ovarian hormones in attenuating fibromyalgia associated muscle hyperalgesia [8]. The authors reported that reduced estrogen level during early menopause phase in fibromyalgia patients is associated with an increased pain perception in comparison to late menopausal patients, suggesting the role of estrogens in fibromyalgia [122].

The fluctuations in pain severity have also been documented to be associated with change in progesterone and testosterone levels. The peak release of progesterone and testosterone was associated with a decrease in pain severity [123]. Investigations on the treatment of fibromyalgia patients with testosterone revealed the pain and the fatigue ameliorative effect of sex hormones. Transdermal application of 1% w/w testosterone gel for consecutive 28 days to premenopausal women with fibromyalgia significantly increased the serum testosterone levels and the raised serum level of testosterone was inversely associated with pain and fatigue symptoms of fibromyalgia [124]. Estrogen was found to be a key modulator of 5-HT in brain [125, 126]. It has been stated clearly that reduced level of 5-HT is associated with increased pain perception and depression in fibromyalgia [28, 34]. The transdermal administration of estradiol is found to revert the cognitive and memory impairment due to depletion of tryptophan and down-regulation of brain serotonergic function [126]. These findings suggest that sex hormones may boost up the 5-HT functioning in the neurons, thereby improving the memory and behavioral effects of serotonin. Literature reveals that men have low level of estrogens. However, the prevalence of fibromyalgia is higher in women, suggesting the dual face effect of estrogens (pro and anti-nociceptive) [127]. The above findings lead to the various possibilities that estrogens are not the sole regulatory aspects of fibromyalgia that differentiate fibromyalgia's prevalence in both sexes, rather the higher levels of testosterone in men as compared to women may also influence the prevalence difference in both sexes.

Role of Opioid Peptides in Fibromyalgia

Endogenous opioids are the self-synthesized opiate like peptide (endorphins, dynorphin and enkephalin) that regulate vital functions, such as relieving pain and depressive symptomsetc. in the body. Exogenous opioids on the other hand, are the substances administered exogenously, but bind with similar opioid receptors to mimic the functions of endogenous opioids [128]. Panerai et al. reported a reduced level of ß-endorphins in the peripheral BMC of fibromyalgia patients [10]. Furthermore, a consistency came from a report delineating that transcranial direct current stimulation therapy (tDCS) decreased the pain perception by 39% in fibromyalgia patients [129]. Moreover, a decrease in Hamilton depression and anxiety scale reading was reported along with an increase in serum ß-endorphin levels, suggesting that enhanced ß-endorphin level might be associated with decreased pain, anxiety and depression [129]. The aforementioned findings were consistent with the earlier report of Ignelzi and Atkinson proposing a role of ß-endorphins in relieving pain [130]. Furthermore, it has been reported that ß-endorphin suppresses the inflammatory phase of nociception, indicating the anti-inflammatory effect of endorphins [131, 132].

However, there have been reports documenting an enhanced level of Met-enkephalin-Arg^6-Phe^7 (MEAP) in the cerebrospinal fluid of fibromyalgia patients. These patients also exhibited a low pain threshold and increased number of tender points in comparison to healthy controls and patients with low back pain [133]. A series of lidocaine injections in the tender points of fibromyalgia patients resulted in a reduction in pain perception along with a decrease in plasma met-enkephalin concentration [134], suggesting the possible pain enhancing potential of enkephalins. Vaeroy et al. also reported an increased level of both pro-enkephalin and pro-dynorphin peptides along with an increase in pain perception in fibromyalgia patients. The authors also reported a complicated interplay between MEAP with dynorphin A and ß-endorphin and also with products of dynorphin A and ß-endorphin breakdown indicating the involvement of these peptides in pain perception [135]. Furthermore, pharmacological treatment with low dose of nalotrexone (LDN) (opioid antagonist) has been reported to be effective in lowering the pain, stress and fatigue symptoms of FMS and decrease ESR suggesting LDN might lower the pain perception through anti-inflammatory pathway manifested through inhibition of microglia [136].

However, a few contradictory reports were also presented before the aforementioned studies, suggesting no involvement of opioid peptides in the pathophysiology of fibromyalgia.Vaeroy et al. and Yunus et al. reported no change in levels of ß-endorphin in CSF and plasma respectively [137, 138]. Further, no significant amalgamation was observed between pain and ß-endorphin levels in fibromyalgia patients [139]. Also, no significant difference in pain sensitivity and mood was observed between fibromyalgia women patients and control women with nalotrexone treatment at a dose of 50 mg [140]. This endorses the contention that LDN manifests its effect through inhibition of inflammatory microglia. However, exhaustive studies are needed to establish the involvement of opioid peptides in FMS.

Chronic Hepatitis C Virus Infection and Fibromyalgia Syndrome: Immunological Similarities

According to ACR 1990 criteria, Kozanoglu et al. evaluated the prevalence of fibromyalgia in chronic HCV infected patients and non-HCV subjects. The results indicated 18.9% HCV infected patients and 5.3% non-HCV subjects were having symptoms of fibromyalgia. Improper sleep, increased number of tender points and fatigue was higher in HCV patients in comparison to non-HCV subjects [141]. Pharmaco-epidemological data have revealed that 15% of the fibromyalgia patients were infected with HCV in a study group comprising 112 patients [142]. In another independent study of the 90 HCV patients, 16% of patients were documented to have symptoms of fibromyalgia [143]. Cacoub et al. has documented that 15% of total 1202 chronic HCV patients studied were also fibromyalgic [144]. Patients with HCV infection exhibit CD4+ and CD8+ responses. Both types of responses were characterized by the release of different subsets of cytokines, i.e. IL-2, IFN-γ, TNF-α (CD8+ cell responses) and IL-4, IL-5, IL-10 (CD4+ cell responses) [145]. Furthermore, Cacciarelli et al. also a reported an increased level of IL-2, IL-4, IL-10 and IFN-γ in chronic HCV infected patients in comparison to control subjects [146]. The prevalence of both of these conditions in one another and an increased cytokine profile in both might be a reason behind a portion of the clinical likenesses.

Fibromyalgia and Gastrointestinal Abnormalities

Literature reveals a correlation between the prevalence of irritable bowel syndrome (IBS) and fibromyalgia. 41.8% of fibromyalgia patients were found to have IBS [147]. Lubrano et al. independently documented a 20% prevalence of fibromyalgia in IBS patients in a study group comprising 130 patients [148]. Chang et al. have reported exacerbation of fatigue and disturbed sleep pattern, the effectiveness of low dose of tricyclic antidepressants,

leading to an improvement in IBS symptoms, thereby suggesting the etiological likenesses among both syndromes [149]. According to the data obtained from Taiwan National Health Insurance Research Database the risk of inflammatory bowel disease (IBD) in fibromyalgia was found to increase by 1.54 fold. Furthermore, fibromyalgia patients receiving tramadol reported a lower incidence of IBD thereby confounding to the association of IBD and fibromyalgia [150]. Increased expression of BDNF has been observed in IBS [151, 152]. Wang et al. reported that an increased level of BDNF, Trk-B and sub-P in colonic mucosa of IBS patients and suggested the implication of Trk-B pathway in mediating BDNF dependent activation of enteroglial cells, leading to visceral hypersensitivity [152]. In recent years, the role of gut microbiota-brain axis has been explored in fibromyalgia [153, 154]. Increased levels of metabolites related to the gut microbiome (hippuric, 2-hydroxyisobutyric and lactic acids) were observed in FMS patients in comparison to control subjects, indicative of an imbalance in the gut microbiome. This finding corroborates to the contention that homeostasis of gut brain axis become affected in stress evoked fibromyalgia [153]. Furthermore, a double blind, randomized, placebo controlled study on fibromyalgia patients by Roman et al. reported a positive modulatory role of probiotics. Forty patients were selected according to ACR criteria (both 1990 and 2010) and were randomly subjected to placebo and probiotic treatment. A significant improvement in impulsivity and decision making was observed with 8 weeks of probiotic administration in comparison to placebo control fibromyalgia patients [154]. Gut-brain axis is a two directional interaction between enteric nervous system and brain. Stress is a major factor that regulates gut microbiota through the HPA-axis [155, 156]. Stress induced CRH plays a vital role in modulating intestinal permeability. Chronic stress is associated with an increased epithelial defect that leads to the leakage of endotoxins into the circulation [155, 156]. Increased leakiness promotes systemic inflammation by the release of proinflammatory cytokines [157]. This suggests that the increased inflammatory response in FMS may be co-related with stress-evoked activation of the gut-brain axis.

The release of pro-inflammatory cytokines from intestinal mucosais also associated with activation of vagus nerve relaying to nucleus tractus solitarium (NTS) located in the medulla oblongata. NTS further activates the HPA axis, resulting in increased hormonal secretions [158]. Kelly et al. also examined the role of gut microbiota in depression. Transplantation of faecal microbiota in the microbiota free rats showed a depression and anxiety like behavior. The biochemical estimations further revealed an enhanced level of plasma kynurenine and kynurenine/tryptophan ratio in transplanted rats as observed in depressed donors [159]. Furthermore, Aizawa et al. examined Bifidobacterium or Lactobacillus count in the gut of patients having bipolar disorder. The authors observed a negative correlation between sleep and cortisol level with gut microbiota [160]. This suggests that alteration in gut microbiota might be linked to improper sleep and co-morbid depression in fibromyalgia. However, exhaustive studies in the coming years may provide a deeper insight into this association.

Mechanisms of Poor Sleep in Fibromyalgia Syndrome

The various studies have reported a poor sleep and fatigue in fibromyalgia syndrome [157–159]. Electroencephalography (EEG) of fibromyalgia patients revealed decreased rapid eye movement (REM) and improper stage 1 sleep [161]. Bennett et al. conducted a questionnaire symptom survey on fibromyalgia patients with symptoms > 4 years and recorded that improper non-restorative sleep was one the aggravating factor, along with morning stiffness, fatigue, pain, memory and concentration problems [162]. A significant number of patients have reported muscular pain, non-retrospective sleep, memory impairment, morning stiffness and fatigue problems [163]. Studies have suggested that improper sleep aggravates the risk of pain symptom [164–169]. Substance-P is known to regulate sleep [170, 171]. An infusion of substance-P at four different time intervals of 20 min each, at night significantly increased the cortisol level, REM sleep latency and duration of stage-1 sleep in comparison to saline treated control group [170]. Furthermore, administration of non-nociceptive dose of Sub-P (1 mM) to the mice, significantly affected the sleep pattern, period and efficiency in comparison to CSF-Sham group [171]. Sub-P also enhances the release of pro-inflammatory cytokines, which may contribute to disturbed sleep pattern [172]. Various studies have also documented the impaired secretion of growth hormone in fibromyalgia [173, 174]. Pavia et al. demonstrated the role of somatostatin in fibromyalgia. It has been suggested that the impaired secretion of growth hormone in fibromyalgia is associated with an enhanced level of somatostatin [175]. Somatostatin is found to be implicated in an improper sleep pattern. Treatment of rats with somatostatin analogue, octreotide was found to reduce non-REM sleep [176, 177].

Discussion

Various reports presented in the current review in order to delineate the different mediators involved in augmentation of various symptoms and co-morbidities associated with fibromyalgia and the possible pathways leading to these symptoms and co-morbidities. The most common presenting symptom has been generalized muscle pain of gradual onset, often following illness or an operation. The criteria established by the American College of Rheumatology in 1990 require that the widespread pain must be present in all four quadrants of the body, as well as the axial skeleton, together with 11/18 tender points [178]. However, the revised criteria for fibromyalgia categorizes the patients as fibromyalgia patients, if they possess widespread pain index is ≥ 7 and symptom scale severity ≥ 5. The pain must be present in 4 out of 5 areas, apart from abdominal, chest and jaw pain and symptoms should persist for at least 3 months [15, 16]. Other co-morbidities of fibromyalgia include depression, anxiety, migraine and GIT abnormalities [15, 91–93, 179]. A lot of work has been put forward to explore the role of other neurotransmitters in the pathophysiology of fibromyalgia syndrome. Several investigators have postulated 5-HT and D_2 receptor dysregulation in fibromyalgia [34, 43, 44]. A reduced level of 5-HT, biogenic amines and their amalgamation with symptoms and co-morbidities associated with fibromyalgia has been ascribed [7, 28, 35]. Serotonin re-uptake inhibitors are employed in the management of fibromyalgia nowadays, since syndrome is associated with the reduction of serotonin, its metabolites and transport in central nervous system, leading to depression, pain and muscular derangements [18, 28, 29, 35]. A genetic polymorphism has been observed in the serotonin transporter gene regulatory region [180]. 5-HT is found to positively regulate the HPA-axis mediated release of CRH [181]. Therefore, the hypo-responsiveness of CRH in fibromyalgia patients might be associated with reduced levels of stimulatory 5-HT in FMS patients. However, some contrary reports were also presented, revealing the enhanced level of CRH in patients with FMS [101, 102].

Dysregulation of neurotransmitters has been documented to precipitate the various symptoms and associated co-morbidities of fibromyalgia, including pain, co-morbid depression and behavioral abnormalities. Depletion of

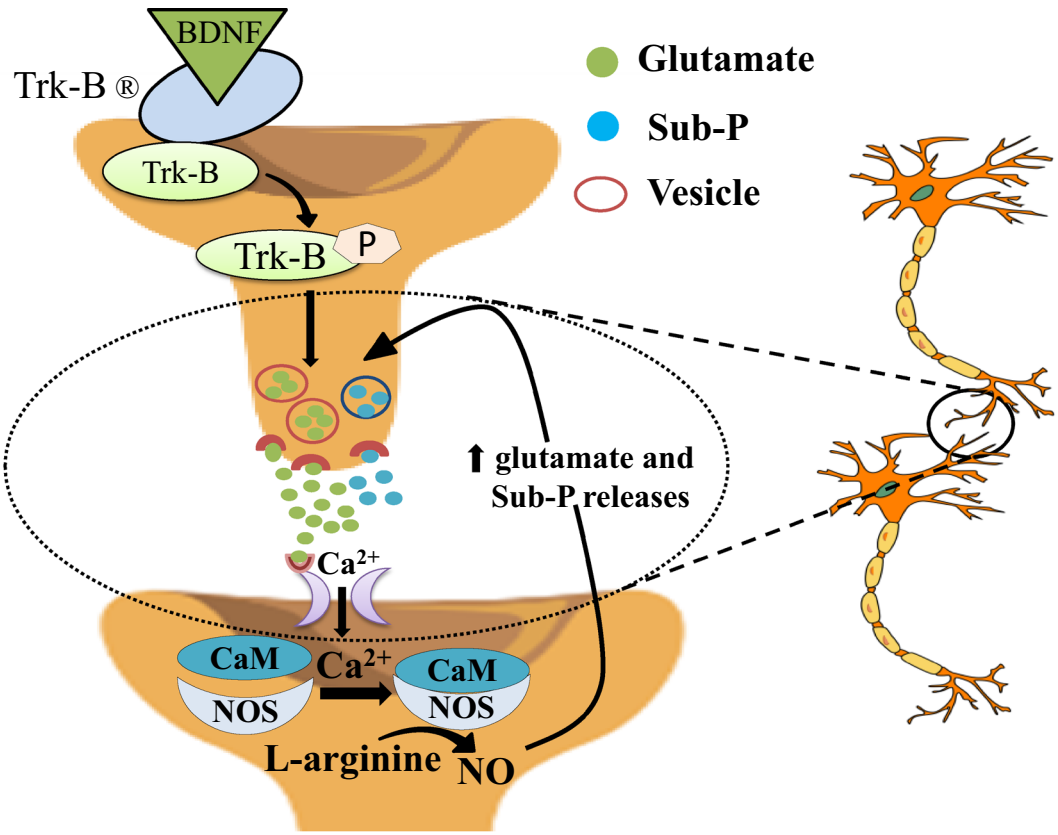

Fig. 1 BDNF induced release of glutamate through phosphorylation of Trk-B residue on Trk-B receptor and calcium dependent CaM-NOS pathway

serotonin, norepinephrine and GABA in the dorsal horn neurons of the spinal cord and increased release of substance-P and NGF that further mediates pain [14]. The hyperactivity of inflammatory (IL-6 and IL-8) as well as anti-inflammatory interleukins (IL-10) has been ascribed in FMS, suggesting the dual presence of inflammatory cascade leading to pain and cognitive impairment along with compensatory anti-inflammatory cascade [22, 24, 73, 74, 79]. The reduced serotonin and enhanced level of Substance-P and pro-inflammatory cytokines have been implicated in problems related to sleep [170, 171, 182–187]. The Sub-P regulates the release of pro-inflammatory cytokines [172]. Therefore, there might be a possibility that an enhanced level of Sub-P might stimulate the release of pro-inflammatory cytokines, thus leading to improper sleep in fibromyalgia patients.IL-8 is a pro-inflammatory cytokine and found to be involved in neutrophil trafficking across vascular walls [81]. Furthermore, a correlation between the enhanced level of TNF-α and endothelial dysfunction has been elucidated by various research groups [72, 84]. TNF-α showed a positive correlation with ADMA in fibromyalgia patients, (a novel risk factor for endothelial dysfunction) [84]. Cytokines might also be implicated in co-morbid migraine. The reports have documented the role of cytokines in the pathophysiology of migraine [94–96, 188]. Thus, the enhanced level of cytokines in FMS might also be a leading cause of co-morbid migraine. Moreover, they were also found to be implicated in the immunological likeness among fibromyalgia and HCV infection [141].

Additionally, the role of BDNF, NO, glutamate and substance-P has also been explored in FMS [11, 23, 102, 189]. It has been reported that NMDA receptor activation results an increased nitric oxide levels through nNOS activation [190, 191]. This NMDA activation has been found to produce nociception via activation of NO pathway [192, 193]. Possible hypothetical pathway leading to pain in fibromyalgia might be that the BDNF binds with a Trk-B receptor that causes a phosphorylation of Trk-B residue on receptor surface, which might enhance the release of NO through activation of the NMDA receptor. The activation of NMDA receptor potentiates the inward movement of calcium, which further activates the calmodulin dependent nNOS that results in an increased production of NO [194–196]. The release of NO at the synaptic cleft further triggers the release of pain mediators such as glutamate and substance-P from pre-synaptic neuron (Fig. 1), thus leading to pain [194, 196]. The enhanced expression of BDNF has also been reported in co-morbid IBS [151,

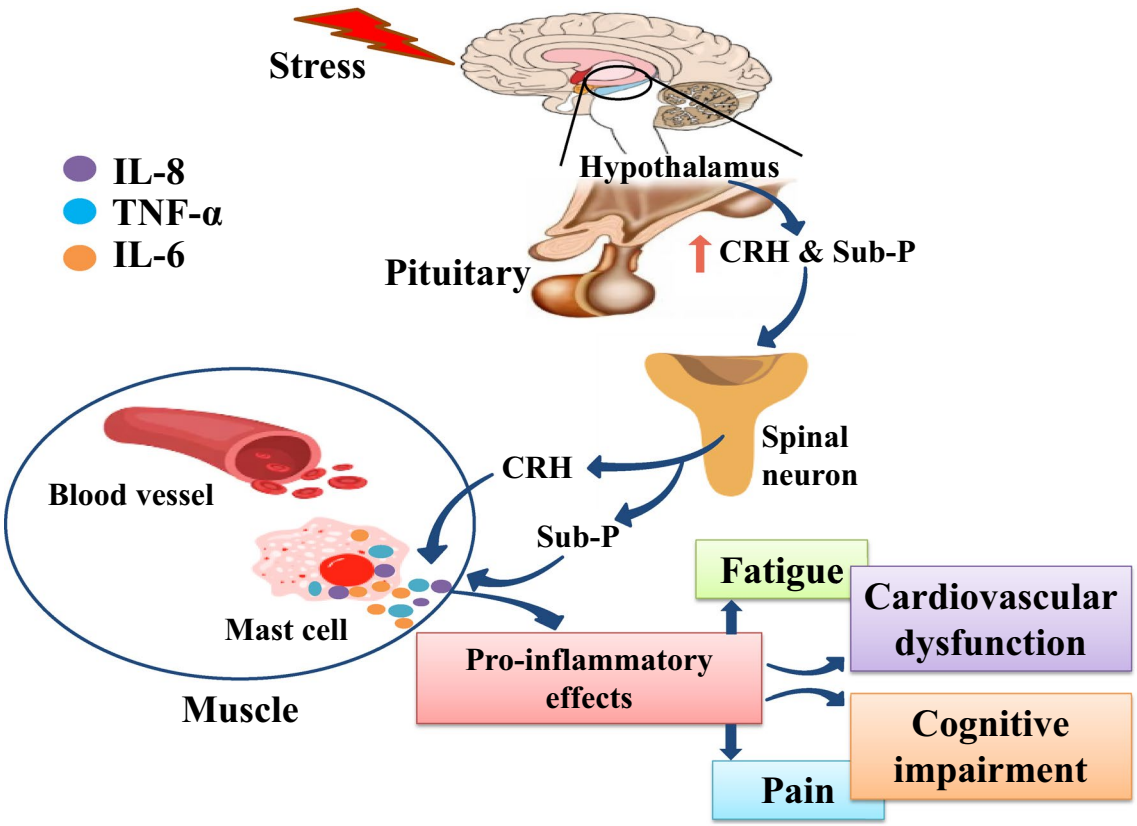

Fig. 2 Stress evoked enhanced levels of CRH and substance-P leading to a stimulatory release of cytokines through activation of mast cells and subsequently resulting in pro-inflammatory effects

152]. Trk-B has been suggested to be involved in BDNF dependent visceral hypersensitivity in IBS [152]. Furthermore, an implicatory association between IBS and HPA axis via gut-brain axis has been reported [154]. The co-existing nature of fibromyalgia and IBS and improvement in CNS activity with probiotics, suggests that gut-brain axis might have an associatory linkage between fibromyalgia and IBS. Outside the brain, the mast cells have been a possible target of CRH, prompting to increased inflammatory processes, leading to pain [197, 198]. According to the study of Tsilioni et al. CRH is an important factor along with substance-P to stimulate mast cells for release of IL-6, IL-8 and TNF-α, which could further enhance the release of CRH and substance-P that leads to pro-inflammatory effects [102], suggesting the possible pathway of an enhanced level of CRH, Sub-P and cytokines (Fig. 2). Although prevalence of fibromyalgia is much higher in females as compared to males, but not much literature is available regarding the role of sex hormones in fibromyalgia. Studies have suggested the antinociceptive and anti-inflammatory effect of estrogen and progesterone to be through up regulation of the serotonergic pathway [126]. Similarly the role of opioid peptides in fibromyalgia is controversial. There are conflicting reports for the role of opioid peptides. Some investigations have suggested pain ameliorative effect of opioid peptides in fibromyalgia while other reports have suggested the pain potentiating effect [10, 128–130, 133–138]. Some reports also suggested the non-involvement of endogenous opioid peptide in fibromyalgia [132, 133].

From the above discussion, it can be concluded that fibromyalgia is a complex disorder, including a wide array of elements in its pathophysiology. The broad central and peripheral components of fibromyalgia includeneurotransmitters, substance-P, NGF, BDNF, HPA axis elements, inflammatory cytokines, reactive oxygen species and gut brain axis.

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