Targeting fibromyalgia pain: brain–spinal cord and peripheral contributions

Fibromyalgia (FM) is a complex chronic pain syndrome with a well-defined clinical phenotype that results from disordered central pain-related mechanisms. The etiology is multifaceted with links to genetic factors, personality, psychological distress, environmental triggers and peripheral musculoskeletal function. Central brain and spinal cord 'top-down' mechanisms dominate the pathophysiology of FM. We review the disordered pain-related neurological processes that are present in FM and discuss treatments that target these relevant mechanisms.

KEYWORDS: brain ■ diffuse noxious inhibitory control ■ DNIC ■ fibromyalgia ■ pain ■ psychological ■ spinal cord ■ stress

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Fibromyalgia (FM) has a typical clinical phenotype characterized by widespread chronic pain and tenderness, fatigue, sleep and cognitive abnormalities, and emotional distress [1,2]. The use of research-based classification criteria has resulted in considerable insight into FM [3] and the use of different diagnostic criteria aids diagnosis in the clinic [4]. All criteria for FM rely only on clinical history and examination. In all societies studied it has a high prevalence and high impact. FM commonly occurs as the sole clinical problem but it may also associate with many other illnesses, including various rheumatic diseases.

Many causes of FM have been considered, ranging from primarily peripheral mechanisms to primarily central ones. For instance, abnormality in muscle was once proposed as a primary generator of pain in FM. Although some peripheral tissue changes are indeed present, current evidence indicates that there is no primary peripheral nociceptive cause for FM [5].

In contrast, FM is now considered to be the prototypical central chronic pain syndrome. A number of processes likely contribute to the FM mechanism, ranging from genetic polymorphisms coding for serotonergic or catecholaminergic systems, to triggering environmental insults such as infection, trauma or psychological distress [6]. We consider that the FM mechanism is generated centrally and this mechanism in turn both causes and modulates the downstream clinical effects, particularly the core features of musculoskeletal pain and tenderness, which contribute to the FM phenotype. Treatment paradigms therefore need to reflect the 'upstream' driving mechanisms of FM.

Relevant anatomical pathways

We commence this article with a brief outline of pain-related pathways that are involved in FM [7]. At the periphery, nociception is initiated by activation of low- and high-threshold nociceptors that transmit via fast conducting A-δ fibers and slow conducting C-fibers, respectively. In turn, these fibers synapse with second order neurons in the dorsal horn of the spinal cord. These include superficial second order neurons that primarily ascend to supraspinal structures and also more deeply place wide-dynamic range neurons that have a broader range of functions. These secondary afferents cross in the medulla and ascend as the medial lemniscus to the thalamus. Several of the thalamic nuclei are concerned with pain – the lateral nuclei deal mainly with sensory/discriminative aspects and the medial nuclei with 'affective' pain. From here, further afferents ascend to primary and secondary sensory cortices, the anterior insula and the cingulate gyrus.

Descending impulses, originating in the emotion-linked brain regions, pass through midbrain structures including the raphe nuclei, in the upper medulla, periaqueductal grey and locus coeruleus, and then back to the dorsal horn via reticulospinal fibers. These descending pathways allow modulation of pain and other sensory input by higher central structures. This pathway has been termed the diffuse noxious inhibitory control (DNIC) pathway.

■ Pain pathways in FM

A number of studies have shown abnormal reactivity to peripheral stimulation in FM. A-δ nociceptor stimulation in FM results in increased cerebral evoked responses in the somatosensory

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cortex [8]. Repetitive stimulation of C nociceptive fibers results in temporal summation in the spinal cord in normal controls, however this process is exaggerated in FM [9]. These observations indicate increased sensitivity to peripheral nociceptive sensory stimuli in FM and reflect the process of central sensitization [10].

In healthy individuals, pain triggers both innate protective reflexes and various brain-related inhibitory mechanisms, including the DNIC system. Patients with FM have disordered function of ascending pain – reflex interactions [11] and also of the descending DNIC system [12,13]. This reflects a change in central brain-related control of spinal cord-related pain processing.

This change in spinal cord sensitivity allows peripheral inputs from pain-generating musculoskeletal tissues to further modulate the FM process. In addition, peripheral sensory inputs of non-noxious nature are more likely to be involved in the clinical features of FM [14].

The role of central sensitization is critical to the pathophysiology of FM. The brain is both the generator of pain-related sensory dysfunction in FM and also the receiver of the pain itself. We therefore start with a review of the brain as a target for FM intervention. In this article, we highlight interventions that target selected components of the FM cascade but in doing so we recognize that many drugs and other interventions will likely influence more than one aspect of the pathway. Figure 1 identifies the relevant parts of these pathways focussing on brain–spinal cord interactions.

The brain in FM

Multiple studies using functional neuroimaging have shown critical differences in central pain processing FM compared with controls, particularly differences in the affective processing of pain.

SPECT techniques, using radiotracers, infer neural activity from localized increases in regional cerebral blood flow (rCBF). A range of rCBF abnormalities have been found in FM, including reduced flow in the dorsolateral frontal cortical areas of both hemispheres, thalamus and head of the caudate nucleus, inferior pontine tegmentum, superior parietal cortex, and the gyrus rectalis [15]. These studies indicate that a range of functional abnormalities related to pain processing occur in FM and involve a variety of areas in the brain.

SPECT studies have shown hyperperfusion of the somatosensory cortex and areas involved in sensory pain processing, but importantly, significant hypoperfusion of the amygdala and anterior insula, areas important in the affective–attentional dimension of the pain response [16]. Differences between FM and depression, a common comorbidity of FM, are seen. Hypoperfusion of the amygdala and anterior insula is also seen in depressed patients, however, changes were not present in the somatosensory cortex. These changes correlated with clinical outcomes at 12 months, including the clinical severity of the FM.

Functional MRI (fMRI) also uses rCBF to demonstrate central neural activation patterns and has revealed that there is increased blood flow to pain-processing areas at a lower threshold in FM patients than controls [17]. Furthermore, fMRI has been used to demonstrate changes in cortical intrinsic connectivity in FM. Areas involved in self-referential thinking and the maintenance of the brains 'resting state' display greater connectivity to regions involved in pain processing in FM compared with healthy controls [18].

Magnetic resonance spectroscopy (MRS) assesses brain metabolism by determining the concentration of certain metabolites such as creatine or glutamine. FM patients have significantly higher levels of glutamate and combined glutamate and glutamine within the right posterior insula compared with controls and this correlates with lower pressure pain thresholds [19]. It is noted that medications that down-regulate glutamine, such as the α-2-δ ligands, are beneficial in FM.

Psychological factors

Several psychological factors have been identified as being more commonly represented in patients with FM than in the general population. These include vulnerable personality, negative life events, catastrophization and passive pain coping mechanisms [20,21]. An increased incidence of anxiety in FM may facilitate this background emotional distress. All these factors link to dysfunctional processing of pain in FM by influencing downward pain control pathways (see 'Descending pathways in FM' section).

In addition, as with other chronic pain disorders, the incidence of depression is greater compared with the general population, although no causative link exists between depression and FM [21]. An increased incidence of anxiety in FM also promotes background emotional distress further adding to the emotional burden to the patient.

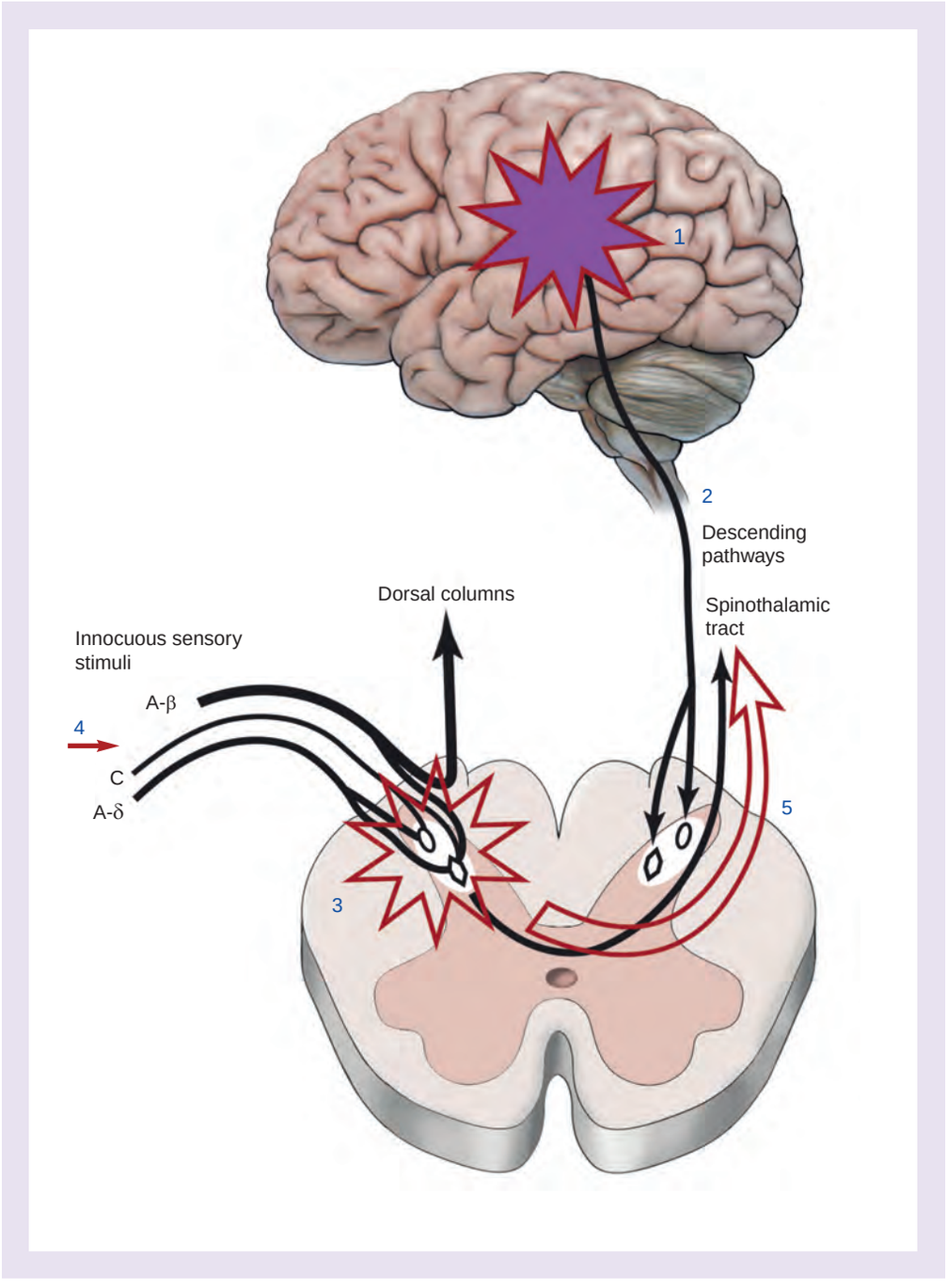

Figure 1. Top-down model of fibromyalgia. Central emotion-related brain areas **(1)** change function of descending pain modulatory system **(2)** causing sensitization of deeply placed pain-related projection neurons in dorsal horn of spinal cord **(3)**. Sensory stimuli have important connections to this region **(3)** and thereby innocuous stimuli **(4)** can 'gain access' to the pain system, with muscle and joint now causing pain. A-β fibers are mechanoreceptors, and C- and A-δ fibers are nociceptive. Star shape indicates sensitization and curved arrow indicates pain.
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Sleep disturbance

Sleep disturbance is very common in FM. Sleep difficulties include initiating and/or maintaining sleep, and unrefreshing sleep [22]. Night pain in FM can disturb sleep and poor quality sleep can modulate pain mechanisms. In healthy volunteers, it has been demonstrated that when sleep patterns are disturbed, specifically slow-wave sleep, temporary musculoskeletal and mood symptoms appear [23–25]. Furthermore, poor sleep can predict pain, which in turn can predict impaired physical functioning, and also predict depression [26].

The stress system

The hypothalamic–pituitary–adrenal (HPA) axis provides a pivotal and dynamic link between our emotions and neuroendocrine function. Multiple studies have explored the link between chronic stress and the subsequent development of FM with its associated neuroendocrine abnormalities [27,28] . Resultant dysfunction of this axis reflects the central mechanisms in FM and also provides a possible cause of associated nonpain FM features, such as fatigue [29].

Exposure to stress during childhood has the effect of raising the 'tone' of the HPA axis, with exaggerated adrenocortical trophic hormone (ACTH) response and exaggerated cortisol response to stressors in later life. In FM, there is abnormal hypersecretion of ACTH in response to stress as well as depressed autonomic function [30] However, FM patients have elevated basal levels of ACTH, and reduced levels of IGF-1, free iodothyronine, growth hormone (GH), estrogen and urinary cortisol [31,32]. This contrasts with anticipated 'chronic stress' response or exaggerated cortisol response. Some of these neuroendocrine and hormonal dysregulations are possibly related to altered levels of 5-hydroxytryptamine in these patients or abnormalities in sleep [33].

While chronic stress may lead to changes in certain hormones and neurotransmitters, resulting in various manifestations of FM such as pain and fatigue, it is also noted that the chronic pain present in FM can also give rise to psychological stress, and thereby also cause changes in neuroendocrine axes.

Other neuroendocrine dysfunction

Some of the symptoms of FM and GH deficiency are similar, including low energy, reduced exercise capacity, dysthymia, muscle weakness and impaired cognition. Evidence that GH deficiency may play a role in FM comes from a randomized, double-blinded, placebo-controlled study in which subjects with FM, who had daily subcutaneous injections of GH over 9 months, showed significant improvement in overall symptoms and tender points [34]. Further studies have not shown such clear outcomes.

Neuropeptide Y may represent the functional sympathetic output of the CNS and has been found to be elevated in FM. Oxytocin has both anxiolytic and antinociceptive properties and has been found to be low in patients with FM and high levels of pain, stress and depression [35]. Their role may be less causal and more a consequence and warrants further investigation.

Targeting treatment: brain

The use of varied psychological and physical treatments to modify higher centre processing has become fundamental in the management of FM.

Education

Education and explanation are core management strategies in FM [36]. They inform the individual and reduce anxiety about the nature of the condition. A successful FM treatment program may need to involve a multidisciplinary team and various modalities individualized for each patient. The team may include the physician, a psychologist, physiotherapist and an exercise physiologist. Typically, once diagnosed, the patients must also be assessed for psychiatric comorbidities, barriers to treatment and other social issues, all of which are likely to impact treatment choices.

Exercise

Exercise is another core management strategy. It likely has both central and peripheral benefits on the FM mechanism (see 'Peripheral contributions' section). Centrally, exercise promotes well-being and control and decreases stress, all beneficial for FM [37,38]. Exercise results in positive modulation of abnormal levels of norepinephrine, endorphins, cortisol and some inflammatory cytokines [39]. Exercise has been shown to reduce symptoms of fatigue and pain and improve sleep in FM. A meta-analysis involving 3180 subjects found statistically significant and clinically important improvements in pain (number needed to treat [NNT] = 9) and physical function (NNT = 5) following a community-deliverable exercise program [40]. The magnitude of the positive effects of physically based treatments was comparable with drug treatment judged effective for arthritis. A Cochrane review found that aerobic-only exercise training has positive effects on global wellbeing, physical function and possibly on pain and tenderness. Strength and flexibility remain underevaluated however, strength training may have a positive effect on FM symptoms [41].

Cognitive behavioral therapy

In most studies, cognitive behavioral therapy (CBT) provides worthwhile improvements in pain-related behavior, coping strategies and overall physical function. Sustained improvements in pain have been most evident when individualized CBT is used to treat patients with juvenile FM [42–44]. Studies show that CBT, as a single treatment modality, is effective but does not

offer any distinct advantage over well-planned group programs of education or exercise, or both. It has a clear place in the treatment of FM as an adjunctive therapy in combination with other modalities, but its role in the management of FM needs further research.

Cognitive behavioral therapy has been shown to attenuate the nociceptor flexion reflex in FM patients [45], implying that modulation of central psychological processes has strong links to downstream pathophysiology of FM.

Mind–body therapies

A number of mind–body therapies appear to tap into important central modulatory mechanisms in FM, although the quality of evidence is variable [46]. Tai chi combines meditation, slow and gentle movements, deep breathing and relaxation, and in one study, compared with wellness education and stretching, tai chi improved pain scores, mood, quality of life, sleep and exercise capacity. Improvements persisted for 24 weeks after the study onset [47]. The mechanism is likely multifactorial but reduction in stress reactivity is likely a key factor.

Dopamine agonists

Dopamine influences sleep, behavior and autonomic arousal via its actions as a centrally acting neurotransmitter. The dopamine agonist pramipexole has shown beneficial effects in a small (n = 60) randomized, double-blind trial, where it reduced pain, fatigue and improved global function [48]. However, owing to the trial limitations, further investigation is required to validate these findings.

Sodium oxybate

Sodium oxybate (SXB) is the sodium salt of γ-hydroxybutyrate (GHB), an endogenous metabolite of γ-aminobutyric acid (GABA) with CNS-depressant properties [49]. It has been shown to increase slow wave sleep and reduce sleep fragmentation in narcolepsy [22]. GHB also modulates activity of noradrenergic, serotonergic, dopaminergic, cholinergic and glutamatergic neurons and promotes GH secretion [50].

Two double-blind randomized-controlled trials (n=339 subjects) showed that SXB improves sleep architecture in patients with FM by reducing α intrusion in nonrapid eye movement sleep (a marker of sleep disruption) and increasing slow-wave sleep [51]. SXB improves sleep, reduces pain and fatigue [52]. A 50% reduction in pain occurred in 40% of patients and more than half described a 30% reduction in the FM impact questionnaire score [53]. SXB has mild side-effects related to CNS depression and has potential for misuse.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) involves repetitive stimulation via a magnetic coil placed in a figure eight over the scalp. rTMS induces analgesic effects both in experimental pain and in other chronic pain conditions, most likely by activating pain modulation pathways. Following a 21-week course of rTMS therapy FM patients significantly improved pain, fatigue, sleep and morning lethargy scores. These clinical changes directly correlated with intracortical inhibition [54]. Benefits continue with ongoing treatment [55]

Descending pathways in FM

As previously indicated, the DNIC pathway refers to powerful signaling pathways initiated by supraspinal structures that activate descending antinociceptive pathways. Dysfunction of this pathway is thought to be fundamental to FM pain mechanisms.

These descending pathways originate in the periaqueductal grey and other midbrain centers. The monoaminergic neurotransmitters (5-hydroxytryptamine also known as serotonin) and norephinephrine (NE) facilitate this pathway. Decreased descending inhibitory 'tone' affecting the dorsal horn pain transmission neurons facilitates the pain sensitization process. This leads to an inability to inhibit irrelevant sensory stimuli, which are then perceived as pain [54,56].

Descending pain inhibition has been demonstrated in humans by the application of a tonic conditioning nociceptive stimulus. Pain inhibition (involving DNIC) is then elicited by means of applying a cold pressor test, involving submerging the patients arm in ice cold water. In healthy patients, DNIC is demonstrated by the reduction in the patient's perception of the initial 'test' stimulus. In multiple studies, FM patients have demonstrated a lower thermal pain threshold and a lesser reduction in the perception of the initial test stimulus after application of the cold pressor test – indicating that DNIC is not functioning normally in FM [13,56,57]. Abnormal attenuation of 'wind-up' pain via C-fiber activation in FM may also involve this dysfunction. The lack of DNIC dysfunction in depression distinguishes it from FM [58].

The rostral anterior cingulate cortex (rACC) is known to be important in descending executive pain modulatory function. Attenuation of rACC function is present in FM. Using fMRI, the cerebral response to individually calibrated pain provocations of a pain-free body region showed FM patients to exhibit higher sensitivity to pain provocation than controls. While there was no difference in activity in brain regions relating to affect or regions with sensory projections from the stimulated body area FM patients failed to respond to pain provocation in the rACC descending pain regulating system further elucidating dysfunction in downwards inhibitory tone [59].

Common neural networks likely link pain and sensory modulation and psychological factors. Patients with higher catastrophizing levels demonstrated higher pain intensities and lower effects of DNIC. This suggests that catastrophizing may have a significant impact on pain modulation via its influence on DNIC [60] and occurs to a far greater extent in women, consistent with the female predominance of FM [61].

Serotonin and NE are the key neurotransmitters of the DNIC pathway. Multiple studies have demonstrated a reduction in both serum and cerebrospinal fluid (CSF) concentrations of serotonergic and NE metabolites in FM [62–64]. The importance of this pathway is further emphasized by the efficacy of compounds that raise serotonin and NE levels in lessening symptoms of FM.

Opioid pathway

In contrast to the significant role of dysfunction of the descending serotonin/NE pathways in promoting FM the descending opioid pathway seems to be functioning normally in response to the pain of FM. In FM, levels of endogenous enkephalins are high, indicating an excess of endogenous opioids [65]. This contrasts with low CSF levels of biogenic amines.

To further delineate the role of opioids in DNIC, μ-opioid receptor (MOR)-PET imaging has been utilized. FM patients have reduced MOR binding potential within the amygdala, the anterior cingulate and the nucleus accumbens [66]. All of these regions play some role in nociception and pain, particularly in the regulation of the affective quality of pain [67]. Because the concentration of endogenous opioids is elevated in the CSF of FM patients, the reduced MORs could be explained owing to high occupancy by endogenous ligands or by down regulation after prolonged stimulation.

Targeting treatment: descending pathways

Serotonin-norepinephrine reuptake inhibitors & tricyclic antidepressants

The reduction in serotonergic and noradrenergic metabolites in the CSF has lead to extensive investigation of medications that target both these neurotransmitters.

Selective serotonin reuptake inhibitors, such as citalopram, are not effective in FM. However, fluoxetine and paroxetine have shown some benefit, particularly at high doses when more effects on the noradrenergic system are present, but there is a paucity of high quality trials [68]. Their effect size was small compared with Tricyclic antidepressants (TCAs) and they had no effect on fatigue. In contrast, drugs that modulate both serotonin and NE show varying degrees of benefit [14]. TCAs, such as amitriptyline, have this property and do have significant impact on the symptoms of pain, sleep disturbances and fatigue of FM [69].

The serotonin NE reuptake inhibitors, with more balanced modulation of serotonin and NE, for example, duloxetine and milnacipran, also have demonstrated efficacy in FM [70].

Typically, in assessing FM pain, achieving a 30% pain response (improvement from baseline) is considered clinically useful, and a 50% pain response is considered clinically significant. High-quality randomized-controlled trials data has shown duloxetine at 60 mg daily resulted in a relative risk 50% reduction in pain of 1.57 (95% CI: 1.20–2.06; NNT = 8, 95% CI: 5–17). Efficacy was dose dependent with 20 mg daily found to be ineffective. Duloxetine was also effective at treating sleep disturbances, but has little effect of fatigue levels [69]. Milnacipran was similarly effective in the treatment of pain, but is more effective in the treatment of fatigue symptoms than duloxetine. Milnacipran has little effect on sleep disturbance. A comparative meta-analysis showed the NNT to result in 30% pain reduction for amitriptyline, duloxetine and milnacipran was 3.54, 8.21 and 10.96, respectively [69,71]. Duloxetine and milnacipran have been shown to sustain benefit over time but there is no long-term data for amitriptyline or other TCAs.

Amitriptyline is considered the first-line agent for the treatment of FM by most international guidelines, with duloxetine and milnacipran being useful alternatives – all drugs should be used in conjunction with lifestyle and psychological therapies [36].

In addition to effects on the DNIC system, the analgesic effects of some TCAs and serotonin NE reuptake inhibitors may be contributed to by the blockade of neuronal voltage gated sodium channels in the periphery [72].

Tramadol plus paracetamol

Tramadol is an atypical opioid analgesic, with a unique mechanism of action combining MOR activity with inhibition of serotonin/NE reuptake. In combination with paracetamol, it has been shown to be effective compared with placebo with an 18% reduction in visual analog scale pain scores compared with placebo. This combination also improved FM impact questionnaire scores [73].

Opioids

In keeping with the above discussed studies which show reduced opioid receptor binding, potential exogenous opiates have been shown in clinical trials and practice to have little efficacy in FM compared with other pain states [74], and are not recommended in clinical guidelines [36].

Central sensitization in FM

There is a generalized lowering of pain sensitivity threshold in FM. Activation of peripheral nociceptor afferent fibers may play a role in the central sensitization [75], however, most evidence suggests that little continuous input is required to maintain the central sensitization. By contrast, powerful modulation from the brain plays the key role [76].

In the context of central sensitization peripheral A-β fibers (normally functioning as mechanoreceptor afferents) interact with sensitized wide dynamic receptor neurons in the dorsal horn of the spinal cord. The result is that everyday movements and sustained postures will now generate pain through functionally 'rewired' mechanoreceptor pathways. The sensory input from deeply placed spinal structures, such as joints in the low neck or back, will activate reflex phenomena when interacting with sensitized spinal cord neurons. This causes regionalized pain and other sensory symptoms as well as regional tenderness – characteristic features of the FM clinical phenotype.

A number of neurotransmitters including substance P (SP) and glutamate, which subsequently activate N-methyl-D-aspartate (NMDA) receptors promoting pain transmission, are up regulated in FM [77,78].

Substance P, a neuropeptide is released from the terminals of specific sensory nerves and binds to NK-1 receptors. It lowers the threshold of synaptic susceptibility in second order spinal neurons that in turn is released by the activation of NMDA receptors in the dorsal horn. SP can travel extensively along the spinal cord to sensitize distant dorsal horn neurons. SP is also closely associated with 5-hydroxytryptamine in the brain, particularly in areas responsible for emotion and pain perception. It has been shown to be at levels threefold greater in the CSF of FM patients [79].

Multiple animal studies have demonstrated increases in glutamate following noxious stimuli which have been correlated with hyperalgesia [76]. This is reversed by administration of the potent NMDA antagonist ketamine [80] in humans. Local pain was induced in patients with FM by injection of an intramuscular injection of hypertonic saline into the tibialis anterior muscle and pain threshold established with single intramuscular (IM) electrical impulses. During the ketamine infusion pain scores using the visual analog scale progressively reduced compared with placebo both at rest (prehypertonic saline) and with IM injection hypertonic saline. Ketamine had no significant effect on single IM electrical stimulation supporting the role of a centrally dysfunctional pain pathway rather than peripheral pain generator.

In summary, central sensitization relates to enhanced excitability of dorsal horn neurons of the spinal cord and is characterized by increased spontaneous neuronal activity, enlarged receptive fields and augmented stimulus responses to those transmitted by large and small caliber primary afferent fibers [81]. In addition, there is spontaneous pain in response to innocuous mechanoreceptor input. This process is facilitated by a number of neurotransmitters, notably SP and glutamate.

Targeting treatments: central sensitization

Pregabalin and gabapentin bind to the α-2-δ subunit of voltage-dependant calcium channels. In regard to FM, they reduce the influx of calcium into sensitized neurons in the spinal cord. This in turn reduces the release of glutamate and SP. Three large meta-analyses [70,82,83] indicate that pregabalin and gabapentin are effective in reducing pain and improving sleep and health-related quality of life in FM [84]. There is more evidence for pregabalin and no comparative studies with gabapentin. Pregabalin has similar efficacy at doses from 300 mg up to 600 mg daily and may cause more side effects (including dizziness and somnolence) at higher doses. Approximately

a third of FM patients have marked improvement of key symptoms through use of the α-2-δ ligands pregabalin and gabapentin [82,83]. Thus, in many studies and in clinical practice, approximately 30% of patients achieve 50% improvement in pain (NNT = 10) and approximately 50% achieve 30% improvement with these drugs (NNT = 7) [85]. These pain outcomes have been shown to correlate with substantial improvements in real-world outcomes such as quality adjusted life years and work attendance [86].

Peripheral contributions

To date, little evidence has been found of peripheral pain generating tissue changes in FM.

Neurogenic inflammation is present in FM and implies local tissue release of vasoactive neuropeptides [87]. SP is usually undetectable in muscle neurons but is present in the neurons of FM muscle [88]. It is likely that these changes are due to sensitized central pain pathways, rather than a fundamental role of peripheral pain generation.

Mast cells are found throughout the human body on skin and mucosal surfaces. They are stimulated to degranulate and release pro-inflammatory cytokines by physical, psychological and chemical triggers (including SP) [89,90]. Skin biopsies in FM patients show inflammatory cytokines and a 14-fold increase in mast cells [91]. Mast cell degranulation can cause local pain and tenderness, headache, flushing and abdominal discomfort [92]. The released inflammatory mediators have been hypothesized to contribute to central sensitization via tonic activation of peripheral nociceptors [91]. It is possible that the augmented degranulation of mast cells may contribute to the cycle of central sensitization, but given the body of evidence supporting a 'top-down' model, it is more likely that the dermal changes represent effect rather than cause.

Other traditional peripheral pain generators, such as osteoarthritis, spinal degenerative disease or muscle trigger points (MTPs), will provide additional inputs into the already sensitized pain system of FM resulting in augmented pain [93]. This is evidenced by the administration of anesthetic epidural blockade eliminating spontaneous pain and tender points and/or MTPs in FM patients [94]. Similarly, a single intramuscular anesthetic injection into the midpoint of the upper trapezius muscle, a common MTP site in FM, significantly increases local pain thresholds and decreases remote secondary heat hyperalgesia in FM patients [93].

Targeting treatment: peripheral contributions

Drugs

Drugs, such as NSAIDs and opioids, which act on peripheral pain generating mechanisms, have not been shown to be effective in FM [36]. However they may be useful in some instances to control input from peripheral pain generators, such as osteoarthritis, that can aggravate and perpetuate central sensitization processes [93].

Exercise

Supervised aerobic exercise training programs have beneficial effects on physical capacity and FM symptoms. Strength training may have some benefits on FM symptoms, but further evaluation is required on flexibility exercise. Exercise aids FM-related stiffness and decreases symptoms locally but also likely has benefits through central pain modulation, both in the brain and in the spinal cord [36,41].

Other

Inputs from a variety of musculoskeletal sources, including MTPs, may respond to different physical approaches with benefit on the patients symptoms [95].

Applying targeted management

Education, exercise and mind-body programs are considered core management strategies for patients with FM. Clinical effects and severity vary in patients and choice of emphasis on different modalities, thus must be flexible. Consideration of medication to modulate sleep, distress, downward pain control and central sensitization may be necessary in many patients. Attention to peripheral pain generators is always necessary [95,96].

Future perspective

Fibromyalgia is a common and high impact disorder. The clinical phenotype is characteristic but likely there are many different pathways to reach this clinical picture. Brain-related changes in function dominate the pathophysiology and these changes will become clearer over time. The links between emotional and psychological responses and the pain control system appear to hold the key to FM. Thus, elucidation of fundamental changes in control and modulation of brain-related control of spinal cord and similar subcenters need to be better characterized. Background genetic factors may influence many of the pain-modulatory centers, including the descending control systems that link to the regions of the brain that are responsive to emotions.

Understanding of the influence of peripheral inputs to the sensitized spinal cord neurons will allow for integration of many physical therapies that activate peripheral nerve, muscle and spine related structures. A revised construct of mind-body interaction is likely to result from clarification of FM mechanisms with significant influence on musculoskeletal health practices in general.

To achieve reversal of FM clinical features a new paradigm of interventions is anticipated – combinations of multitargeted drugs, physical therapies and focused psychological strategies. Effective management of FM and related disorders, with full restoration of function, is now seen to be an achievable goal.

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Executive summary

- Fibromyalgia (FM) is a common chronic pain disorder characterized by widespread pain and tenderness, fatigue, poor sleep, cognitive dysfunction and emotional distress.
- There is considerable evidence to indicate that change in the emotion-related part of the brain plays an important role in initiating and modulating the FM mechanism.
- Descending modulatory influences from the brain to the spinal cord become dysfunctional in FM allowing for increased sensitivity and altered sensory processing to otherwise innocuous sensory stimuli, resulting in pain being not due to a peripheral nociceptive cause.
- Modalities that target and modulate components of this centrally driven process will best treat the mechanism causing FM.
- Education, exercise and psychological-related approaches all modulate central FM mechanisms and are considered essential background therapies.
- Some effective drugs, such as sodium oxybate and some effective treatments, such as magnetic stimulation appear to have primary effects on the brain mechanisms.
- Other effective drugs, such as serotonin-norepinephrine reuptake inhibitors appear to impact brain–spinal cord modulatory mechanisms.
- Other effective drugs, such as the α-2-δ ligands target the dorsal horn sensitization process.
- Decreasing nociceptive input from peripheral pain generators is important but not the key element of management.
- Combinations of targeted therapies are likely to improve outcomes in FM patients.

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