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Narrative Review: The Pathophysiology of Fibromyalgia

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Primary fibromyalgia is a common yet poorly understood syndrome characterized by diffuse chronic pain accompanied by other somatic symptoms, including poor sleep, fatigue, and stiffness, in the absence of disease. Fibromyalgia does not have a distinct cause or pathology. Nevertheless, in the past decade, the study of chronic pain has yielded new insights into the pathophysiology of fibromyalgia and related chronic pain disorders. Accruing evidence shows that patients with fibromyalgia experience pain differently from the general population because of dysfunctional pain processing in the central nervous system. Aberrant pain processing, which can result in chronic pain and associated symptoms, may be the result of several interplaying mechanisms, including central sensitization, blunting of inhibitory pain pathways, alterations in neurotransmitters, and psychiatric comorbid conditions. This review provides an overview of the mechanisms currently thought to be partly responsible for the chronic diffuse pain typical of fibromyalgia.

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Fibromyalgia is a chronic pain syndrome characterized by diffuse musculoskeletal achiness, stiffness, and exaggerated tenderness at 18 specified tender points. It is a common syndrome with familial aggregation (1, 2) and is found in approximately 2% of the U.S. population (3.4% of women and 0.5% of men) (3). Although the concept of fibromyalgia dates back to the turn of the 20th century, the modern concept of fibromyalgia as a pain syndrome in the absence of otherwise apparent organic disease was established by Graham (4) in the 1950s. However, it was not until 1990 that an American College of Rheumatology committee (5) established the following criteria for a diagnosis of fibromyalgia: a history of widespread pain (involving all 4 limbs and the trunk) and mild or greater tenderness to digital palpation of at least 11 of 18 specified tender points. Despite this restricted definition (originally intended for use only in clinical studies), the core features of pain and tenderness are almost invariably accompanied by other symptoms, the most common of which are poor-quality sleep, morning stiffness, and fatigue. Although the establishment of the American College of Rheumatology criteria led to a proliferation of fibromyalgia research, this research has not, unfortunately, cleared the murky waters surrounding fibromyalgia. In fact, 17 years after the American College of Rheumatology committee established the criteria for fibromyalgia (5), no consensus exists on the syndrome's cause, its treatment, or even whether it merits consideration as a distinct clinical entity (6, 7).

Fibromyalgia may be a syndrome of dysfunctional central pain processing, and the neurologic mechanisms responsible for maintaining central pain states are now being studied. The precipitants of chronic widespread pain are unknown, but fibromyalgia seems to be a final common pathway for a myriad of conditions, or combinations thereof, ranging from the psychosocial to the mechanical to the biological. Anxiety, depression, or somatizing personality traits may predispose some patients with fibromyalgia to the development or maintenance of the syndrome (8). In other patients, physical or psychological trauma (9) or certain viruses (hepatitis B virus [10], hepatitis C virus [11], and HIV [12, 13]) may be partly responsible for initiating the events that lead to fibromyalgia.

Because of the complexity of its cause, fibromyalgia is best understood from a multidisciplinary perspective and an overly reductionist approach may be premature. For example, although it might be expedient to overlook psychological factors in trying to explain the pathogenesis of fibromyalgia, psychological processes alter (and are altered by) neurohumoral processes, such as the hypothalamic–pituitary–adrenal axis (14–18). The crosstalk and reciprocal relationships between the higher and lower cerebral cortices, between the central nervous and endocrine systems, and between the central and peripheral nervous systems demand that both investigators and clinicians remain open to the complexity of the syndrome. Our review examines some putative aberrant processes that may lead to fibromyalgia, including potential abnormalities in peripheral tissue (that is, muscle), changes in pain processing within the spinal cord, changes in pain modulation in the central nervous system, alteration in neurotransmitters, neurohumoral abnormalities, and psychiatric associations (**Table**). We also briefly review some published hypotheses about possible precipitants of fibromyalgia.

Methods

We reviewed the mechanisms and pathophysiology of the fibromyalgia syndrome by searching English-language publications in PubMed and references from relevant articles published between 1970 and 2006. For any study to be included in our review, we had to reach a group consensus. The main search terms were *fibromyalgia, fibrositis, chronic diffuse pain, chronic widespread pain, pathophysiology, etiology, mechanism(s),* and *central sensitization.* We se-

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Table. **Pathophysiology of Fibromyalgia: Potential Mechanisms**

Mechanism	Description
Central sensitization	Amplification of pain in the spinal cord via spontaneous nerve activity, expanded receptive fields, and augmented stimulus responses
Abnormalities of descending inhibitory pain pathways	Dysfunction in brain centers (or the pathways from these centers) that normally downregulate pain signaling in the spinal cord
Neurotransmitter abnormalities	Decreased serotonin in the central nervous system may lead to aberrant pain signaling; this may partly be explained by a serotonin transporter polymorphism Decreased dopamine transmission in the brain may lead to chronic pain through unclear mechanisms
Neurohumoral abnormalities	Dysfunction in the hypothalamic–pituitary–adrenal axis, including blunted cortisol responses and lack of cortisol diurnal variation, is associated with (but is not specific for) fibromyalgia
Psychiatric comorbid conditions	Patients with fibromyalgia have increased rates of psychiatric comorbid conditions, including depression, anxiety, posttraumatic stress, and somatization; these may predispose to the development of fibromyalgia

lected articles on the basis of quality, relevance to the illness, importance in illustrating a proposed pathophysiology, or the level of attention that they have previously received in the field. Our review was not funded.

Overview of Pain Pathways

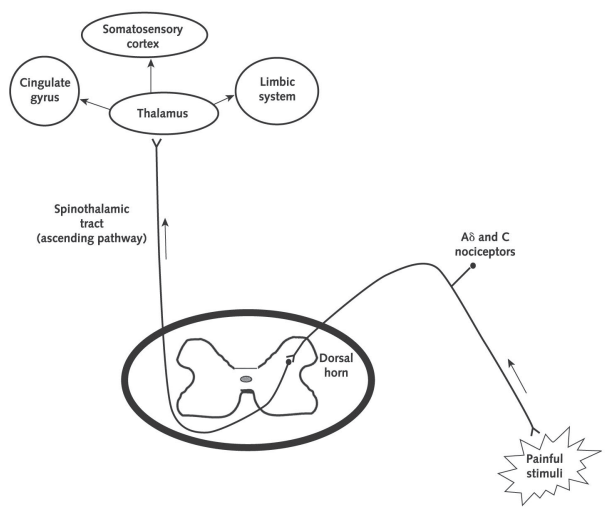
Because altered processing of pain is probably a contributor to the pathogenesis of fibromyalgia, a brief review of normal pain pathways is warranted (**Figure**). Nociceptive information arrives in the spinal cord via primary afferent nerves that converge on second-order afferent neurons in the spinal cord. The latter neurons constitute the primary ascending pain pathways (that is, spinothalamic tracts) and end at the thalamus. The thalamus distributes nociceptive information to the somatosensory cortex, where the sensory–discriminative aspect of pain is processed. It also distributes the information to other subcortical brain centers, such as the anterior cingulate gyrus (19) and the amygdala (20, 21), where affective–motivational information about pain is processed (22, 23).

Primary information carried by the ascending nociceptive pathway is modulated by several distinct descending pathways (24). These pathways originate from many areas in the brain, including the periaqueductal gray area (25), locus ceruleus (26), and hypothalamus. Although how these descending inhibitory pathways affect pain is not yet completely understood, we know that they strongly influence pain perception (27, 28).

Patients with Fibromyalgia Experience Pain Differently from Unaffected Individuals

Many clinical studies have found differences in pain processing between patients with fibromyalgia and healthy persons. Although these persons have similar thresholds for sensing normal stimuli (pressure, heat, and cold), the threshold at which stimuli become painful is lower in patients with fibromyalgia. Several studies have demonstrated this phenomenon by using subjective indices of pain measurement (29–31). More recently, investigators have objectively documented a lower pain threshold in patients with fibromyalgia by using a pain measure known as the nociceptive flexion reflex, a validated tool for studying central and chronic pain states and the effects of centrally acting analgesic drugs (32, 33). This reflex is measured (electromyographically) as the withdrawal of a proximal leg muscle (short head of the biceps femoris) in response to an electrical stimulus applied directly to the sural nerve (34). The nociceptive flexion reflex threshold refers to the level of stimulus that generates a measurable withdrawal response. In a study by Desmeules and colleagues (35), patients with fibromyalgia had a statistically significant reduction in nociceptive flexion reflex threshold compared with control participants, a finding reproduced by Banic and colleagues (36).

Figure. **The ascending pain pathway.**



Nociceptive information arrives in the spinal cord via primary afferent nerves (C and Aδ fibers that converge on second-order afferent neurons in the spinal cord). These second-order neurons, which make up the spinothalamic tract (the primary ascending pain pathway), end at the thalamus. Neurons from the thalamus then distribute nociceptive information to the somatosensory cortex, where the sensory–discriminative aspect of pain is processed, and to other subcortical brain centers, such as the cingulate gyrus and the limbic system, where affective–motivational information about pain is processed.

Neuroimaging of the brain has also objectively shown differences in central nervous system responses to pain between patients with fibromyalgia and healthy persons, which we will discuss later.

In summary, subjective testing of pain, objective evaluation of peripheral pain reflexes, and brain imaging indicate that patients with fibromyalgia experience pain differently from healthy individuals and have physiologically lower pain thresholds than those of healthy individuals.

PATHOPHYSIOLOGY OF FIBROMYALGIA

Role of Peripheral Tissues

Although the current opinion among most investigators is that fibromyalgia is not a disorder of the peripheral tissues, many studies have suggested that fibromyalgia may manifest as abnormal histopathologic findings in peripheral muscle (37). Fibromyalgia researchers studying muscle pathology have focused on altered muscle metabolism—in particular, high-energy phosphate metabolites. An early study (38) suggested that these metabolites (for example, adenosine triphosphate and adenosine diphosphate) were lower in tender points of muscle than in the same anatomical locations in control participants. However, muscle detraining results in decreased levels of these compounds (39) and patients with fibromyalgia are typically deconditioned (40). Because these studies did not match the levels of aerobic fitness of healthy control participants with those of patients with fibromyalgia, their results must be viewed skeptically.

More recently, studies have investigated fibromyalgia muscle metabolism by using magnetic resonance spectroscopy, a technique that allows for noninvasive measurement of phosphate metabolites under dynamic conditions. To our knowledge, only 1 study has been performed under dynamic conditions while being properly controlled according to the aerobic fitness levels of patients with fibromyalgia. That study found no difference in high-energy phosphate levels between patients with fibromyalgia and control participants (41).

In conclusion, earlier studies attributing the cause of fibromyalgia to peripheral tissue pathology were methodologically flawed and none has been validated. Despite the accumulating evidence against the notion that fibromyalgia is caused by peripheral lesions, groups are still searching for and publishing information on such abnormalities (42, 43). These studies should be held to a high evidentiary standard.

Role of the Central Nervous System

By the early 1990s, investigators finally agreed that the pathophysiology of fibromyalgia was probably due to aberrant central pain mechanisms (44). Researchers have since demonstrated that various central nervous system processes in the brain and the spinal cord manifest abnormalities in patients with fibromyalgia.

Imaging the Fibromyalgic Brain: Aberrant Responses to Pain Seen on Functional Neuroimaging

Neuroimaging studies have shown objective differences in brain responses to pain between patients with fibromyalgia and healthy control participants. Gracely and colleagues (45) used functional magnetic resonance imaging to document that painful peripheral stimuli (pressure applied to the thumbnail bed) increased cerebral blood flow to many common areas in patients with fibromyalgia and control participants. However, these areas had increased blood flow at much lower thresholds in patients with fibromyalgia. On the other hand, at pressures causing pain in patients with fibromyalgia but not in control participants, 2 areas of the brain were active (that is, had increased cerebral blood flow) only in the control group, suggesting that patients with fibromyalgia may demonstrate blunting of descending inhibitory pathways (further discussed later). Functional magnetic resonance imaging has also demonstrated that, compared with healthy control participants, patients with fibromyalgia experience increased brain activity in pain-relevant areas not only while receiving painful and nonpainful tactile stimuli but also while at rest (46). In other studies, positron emission tomography scans of the brains of patients with fibromyalgia demonstrate tonic reduction in baseline thalamic metabolic activity, even in the absence of painful stimuli, suggesting intrinsic abnormalities of initial pain signal processing (47, 48). However, researchers have also demonstrated decreased thalamic activity in chronic neuropathic pain, suggesting that abnormalities of thalamic function may be a signature of chronic pain in general and may not be unique to fibromyalgia (49, 50). Moreover, the abnormalities found in functional imaging of patients with fibromyalgia have not been consistent across studies.

In summary, several studies have found differences between patients with fibromyalgia and control participants through functional neuroimaging. However, they have not always demonstrated the same discrepancies (47, 48, 51). Further and larger studies are therefore needed.

Central Sensitization: Amplification of Pain as a Mechanism for Fibromyalgia Discomfort

By the early 1990s, investigators finally agreed that the pathophysiology of fibromyalgia was probably due to aberrant central pain mechanisms because no peripheral abnormalities could be found (44). The possibility that normal peripheral pain could become amplified because of nervous system dysfunction was proposed as early as 1944, when Elliot (52) suggested that the process may involve the spinal cord and thalamus. An underlying mechanism for hyperalgesia may be what is termed central sensitization, that is, enhanced excitability of the spinal cord neurons that transmit nociceptive information to the brain. Central sensitization implies spontaneous nerve activity, expanded receptive fields (resulting

in a larger geographic distribution of the pain), and augmented stimulus responses (such as abnormal temporal summation [53]), within the spinal cord. Abnormal temporal summation, or "wind-up," is the phenomenon whereby after an initial painful stimulus, subsequent equal stimuli are perceived to be more intensely painful. This magnified "second pain," which occurs in everyone, is exaggerated in patients with fibromyalgia (54).

The receptor thought to be responsible for these phenomena is the *N*-methyl-D-aspartic acid (NMDA) receptor (55–57), which is found at the postsynaptic membrane in the dorsal horn of the spinal cord. These receptors are normally inactive and do not respond to initial acute stimuli. However, after repeated neuronal depolarization, the receptors undergo activation. Experimental evidence from animal and human studies have shown that NMDA receptors are responsible for wind-up and central sensitization. Treating rats with an NMDA-receptor antagonist prevents wind-up (58). In patients with fibromyalgia, the NMDA-receptor antagonist ketamine attenuates wind-up, muscular hyperalgesia, referred pain, and muscle pain at rest (59). The NMDA-receptor antagonist dextromethorphan (a common ingredient in cough medicine) was also recently shown to reduce experimentally induced wind-up in patients with fibromyalgia and control participants (60).

In summary, mounting evidence indicates that patients with fibromyalgia experience abnormal pain amplification at the level of the spine, although the specific abnormalities leading to amplification have not been completely elucidated.

Dysregulation of Descending Inhibitory Pain Pathways: Taking the Brakes Off of Pain

Spinal sensitization to pain may also be related to abnormalities in descending efferent pathways. In healthy persons, signals originating in the brain downregulate spinal cord responses to painful stimuli. This modulatory response (also called descending inhibitory pathways or diffuse noxious inhibitory controls) seems to be dysregulated in patients with fibromyalgia. Some small studies (61, 62) have shown that, unlike healthy persons, patients with fibromyalgia do not modulate pain when noxious stimulation is applied, suggesting dysfunction in the many neural systems that contribute to the descending inhibitory pathways. In addition, pain-facilitating descending pathways may play a role in chronic pain states, such as fibromyalgia (24).

Glial Cells and the Modulation of Pain

Glial cells, long thought to be metabolically inactive support cells in the nervous system, are now recognized as playing a substantial role in modulating pain signaling (63). Glial cells and astrocytes are activated by stimuli that induce pain, such as nerve trauma, subcutaneous irritation, and intraperitoneal inflammation (64), and by neurotransmitters involved in pain signaling (63). In addition to being receptors for neurotransmitters, glial cells express receptors for bacteria and viruses (65, 66), which may explain why infection with neurotropic organisms, such as HIV, is frequently associated with fibromyalgia or other chronic pain syndromes.

Glial cells release many neuroactive substances on activation by painful stimuli, including nitric oxide, prostaglandins, leukotrienes, nerve growth factors, excitatory amino acids, and reactive oxygen species (67). Activated glia upregulate release of substance P and other excitatory amino acids from primary afferent neurons in the spinal cord and enhance the excitability of pain transmission neurons. In addition, microglia and astrocytes release proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α (68). Blocking the actions of these cytokines prevents or reverses exaggerated pain states (64).

Finally, because of the several connections that exist between groups of glia and the types of transmitters they release, activation of glial cells may cause expansion of the pain field or extraterritorial pain.

In summary, glial cells surrounding pain neurons can alter and enhance the signaling and perception of pain. Indeed, inhibition of glial activation prevents exaggerated pain states (69, 70). Although a role for glia in fibromyalgia pathogenesis is attractive, studies of glial responses in fibromyalgia remain to be conducted.

Involvement of Neurotransmitters

Serotonin. Serotonin, a neurotransmitter derived from tryptophan, is produced by neurons in the brainstem. Serotonergic neurons project from the posterior raphe nucleus to the medulla and spinal cord and from the anterior raphe nucleus and make connections throughout the cortex, limbic system, and thalamus. Serotonin is thus widely distributed and has inhibitory effects on several pain pathways. Increased serotonin in the brain leads to blunted pain signaling via decreased release of substance P in the spinal cord.

Measurements of serum serotonin levels in patients with fibromyalgia have yielded conflicting data. Although some small studies (71, 72) showed decreased serum serotonin levels in patients with fibromyalgia, decreased levels were also found in patients with osteoarthritis. A larger study (73) found no statistically significant difference between patients with fibromyalgia and pain-free persons (73). However, the relevance of these studies may be questioned because whether serum serotonin levels reflect those in the central nervous system is unknown.

Two studies have investigated central nervous system serotonin levels in patients with fibromyalgia. Russell and colleagues (74) found no statistically significant difference in serotonin levels in cerebrospinal fluid between women

with fibromyalgia and unmatched control participants. On the other hand, Houvenagel and colleagues (75) compared serotonin levels in cerebrospinal fluid in patients with fibromyalgia with those in patients with lower back pain and pain-free persons. In the study, patients with fibromyalgia had statistically significantly lower levels of serotonin in cerebrospinal fluid than did persons in either control group. Because these studies were small and their results were not concordant, no definite conclusions can be drawn.

Other studies have examined whether patients with fibromyalgia express a recently discovered polymorphism ("S" and "L" for "short" and "long," respectively) in the serotonin transporter (*5-HTT*) gene. The S allele is found in greater frequency in patients with anxiety traits and affective and obsessive–compulsive disorders. Offenbaecher and colleagues (76) observed an increased frequency of the S/S genotype in a group of patients with fibromyalgia compared with that of healthy control participants. Of note, the S/S subgroup showed higher levels of psychological distress and depression. Cohen and colleagues (77) genotyped the *5-HTT* gene in patients with fibromyalgia and healthy control participants and found a statistically significant higher expression of the S/S genotype in patients with fibromyalgia (77). These patients, as in Offenbaecher and colleagues' study, also had higher levels of psychological distress. In contrast, Gursoy (78) compared *5-HTT* polymorphisms in another group of patients with fibromyalgia who had normal psychological profiles with those of a cohort of healthy control participants and observed no statistically significant differences.

Taken together, these studies identified no differences between mentally healthy patients with fibromyalgia and healthy control participants. However, they suggest differences between control participants and the subset of patients with fibromyalgia with anxiety traits. Thus, aberrant serotonin signaling may link anxiety and chronic pain, which indicates that anxiety may be causatively linked to pain. Nonetheless, altered serotonin levels alone are probably insufficient to explain the pain state in fibromyalgia.

Dopamine. A recent review by Wood (79) focused on the mesolimbic dopaminergic system as a possible contributor to central pain states. In animal models, acute stress states activate mesolimbic dopamine neurons and induce analgesia. Prolonged stress, however, decreases mesolimbic dopaminergic output and, in turn, creates a hyperalgesic state. A recent study (80) comparing the response of female patients with fibromyalgia and healthy control participants to buspirone showed an augmented prolactin response in the fibromyalgia group. Researchers attributed this to altered dopamine sensitivity in the patients with fibromyalgia. However, the study was small and further work is needed before any conclusions can be drawn about the role dopamine may play in fibromyalgia.

Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal axis plays a central role in the physiologic response to stress (81). Studies have shown that the hypothalamic–pituitary–adrenal axis in patients with fibromyalgia is disturbed, including evidence of elevated cortisol levels lacking diurnal fluctuation (82, 83) and blunted cortisol secretion in response to stress and corticotropin-releasing hormone stimulation testing (82, 84, 85). However, these findings are not specific to patients with fibromyalgia: They are also seen in patients with depression (86) and patients with a history of child abuse (87) who do not have fibromyalgia.

PSYCHIATRIC ASPECTS OF FIBROMYALGIA

Patients with fibromyalgia have an elevated incidence of psychiatric comorbid conditions, and observational studies implicate psychopathology as playing a role in fibromyalgia in some, but not all, patients (88). Fibromyalgia subgroups with different psychiatric diagnoses may respond differently to therapies and may benefit from treatments that account for their psychiatric conditions.

Depression

Much has been written about the connection between depression and pain, so it is no surprise that much has also been written about the connection between depression and fibromyalgia (89). In primary care practices, more than one half of all patients with depression present with purely somatic symptoms (90–93) and most of these symptoms are pain (94, 95). The presence of depression worsens pain outcomes and vice versa; the reciprocal relationship between depression and pain is probably explained by their common pathways and neurotransmitters (89). Patients with fibromyalgia have increased rates of depression, which has been thoroughly detailed in several previous reviews (96, 97). Antidepressants, which help normalize norepinephrine and serotonin responses, are mainstays of fibromyalgia therapy. Despite substantial overlap between depression and fibromyalgia, most patients with fibromyalgia are not clinically depressed and fibromyalgia is therefore an independent but overlapping entity.

Anxiety and Somatization

Patients with nonorganic somatic symptoms have elevated rates of psychological distress, anxiety and depression, and functional impairment. The more unexplained somatic symptoms a patient presents with, the more psychiatric comorbid conditions she or he is likely to have (98). Cross-sectional studies of fibromyalgia have shown elevated rates of anxiety and somatization. However, because these studies examined the psychiatric profiles of patients with known fibromyalgia, it is not possible to determine whether these patients had a psychiatric comorbid condition causing fibromyalgia or whether the pain state led to psychiatric distress. McBeth and colleagues recently published the first population-based prospective study in-

dicating that certain psychiatric traits may actually precede the development of chronic widespread pain, which is often a study surrogate for fibromyalgia (99). Patients initially completed a detailed pain questionnaire and a battery of psychosocial instruments. At 12-month follow-up, the patients again reported on pain status. Patients who were pain-free at the beginning of the study but whose psychosocial battery indicated a tendency for somatization were statistically significantly more likely to develop chronic widespread pain within the next 12 months (100).

Posttraumatic Stress

The presence of tender points in patients is closely associated with their current anxiety, and patients with a history of psychological trauma associated with anxiety (for example, childhood trauma or sexual abuse) have an increased number of tender points (98). Indeed, several studies have documented that patients with fibromyalgia are more likely to have experienced abuse. Moreover, patients with fibromyalgia have increased rates of posttraumatic stress disorder. Two recent studies (101, 102) surveying for posttraumatic stress symptoms in consecutively presenting patients with fibromyalgia found a high percentage of these symptoms (57% [101] and 56% [102]). Traumatic events in the lives of patients with fibromyalgia should therefore be explored because they may be contributing to current pain and distress.

In summation, fibromyalgia is frequently associated with psychiatric comorbid conditions, which may contribute to the development or persistence of symptoms or both. Although it was previously unclear whether fibromyalgia led to psychiatric disease or vice versa, evidence is accruing that psychiatric illness (for example, anxiety, somatization, and posttraumatic stress) predisposes to the development of the syndrome.

Possible Precipitants of Fibromyalgia

Despite the difficulty inherent in addressing cause in the absence of a defined pathogenesis, many researchers have attempted to examine the triggers that lead to fibromyalgia.

Infection

A few studies suggest that viral infection may precipitate fibromyalgia in some patients. For example, patients with hepatitis C (11, 103, 104) and HIV (12, 13) have been found to have higher rates of fibromyalgia than the general population. It is presently unclear how or why viruses might trigger fibromyalgia, but central nervous system cytokine activation via viral neurotropism and subsequent glial activation may play a role (105, 106).

Physical Trauma

Several retrospective studies suggest that physical trauma can precipitate fibromyalgia (107–110). However, the problem with retrospective studies is that of selective memory: It is arguably easy for a patient to pick an event that "triggered" his or her fibromyalgia when prompted to do so. Buskila and colleagues (9) prospectively followed a cohort of patients with traumatic cervical spine injury (whiplash from motor vehicle accidents) for the development of fibromyalgia, and a relatively high percentage of patients (22%) developed the condition (9). However, most positive tender points in this group of patients were found around the injured area (the neck), suggesting that the pain was predominantly local, was distinct from classic fibromyalgia, and was possibly related directly to a mechanical difficulty. Another limitation of the study was that many participants had self-referred for their cervical spine injury. Thus, the cohort may have been self-selected to be more anxious and worried about their health than the average patient with whiplash or to have reasons for secondary gain and therefore were more predisposed to fibromyalgia. A more recent study (111) prospectively followed a cohort of 153 patients with whiplash (diagnosed in an emergency department) for 15 months, and only 1 patient developed fibromyalgia.

Conclusion

The study of the pathophysiology of fibromyalgia presents a unique and complex set of challenges, beginning with the nosology of the illness. To date, the most productive approaches to studying pain mechanisms in fibromyalgia have come mostly from applying tools used in studying other forms of chronic pain. Indeed, accumulating evidence suggests that fibromyalgia probably results from abnormal central pain processing rather than a dysfunction in the peripheral tissues where such pain is perceived. Several mechanisms may be involved, including central sensitization, suppression of descending inhibitory pathways, excessive activity of glial cells, and abnormalities of neurotransmitter release or regulatory proteins or both. These mechanisms are probably not mutually exclusive.

What is most clear is that patients with fibromyalgia experience pain differently than the general population, and they do so in the absence of disease. On the basis of the known and putative precipitants (and the conditions associated with fibromyalgia), emotional or psychiatric disturbance or both may effect and modulate pain processing to produce fibromyalgia in many patients. To be effective, future therapies for fibromyalgia will need to address the pain pathways involved in fibromyalgia; its associated comorbid conditions; or, more likely, both.

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