Central Sensitivity Syndromes: Mounting Pathophysiologic Evidence to Link Fibromyalgia with Other Common Chronic Pain Disorders

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Abstract:

The aim of this study was to review emerging data from the fields of nursing, rheumatology, dentistry, gastroenterology, gynecology, neurology, and orthopedics that support or dispute pathophysiologic similarities in pain syndromes studied by each specialty. A literature search was performed through PubMed and Ovid using the terms fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, irritable bladder/interstitial cystitis, headache, chronic low back pain, chronic neck pain, functional syndromes, and somatization. Each term was linked with pathophysiology and/or central sensitization. This paper presents a review of relevant articles with a specific goal of identifying pathophysiologic findings related to nociceptive processing. The extant literature presents considerable overlap in the pathophysiology of these diagnoses. Given the psychosomatic lens through which many of these disorders are viewed, demonstration of evidence-based links supporting shared pathophysiology between these disorders could provide direction to clinicians and researchers working to treat these diagnoses. “Central sensitivity syndromes” denotes an emerging nomenclature that could be embraced by researchers investigating each of these disorders. Moreover, a shared paradigm would be useful in promoting crossfertilization between researchers. Scientists and clinicians could most effectively forward the understanding and treatment of fibromyalgia and other common chronic pain disorders through an appreciation of their shared pathophysiology.

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A literature search was performed through PubMed and Ovid using the following search terms: fibromyalgia, temporomandibular disorder, irritable bowel syndrome, irritable bladder syndrome, interstitial cystitis, headache, chronic low back pain, and chronic neck pain. Each term was then linked to the terms pathophysiology and/or central sensitization. Eight hundred forty-nine relevant articles were reviewed with a specific goal of identifying pathophysiological findings related to nociceptive processing. One hundred seventy-six articles were original research, and 48 were major reviews or consensus statements. The bibliographies of these articles as well as unpublished peer-reviewed abstracts from major relevant scientific proceedings were also evaluated. Ultimately, 78 articles were chosen based on predetermined methodologic criteria, such as research with a theoretic framework based on known pathophysiological mechanisms, inclusion of subjects who met specialty-specific diagnostic criteria but were free of confounding comorbidities, and use of valid and reliable psychophysical testing modalities. Scientific reviews that addressed central sensitization in chronic pain disorders and used similar methodologic criteria also were included.

**PATHOPHYSIOLOGY**

The notion that persistent pain may lead to neuroplastic changes within the peripheral and central nervous system is now firmly established. It was originally observed, in animals, that repetitive C-fiber stimulation exponentially increases dorsal horn stimulation, such that the same level of stimulus produces a progressive increase in activation of second order neurons projecting to the brain (Mendell, 1966; Yunus, 2008). This phenomenon, termed "windup," represents one major mechanism through which ongoing pain produces a hyperexcitable state within the central nervous system. It is now understood that pain impulses originating in peripheral nerve endings ("nociceptors") activate both A-delta and C-nociceptive fibers. These are the nerve fibers that carry the nociceptive impulse to dorsal horn neurons in the spinal cord. Some of these neurons are multimodal and respond to the sensations of touch, pressure, temperature, and pain and are therefore called wide dynamic range neurons. Chronic pain causes a persistent activation of A-delta and C fibers, stimulating the release of neurotransmitters and neuromodulators (i.e., substance P, nerve growth factor, calcitonin gene-related peptide, glutamate, and aspartate) into the dorsal horn synapse (Urban & Gebhart, 1999). Influx of these neurochemicals sensitizes the WDR neurons such that they become hyperexcitable, responding to lower levels of nociceptive stimuli (i.e., hyperalgesia) as well as some previously nonpainful stimuli (i.e., allodynia) (Eide, 2000). Expansion of receptive fields represents another important mechanism through which central sensitization modulates the expression of hyperalgesia. This occurs as a result of prolonged excitation of WDR neurons, which in turn activates adjacent neurons, thus expanding their receptive fields beyond the site.
of the original injury. Clinically, this results in pain being experienced by stimulation of locations that had not previously provoked a pain response (Coderre, Katz, Vaccarino, & Melzack, 1993; Nielsen & Henrikson, 2007).

Although our understanding of the development of chronic pain states and hyperalgesia has traditionally focused on transmission of pain through ascending pathways (from the periphery to spinal and supraspinal centers), a growing body of research expands our understanding of descending influences on the generation and maintenance of sensitization (Heinricher, Tavares, Leith, & Lumb, 2009; Tracey & Dunckley, 2004). The periaqueductal gray–rostral ventromedial medulla (PAG-RVM) system is central to the descending modulation of pain. The descending inhibitory (antinociceptive) influences of this system have long been reported (Mayer, Wolfe, Akil, Carder, & Liebeskind, 1971). The first evidence came from studies demonstrating that stimulation of the PAG produced profound analgesia in rats (Porreca, Ossipov, & Gebhart, 2002). Further study demonstrated that the PAG-RVM involved stimulation of descending serotonergic, noradrenergic, and opioid pathways that affect an analgesic response at the level of the dorsal horn. Diffuse noxious inhibitory control (DNIC) represents one model in which nociceptive stimuli activate the PAG and RVM, producing descending inhibitory control (Marchand, 2008). DNIC is also described as counterirritation, in which one noxious stimulus inhibits the perception of a second painful stimulus (Campbell et al., 2008). Stress, attention and expectation can also activate endogenous inhibitory mechanisms, as demonstrated in the placebo literature (Benedetti, 2006).

Persuasive evidence suggests that descending pathways can play a facilitatory as well as an inhibitory role (Suzuki, Rygh, & Dickenson, 2004). Descending control through the RVM represents a balance between enhancing and inhibiting nociception and may shift to play a more pronociceptive role under certain conditions. There is reasonable evidence that descending facilitation also plays a contributory role in central sensitization and the development of widespread hyperalgesia (Heinricher et al., 2009). The neurophysiology of this system posits that under prolonged nociceptive input, neurons in the RVM undergo changes in excitability that can in some circumstances serve to maintain central sensitization (Gebhart, 2004). Neurons in the RVM are classified into “ON-cells,” “OFF-cells,” and “NEUTRAL-cells”. ON-cells play a role in descending facilitation, whereas OFF-cells correspond to nociceptive inhibition (Porreca et al., 2002). Although the role of NEUTRAL-cells is less clear, one theory proposes that they are recruited to become either ON- or OFF-cells, perhaps playing a role in the shifting balance between RVM inhibition or facilitation (Heinricher et al., 2009). A shift in balance where ON-cells become more active is characterized by a decreased nociceptive threshold as descending facilitation predominates. Thus, in the face of persistent nociceptive input, excitatory changes within the neurons of the RVM could produce an imbalance in facilitatory influences that maintain a hyperalgesic state (Porreca et al., 2002). Therefore ascending alterations characteristic of central sensitization along with the abnormal descending modulation combine to initiate and maintain widespread hyperalgesia.

Although FM, TMD, IBS, IC, headache, chronic low back pain, and chronic neck pain all display characteristics of central sensitization, pain processing alterations in these disorders could come secondary to ongoing painful input or represent a primary mechanism of the disease (Ness, Powell-Boone, Cannon, Lloyd, & Fillingim, 2005). Whether pain processing abnormalities are secondary to or precede the development of these chronic pain disorders remains an important area of research and could vary by pain processing disorder. Some of these conditions arise from pathologic changes in the periphery which lead to centralized changes in nociceptive processing, but peripheral instigators are more difficult to identify in other disorders. The following sections will review findings of central sensitization in these conditions.

**FIBROMYALGIA**

It has become a generally accepted paradigm that central sensitization and impaired descending pain modulation are two underlying mechanisms causing widespread hypersensitivity to pain in FM (Perrot, Dickenson, & Bennett, 2008; Staud & Rodriguez, 2006). Attributes of FM that support the role of central sensitization include decreased pain thresholds and enhanced sensitivity outside of typical tender point locations, expansion of pain receptive fields, increased levels of substance P and nerve growth factor in the cerebral spinal fluid, abnormal windup, and prolonged pain after cessation of painful input (Dadabhoy, Crofford, Spaeth, Russell, & Clauw, 2008; Giovengo, Russell, & Larson, 1999; Staud & Domingo, 2001). As noted earlier, windup describes the changes that occur after ongoing painful input resulting in increased excitability of dorsal horn neurons, enhanced responsiveness to painful and nonpainful input, and an increase in spontaneous activity (Staud, Price, Robinson, Mauderli, & Vierck, 2004). This phenomenon is a normal occurrence to painful stimuli, but FM patients demonstrate enhanced windup with
a greater degree of neuronal excitability and prolonged after sensations (Staud, 2007). This means that WDR neurons have a lower firing threshold and take longer to resolve following cessation of the stimuli. Research demonstrates that substance P levels in FM patients are two- to threefold that of healthy controls (Russell, 1998; Russell & Bieber, 2006). Substance P, along with excitatory amino acids, such as glutamate and aspartate, enhance the transmission of pain through the primary afferent neurons (Larson, Giove, Russell, & Michalek, 2000). Increased levels of substance P can induce hyperalgesia and allodynia by lowering the firing threshold of spinal cord neurons and extend long distances from the pain locus (Bennett, 1999). The proposed neuroplastic changes that result from central sensitization have been visualized in FM patients with functional magnetic resonance imaging (fMRI). Gracely, Petzke, Wolf, and Clauw (2002) investigated fMRI changes in FM patients and healthy control subjects while applying slow controlled pressure to the thumbnail. When applying 2 kg of pressure, FM patients rated the experience as significantly more painful and demonstrated activation of significantly more pain-related brain areas compared with the control subjects. Research of this kind provides persuasive visual evidence for brain neuroplastic changes in FM patients. Furthermore, a positron-emission tomography study performed without noxious stimuli found a significant hyperperfusion in regions of the brain involved in the sensory dimension of pain processing, whereas hypoperfusion was noted in areas associated with the affective-attentional dimension (Guedj et al., 2007).

A growing body of evidence also indicates that FM is characterized by a dysfunction in descending pain inhibition (Vierck, 2006). Studies report low levels of the serotonin metabolite 5 hydroxy-indole-acetic acid (5HIAA) in the cerebrospinal fluid of FM patients (Russell, Vaeroy, Javors, & Nyberg, 1992) and an overall dysfunction in serotonergic neurotransmission (Coaccioli et al., 2008). Serotonin plays an important role in modulating the descending inhibitory system. A deficit in the DNIC system, modulated in part by serotonin, of patients with FM adds evidence for impaired central inhibition in this disorder. Research on DNIC in healthy populations demonstrates that pressure pain thresholds in the leg decrease when inducing ischemic pain in the arm in healthy controls, indicating that pain in the arm activates descending inhibition, which inhibits pain in the leg (Kosek & Hansson, 1997). When applying the same procedure to patients with FM, pressure pain thresholds remained the same, indicating a deficit in descending inhibition. These results have been confirmed using a spatial summation procedure, in which cold pressor pain to a large area activated descending inhibition in healthy control subjects but not in patients with FM (Julien, Goffaux, Arsenault, & Marchand, 2005). These findings demonstrated that pain-inhibitory systems are not effectively activated during spatial summation in patients with FM compared with healthy control subjects. Research of this nature provides evidence for abnormalities in both the ascending and descending pathways in patients with FM.

Although the presence of central sensitization in FM has been well established, the mechanism by which this sensitization occurs is less clear. As noted, central sensitization occurs owing to ongoing C-fiber stimulation, or painful input, resulting in sustained increases in the excitability and responsiveness of neurons in the spinal cord (Zusman, 2002). While pain processing abnormalities such as deficient endogenous pain inhibition (Julien et al., 2005) have been proposed to enhance the intensity of nociception in patients with FM, research is less clear on the mechanism generating the ongoing nociceptive input needed to initiate central sensitization (Vierck, 2006). Several researchers propose that regional or focal chronic pain might produce the sustained noxious input that results in hypersensitivity of the central nervous system (Bennett, 2005; Lidbeck, 2002; Staud, 2007). This hypothesis proposes that longstanding bombardment of spinal cord neurons by A-beta and C fibers as a result of ongoing focal pain conditions gives rise to the neuroplastic changes characteristic of central sensitization (Mecus & Nijs, 2007; Nielsen & Henriksson, 2007), making regional pain conditions a possible instigator for the altered pain processing of FM. In fact, it has been proposed that regional pain syndromes precede the development of widespread pain in most patients with FM (Nielsen & Henriksson, 2007). This proposal is supported by the fact that FM is frequently associated with several focal pain conditions that also have evidence of being characterized by altered pain processing, including TMD, IBS, IC, headaches, back pain, and neck pain (Staud, 2007). These peripheral pain generators could provide the necessary tonic nociceptive input that leads to abnormal pain processing within the central nervous system. Indeed, generalized hyperalgesia has been confirmed in several of these disorders. Peripheral sensitization manifests only at the pain locus, whereas central sensitization is detected in healthy tissue distant from the pain locus. Hypersensitivity not localized to the area of ‘injury’ indicates underlying changes in the central nervous system that might be explained by central sensitization. Several research studies have reported evidence of centrally
mediated pain processing abnormalities in these FM comorbidities.

**TEMPOROMANDIBULAR JOINT DISORDER**

A growing body of literature on TMD demonstrates that some individuals with this condition display alterations in central nervous system pain-regulatory systems (Sarlani & Greenspan, 2005). Individuals with this disorder show enhanced sensitivity to a wide range of experimental pain modalities both at the temporomandibular region and at sites distant from the head and neck region, demonstrating a generalized alteration in nociceptive processing (Maixner, Fillingim, Booker, & Sigurdsson, 1995; Sarlani & Greenspan, 2003). Subjects with TMD display decreased pressure pain thresholds both contralaterally and ipsilaterally to the site of orofacial pain, suggesting the presence of centrally mediated pain (Reid, Gracely, & Dubner, 1994). Subjects with TMD also exhibit enhanced temporal summation to noxious stimuli and impaired central inhibitory mechanisms (Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998) perhaps suggesting an imbalance between descending inhibitory and facilitatory pathways in individuals with TMD (Sarlani & Greenspan, 2003). Supporting this notion are separate studies finding that ischemic pain and cold pressor tasks engaged pain inhibitory systems in healthy control subjects but not in subjects with TMD, suggesting dysfunction in the DNIC system (King et al., 2009; Sigurdsson & Maixner, 1994). Taken together, these findings provide evidence of altered nociceptive processing related to peripheral and central sensitization and impaired descending modulation of pain, similar to mechanisms found in patients with FM. Recent evidence shows that enhanced pain sensitivity may precede and even act as a genetic risk factor for the development of TMD. In a recent prospective cohort study (Diatchenko et al., 2005), healthy women under went experimental pain testing and genetic analysis. Analyses demonstrated that single-nucleotide polymorphisms of the gene that codes for catecholamine-O-methyltransferase (COMT), an enzyme whose functions include the regulation of levels of catecholamines and enkephalins, was associated with experimental pain sensitivity. Three genetic variants of the COMT gene corresponded with individuals presenting with high pain sensitivity, average pain sensitivity, and low pain sensitivity. The presence of a COMT genetic variant associated with low pain sensitivity decreased an individual’s risk of developing TMD by 2.3 times. That study demonstrated that enhanced pain sensitivity in healthy adults predicted the development of TMD and that genetic variations accounting for different levels of catecholamines and enkephalins affected both pain sensitivity and risk of TMD. Future research of this kind is needed to elucidate this relationship in other disorders of pain processing.

**IRRITABLE BOWEL SYNDROME**

Patients with IBS demonstrate similar findings of localized and widespread hypersensitivity. Studies using stimulation of local nociceptors by rectal distention have found reduced local pain thresholds, enlarged referral patterns, and enhanced spinal transmission of nociceptive signals (Coffin, Bouthassira, Sabate, Barbe, & Jian, 2004). Further research illustrates that IBS patients experience cutaneous hypersensitivity extending to the site of orofacial pain, suggesting the presence of centrally mediated pain (Reid, Gracely, & Dubner, 1994). Taken together, these findings provide evidence of altered nociceptive processing related to peripheral and central sensitization and impaired descending modulation of pain, similar to mechanisms found in patients with FM. Recent evidence shows that enhanced pain sensitivity may precede and even act as a genetic risk factor for the development of TMD. In a recent prospective cohort study (Diatchenko et al., 2005), healthy women underwent experimental pain testing and genetic analysis. Analyses demonstrated that single-nucleotide polymorphisms of the gene that codes for catecholamine-O-methyltransferase (COMT), an enzyme whose functions include the regulation of levels of catecholamines and enkephalins, was associated with experimental pain sensitivity. Three genetic variants of the COMT gene corresponded with individuals presenting with high pain sensitivity, average pain sensitivity, and low pain sensitivity. The presence of a COMT genetic variant associated with low pain sensitivity decreased an individual’s risk of developing TMD by 2.3 times. That study demonstrated that enhanced pain sensitivity in healthy adults predicted the development of TMD and that genetic variations accounting for different levels of catecholamines and enkephalins affected both pain sensitivity and risk of TMD. Future research of this kind is needed to elucidate this relationship in other disorders of pain processing.

**INTERSTITIAL CYSTITIS**

Although there have been relatively few psychophysical studies investigating widespread hypersensitivity in IC (Ness et al., 2005), available evidence supports the hypothesis that central pain amplification plays a predominant role in maintaining the symptoms of this disorder (Twiss et al., 2009). Studies show that compared with healthy control subjects, subjects with IC have significantly lower pressure pain thresholds at the masseter, trapezius, and ulnar muscles and significantly decreased tolerance of ischemic arm pain, demonstrating generalized hypersensitivity to various noxious stimuli (Ness et al., 2005; van de Merwe et al., 2008). A recent review (Klumpp & Rudick, 2008) investigating the pathophysiology underlying the pain of IC proposed that peripheral sensitization of bladder C fibers first occurs due to ongoing exposure to sensitizing factors such as
histamine, bradykinin, nerve growth factor, and tumor necrosis alpha. Hyperexcitability of peripheral pain fibers leads to persistent activation of spinal cord neurons, causing a temporal summation of nociceptive input that is centrally maintained and no longer needs peripheral input from the bladder. This potential progression leading to the development of generalized hyperalgesia in IC could occur in other regional disorders of pain processing.

HEADACHE

Several psychophysical studies report that sensitization of the central nervous system represents one underlying mechanism in the pathophysiology of headaches (Buchgreitz, Lyngberg, Bendtsen, & Jensen, 2006). This research demonstrates enhanced sensitivity to various modes of painful and nonpainful stimuli in individuals with migraines and tension-type headaches. For example, one study found that a portion of migraine headache patients had periorbital cutaneous allodynia in response to nonnoxious stimuli (Burstein, Yarnitsky, Goor-Aryeh, Ransil, & Bajwa, 2000). These authors also report findings of allodynia beyond the referred pain area into the ipsilateral head and forearm in a subset of subjects, suggesting hyperexcitability of spinal and supraspinal pain pathways that is characteristic of central sensitization. Findings of widespread hypersensitivity during and outside of migraine attacks add evidence to the proposition that migrainous central sensitization results as a consequence of increased excitability of medullary dorsal horn neurons which can be sustained despite cessation of peripheral input (de Tommaso et al., 2002). A recent population study found that a subject’s degree of tenderness was positively associated with headache frequency (Buchgreitz et al., 2006). Those authors proposed that this relation between enhanced pain perception and headache chronicity is due to the development of central sensitization from prolonged nociceptive input, a hypothesis supported by work done in the chronic low back pain (Flor, 2003; Natvig, Bruusgaard, & Eriksen, 2001) and FM (Forseth, Husby, Gran, & Forre, 1999) populations. Fibromyalgia is a common concomitant diagnosis in patients with chronic headache (de Tommaso et al., 2009).

CHRONIC LOW BACK PAIN

A substantial amount of work has been done investigating the development of central sensitization in spinal pain disorders such as low back and cervical pain. One group of researchers reported the presence of generalized hyperalgesia in these axial pain disorders by using pressure algometry to assess pressure pain thresholds in patients with chronic low back pain, patients with chronic whiplash pain, and healthy control subjects (Laursen, Bajaj, Olesen, Delmar, & Arendt-Nielsen, 2005). Pressure was systematically applied to seven body locations, including sites in the arm, back, finger, and lower leg. They found that patients with spinal pain exhibited significantly lower pressure pain thresholds in all locations compared with healthy control subjects. Specific to low back pain, a wide body of literature has documented widespread changes in pain processing through experimental pain procedures applied to the back and a peripheral site, such as an extremity. These studies have used electrical stimulation (Flor, Diers, & Birbaumer, 2004; Wilder-Smith, Tassonyi, & Arendt-Nielsen, 2002), heat stimuli (Kleinbohl et al., 1999), and pressure (Clauw et al., 1999) to demonstrate decreased pain thresholds and tolerance in subjects with low back pain. Patients with chronic low back pain also displayed generalized deep tissue hyperalgesia through the use of hypertonic saline–induced muscle pain followed by pressure algometry (O’Neill, Manniche, Graven-Nielsen, & Arendt-Nielsen, 2007). That study found that, compared with control subjects, individuals with low back pain experienced decreased pressure pain thresholds, higher pain responses, longer duration of pain, and more widespread pain in response to the experimental pain procedure. The authors proposed that the continuous nociceptive input provided by the chronic low back pain might have initiated central sensitization.

Recent imaging studies of chronic low back pain have documented neuroplastic changes in the brain, providing further evidence of altered physiologic processing at the supraspinal level. Functional MRI testing on subjects with idiopathic low back pain and healthy control subjects demonstrated that 2 kg pressure at the thumbnail in the healthy control group caused only mild pain and resulted in an increase in fMRI signaling at only one pain-related cortical region (Giesecke et al., 2004). The same amount of pressure applied to subjects with low back pain resulted in moderate pain and produced increased fMRI signaling at five pain-related brain regions. Another research team has used magnetic source imaging to document enhanced cortical reactivity and an expansion of cortical representation in response to nociceptive input in patients with chronic back pain (Flor, 2003; Flor, Braun, Elbert, & Birbaumer, 1997). That research showed increased cortical reactivity which correlated with increased duration of pain; furthermore, the cortical representation of the back was enlarged in patients with chronic back,
such that representation of the back extended into neighboring cortical areas such as the leg and foot.

**CHRONIC NECK PAIN**

Similar to studies documenting widespread hyperalgesia and central sensitization in chronic low back pain, several reports document altered pain processing in individuals with chronic neck pain. Psychophysical testing has demonstrated enhanced sensitivity to stimuli within the cervical region and periphery when applying pressure pain (Banic et al., 2004; Herren-Gerber et al., 2004; Koelbaek Johansen, Graven-Nielsen, Schou Olsen, & Arendt-Nielsen, 1999), electrical stimulation (Curatolo et al., 2001; Sheather-Reid & Cohen, 1998), and thermal stimulation (Johnston, Jimmieson, Jull, & Souvlis, 2008). Taken together, these studies demonstrated that tonic pain from a peripheral source may result in abnormal central pain processing, such that hypersensitivity is no longer dependent on peripheral input or confined to a particular region of the body (Staud, 2007; Vierck, 2006). The demonstration of decreased pain tolerance and thresholds, hyperalgesia, and allodynia at both focal pain and healthy tissue sites suggests maintenance of sensitization through central rather than peripheral mechanisms.

The demonstration of central sensitization in some individuals with regional pain disorders provides a putative unifying factor between some focal pain syndromes and the widespread pain of FM. It is likely that in some individuals, changes in central pain processing in regional pain states summate to become widespread. Thus, contemporary notions of chronic pain states posit a continuum of pain ranging from focal to widespread. On one end of the continuum is pain that is well localized, perhaps of shorter duration, and on the opposite end of the spectrum is pain that has become chronic and widespread (Macfarlane, 1999). Indeed, several studies have reported the emergence of CWP and FM from chronic low back or neck pain. The frequency with which post-whiplash injury patients develop CWP has been reported to be from 8% (Wynne-Jones, Jones, Wiles, Silman, & MacFarlane, 2006) to 21% (Holm et al., 2007), and another study (Buskila, 1997) reported that 22% developed FM after injury. One study investigating the development of FM from chronic low back pain reported that 24.5% of subjects transitioned to FM (Lapossy et al., 1995). Similarly, research has shown that 15% (Macfarlane et al., 1999) to 52% (Mayer, Towns, Neblett, Theodore, & Gatchel, 2008) of patients presenting with chronic low back pain met American College of Rheumatology diagnostic criteria for FM. Evidence of the development of CWP or FM from a regional pain disorder, taken together with research documenting the presence of central sensitization within several focal pain conditions, provides support for a continuum of pain ranging from local to widespread.

**A UNIFYING HYPOTHESIS**

A persuasive body of evidence now demonstrates that sensitization represents a unifying pathophysiologic mechanism among these painful disorders. It has been proposed that these syndromes have more in common than previously thought, specifically that they are characterized by a dysregulation of peripheral afferents and central nervous system pathways. Given the shared pathophysiologic mechanisms, these disorders have been termed “central sensitivity syndromes” (CSS) (Yunus, 2008). This underlying connection not only may explain why individuals with these peripheral disorders sometimes develop widespread hyperalgesia, but could also provide the rationale for why CSS often overlap with one another (Vierck, 2006). Epidemiologic studies have demonstrated that 75% of patients with FM meet TMD criteria and 18% of TMD patients meet FM criteria (Plesh, Wolfe, & Lane, 1996), and 32% of FM patients present with IBS and 32% of patients with IBS meet criteria for FM (Sperber et al., 1999). Similarly 55% of FM patients in one study presented with tension headaches (Campbell, Clark, Tindall, Forehand, & Bennett, 1983). Although further research is needed to conclusively establish the precise mechanisms of altered pain processing in these syndromes and to explore the presence of central sensitization in other pain disorders (Yunus, 2007), increased research is also needed to understand who is at risk for the development of centrally mediated pain disorders.

The current hypothesis posits that these disorders emerge in an individual patient when a complex interaction of genetic predisposition, enhanced pain perception, and heightened psychologic distress combines with certain environmental factors (Datchenko et al., 2006). Some caution regarding the generalizability of the CSS tag is warranted, because these individual syndromes present as focal pain complaints. For example, IC has characteristic diagnostic features at cystoscopy in terms of punctuate vascular glomerulations, pain on hydrodistention, and morphologic findings in bladder biopsies (van de Merwe et al., 2008). This may well imply that each individual CSS is driven by a specific peripheral pain generator. Further research recognizing the complex interplay between genetics, peripheral pain generators, dysfunctional pain processing, psychologic factors, and environment triggers will be integral to understanding why a subset of individuals develop chronic
pain syndromes characterized by abnormal pain processing and why a portion of those patients with localized pain disorders go on to develop WSP or FM.

In summary, a wide body of research evidence has persuasively demonstrated a connection between FM and some regional pain disorders, namely, the development of altered pain processing. An increased understanding of the basic pathophysiological mechanisms shared by these pain disorders now permits a paradigm shift where research and treatment findings in one central sensitivity syndrome might be applied to other syndromes. Collaboration among researchers and clinicians interested in these disorders will not only accelerate progress in developing mechanistic models but also assist in recognizing common risk factors for regional CSS and widespread pain disorders such as FM. Because CSS are the most common conditions a future physician will treat (Yunus, 2008), expanding insights into these perplexing disorders will positively affect the healthcare community in general.

REFERENCES


