The Science of Fibromyalgia

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Fibromyalgia (FM) is a common chronic widespread pain disorder. Our understanding of FM has increased substantially in recent years with extensive research suggesting a neurogenic origin for the most prominent symptom of FM, chronic widespread pain. Neurochemical imbalances in the central nervous system are associated with central amplification of pain perception characterized by allodynia (a heightened sensitivity to stimuli that are not normally painful) and hyperalgesia (an increased response to painful stimuli). Despite this increased awareness and understanding, FM remains undiagnosed in an estimated 75% of people with the disorder. Clinicians could more effectively diagnose and manage FM if they better understood its underlying mechanisms. Fibromyalgia is a disorder of pain processing. Evidence suggests that both the ascending and descending pain pathways operate abnormally, resulting in central amplification of pain signals, analogous to the "volume control setting" being turned up too high. Patients with FM also exhibit changes in the levels of neurotransmitters that cause augmented central nervous system pain processing; levels of several neurotransmitters that facilitate pain transmission are elevated in the cerebrospinal fluid and brain, and levels of several neurotransmitters known to inhibit pain transmission are decreased. Pharmacological agents that act centrally in ascending and/or descending pain processing pathways, such as medications with approved indications for FM, are effective in many patients with FM as well as other conditions involving central pain amplification. Research is ongoing to determine the role of analogous central nervous system factors in the other cardinal symptoms of FM, such as fatigue, nonrestorative sleep, and cognitive dysfunction.

***Mayo Clin Proc.* 2011;86(9):907-911**

ACR = American College of Rheumatology; CSF = cerebrospinal fluid; FM = fibromyalgia

Fibromyalgia (FM) is estimated to affect more than 5 million Americans (2%-5% of the adult population),[1,2] making it one of the most common chronic widespread pain disorders in the United States.[3] Fibromyalgia is the second most common disorder observed by rheumatologists (after osteoarthritis)[4] and accounts for a substantial subpopulation of patients in the primary care setting, where many patients with FM typically first present and seek ongoing care. Fibromyalgia is a persistent and debilitating disorder that can have a devastating effect on people's lives, affecting their ability to work and engage in everyday activities, as well as their relationships with family, friends, and employers.[5] This painful disorder also imposes large economic burdens on society.[6,7]

Our understanding of FM has increased substantially in recent years; it is no longer accurate to state that FM is "poorly understood."[8] Extensive research suggests that the most prominent symptom of FM, chronic widespread pain, is neurogenic in origin. The pain seems to result from neurochemical imbalances in the central nervous system that lead to a "central amplification" of pain perception characterized by allodynia (a heightened sensitivity to stimuli that are not normally painful) and hyperalgesia (an increased response to painful stimuli). Neuroimaging studies support this research, showing that FM is associated with aberrant processing of painful stimuli in the central nervous system. Functional magnetic resonance imaging studies of the brain demonstrate that a pain response can be elicited in patients with FM using a much lower pain stimulus than that needed for healthy controls.[9,10] Similar findings of diffuse hyperalgesia and allodynia, noted with both experimental pain testing and functional neuroimaging, have been noted in a number of different chronic pain states, such as irritable bowel syndrome, interstitial cystitis, temporomandibular joint disorder, and even osteoarthritis. This suggests that the same central nervous system findings that play a central role in FM are actually seen in a variety of chronic pain conditions.

Although awareness and understanding of FM have improved, it is thought that FM remains undiagnosed in as many as 3 of 4 people with the disorder (Data on file. *Decision Resources* report 2009. Pfizer, New York, NY). Greater understanding of the disorder and its management can enable clinicians to more effectively care for their patients with FM and achieve better outcomes. This concise review was developed by the FibroCollaborative, a diverse group of leading experts on FM, to provide practical guidance regarding the current understanding of FM pathophysiology and how it relates to FM symptomatology, diagnosis, and management approaches.

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Group Information: A complete list of the members of the FibroCollaborative was published in *Mayo Clinic Proceedings* (2011;86[5]:457-464).

Dr Clauw has received grants/research support from Pfizer and Forest Laboratories. He is a consultant and a member of the advisory boards for Pfizer, Eli Lilly and Company, Forest Laboratories, Cypress Biosciences, Pierre Fabre Pharmaceuticals, UCB, and AstraZeneca. Dr Arnold has received grants/research support from Eli Lilly and Company, Pfizer, Cypress Biosciences, Wyeth Pharmaceuticals, Boehringer Ingelheim, Allergan, and Forest Laboratories. She is a consultant for Eli Lilly and Company, Pfizer, Cypress Biosciences, Wyeth Pharmaceuticals, Boehringer Ingelheim, Forest Laboratories, Allergan, Takeda, UCB, Theravance, AstraZeneca, and sanofi-aventis. Dr McCarberg has received honoraria from Cephalon, Eli Lilly and Company, Endo Pharmaceuticals, Forest Laboratories, Merck & Co, Pfizer, and Purdue Pharma. The FibroCollaborative group was sponsored by Pfizer.

A question-and-answer section appears at the end of this article.

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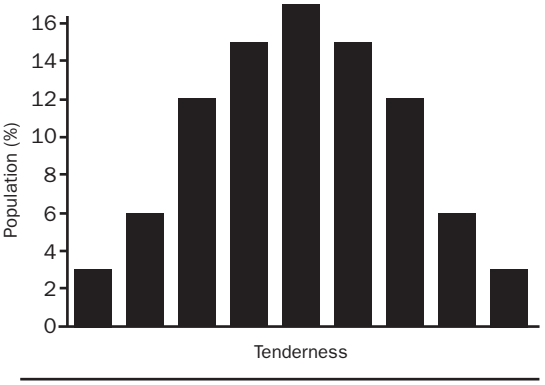

- As with most other physiological processes, the processing of pain and other sensory information by the brain and spinal cord is governed by a "volume control setting"
- Volume control is likely set genetically and modified by environmental influences
- The higher the volume control setting, the more pain experienced, irrespective of peripheral nociceptive input

FIGURE 1. Pain sensitivity in the general population. From *Rheum Dis Clin N Am*,[13] with permission from Elsevier.

NORMAL PAIN PROCESSING

In normal pain processing, the perception of pain involves 2 main groups of neural pathways: ascending and descending pathways.[8] Peripheral nerves transmit sensory signals, including nociceptive (pain-inducing) signals, to the spinal cord for transmission via the ascending nociceptive pathway to the brain for processing. Nociceptive signals are emitted when specialized receptors in the peripheral nerves called *nociceptors* are activated by stimuli such as temperature and physical pressure or impact. In the general population, perception of pain displays a normal distribution on a bell curve (Figure 1).

Descending pain modulatory pathways send both facilitatory and inhibitory signals from the brain to the spinal cord and to the periphery, either increasing or decreasing the "volume control" on incoming nociceptive signals reaching the brain. Signals in these pathways are mediated and propagated by a number of neurotransmitters and neurochemicals (eg, norepinephrine, serotonin).[8,11]

PAIN PROCESSING IN FM

In patients with FM, the 2 main pain pathways operate abnormally, resulting in central amplification of pain signals.[8,11] (This concept is also referred to in the medical literature as *central sensitization;* however, the FibroCollaborative consensus is that the term *central sensitization* has been previously used to describe a specific spinal pain mechanism, in which an initial nociceptive focus leads to regional pain amplification, and thus the term *amplification* is more appropriate because it acknowledges that many neurophysiological processes can result in this phenomenon). The origin of this pain amplification process is not fully understood but is certain to be multifactorial. Peripheral pain generators likely play some role, but most current research suggests a strong central nervous system component that is or becomes largely independent of peripheral nociceptive input. Figuratively, it is as if the "volume control setting" for pain is abnormally high in FM, the result of both increased excitability of central neurons and reduced pain inhibitory mechanisms. This analogy may be a helpful way to explain central amplification in FM to patients.

Similar to most other physiological processes, the "volume control setting" for how the brain and spinal cord process nociceptive and other sensory information varies tremendously between individuals in the population. Central amplification is likely determined at least partially by genetics and modified by environmental influences.[12] Individual variation in this distribution of pain or sensory sensitivity determines, at least in part, the lifetime susceptibility to pain or other sensory symptoms as well as symptom severity.[13] In the population of patients with FM, perception of pain is skewed to the right on a bell curve (Figure 1). The farther to the right along this distribution, the higher the "volume control setting" and pain intensity becomes, irrespective of peripheral nociceptive input.[13]

CENTRAL AMPLIFICATION AND FM SYMPTOMATOLOGY

Central nervous system dysfunction can help explain the heterogeneous constellation of symptoms and other clinical aspects of FM, including chronic widespread pain and tenderness. Patients display both hyperalgesia and allodynia. The 1990 American College of Rheumatology (ACR) classification criteria required 3 months or greater of widespread pain and pain on palpation of at least 11 of 18 tender point sites. The 1990 ACR criteria have been used to identify patients for clinical trials and to diagnose FM in patients in clinical settings.[14] The 2010 ACR clinical criteria for fibromyalgia, an alternative approach to diagnosing fibromyalgia in the clinic, include a widespread pain index and a symptom severity scale and eliminate the tender point examination.[15]

Patients with FM exhibit not only sensitivity to pressure but also a decreased threshold/increased sensitivity to a number of other sensory stimuli, including heat, cold, auditory, and electrical stimuli.[13] Additionally, FM is frequently accompanied by other, associated conditions that may also share these pathophysiological features with FM,

including irritable bowel syndrome, tension-type headache and migraine, temporomandibular disorder, chronic pelvic pain, vulvodynia, and interstitial cystitis, painful bladder syndrome, chronic prostatitis, and prostadynia.[11]

PHARMACOLOGICAL MECHANISMS FOR ANALGESIA

Analgesic agents such as nonsteroidal anti-inflammatory drugs and acetaminophen that act primarily through peripheral mechanisms are less effective for "central" pain conditions such as fibromyalgia than they are for pain due to peripheral nociceptive input. However, peripherally acting treatments may be appropriate in certain circumstances (eg, concurrent peripheral pain due to damage or inflammation of tissues from certain conditions) because it has recently been shown that the central amplification of FM can be somewhat improved by such treatments.[16]

Pharmacological agents that act centrally in ascending and/or descending pain processing pathways can be effective in many patients with FM as well as in patients with other conditions involving central pain and sensory amplification.[8] The complexity of the pathways and neurochemical abnormalities involved in FM varies from person to person, resulting in the fact that no single class of drug will work in all individuals with fibromyalgia. As with other analgesic agents and other medical conditions such as hypertension, individual patients with FM tend to respond well to certain classes of drugs but not others.[13] This analogy can be helpful in discussions with patients about treatment options, expectations regarding the need to individualize treatment, and the possibility that more than one approach may need to be explored before the right treatment or combination of therapies is found.

MECHANISMS OF FM PAIN

An extensive and growing body of evidence supports central amplification as the underlying process for chronic widespread pain in FM. Pain threshold studies show that patients with FM perceive pain at a lower threshold than healthy controls, eg, in response to pressure (dolorimetry) on some area of the body.[17] Neuroimaging data demonstrate greater regional cerebral blood flow in areas of the brain associated with pain processing at lower pain-producing pressures than healthy controls (Figure 2).

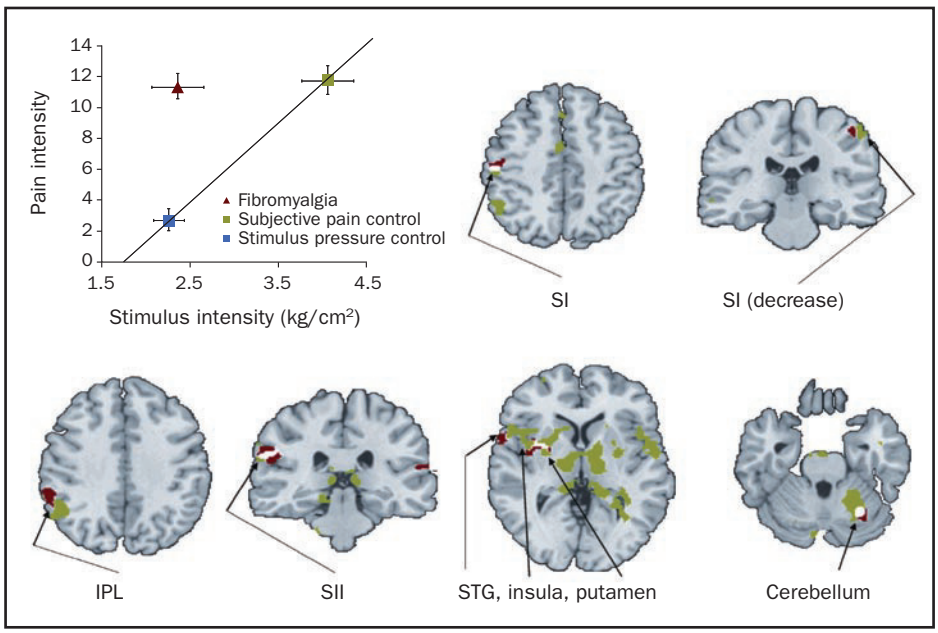

FIGURE 2. Neuroimages of regional cerebral blood flow in areas of the brain associated with pain processing in patients with fibromyalgia and controls. These images reflect responses to stimuli during pain scans. The effects of pressure applied to the left thumb sufficient to evoke a pain rating of 11 (moderate) are compared with the effects of innocuous pressure in patients with fibromyalgia (red) and controls (green), with overlapping activations in yellow. Significant increases in the functional magnetic resonance imaging signal (arrows) resulting from increases in regional cerebral blood flow are shown in standard space superimposed on an anatomic image of a standard brain. Similar pain intensities, produced by significantly less pressure in patients with FM, resulted in overlapping or adjacent activations in the contralateral primary somatosensory cortex (SI), inferior parietal lobule (IPL), secondary somatosensory cortex (SII), superior temporal gyrus (STG), insula, and putamen, as well as in the ipsilateral cerebellum.
From *Arthritis Rheum*,[9] with permission from John Wiley and Sons.

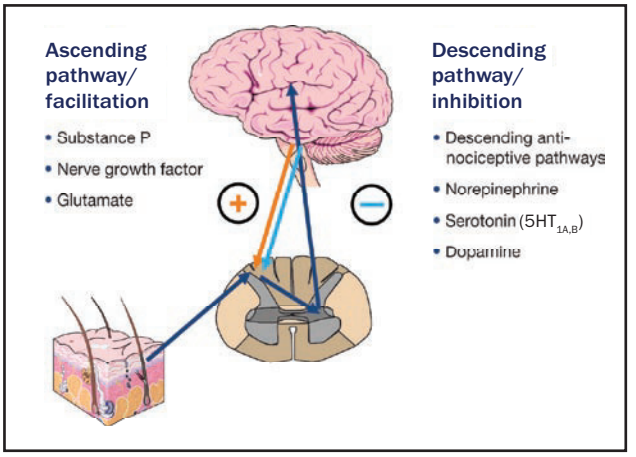

FIGURE 3. Neural pathways and neurotransmitters that influence pain sensitivity.
Adapted from *Rheum Dis Clin N Am*,[13] with permission from Elsevier.

On the molecular level, patients with FM exhibit changes in levels of neurochemicals and receptors associated with increased signaling in ascending (pro-nociceptive) pathways and decreased signaling in descending (anti-nociceptive) pathways (Figure 3).[13] Increased levels of neurotransmitters in the cerebrospinal fluid (CSF) indicate increased signaling in ascending, pro-nociceptive pathways. Neurotransmitters that generally act to increase ascending input, including substance P, nerve growth factor, and brain-derived neurotrophic factor, are present in higher levels in the CSF of patients with FM than healthy controls. Additionally, levels of glutamate and other excitatory amino acids have been shown to be elevated in both the CSF and brain in individuals with fibromyalgia. Glutamate acts on *N*-methyl-D-aspartate receptors to produce increased pain "wind up," a phenomenon of progressively increased central pain amplification after repeated painful stimulation, resulting in greater hyperalgesia and allodynia.

In patients with FM, the activity of descending, anti-nociceptive pathways is also decreased, as evidenced by lower CSF levels of metabolites of serotonin, norepinephrine, and dopamine.[18] In contrast to low levels of these anti-nociceptive neurotransmitters, opioid levels are increased[19] and opioid receptor binding is decreased,[20] with the net effect that baseline endogenous opioidergic activity is *increased* in fibromyalgia. The findings of decreased opioid receptor availability (likely due to the high endogenous release of opioids) may help explain why opioids, although appropriate in certain circumstances, are overall less effective in treating FM and other central pain states.

Many of these same neurotransmitters and neuroprocessing mechanisms also influence mood, energy, and sleep. Similar imbalances of these neurotransmitters in different brain regions may help to explain, at least in part, the mood disorders, sleep dysfunction, and fatigue frequently associated with FM.

Additional mechanisms involved in FM pain are an area of active research. Contributory factors that may be associated with increased pain perception in FM and other chronic pain states include abnormal autonomic function, hypothalamic-pituitary-adrenal axis abnormalities,[21] neurogenic inflammation (glial cell activation),[22] and gray matter loss.[23]

CONCLUSION

Research to elucidate the mechanism underlying FM pain continues on many fronts. Investigation is ongoing to determine whether the other cardinal symptoms of FM, fatigue and nonrestorative sleep, can be explained by central amplification, are secondary to pain, or are caused by some other pathophysiological process. Also, similar neurotransmitter abnormalities may lead to multiple associated symptoms (eg, sleep/mood dysfunction, memory problems) and may therefore account for some of the hallmark symptoms of FM. Other areas of research include identification of possible subsets of patients who respond better to one type of therapy than to others and elucidation of disease progression in FM. Of particular interest is whether FM progresses without adequate treatment and whether treatment could be not only symptom-relieving but disease-modifying.

In the meantime, advances in the understanding of the pathophysiology of FM enable practitioners to more quickly and accurately recognize and diagnose the disorder. Explanation of the pain mechanisms of FM to patients in layman's terms may result in increased confidence in treatment and more effective management. Ongoing research will provide additional insight into FM and further eliminate the perception that this debilitating disorder is "poorly understood" and difficult to manage.

Editorial support was provided by Gayle Scott, PharmD, of UBC Scientific Solutions and funded by Pfizer.

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Questions About Fibromyalgia

1. Which <u>one</u> of the following refers to changes in pain pathways in patients with fibromyalgia (FM) and other chronic pain disorders?
   a. Peripheral decompensation
   b. Peripheral sensitization
   c. Central amplification
   d. Central maladaption
   e. Central generation

2. Which <u>one</u> of the following statements is <u>true</u> regarding nociceptive and neurogenic pain?
   a. Nociceptive pain is peripherally generated
   b. Neurogenic pain is more commonly associated with psychoses
   c. Nociceptive pain perception declines with aging
   d. Neurogenic pain usually responds well to opioids
   e. Nociceptive pain is heightened in women

3. Which <u>one</u> of the following statements <u>best</u> describes the mechanism of action of agents likely to provide pain improvement in patients with FM?
   a. They bind irreversibly to opioid receptors
   b. They block prostaglandin receptors
   c. They act centrally in ascending and/or descending pain pathways
   d. They bind reversibly to opioid receptors
   e. They combine both peripherally acting (eg, acetaminophen) and centrally acting analgesics (eg, oxycodone)

4. Which <u>one</u> of the following <u>best</u> describes pain perception in patients with FM?
   a. Allodynia and hyperalgesia
   b. Paradoxical hypoalgesia
   c. Allopathy and central hyperalgesia
   d. Allodynia and hyperalgesia
   e. Allodynia and peripheral hyperalgesia

5. Which <u>one</u> of the following is the <u>most likely</u> cause of the pain, tenderness, and sleep and mood disturbances common in patients with FM?
   a. Early neuronal changes typical of dementia
   b. Decreased levels of neurotransmitters in the cerebrospinal fluid
   c. Decreased glutamate in the brain
   d. Increased activity of anti-nociceptive pathways
   e. Central amplification of pain signals

Correct answers: 1. *c*, 2. *a*, 3. *c*, 4. *a*, 5. *e*