Published in final edited form as:
Best Pract Res Clin Rheumatol. 2011 April ; 25(2): 155–164. doi:10.1016/j.berh.2010.01.010.

Peripheral Pain Mechanisms in Chronic Widespread Pain

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Abstract

Clinical symptoms of chronic widespread pain (CWP) conditions including fibromyalgia (FM), include pain, stiffness, subjective weakness, and muscle fatigue. Muscle pain in CWP is usually described as fluctuating and often associated with local or generalized tenderness (hyperalgesia and/or allodynia). This tenderness related to muscle pain depends on increased peripheral and/or central nervous system responsiveness to peripheral stimuli which can be either noxious (hyperalgesia) or non-noxious (allodynia). For example, patients with muscle hyperalgesia will rate painful muscle stimuli higher than normal controls, whereas patients with allodynia may perceive light touch as painful, something that a “normal” individual will never describe as painful. The pathogenesis of such peripheral and/or central nervous system changes in CWP is unclear, but peripheral soft tissue changes have been implicated.

Indirect evidence from interventions that attenuate tonic peripheral nociceptive impulses in patients with CWP syndromes like FM suggest that overall FM pain is dependent on peripheral input. More importantly, allodynia and hyperalgesia can be improved or abolished by removal of peripheral impulse input. Another potential mechanism for CWP pain is central disinhibition. However, this pain mechanism also depends on tonic impulse input, even if only inadequately inhibited. Thus a promising approach to understanding CWP is to determine whether abnormal activity of receptors in deep tissues is fundamental to the development and maintenance of this chronic pain disorder.

Conclusions—Most CWP patients present with focal tissue abnormalities including myofascial trigger points, ligamentous trigger points, or osteoarthritis of the joints and spine. While not predictive for the development of CWP these changes nevertheless represent important pain generators that may initiate or perpetuate chronic pain. Local chemical mediators, including lactic acid, ATP, and cytokines seem to play an important role in sensitizing deep tissue nociceptors of CWP patients. Thus the combination of peripheral impulse input and increased central pain sensitivity may be responsible for wide-spread chronic pain disorders including FM.

Keywords

Nociception; Chronic widespread pain; Fibromyalgia

Chronic Widespread Pain (CWP)

The prevalence of chronic pain in the general population is high, seems to increase with age [1,2], and is usually assessed by cross-sectional studies utilizing screening questionnaires

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sent to a random sample of subjects [2]. These questionnaires collect information about demographic data, diagnosis, current pain, pain during the previous month, recurring pain, pain duration, location, frequency, intensity, pain at rest or during movement, occupational status, working hours per week, use of health care for pain, and disability pensions. Often the respondents also mark the location of their pain on drawings of the human body. Several studies have found that large parts of the general population (34.5% to 53.7%) report pain of more than three months duration regardless of intensity (chronic pain) [2,3]. The prevalence of chronic pain is consistently higher among women than men and appears to become more prevalent with age [4]. The highest chronic pain prevalence (88%) has been observed in subjects 65–74 years old [5]. In contrast, individuals who have CWP or fulfill the 1990 classification criteria for FM have more severe symptoms – higher pain intensity, fewer pain-free periods, and more pronounced pain-related interference in everyday life – and consequences for daily life. The population prevalence for CWP has been estimated at 10% [3,6] and for FM at 2.5% [7]. It has been postulated that FM represents the extreme end of the CWP spectrum in the general population. However, only few studies have assessed the similarities and differences in pain experiences between patients fulfilling the ACR criteria for FM and those with CWP.

Fibromyalgia Syndrome (FM)

FM patients encountered in clinical practice are not necessarily representative of patients in the general population because these patients differ in pain severity and lifetime psychiatric diagnoses from FM patients found in the community [8,9]. Similar findings have been documented for CWP [10]. FM is a chronic pain syndrome, that is defined by wide-spread pain for more than three months and the presence of more than ten out of eighteen tender points [11]. Additionally, almost all FM patients complain of disturbed sleep, distress, and pronounced fatigue. The latter features have been included in the preliminary 2010 FM Criteria [12]. FM is a chronic illness that disproportionately affects women [9:1 ratio of women to men affected]. Like many other syndromes FM has no single specific feature but represents a symptom complex of self reported or elicited findings.

Pathogenesis of CWP and FM

Similar to CWP, FM pain appears to depend on impulse input from deep tissues, particularly muscles. In genetically susceptible individuals, such tonic impulse input results in peripheral sensitization as well as neuroplastic changes of the central nervous system (CNS), termed central sensitization. During central sensitization, a cascade of transcriptional and translational events leads to heightened sensitivity (hyperalgesia and/or allodynia) of second and higher order neurons and expansion of their receptive fields. It is unclear at this time, why such changes are long-lasting or even permanent in FM and CWP patients. One likely mechanism is the abnormal response of chronic pain patients to stressful events. Specifically, altered neuroendocrine and autonomic nervous system (ANS) function appears to play an important role in the pathogenesis of CWP [13–15]. Disturbances of neuroendocrine and ANS function can trigger many symptoms that are commonly observed in FM and CWP, including pain, fatigue, insomnia, mood disorders, weakness, and orthostatic intolerance. A number of studies that have examined coordinated hypothalamic-pituitary-adrenal (HPA) axis and ANS functioning showed hyporeactivity to applied stress in FM [16–21]. This altered neuroendocrine responsiveness seems to result from changes in hypothalamic function, not from a primary adrenal defect. Thus neuroendocrine alterations are most likely involved in the pathophysiology of FM and contribute to its ongoing symptomatology. Due to the fact that pain is not only worsened by chronic stress but is also an important stressor in its own right, reductions in stress will likely have a positive effect on chronic pain and FM/CWP.

Role of Muscle Impulse Input for CWP

Although, there are no detectable nociceptors in muscle fibers [22–24] muscle stimuli can elicit pain. Nociceptive afferent fibers including A-delta and C-fibers can be found in muscles as dense innervations of vascular structures [25–27]. Whereas chronic degenerative muscle disorders are not painful, inflammatory myopathies can result in sensitization of pain receptors that may elicit pain. Hypoxia in combination with muscle activity as well as energy depletion can also cause pain. Thus, if nociceptors in deep tissues of CWP patients are sensitized by inflammatory or non-inflammatory mechanisms, hyperalgesia can occur. Importantly, mechanical hyperalgesia is a characteristic feature of so-called “tender points” which are a hallmark of FM and part of the 1990 classification criteria of the American College of Rheumatology for this syndrome [11]. There is a large body of evidence for a generalized lowering of pressure pain thresholds in FM patients [28–32], and the mechanical allodynia of FM patients is not limited to tender points but appears to be widespread [31–33]. In addition, almost all studies of FM patients have shown abnormalities of pain sensitivity while using different methods of sensory testing.

Not only is the mechanical hyperalgesia of FM patients likely a consequence of abnormal input from sensitized peripheral tissue receptors and resultant central sensitization, but the underlying pain mechanisms can be readily evaluated by psychophysical testing. Specifically, if central sensitization is dependent on peripheral impulse input, it should be short-lived after receptor activation [34]. Infrequently, however, tonic impulse input can change pain pathways and become independent of peripheral input [35]. One particular psychophysical method, temporal summation of pain (TS) has been used for testing of central pain sensitivity in FM patients [36–38]. Several studies that used this method, seem to indicate that TS is enhanced in FM and that the increased central pain sensitivity of FM patients attenuates much slower than seen in normal subjects [36]. Although direct neurophysiological evidence of tonic input from deep nociceptors is lacking at this time, indirect evidence strongly suggests abnormally sustained impulse input from muscle receptors in FM patients [37,39,40].

Role of Myofascial Trigger Points for Overall Pain

Local pain of CWP and FM patients is often related to the presence of myofascial trigger points (MTP) which can be classified as either active or latent. Whereas active MTP are characterized by spontaneous pain, latent MTP are clinically silent but usually have all the other clinical characteristics of active MTP, including taut bands and twitch response [41–43]. Active MTP are associated with local and referred pain and a characteristic twitch response after manual or needle stimulation [41,42]. Both active and latent MTrPs show spontaneous electrical activity at rest during needle electromyography [44], indicating that objective electrophysiological methods can be used to document the existence of MTP. Unfortunately, there is no pathologic or laboratory test for identifying MTP. The development of MTP is often associated with injuries to muscle fibers. Such injury may include traumatic events or repetitive microtrauma to muscles. MTP cause pain and spasms in the muscle or muscle fibers. Several studies have demonstrated the presence of large numbers of active MTP in FM patients [45,46] and one study has shown the ability of active, but not latent MTP counts to predict overall spontaneous pain intensity in patients with FM [47]. However, highly variable numbers of trigger points in individual patients have been reported between different examiners [46].

Further support for the important role of muscle abnormalities for CWP is provided by several injection studies of MTP with local anesthetics [48,49] The results of these studies showed that local treatment of peripheral pain generators of CWP patients not only relieved

local symptoms but also significantly improved overall pain and tenderness. In addition, local muscle injections increased mechanical and electrical pain thresholds of adjacent as well as remote body areas of CWP patients. This effect was not seen in patients undergoing placebo treatments.

Effects of Local Pain on Generalized Pain Sensitivity

It is well known that small areas of local pain can have enhancing effects on overall pain sensitivity. This effect, however, depends on several factors including the duration of pain. In contrast to short lasting dental pains which do not enhance pain sensitivity of distal sites like the arms [50], chronic pain from myofascial temporomandibular disease can profoundly increase pain sensitivity of remote areas [51]. Generalized hyperalgesia has also been described in patients with local pain syndromes including whiplash injury [52], irritable bowel syndrome [53], back pain [54], and pelvic pain [55]. Some of these changes can be explained by increasing recruitment of central neurons that become activated by nociceptive stimulation [56,57] as well as by enhanced spatial summation [58]. Another local pain mechanism is spatial referral, i.e. tonic impulse input from local tissues can result in pain of remote areas and increased pain intensity. Thus, painful input from tonic impulse input can summate with input from acute injuries resulting in wide-spread pain. Furthermore, spatial summation mechanism seem to be abnormal in FM. Whereas this important pain mechanism appears to be normal during low-grade nociceptive input [59] spatial summation of pain seems to be unlimited during intense pain stimuli [60]. Spatial summation of pain can be reduced by tissue injections with local anesthetics. However, the results of local anesthetics on pain and hypersensitivity of muscle pain are mixed. Whereas injections of local anesthetics into trigger points attenuated whiplash pain, mechanical hyperalgesia at remote sites was not affected [61]. In contrast, rectal application of lidocaine to IBS patients abolished rectal hyperalgesia and cutaneous pain sensitivity within lumbar dermatomes [62]. Thus, in some chronic pain conditions, like FM or whiplash pain generalized hypersensitivity may depend on minimal impulse input from muscles. It is unknown at this time whether central pain mechanisms like spatial summation and referred pain play important roles for the wide-spread sensitization associated with FM. Thus different pain mechanisms must be considered for the generalized hypersensitivity associated with chronic pain and FM.

Muscle Metabolites and Pain

A likely source of nociceptive input accounting for FM pain is muscle tissue. Several types of muscle abnormalities have been reported in FM patients including the appearance of ragged red fibers, inflammatory infiltrates, and moth-eaten fibers. Possible mechanisms for such muscle changes may include repetitive muscle microtrauma, which could contribute to the postexertional pain, MTP, and other painful symptoms experienced by these patients. In addition, prolonged muscle tension and ischemia have been detected in muscles of FM patients. Investigations using ^{31}P nuclear magnetic resonance (NMR) spectroscopy have shown that FM patients display significantly lower phosphorylation potential and total oxidative capacity in the quadriceps muscle during rest and exercise [63]. FM patients also exhibit significantly lower levels of muscle phosphocreatine and ATP, as well as a lower phosphocreatine/inorganic phosphate ratio.

Changes in muscle pH related to ischemia can provide powerful mechanisms for the sensitization of spinal and supraspinal pain pathways. Recent studies have shown that low pH has a profound effect on the initiation and perpetuation of muscle pain [64]. Repeated acid injections into rat muscle produced a bilateral, long-lasting, mechanical hyperalgesia that was maintained without continued muscle nociceptive input and did not produce

damage to muscle tissue. Furthermore, this secondary mechanical hyperalgesia was maintained by neuroplastic changes in the central nervous system, even after the cessation of nociceptive activity. The initiation of hyperalgesia occurred in response to repeated intramuscular injection of acidic saline, suggesting that this process involves activation of ASICs or the capsaicin-sensitive TRPV1 channel in muscle. Thus, a more acidic milieu may activate ASIC1 or ASIC3 muscle nociceptors, which in turn could produce mechanical hyperalgesia [65]. Because nociceptive input from muscles is very powerful in inducing and maintaining central sensitization muscle abnormalities may strongly contribute to this important mechanism of pain amplification.

Role of Abnormal Muscle Microcirculation

The blood flow of muscles, particularly the trapezius, seems to be reduced in FM [66]. Muscle microcirculation can be measured by Doppler ultrasound [66,67], xenon-133 clearance [68], or oxygen multipoint electrodes on the muscle surface of FM patients [69]. The trapezius and brachioradialis muscles have been most frequently studied. Tissue oxygen pressures are reported to be abnormal in FM patients compared to normal controls [70]. These results suggest abnormal capillary microcirculation, at least in the upper part of the body. In addition, decreased blood flow in the tender point areas of FM patients has also been reported using intramuscular needle electrodes. These blood flow abnormalities, however, do not appear to result from diminished capillary density. On the contrary, capillary density of trapezius muscles [71] was increased compared to lower extremity muscles including the vastus lateralis [72]. Other reported muscle abnormalities include increased thickness of the capillary endothelium of FM patients [73]. These changes may be either the cause or effect of localized hypoxia. The microcirculation of muscles is not only regulated by locally produced metabolites, humoral factors, but also the ANS. This important role of the ANS for chronic muscle pain was demonstrated by stellate ganglion blockade which abolished pain and tender points of FM patients whereas sham blockade was ineffective [74].

Thus, muscular ischemia appears to be a relevant mechanism for chronic muscle pain, either focal or generalized. Hypoxia of muscle tissue, exacerbated by contraction, is highly effective in activating unmyelinated muscle nociceptors [75]. Furthermore, muscular blood flow of FM patients can not only be completely abolished by isometric or isokinetic exercise [66] but also seems to recover very slowly [76]. Such findings may explain why pain is abnormally increased for FM patients during and after exercise [68,77]. Several lines of evidence support the fact that strenuous or intensive exercise can contribute to FM patients' hyperalgesia and pain. For example, isometric contractions can increase the mechanical pain sensitivity of FM patients' exercised muscles [hyperalgesia], but render muscles of normal control subjects hypoalgesic [40]. Similarly, FM patients show increased heat hyperalgesia after exercise, whereas healthy controls become less sensitive [78]. These findings suggest that certain types of exercise can increase the tonic nociceptive input from FM muscles resulting in peripheral and central sensitization. Whereas strenuous exercise seems to activate powerful antinociceptive mechanisms in normal control subjects, this stress mechanism appears to be either dysfunctional or insufficient to overcome tonic muscle pain in FM.

Mechanisms of Pain in CWP

Pain in CWP is consistently felt in deep tissues and is related to sensitization of peripheral and central nervous system (CNS) pain pathways. Neurotrophins like nerve growth factor (NGF) and tachykinins like SP are elevated in the cerebro-spinal fluid (CSF) of FM patients [79]. NGF and SP not only enhance the sensitivity of nociceptors but also are associated

with inflammatory regulation [80]. Specifically, administration of recombinant human NGF to pain-free volunteers can result in mild to moderate back pain [81]. Several neuropeptides, in particular SP can induce the expression of cytokines which may sensitize peripheral nerve endings [82]. Not surprisingly, elevated levels of cytokines in peripheral blood and skin have been reported in FM patients [83,84]. These cytokines include IL-1ra, IL-8, and IL-6. Of these cytokines, IL-8 is of particular interest because it can not only increase nociceptive sensitivity but is also involved in the activation of the sympathetic nervous system [85].

Role of Peripheral and Central Pain Mechanisms

Increasing evidence points towards multiple initiating factors for hyperalgesia in FM, in particular psychological and physical stress, including traumatic injuries [86,87]. Once hyperalgesia has been established little continuous tonic impulse input seems to be required for its maintenance. Several studies have demonstrated abnormalities of pain processing in patients with FM, such as alterations of N-methyl-D-aspartate receptors or monoaminergic modulation in the spinal cord [18,39,88,89]. Furthermore, abnormal increases in temporal summation of pain, expansion of receptive fields and hyperalgesia, as well as dysfunctional descending nociceptive modulation, have been described in patients with FM [36,90–93] and other chronic musculoskeletal pain disorders [94,95]. These findings suggest that central sensitization of nociceptive afferent pathways seems to play an important role for the sensory abnormalities of FM/CWP patients [96,97].

Many FM studies related to pain and hyperalgesia clearly point to spinal mechanisms, consistent with the observation that FM patients have enhanced responses to somatic and cutaneous stimuli throughout the pain matrix of the brain, including the thalamus [38,98,99]. However, on the basis of this evidence, it is not clear whether such enhanced responses are the result of facilitating mechanisms within the brain, spinal sensitization maintained by tonic impulse input from somatic tissues, or abnormal mechanisms of descending facilitation from the brain to the spinal cord and/or somatic tissues. Several neuroimaging studies of FM patients during painful mechanical stimulation showed increased activity of pain processing brain regions such as rostral anterior cingulate cortex (ACC) and prefrontal cortical areas [100,101]. Such findings, however, do not prove that hyperalgesia in FM is the result of enhanced pain processing at higher cerebral levels. Mostly, because such brain activity may reflect selective cognitive effects, rather than enhanced activity of ascending pain pathways to the brain [102].

Summary

Although muscle biopsy studies do not conclusively show specific abnormalities for CWP syndromes like FM, the presence of moth-eaten fibers, ragged red fibers and type II fiber atrophy indicates that muscles are likely involved in the pathogenesis of CWP [103–107]. Abnormalities of muscle perfusion in FM may result in lowered pH during mild to moderate muscle load sufficient for activation of muscle nociceptors. Such changes have been reported in the local milieu of MTPs [108] which are almost always present in FM patients [47]. Additional muscle abnormalities, including mitochondrial changes, or changes in muscle metabolism, may contribute to sensitization of muscle nociceptors and thereby cause pain, fatigue and muscle weakness. Altogether, this may result in peripheral sensitization of afferent pain pathways which then provide tonic impulse input to central pathways resulting in central sensitization.

Besides the important role of peripheral impulse input for CWP, it is also important to consider the important influences of central pain mechanisms, such as pain-inhibitory and pain-facilitating pathways, as well as the cortical and subcortical processes related to chronic

pain. A better understanding of the interaction between peripheral and central factors will be necessary before a full understanding of CWP can be achieved.

Acknowledgments

Supported by NIH grant AR-053541.

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