

Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition

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Chronic musculoskeletal pain has biological, psychological and social components. This review deals with the biological factors, with emphasis on the fibromyalgia syndrome (FMS). Studies on central sensitization of pain-transmitting neurons, changes in endogenous pain modulation that give rise to pain disinhibition, referred pain, pain-related decrease in muscle strength and endurance, and pain generators in deep tissues are reviewed. In FMS there is strong scientific support for the statement that the biological part of the syndrome is a longstanding or permanent change in the function of the nociceptive nervous system that can be equated with a disease. Further research is necessary in order to determine which methods are best for diagnosis of the pain hypersensitivity in clinical practice. FMS may be the far end of a continuum that starts with chronic localized/regional musculoskeletal pain and ends with widespread chronic disabling pain.

Key words: fibromyalgia; chronic muscle pain; central sensitization; pain disinhibition; referred pain; motor responses in pain.

Widespread hypersensitivity in chronic musculoskeletal pain conditions means general reduction in pressure pain thresholds (PPTs) assessed from many sites. The decrease in pain thresholds may be slight to moderate or pronounced. If pronounced,

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non-noxious stimuli may give rise to pain (allodynia), and noxious stimuli may cause pain that lasts longer and has higher intensity than normal (hyperalgesia). The allodynia/hyperalgesia can be localized, regional, or widespread. Widespread pain combined with widespread allodynia/hyperalgesia is seen in disorders such as fibromyalgia syndrome (FMS). If there is widespread muscle pain but no widespread allodynia/hyperalgesia, the condition is termed chronic widespread pain (CWP). This chapter will focus mainly on FMS. Myofascial pain will not be discussed as it is dealt with in other chapters of this book. The pathogenesis of FMS is often described as unknown, but today this is not entirely true. In spite of the fact that there are still gaps in our knowledge, we know enough about pathogenetic mechanisms of pain and pain hypersensitivity to argue that the permanent or longstanding pain hypersensitivity can be regarded as a disease involving the nociceptive nervous system. These arguments will be discussed in this article. Comprehensive reviews on FMS have recently been published.^{1,2}

FMS

FMS has biological, psychological and social components. The pain signals from the periphery reach (in the cortex) both somatosensory areas, where pain localization, pain duration and pain intensity are perceived, and other areas, e.g. limbic structures where the emotional responses to pain are perceived and interpreted.³ The psychological factors are always there, as are the social consequences, but these factors are not necessarily the primary causes for the pathological pain hypersensitivity. The many symptoms of FMS could be explained by the fact that there are bidirectional connections between the nociceptive nervous system and the immune system, the sleep-regulating system, and the stress-regulating systems. Furthermore it has recently been described that descending facilitatory pathways may cause widespread hypersensitivity.⁴

THE BIOLOGICAL COMPONENTS

Central sensitization

Sensitization of pain transmission neurons in the CNS, especially the wide-dynamic-range neurons (WDR) in the dorsal horn, is a normal event in acute pain. It becomes pathological if it is longstanding or permanent, as it does in FMS. Permanent central sensitization is considered to be an expression of neuronal plasticity in primary sensory and dorsal-horn neurons, especially the WDR neurons. The WDR neurons change in structure, phenotype, function and biochemistry. A-beta fibres get qualities that are similar to those of C-fibres, and touch or slight pressure becomes painful.⁵ Pain is normally a result of stimulation of high-threshold neurons by noxious stimuli. The stimulus (pressure)–response (pain) function is a power function. The stimulus–response function when low-threshold neurons are stimulated is linear. Bendtsen et al. found that the stimulus (pressure)–response (pain) function in patients with FMS is linear, indicating that stimulation of A-beta nerves gives rise to pain.⁶

Neuronal plasticity is activity-dependent. In most patients with FMS the widespread pain is preceded by chronic localized musculoskeletal pain. The origin of the pain can be in muscles, joints and ligaments, and the most likely activity that could give rise to changes caused by neuronal plasticity is longstanding bombardment of neurons in the spinal cord by impulses in pain-transmitting C-fibres and A-beta fibres. A tonic activity

in C-fibres and A-beta fibres could maintain central sensitization. Epidural lumbar blockade by lignocaine completely eradicated pain and allodynia in the nine FMS patients studied.⁷ This indicates that pain may be evoked and not spontaneous not only at onset of FMS but also late in the course of the disorder. This does not exclude the possibility that pain in FMS also can be spontaneous. Mense discusses the idea that decreased levels of nitric oxide at the spinal level can induce spontaneous pain.⁸ Activation of N-methyl-D-aspartate (NMDA) receptors on WDR neurons is one step in the development of central sensitization, and in patients with FMS who are ketamine responders it is likely that the response is due to a reduced central sensitization at the spinal level.⁹ (Ketamine is an NMDA-receptor antagonist, and a ketamine responder is a person in whom infusion of ketamine reduces pain by 50% or more.) The same conclusion can be drawn from the fact that temporal summation/integration of pain signals from deep tissues and the temporal summation in patients with FMS are attenuated by antagonists to NMDA receptors.^{10,11} Temporal summation means that repetitive stimulation at frequencies lower than 5 Hz by identical stimuli gives rise to gradually increasing pain responses. Activation of NMDA receptors on WDR neurons can cause additional release of neuropeptides such as substance P, and these substances can diffuse in the spinal cord and result in the spread of pain.¹²

Pain disinhibition

Pain disinhibition is a result of a change in the endogenous descending pain-modulating system. The descending system includes a nervous network that links the periaqueductal grey and the rostral ventromedial medulla with the spinal cord. Ren and Dubner¹³ regarded activity-dependent plasticity and descending modulation as having a protecting function. Early facilitation enhances nocifensive escape behaviour. Late inhibition creates conditions that are good for healing of an injury.¹³ The feedback to the descending tracts comes partly from collaterals from ascending pain-transmitting tracts and partly from tracts from cortex and hypothalamus. In persons with permanent pain hypersensitivity there could be a continuous stimulation of both facilitatory and inhibitory tracts that would result in increased pain if activity in inhibitory tracts decreases or if activity in facilitatory tracts increases. Pain hypersensitivity due to changes in the function of descending tracts can be present in both FMS with onset in the periphery and FMS that starts in the brain. The endogenous pain modulation in FMS is impaired as compared to healthy controls.^{14,15} As the descending facilitatory pathways originating in the frontal cortical areas have been shown to cause generalized increased neuronal responses along the neuroaxis, this has for the first time indicated that emotions such as fear may drive the development of widespread pain and sensitization.¹⁶

Peripheral sensitization and pain generators in deep tissues

Opinions on the importance of peripheral factors for the pathogenesis of the FMS symptoms differ. It is claimed by some that there are no significant changes in the muscles in FMS. In a recent comprehensive review in *Pain*, Vierck maintains another view.¹ He points out 'central sources of sensitization or disinhibition should be regarded as the primary cause of FM pain only if peripheral activation of these mechanisms can be ruled out'. There is currently a large number of studies showing that there are changes, especially in intramuscular microcirculation and in muscle energy metabolism, that could be the excitatory drive for the changes found in the nociceptive system in

the CNS and for multifocal pain in the muscles.^{17–19} In a study by Elvin et al²⁰, the muscle blood flow in patients with FMS was studied with contrast-medium-enhanced colour Doppler technique. The flow response was lower and of shorter duration following dynamic and static exercise in FMS patients than in healthy controls. The authors state that their results indicate that muscle ischaemia can contribute to pain in FMS. Other studies support the idea that decreased relaxation between contractions, which has been found in patients with FMS, means that not only static but also dynamic muscle contractions will cause ischaemic pain.¹⁷

The fact that localized or regional pain in most patients with FMS precedes the widespread pain supports the notion that FMS can develop from localized pain. In some instances FMS develops from local muscle pain of known origin: for example, osteoarthritis, rheumatoid arthritis (RA) or chronic myopathies.^{21–23} In RA, osteoarthritis and chronic idiopathic back pain, decreased PPT has been found in areas outside the area of pain.^{21,22,24} In back pain, the results of functional magnetic resonance imaging (fMRI) studies have been similar to those described in FMS, namely that pain areas in the brain are activated by stimuli that do not cause any activation in healthy controls. Pain that is of the same intensity in both patients and controls gives the same activation pattern in both groups.²⁴

A promising method for revealing pathology in muscles could be microdialysis in painful muscles in order to determine concentrations of substances that could be pain-provoking. Rosendal et al²⁵ found that in work-related trapezius myalgia increased levels of 5-hydroxytryptophan (5-HT) and glutamate were correlated with pain intensity and reduction in PPTs.

Referred pain

Recordings from dorsal-horn neurons in animals have revealed that within minutes after application of a noxious stimulus to a receptive field in a muscle, new receptive fields at a distance from the original receptive field emerge.^{26,27} That is, following nociceptive input, dorsal-horn neurons that were previously responsive to only one area within a muscle begin to respond to nociception from areas that previously had not provoked a response. The appearance of new receptive fields could indicate that latent convergent afferents on the dorsal-horn neuron might be opened by noxious stimuli arising from muscle tissue⁸, and that this facilitation of latent convergence of connections could appear as referred pain. Recent observations from the same group have demonstrated that substance P released from the ends of primary afferents plays a role in the connectivity in the dorsal horn⁸. Furthermore, an expansion of the receptive fields proximal to the normal receptive field was found in a study where experimental myositis was induced, and afterwards application of antagonists to three different neurokinin receptors were effective in preventing the induced hyperexcitability.²⁷ This is the central hyperexcitability theory for referred pain proposed by Mense.⁸ The theory is consistent with several of the characteristics of referred muscle pain (dependency on stimulus and a delay in appearance of referred pain compared with local primary pain). However, if the emergence of new receptive fields is construed as the neurophysiological basis for referred pain, the fact that such fields are sometimes proximal to a site of nociceptive input conflicts with the majority of studies on experimentally induced referred pain in healthy subjects.^{29–38} These studies demonstrate the development of referred pain distal to a site of induced pain, but not proximal to it. Clinical studies looking at the spread of experimentally induced referred pain in patients

suffering from whiplash syndrome and fibromyalgia have demonstrated proximal as well as distal referral of pain.^{39,40} In only one study have we seen proximal spread of referred muscle pain following intramuscular injection of capsaicin in a few healthy volunteers. A possible explanation of the divergence between findings in healthy humans versus findings in people with clinically significant pain is that pre-existing pain in the latter might have induced a state of hyperexcitability in the spinal cord, resulting in proximal and distal referral compared to the predominant distal referral in healthy subjects.

The hyperexcitability theory^{8,27,41,42} is based on animal studies where receptive fields appeared within minutes. This does not fit exactly with the development of referred pain in humans that occurs within seconds. We think, however, that the idea of latent connections between dorsal-horn neurons is convincing.

The involvement of peripheral input from the referred pain area is not clear. Anaesthetizing this area has produced reductions in referred pain intensity in some studies, but no effects in others. For example, Laursen et al.³⁴ found that it is possible to induce referred pain to limbs with complete sensory loss due to an anaesthetic block. Conversely, Vecchiet et al.⁴³ demonstrated that infiltration of muscle tissue with anaesthetics 30 minutes after injection of hypertonic saline (i.e. no ongoing pain) completely reversed cutaneous and muscular hyperalgesia. This effect of a peripheral block on muscle hyperalgesia could suggest peripheral sensitization. Alternatively, deep and especially cutaneous hyperalgesia after muscle pain might be caused by a central mechanism where peripheral input is needed, which is also a necessary condition for referred pain.⁴⁴ Recently, we found hyperalgesia to pressure distal to the referred pain area produced by experimental pain induced in the tibialis anterior muscle.⁴⁵ The referred hyperalgesic area was innervated by the deep peroneal nerve, which also innervates the tibialis anterior muscle. This suggests involvement of summation between muscle afferents and the somatosensory afferents from the hyperalgesic area, with facilitation by central sensitization.

In summary, referred pain probably reflects a combination of central processing and peripheral input. As far as central processing is concerned, research conducted in relation to the central hypersensitivity theory supports the role of altered functioning in the dorsal horn as a contributor to referred pain. It is also likely that supraspinal mechanisms contribute to referred pain, although they have not been extensively studied. Also, there are many questions about referred pain that have not yet been fully resolved by research, and have not been incorporated into theories of referred pain. In the clinic it is difficult to establish whether pain in a particular muscle is primary, in the sense that it is due to causes in the painful muscle, or whether the pain is referred. Pain may be referred to a muscle not only from other muscles but also from tissues such as nerves or viscera.

Motor responses

The completely resting muscle is characterized by the absence of any electromyographic (EMG) activity. However, with the jaws at rest there is weak EMG activity present in the human jaw-closing muscles.⁴⁶ This might serve to counteract the effects of gravity on the lower jaw, i.e., postural activity. There is a general consensus that healthy, non-painful jaw muscles exhibit only very low levels of EMG activity, in the range of 3–5 μ V, but there is no scientific evidence for any exact threshold values.⁴⁷

In a recent study, we recorded the resting muscle activity by intramuscular wire and surface electrodes during saline-induced muscle pain.⁴⁸ In this study there was

a transient increase in the EMG activity during infusion of hypertonic saline compared with infusion of isotonic saline. After the infusion and during ongoing muscle pain there was no significant difference in the resting EMG level. Ongoing muscle pain did not produce sustained increased EMG activity. Moreover, experimental muscle pain does not cause any changes in resting EMG activity between repeated maximal voluntary contractions (MVC).⁴⁴ Elert et al⁴⁹ reported an increase in the resting EMG activity between contractions in fibromyalgia patients. Others report no increase in the resting muscle EMG activity in fibromyalgia⁵⁰, temporomandibular disorders⁵¹, and low-back-pain patients.^{52,53} Observation of muscle spasms in a referred pain area from trigger-point activation is also reported.⁵⁴ In addition, saline-induced muscle pain produced increased resting muscle activity in muscles away from the painful muscle^{55,56}, but this finding was inconstant and based on limited material.

Increased postural EMG activity has for a long time been believed to play a very important role in the pathophysiological mechanisms in many muscle pain disorders. Increased EMG activity in painful muscles would also intuitively explain the clinical impression of increased tension or hardness in the same muscles. Recently, evidence was presented for increased hardness of pericranial muscles in patients with tension-type headache.⁵⁷ Travell et al.⁵⁸ are usually given credit for the description of the 'vicious cycle' which proposed a mutually reinforcing relationship between chronic pain and muscle hyperactivity. In this respect, confusion in the terminology has existed for a long time, since the terms 'muscle tension', 'muscle spasms', 'muscle contractures', and 'muscle hyperactivity' have been used interchangeably but can represent entirely different conditions. DeVries⁵⁹ suggested that muscle pain and soreness were caused by tonic local spasm of motor units, and that the pain reflex sustained the tonic muscle contraction, setting up a vicious cycle. Later, Johansson and Sojka⁶⁰ presented a model to explain the muscle tension and pain, which integrated the gamma-motor-neuron system in the pathophysiological mechanism. Mense⁴² discussed a modified vicious cycle concept in which the main component was local ischaemia. It was pointed out, however, that at present there is no evidence for the suggested chain of events. Finally, Mense and Simons⁶¹ have proposed that tension in painful muscles is electrically silent and that muscle contracture and not contraction could cause tension. The minute loci or trigger points could be associated with localized EMG activity⁵⁹, but the question of increased EMG activity in trigger points of jaw-closing muscles has not been unambiguously answered yet.⁶²⁻⁶⁵

The MVC during saline-induced muscle pain is significantly lower than the control condition.^{54,66} A clinical demonstration of the observed decrease in muscle strength during voluntary isometric contractions of a painful muscle has also been made in fibromyalgia⁶⁷⁻⁶⁹, temporomandibular disorder⁷⁰, and low-back-pain patients.^{71,72} In fibromyalgia patients, the reduction in strength is suggested to be due to a deficient central activation of motor units, because supramaximal stimulation of the ulnar nerve shows no difference in the strength of the adductor pollicis muscle between patients and a control group.⁶⁸ The nociceptive activity most likely modulates the motor neuron firing, as there is a correlation between pain intensity and EMG changes.^{73,74}

During a static contraction (80% of the MVC before pain), muscle pain causes a significant reduction in endurance time.⁴³ Contractions at 10% MVC after injection of hypertonic saline were previously found to cause no changes in EMG activity.⁷⁵ Sub-maximal static contraction of the trapezius muscle in patients with unilateral shoulder pain produces progressively increased EMG amplitude until endurance is reached, but the recordings from the painful and non-painful side are similar.⁷⁶ The different findings between submaximal and maximal contractions⁴⁴ might be explained by changes in the

descending neural drive to motor neurons. The descending neural drive cannot be voluntarily increased during MVC, and an inhibitory mechanism controlling the motor neurons might therefore explain decreases in MVC. When submaximal contractions are performed, it might be possible to increase the voluntary neural drive and consequently compensate the potential inhibitory mechanism.

In accordance with experimental findings⁴⁴, the endurance time is decreased in muscle pain patients.^{77–80} The decline of motor neuron firing in fatigued muscles is proposed to be reflex-mediated by group III and IV excitation.^{81,82} Thus, a similar mechanism may be involved in muscle pain, as a decreased endurance time is demonstrated during saline-induced muscle pain.⁴⁴ In clinical studies various physiological factors within the muscle (e.g. microcirculation) could influence endurance time⁸³, and this may be impaired in patients.

The relationship between work-related muscle pain and muscle activity has been studied extensively in an attempt to find a valid predictor for the development of myalgia. The question is why some people develop myalgia when performing work at low levels of force. A decreased frequency of unconscious gaps in the low-level EMG activity was recently found to predict the patients who developed myalgia.⁸⁴ Experimental models of muscle pain have also been used in occupational settings (low load, repetitive work) where it was found that saline-induced neck muscle pain caused a decreased working rhythm and a muscle coordination change which could be interpreted as protective.⁸⁵

THE TWO MAIN SUBGROUPS OF FMS

There are two main subgroups of FMS. The first subgroup is characterized by widespread pain that is preceded by longstanding localized or regional musculoskeletal pain. Pain generators may be present in muscles or joints or tendons or ligaments. In the other subgroup the primary cause is in the brain. It is clinically important to differentiate between these subgroups. To identify pain generators and to try to eliminate them is part of the treatment in patients where the widespread pain is preceded by chronic localized/regional pain. In patients with onset in the CNS the pain hypersensitivity is caused by changes in the CNS and the muscle pain may in this case be secondary. The nature of these stimuli may differ from one pain site to another and from one time to another. This is illustrated by the fact that, for example, a drug may have good effect at one pain site but not at another, and at one time but not at another, in patients with FMS. The psychological and social symptoms may not differ between the two subgroups. In both groups a common feature is chronic stress. It is, however, not obligatory with psychological distress in FMS. Giesecke et al⁸⁶ studied the correlation between degree of tenderness and psychological/cognitive factors and could identify three subgroups. In the first subgroup the patients had extreme tenderness but no obvious psychological symptoms. In the second group the patients had moderate tenderness and no psychological distress. In the third group the psychological symptoms were prominent, but the pain sensitivity was only moderately increased.

Onset in the periphery: the bottom-to-top model

FMS patients where widespread pain is preceded by chronic localized/regional muscle pain – and this includes most FMS patients – belong to this subgroup. Central sensitization and pain disinhibition cause widespread pain hypersensitivity and widespread pain. The chronic stress and the psychosocial problems are secondary to chronic continuous pain.

Onset in the brain: the top-to-bottom model

The other possibility is that the onset of FMS is in the brain. Psychological factors that give rise to chronic stress may initiate the chain of events that leads to FMS. In this group pain disinhibition could be the main pathogenetic factor. The chronic stress may be a result of the cumulative effects of day-to-day stresses. Chronic or longstanding muscle pain of moderate or pronounced intensity is an allostatic load (allostasis: the ability to achieve stability through change). One effect of allostatic load can be decreased function in the immune system.⁸⁷ Infections can sometimes be associated with onset of FMS.

A disturbed sleep pattern is found in most patients with FMS.⁸⁸ This might be secondary to the pain, but some researchers consider that it could also play a role in the onset of FMS. Several neurochemicals have shown abnormal values in different body fluids. In particular, changes in the serotonin metabolism have been discussed as factors that could be involved in the pathogenesis of FMS.⁸⁹

Neuroendocrine aberrations have been found in subgroups of patients with FMS, but it is uncertain whether they cause the pain hypersensitivity or are secondary to constant pain.⁸⁹

Biological changes in the stress-regulating system (HPA axis and the sympathetic nervous system) have been found in a subgroup of patients. There is an increased resting sympathetic tone but a blunted response to stressors.⁹⁰

Glial cells have more than a supportive function. Activation of astrocytes and microglia can contribute to exaggeration of pain and pain sensitivity.⁹¹ Whether activation of glial cells is important for the pathogenesis of pain and allodynia in FMS is currently unknown. Substances that can cause pain hypersensitivity may be released not only from neurons but also from glial cells.⁹¹ Cytokines are the signal substances in the immune system. Release of proinflammatory cytokines such as interleukin-1 β can induce cyclo-oxygenase 2 (COX2) and prostaglandin E2 (PGE2). When PGE2 reacts with its receptors on neurons and glial cells in the CNS, the result could be increased neuronal excitability and allodynia/hyperalgesia. Increased levels of cytokines have been found in patients with FMS.⁹² Theoretically cytokines may play a role in the pathogenesis of FMS when muscle damage, inflammation or stress contributes to pain and pain hypersensitivity. It is possible that blood-borne proinflammatory cytokines from damaged or inflamed muscle can reach the brain and the cerebrospinal fluid, and in the brain cause increased neuronal excitability.^{93,94}

The psychological distress and the social consequences of continuous pain could be similar in the two subgroups.

The treatment principles are the same in the two subgroups. It is important to remember that the factors that caused the onset of FMS may still be present later on in the course of the syndrome, and these factors may require special treatment.

METHODS FOR DETECTING PAIN HYPERSENSITIVITY IN RESEARCH AND IN THE CLINIC

In the clinic

In all longstanding or chronic muscle pain conditions examination with respect to the presence and spread of pain hypersensitivity is mandatory. The ideal method should be easy to perform, reliable, not time-consuming, and not expensive. The most

commonly used method is to estimate PPT. The pressure at which conversion from painless pressure to painful pressure occurs is the pressure pain threshold. An area with decreased PPT is a tender point (TP). The application of pressure by the tip of the thumb or by algometers or dolorimeters at first elicits an awareness of pressure. As the pressure is increased, the subject experiences pain. The method is denoted 'the ascending method'. The American College of Rheumatology (ACR) classification criteria for FMS⁹⁵ requires 11 TPs or more out of 18 specified anatomical sites. The ascending method for estimation of number of TPs is a screening method for spread of allodynia. The results depend both on the level of PPT and on degree of pain perception which in turn can be influenced by psychological factors. For a more accurate measure of PPT that is not influenced by psychological factors, stimuli have to be applied in a random order.⁹⁶ In a recent study by Maquet et al⁹⁷, PPT was determined by using a pressure dolorimeter in patients with FMS and in healthy controls. The intra-individual coefficient of variation between two successive measurements sessions reaches 17% for healthy females, 13% for healthy males, and 24% for patients with FMS. PPT reference values for the different TP sites are given. The tender point score in patients with FMS averaged 60% of the values in the healthy controls. This study points to the conclusion that correctly performed dolorimetry could be a more accurate method in the clinic than the manual palpation method. Vargas et al⁹⁸ have recently published results from a study where they tested sphygmomanometry as a possible screening method for FMS. They found that pain during standardized blood-pressure testing was strongly associated with the diagnosis of FMS. Diagnostic sensitivity was 0.7 and specificity 0.96.

A recent study by Laursen et al.⁹⁹ assessed PPT in a number of chronic pain patients (fibromyalgia, whiplash, rheumatoid arthritis, endometriosis) and found that FMS and whiplash patients had the lowest thresholds on average, but that the other groups also showed significant generalized hypersensitivity (Figure 1).

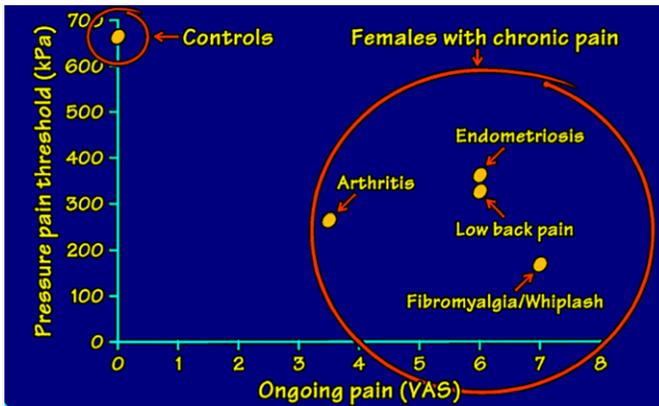


Figure 1. Decreased pressure pain threshold (PPT) is found in many chronic musculoskeletal pain conditions and also in visceral pain. In fibromyalgia (FMS) and in whiplash-associated pain the decrease in PPT reaches the level of allodynia, but in other pain conditions there may be a reduced pain threshold but not generalized allodynia. The figure shows the median and range of PPT plotted against the median rating (VAS) of the clinical pain. The figures are a mean of values obtained at seven sites. An electronic algometer was used. Based on Laursen et al. (2005, *European Journal of Pain* 2005; 9: 267–275) with permission.

Methods used in research

The different methods for demonstrating pathological pain processing in FMS are listed in Table I. The bottom line is that there are reliable quantitative methods for diagnosing the pathological pain processing in the FMS. That these methods are not employed in clinical practice may, for some methods, be due to a lack of reference values, and the fact that the methods are time-consuming and consequently costly. In future some patients with suspected FMS, where an exact diagnosis for clinical or legal reasons is important, may have to be referred to special pain laboratories.

A paradigm for experimental muscle pain: technique and typical findings

During the past 10 years extensive research has been done on experimentally induced muscle pain in normal human volunteers. In a typical study, subjects receive an injection of hypertonic saline (5%) e.g. into the tibialis anterior muscle. The subject is then asked to indicate the location of their resultant pain on human figure drawings, and to indicate the severity of their pain at various sites on a 10-cm visual analogue scale. The pain ratings are provided repeatedly (e.g. every 5 seconds).¹⁰

Subjects typically indicate pain both immediately around the injection site (primary pain) and over the ventral aspect of the ankle (referred pain) if the saline is injected into the anterior tibialis muscle. Pain at the primary site is typically rated as more severe than pain at the referred site.

Within this general paradigm, the effects of a host of modifications can be examined. Muscles other than the tibialis anterior can be studied. In particular, extensive research has been done on the effects of injections into the masseter muscle.¹⁰⁹ Pain can be provoked by intramuscular electric stimulation, and by a variety of chemicals other than hypertonic saline. These include capsaicin, bradykinin, serotonin, and substance P.^{110,111} Following injections, pain threshold and pain tolerance can be studied in response to several different sensory modalities, including pressure, thermal

Table I. Methods used in research in studies on mechanisms of pain hypersensitivity and pain in fibromyalgia syndrome (FMS). All the studies support the idea that there is a change in function of the nociceptive nervous system in FMS.

- Pharmacological analyses and response to experimentally evoked muscle pain (tests for pain intensity, pain thresholds, temporal summation and wind-up, and area of referred pain)¹⁰⁰
- Tests of responses to electro-cutaneous stimulation¹⁰¹
- Determining thresholds for eliciting pain withdrawal reflex¹⁰²
- Diagnostic epidural block⁶; brain imaging (SPECT, fMRI)^{103,104}
- Tests for pain generators in the muscle^{7,18,21}
- Test for neuroendocrinological aberrations²⁹
- Tests for the correlation between stimulus (pressure) and response (pain)⁶
- Tests of somatosensory evoked potentials¹⁰⁵
- Tests for modulation of pain thresholds during and following isometric contractions^{14,15}
- Tests for diffuse noxious inhibitory control (DNIC)¹⁰⁶
- Quantitative sensory testing¹⁰⁷
- Tests for level of substance P in the cerebrospinal fluid¹⁰⁸

SPECT, single photon absorptiometry; fMRI, function magnetic resonance imaging.

stimuli, and electric stimulation.¹¹² Experiments can be carried out on both normal subjects and patients with significant musculoskeletal pain: e.g. patients with fibromyalgia or persistent neck pain following whiplash injuries.¹⁰²

PREDISPOSING FACTORS

Not all people with chronic localized or regional muscle pain develop FMS. Predisposing factors may be a prerequisite for developing FMS. Hereditary factors might be important. Serotonin- and dopamine-related genes could have a role in the development of FMS.¹¹³ People with low pain thresholds caused by acquired or genetic factors may be at greater risk of getting FMS than those with higher pain thresholds. People with localized/regional musculoskeletal pain may be predisposed to developing FMS (see Figure 1). The values for pressure pain thresholds in healthy people differ from one individual to another and from one site to another. Healthy women have a lower pressure pain threshold than healthy men, which might contribute to the high prevalence of FMS in women.^{97,114} Severe mental and physical trauma may cause an increased sensitivity to stress, which in turn might contribute to stress-induced FMS.

SUMMARY: IS FMS A DISEASE?

Central sensitization of pain-transmitting neurons and pain disinhibition as described above can be a feature of chronic muscle pain of different origins. When the pain hypersensitivity is longstanding or permanent, there is a change in function of the nociceptive nervous system that could be equated with a disease.^{115,116} When pain hypersensitivity is widespread and combined with multifocal muscle pain that is more or less continuous and present at rest, FMS is present according to the ACR 1990 classification criteria. Pain hypersensitivity is mainly central, but peripheral sensitization may also be present. In order to explain the muscle pain in FMS, which as a rule is not strictly symmetrical and has varying localizations, peripheral factors have to be taken into account. The pain in FMS is not generalized pain but localized pain at many sites.

Confirming the diagnosis of fibromyalgia as a disease is a two-step procedure: (1) diagnosis of pain hypersensitivity, and (2) diagnosis of pain generators in deep tissues.

We like to underline that the biological, psychological and social components of FMS should be diagnosed and treated separately. Currently the biological component can be regarded as the main component for pain and pain hypersensitivity, but the psychological and social components may be the most important targets for treatment.

Patients with FMS often complain that they are met with distrust when they seek help for their many symptoms. Knowledge of the biological component of FMS is sometimes lacking among health personnel. FMS is considered an illness where the pain amplification and the pain have primary psychological and/or social causes. Recognition of the biological component of FMS, especially among primary care doctors and rheumatologists, could be a prerequisite for improved care of the patients.

Research agenda

- the biological component of FMS can be regarded as a pain hypersensitivity disease which ought to be diagnosed with reliable methods. Further research is necessary to establish which of the many quantitative methods used in research could be adapted to clinical practice

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