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CLINICAL HYPOTHESIS

Fascia: A missing link in our understanding of the pathology of fibromyalgia

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Summary Significant evidence exists for central sensitization in fibromyalgia, however the cause of this process in fibromyalgia—and how it relates to other known abnormalities in fibromyalgia—remains unclear. Central sensitization occurs when persistent nociceptive input leads to increased excitability in the dorsal horn neurons of the spinal cord. In this hyperexcited state, spinal cord neurons produce an enhanced responsiveness to noxious stimulation, and even to formerly innocuous stimulation.

No definite evidence of muscle pathology in fibromyalgia has been found. However, there is some evidence for dysfunction of the intramuscular connective tissue, or fascia, in fibromyalgia. This paper proposes that inflammation of the fascia is the source of peripheral nociceptive input that leads to central sensitization in fibromyalgia. The fascial dysfunction is proposed to be due to inadequate growth hormone production and HPA axis dysfunction in fibromyalgia.

Fascia is richly innervated, and the major cell of the fascia, the fibroblast, has been shown to secrete pro-inflammatory cytokines, particularly IL-6, in response to strain. Recent biopsy studies using immuno-histochemical staining techniques have found increased levels of collagen and inflammatory mediators in the connective tissue surrounding the muscle cells in fibromyalgia patients.

The inflammation of the fascia is similar to that described in conditions such as plantar fasciitis and lateral epicondylitis, and may be better described as a dysfunctional healing response. This may explain why NSAIDs and oral steroids have not been found effective in fibromyalgia.

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Inflammation and dysfunction of the fascia may lead to central sensitization in fibromyalgia. If this hypothesis is confirmed, it could significantly expand treatment options to include manual therapies directed at the fascia such as Rolfing and myofascial release, and direct further research on the peripheral pathology in fibromyalgia to the fascia.

Introduction

The etiology of fibromyalgia—a disorder characterized by widespread muscle pain and tenderness at specific soft-tissue tender points—remains unclear. However, in the past decade evidence for abnormal pain processing in fibromyalgia has significantly advanced our understanding of this disorder. In 2002, a functional MRI study demonstrated that it took much less thumbnail pressure in fibromyalgia patients to activate the pain sensing areas of the brain compared to controls (Gracely et al., 2002). Another study found that fibromyalgia patients experienced stronger pain and larger areas of referred pain after intramuscular injection of hypertonic saline (Sorensen et al., 1998). Other research has shown abnormal temporal summation and wind-up of pain in fibromyalgia (Staud et al., 2004). These findings demonstrate that in fibromyalgia the central nervous system has an exaggerated response to pain, a phenomenon called central sensitization.

Central sensitization is caused by repeated or sustained noxious input to the dorsal horn neurons leading to increased neuronal responsiveness or central sensitization. In fibromyalgia, however, no evidence of muscle pathology has been described, leading to speculation that the central sensitization in fibromyalgia may occur spontaneously though some as yet unknown mechanism (Ji et al., 2003).

Others argue that myofascial trigger points cause the central sensitization in fibromyalgia (Staud, 2008).

However recent biopsy studies have found increased levels of collagen and inflammatory mediators in the fascia of fibromyalgia patients. This paper proposes that dysfunction and inflammation of the intramuscular connective tissue, or fascia, leads to the central sensitization seen in fibromyalgia.

Central sensitization

Central sensitization, a state of heightened sensitivity in the spinal cord, is thought to be a physiologic adaptation of the nervous system to sustained painful input. It is the end result of a complex neuronal response to peripheral nerve injury or tissue inflammation. Recent studies support an important role for dorsal horn glial cells (support cells for neurons) and NMDA receptors in producing abnormal pain sensitivity in the spinal cord (Watkins et al., 2001; Dickenson and Sullivan, 1987).

In lab animals, central sensitization can be induced by injecting inflammatory chemicals into muscle, and by damaging peripheral nerves. Central sensitization has also been described in many chronic pain conditions, including endometriosis (Bajaj et al., 2003), peripheral arterial disease (Lang et al., 2006), and chronic low back pain (O'Neill et al., 2007). In these conditions there is a known source of persistent nociceptive input that keeps the CNS in a continued state of sensitization. One group showed that central sensitization associated with painful hip osteoarthritis normalized following successful hip replacement surgery (Kosek and Ordeberg, 2000).

What causes central sensitization in fibromyalgia?

Since patients with fibromyalgia complain of sore, painful muscles, investigators have long been searching for muscle pathology in fibromyalgia. These studies have included muscle biopsies with structural and ultra-structural observation, magnetic resonance imaging and metabolic studies, electromyography, and studies of blood flow and muscle strength. For the most part these studies have not shown consistent differences between healthy and fibromyalgia muscles. In Simm's rigorous review of 32 studies of muscle in fibromyalgia he states 'Although controversy persist, the weight of evidence from studies that are methodologically sound suggests that muscles are not abnormal' (Simms, 1996).

Others still argue that peripheral pain mechanisms must play an important role in fibromyalgia pain. 'Central sensitization has to have an initial genesis and nociceptive stimuli from painful foci in muscle are increasingly recognized as being relevant to the development of fibromyalgia' (Bennett, 2004). Supporting the idea that there are soft-tissue abnormalities in fibromyalgia is the distribution of pain, which is not uniform as one would expect if the pain was generated solely from a spontaneous central nervous system hypersensitivity, but is most prevalent in certain areas of the soft-tissue, especially the shoulders, chest, and lower back (Starz et al., 2008). The often observed worsening of fibromyalgia pain after an episode of muscle overuse also argues for a peripheral pathology in FM.

Myofascial trigger points have been suggested as the peripheral source of painful input leading to central sensitization in fibromyalgia. Myofascial trigger points are discrete painful spots located in a palpable taut band of skeletal muscle, classified as active if they cause pain at rest, and latent if they are painful only with palpation (Simons et al., 1999). However, attributing the central sensitization seen in fibromyalgia solely to trigger points is problematic. Not all patients with fibromyalgia have trigger points, and not all patients with trigger points have fibromyalgia. One study found 68% of fibromyalgia patients had identifiable trigger points (Granges and Littlejohn, 1993), and another found trigger points in only 38% of fibromyalgia subjects examined (Wolfe et al., 1992). Myofascial trigger points are also quite common—33–54% of completely asymptomatic individuals have latent trigger points (Sola et al., 1955; Schiffman et al., 1990).

Background

The symptoms of fibromyalgia have historically been described by many different terms, including 'Chronic

Rheumatism' and 'Muscular Rheumatism'. In a review article in 1904, Stockman described the symptoms of chronic rheumatism as 'pain, aching, stiffness, a readiness to feel muscular fatigue, interference with free muscular movement, and very often a want of energy and vigour' (Stockman, 1904). Chronic rheumatism was not thought by Stockman to affect the joints themselves, but rather the fibrous tissues structures of the muscles. He attributed chronic rheumatism primarily to infectious causes, particularly rheumatic fever and influenza, but also noted some cases with no infectious etiology.

Stockman notes the work of Balfour and Scudamore, two British physicians who separately in the early 19th century put forward the idea that the pain of muscular rheumatism occurs as a result of thickenings developing in the fibrous connective tissue of muscle.

Sir William Gowers attributed symptoms of muscular rheumatism to the 'inflammation of fibrous tissue', and proposed that the condition should be called 'fibrositis' (Gowers, 1904).

Due to lack of evidence of peripheral inflammation, in 1976 the term 'fibromyalgia' was proposed, and ultimately adopted by the American College of Rheumatology when they released formal diagnostic criteria for the condition in 1990 (Wolfe et al., 1990). However the current terminology still reflects the concept of connective tissue abnormality in fibromyalgia, as the name is composed of the Latin words for fiber, muscle, and pain.

Allopathic medicine has historically regarded fascia as relatively inert. According to a recent article in Science magazine 'medical books barely mention fascia and anatomical displays remove it' (Grimm, 2007). However in osteopathic medicine, the fascia has long been recognized as a potential cause of pain and soft-tissue dysfunction. As one osteopath writes 'The whole of OMT [osteopathic manipulative treatment] has been concerned, purposefully or not, with manipulation of the fascia' (Danto, 2003).

Fascia

Fascia is the dense connective tissue that envelopes muscles grossly, and also surrounds every bundle of muscle fibers and each individual muscle cell. This connective tissue is inextricably linked with the muscle, and is continuous with the tendons and periosteum (Figures 1 and 2).

The fascia is composed of cells—including fibroblasts, macrophages and mast cells—and extracellular matrix. The extracellular matrix (ECM) is composed of ground substance and collagen and elastin fibers. Fascia is essentially a dense gel (the ground substance) in which cells and fibers are suspended, giving it colloidal properties.

Fascia is richly innervated—a histological study found nerve fibers in all specimens of the deep fascia, including a variety of both free and encapsulated nerve endings, especially Ruffini and Pacini corpuscles (Stecco et al., 2006). In fact muscle innervation is primarily located in the fascia: consisting of 25 percent stretch receptors of muscle cells, and 75 percent free nerve endings in intramuscular fascia, and in the walls of blood vessels and tendons (Bonica, 1990).

The principal cell of the connective tissue is the fibroblast, which produces the extracellular matrix, in addition

Figure 1 Published with kind permission of Ron Thompson.

to its roles in regulation of inflammation and wound repair. Fibroblast activation is induced by various stimuli that occur with tissue injury. Activated fibroblasts isolated from the site of a healing wound will continue to secrete higher levels of ECM and proliferate more rapidly than fibroblasts obtained from normal tissue. Fibroblasts are also an important source of ECM degrading proteases, and have

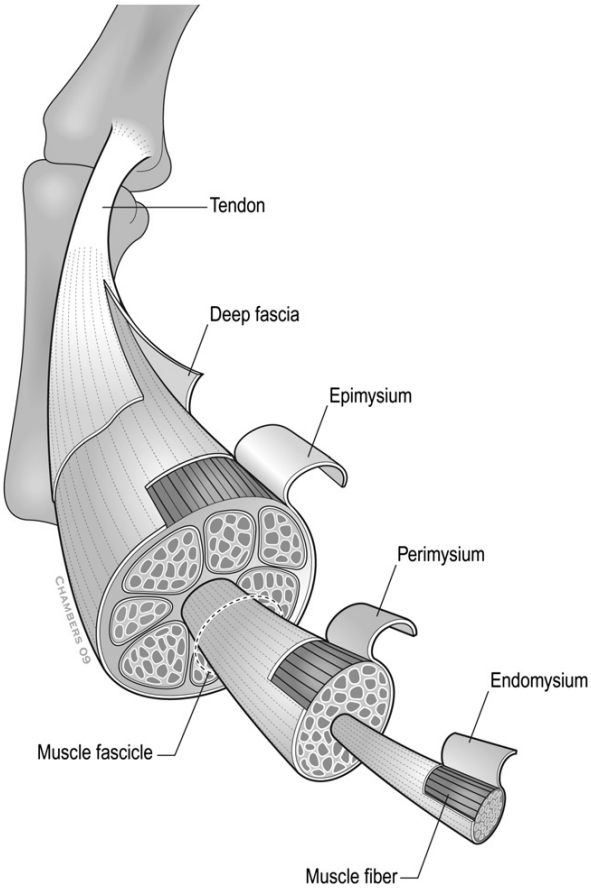

Figure 2 Structure of skeletal muscle, illustrating the layers of surrounding connective tissue known as the fascia, which includes the deep fascia, epimysium, perimysium and endomysium.

a crucial role in maintaining homeostasis and repair in the ECM (Kalluri and Zeisberg, 2006).

Fascia has been demonstrated in vitro to have some contractile behavior. Some fibroblasts, called myofibroblasts, express alpha-smooth-muscle actin and are able to contract (Schleip et al., 2005, 2006). Increased expression of smooth-muscle actin is thought to be triggered by mechanical stimulation and inflammation in order to promote wound healing and tissue repair.

Fibroblasts also respond to mechanical stretch with hyperplasia and secretion of inflammatory cytokines (Skutek et al., 2001). Using in vitro models, Dodd et al. demonstrated that fibroblasts respond to acyclic mechanical strain by altering shape and alignment, undergoing hyperplasia and secreting inflammatory cytokines, including IL-6 (Dodd et al., 2006).

Fibroblasts have a vital role in the regulation of inflammation. Dysregulation of fibroblasts has been implicated in the chronic inflammation seen in rheumatoid arthritis. Synovial fibroblasts isolated from rheumatoid arthritis joints were found to secrete increased amounts of NF-κB, a transcription factor that 'appears to play a critical role in perpetuating both tissue hyperplasia and the inflammatory response at sites of chronic inflammation' (Miagkov et al., 1998; Buckley et al., 2001).

Fibrosis and adhesions

One of the hallmarks of connective tissue, including fascia, is its mutability and remodeling in response to mechanical stress. However, under certain conditions—excess mechanical stress, inflammation or immobility—this process can result in excessive and disorganized collagen and matrix deposition resulting in fibrosis and adhesions (Langevin, 2008).

In plantar fasciitis and tendinitis of the elbow these types of changes have been reported. Two series of surgical biopsies in patients with plantar fasciitis reported fascial thickening, collagen disorganization and increased fibroblasts. Jarde et al. (2003) in a report on 38 cases of plantar fasciitis noted 'collagen degeneration with fibers losing their longitudinal arrangement and presenting with a haphazard orientation, with an increase in fibroblastic cellular density'. They also noted microcalcifications in the fascia of a few of the surgical specimens. The authors found that these lesions were similar to those found in cases of tendon injury.

Tendons are essentially a denser version of intramuscular fascia with the same components of fibroblasts, collagen and extracellular matrix. According to a review of the histopathological changes found in lateral epicondylitis, the most common findings were hypertrophy of fibroblasts and abundant disorganized collagen (Kraushaar and Nirschl, 1999).

A biopsy study of the thoracolumbar fascia in chronic mechanical low back pain found evidence suggestive of fascial inflammation, in particular degenerative changes in the collagen fibers and microcalcifications in the fascia (Bednar et al., 1995). In an ultrasound-based comparison, chronic low back pain patients had approximately 25% thicker perimuscular connective tissue in the thoracolumbar fascia than healthy controls (Langevin et al., 2009).

Eosinophilic fasciitis, a rare condition resulting in widespread eosinophilic infiltration and inflammation of the fascia results in significant fibrosis of the fascia. 'Adhesions seen in eosinophilic fasciitis, which develops grossly thickened fascia and fibrosis are indicative of the potential for fascial inflammation to cause adhesions' (Franklyn-Miller et al., 2009).

Evidence for fascial dysfunction in fibromyalgia

When Stockman examined muscle biopsy studies of patients with 'chronic rheumatism' in 1904, he found inflammatory hyperplasia of the connective tissue. Specifically he described a section of inflamed perimysium which on light microscopic evaluation consisted of a 'proliferated and oedematous fibrous tissue with an amorphous matrix', leading him to conclude that 'the essential pathological changes in chronic rheumatism are confined to white fibrous tissue' (Stockman, 1904). However, Collins later examined Stockman's published illustrations and noted 'scarcely more variation in fibrous tissue structure than can be encountered normally in different situations in the human body'. Collins also examined 7 'typical fibrositic' nodules under light microscopy and found no evidence of inflammation (Collins, 1940). Both of these early studies suffered from methodological flaws including lack of controls groups and poorly defined diagnostic criteria.

More recent studies of FM muscle using standard histopathology techniques under light microscopy have not shown any consistent pathology (Lindh et al., 1995; Drewes et al., 1993). However one group described a 'network of reticular fibers connecting muscle fibers' causing a 'rubber-band like' constriction of muscle fibers seen under light microscopy (Bartels and Danneskold-Samsoe, 1986).

Electron microscopic studies—which examine the myofibrils and sarcomeres that make up individual muscle cells—have also not shown any differences between fibromyalgia muscles and controls (Yunus et al., 1989a).

While no consistent abnormalities have been found at either the ultrastructural or structural level of muscle cells using standard techniques, two recent studies using specialized immuno-histochemical staining techniques focused on the intramuscular connective tissue have discovered some intriguing abnormalities.

Spaeth et al. describe an increase in collagen IV surrounding the muscles of fibromyalgia patients. Comparing immuno-stained muscle biopsies from 25 fibromyalgia patients to 26 healthy controls, they described a 'slight, but significant increase in collagen surrounding the muscle cells of the fibromyalgia patients' (Spaeth et al., 2005).

Ruster et al. also found increased levels of collagen in the endomysium in fibromyalgia muscles, and in addition describe evidence for endomysial inflammation and tissue damage. Specifically, they note elevated levels of N-carboxymethyllsine (CML), an advanced glycation end-product (AGE) that is considered to be a marker of oxidative stress and tissue damage, in the fascia of fibromyalgia patients.

'CML staining was stronger in the fibromyalgia patients, and was detected primarily in the **interstitial tissue between the muscle fibers'** (emphasis added). They reported increased staining of collagen types I, II, and VI in the interstitial tissue compared to healthy subjects and found 'the collagens and CML were co-localized, suggesting that the AGE modifications were related to collagen'. In addition, they found increased levels of CD-68 positive macrophages and activated NF-κB in the interstitial tissue of fibromyalgia muscles (Ruster et al., 2005). As described earlier, NF-κB is a transcription factor that plays an important role in the regulation of fibroblast hyperplasia and cytokine release, and high levels of NF-κB have also been reported in synovial fibroblasts from rheumatoid joints (Miagkov et al., 1998).

This immuno-histochemical evidence is suggestive of fascial inflammation in fibromyalgia. As described earlier, focal fascial inflammation has been described in other conditions as plantar fasciitis and low back pain. Giesecke et al. found evidence for central sensitization in idiopathic chronic low back pain patients (Giesecke et al. 2004). Since local myofascial inflammation as described in chronic low back pain could be a trigger of central sensitization, it is possible that a more generalized fascial inflammation could lead to central sensitization as well. In fact peripheral afferent nociceptors of muscle, the majority of which reside in the fascia, have been shown to be highly effective at causing central sensitization (Wall and Woolf, 1984).

Growth hormone and sleep abnormalities

Moldofsky was able to cause symptoms of fibromyalgia—widespread muscle pain and fatigue—in healthy patients by depriving them of deep (slow-wave) sleep experimentally (Moldofsky and Scarisbrick, 1976). These symptoms resolved once subject were again allowed deep sleep. Sleep studies have demonstrated that fibromyalgia patients experience reduced deep sleep that is frequently interrupted with alpha-waves which are normally associated with states of wakefulness (Moldofsky et al., 1975).

Growth hormone is primarily secreted during deep sleep and after exercise, and is responsible for regulating the healing and maintenance of tissues. Nearly 70% of total GH secretion occurs at night, and GH secretion 'will not occur if sleep stage III or IV is prevented by awakening the subject' (Felig et al., 1995).

Reduced 24 h secretion of GH in FM has been reported, with the decrease most noticeable during the night when GH secreted in the patients was much lower than in controls (Leal-Cerro et al., 1999). Another group also found reduced GH secretion during sleep compared to controls (Landis et al., 2001). More than 90% of fibromyalgia patients have inadequate growth hormone response to exercise (Paiva et al., 2002) and one third have significantly low circulating IGF-1 levels (Bennett et al., 1992). Human growth hormone replacement in FM patients resulted in significant improvement of symptoms and reduction in tender points in one study (Bennett et al., 1998).

Some of the clinical features of FM are similar to those described in adult GH deficiency syndrome including fatigue, muscle weakness, impaired exercise tolerance and depression. Unlike FM, pain is not a major feature described in adult GH deficiency syndrome. However treatment with GH has been reported to improve pain levels in adult GH deficient patients (Cuneo et al., 1998). These conditions may not be directly comparable, however, because true adult GH deficiency is usually acquired due to pituitary damage and is generally accompanied by multiple other pituitary hormone deficiencies. In contrast, fibromyalgia patients have normal pituitary responses but have subtle alterations in hypothalamic control of growth hormone release (Leal-Cerro et al., 1999).

Fibroblasts have growth hormone receptors, and in response to growth hormone secrete many important locally acting growth factors, such as IGF-1 (Murphy et al., 1983; Oakes et al., 1992). Fibroblasts play a central role in wound healing, and IGF-1 is a major physiological mediator of normal wound healing (Suh et al., 1992) A study of wound healing in rats revealed increased IGF-1 immunoreactivity in fibroblasts, epidermal cells and macrophages in the incisional area (Todorovic et al., 2008). Improved wound healing and increased staining for IGF-1 in healing tissue have been reported after administration of recombinant human growth hormone (Gilpin et al., 1994; Herndon et al., 1995). Local IGF-1 administration has also been found to improve wound healing (Suh et al., 1992; Beckert et al., 2007).

An intriguing study of gamma-hydroxybutyrate, a medication known to increase slow wave sleep, was found to both increase growth hormone levels and improve wound healing in rats (Murphy et al., 2007). This medication has also shown benefit in recent human studies of patients with FM as well, and the improvements in sleep significantly correlated with improvements in pain scores (Russell et al., 2009).

Hypothesis

Fascial dysfunction and inflammation may lead to the widespread pain and central sensitization seen in fibromyalgia. This paper proposes that the fascial dysfunction in fibromyalgia could be caused by chronic tension in the fascia and an impaired fascial healing response due to inadequate growth hormone stimulation. In genetically prone individuals, a trauma may trigger prolonged dysfunction of the stress response. This chronic autonomic arousal and hypervigilance may cause excess fascial tension, interfere with deep sleep and impair growth hormone release (Figure 3).

There seems to be a genetic component to fibromyalgia—first-degree relatives of patients with fibromyalgia are 8.5 times more likely to have fibromyalgia than relatives of patients with rheumatoid arthritis (Arnold et al., 2004). An association between trauma and fibromyalgia has also been reported, with one study finding that 'physical trauma in the preceding 6 months is significantly associated with the onset of FM' (Al-Allaf et al., 2002).

Hyperactivity of the stress response has also been described in fibromyalgia, with dysfunction of both hypothalamic—pituitary—adrenal axis and of the autonomic nervous system (Adler et al., 1999; Cohen et al., 2000). Hyperactivity of the HPA axis can also cause a blunted growth hormone response (Jones et al., 2007).

Chronic sympathetic dominance of the nervous system may also promote chronic tension in the fascial system.

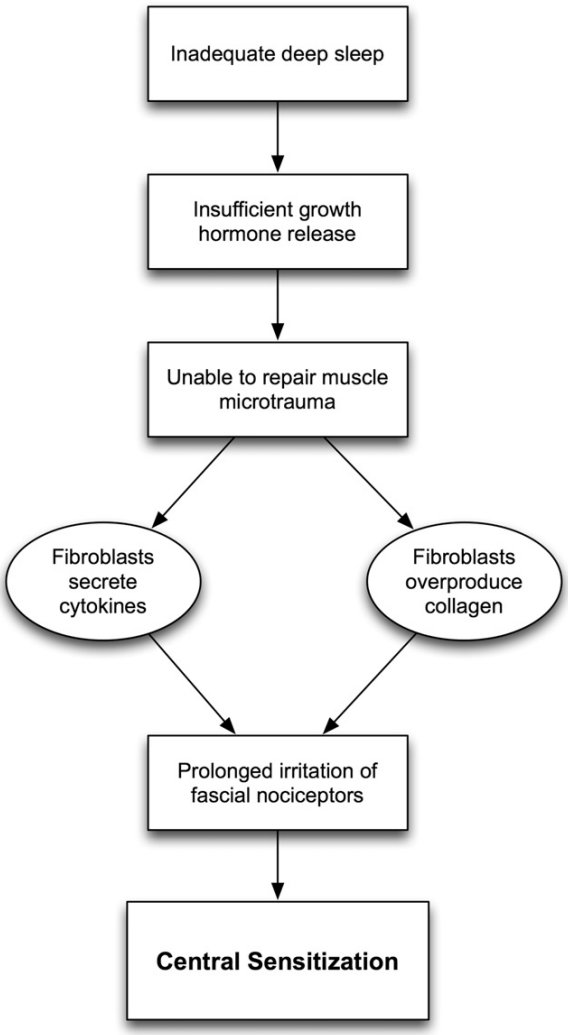

Figure 3 Proposed etiology of central sensitization in fibromyalgia.

Fascia has recently been shown to be able to have significant contractile force in vitro, and this fascial contractility is though to contribute to the incredible feats of strength humans can perform in emergencies—situations in which the sympathetic nervous system is also dominant (Schleip et al., 2005; Schleip et al., 2006).

In response to chronic excess fascial tension, fibroblasts would likely overproduce collagen and extracellular matrix in a continuous attempt to respond to the increased mechanical stress. However due to inadequate growth hormone stimulation of fibroblast there may be an impaired fascial healing response resulting in chronic fascial inflammation; there is 'a critical role for fibroblasts in regulating the switch from acute to chronic inflammation in tissues' (Buckley et al., 2001).

This widespread dysfunctional fascial healing response could be considered a 'bodywide fasciitis' as compared to the more focal fasciitis seen in other conditions such as plantar fasciitis. The tender points of fibromyalgia may reflect areas that suffer the greatest microtrauma and mechanical stress from daily activities, and thus have higher levels of fascial inflammation. The areas near muscle/tendon junctions are particularly susceptible to microinjuries from mechanical forces. In fact, six of the 18 tender points used to define the condition occur in or near areas of tendinous insertions, namely those at the sub-occipital muscle insertions, near the epicondyles and at the medial fat pad of the knee (Figure 4a and b).

Anti-inflammatories in fibromyalgia

If fascial inflammation exists in FM, why are non-steroidal anti-inflammatory medications (NSAID) and corticosteroids ineffective? No improvement in fibromyalgia symptoms was reported with prednisone 15 mg per day for two weeks, or with the NSAID medications ibuprofen and naproxen (Clark et al., 1985; Goldenberg et al., 1986; Yunus et al., 1989b).

This paper argues that there is indeed fascial inflammation in fibromyalgia, but that it is a type of inflammation that is not responsive to oral NSAIDs or corticosteroids. The fascial inflammation proposed to exist in fibromyalgia is similar to that described in chronic overuse injuries such as lateral epicondylitis and plantar fasciitis. This inflammation is attributed to cumulative microtrauma that overwhelms the tissue's ability to repair itself, resulting in a chronic inflammatory reaction that may be more appropriately termed a 'dysfunctional healing response'.

The response to injury of connective tissue, including fascia, ligaments and tendons, occurs in three phases (Kumar, 1999).

1) Inflammatory phase—invasion of polymorphonuclear cells and monocytes/macrophages, and release of prostaglandin and cytokines
2) Proliferative phase—fibroblasts activated to produce collagen and extracellular matrix that is laid down in disorganized fashion
3) Remodeling phase—progressive maturation and alignment of collagen fibers and remodeling of extracellular matrix

The anti-inflammatory effect of NSAIDs is due to their interference with prostaglandin production, thus they are effective in the initial inflammatory phase of injury repair. NSAIDs have been shown to be helpful in decreasing pain and swelling in acute soft-tissue injuries, but not in chronic soft-tissue inflammation (Heere, 1987). A randomized controlled trial of NSAIDs in plantar fasciitis found that both placebo and NSAID group improved over time, and there was no statistical difference between the groups at 1, 2 or 6 months (Donley et al., 2007). Another randomized controlled study found no difference between placebo and NSAID treatment in chronic achilles tendinopathy (Astrom and Westlin, 1992).

Local corticosteroid injections have shown effectiveness in overuse injuries but this effect tends to be short-lived. A randomized controlled trial of steroid injections in plantar fasciitis found a statistically significant pain reduction at 1 month in the treatment group that had disappeared by 3 months post treatment (Crawford et al., 1999). In lateral epicondylitis steroid injections also provide

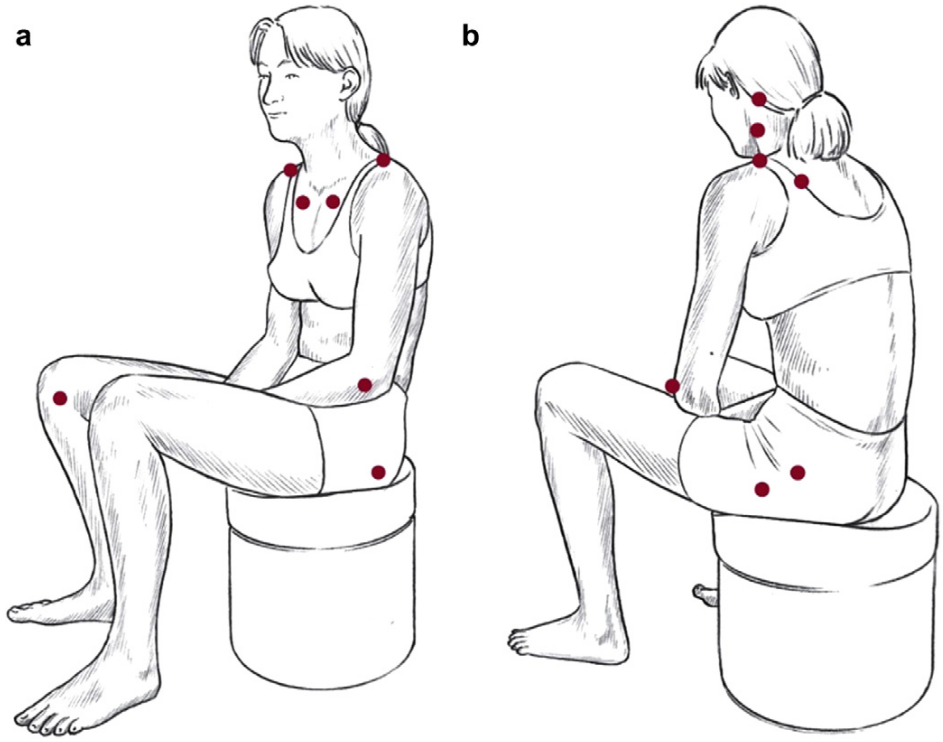

Figure 4 a and b: 18 tender points of fibromyalgia as established by 1990 ACR criteria (Wolfe et al., 1990).

only temporary improvement, and 'the significant short-term benefits of corticosteroid injections are paradoxically reversed after six weeks with high recurrence rates' (Bissett et al., 2006).

In an animal model of chronic muscle inflammation created by injecting inflammatory stimulants into the hamstrings of mice, neither NSAIDs nor high-dose oral corticosteroids were effective in reducing inflammation. The inflammation could only be reduced by local corticosteroid injection directly into the muscle (Green and Mangan, 1980). Notably, while NSAIDs and oral steroids have been tested in FM, the effectiveness of local steroid injections in FM has not been assessed.

NSAIDs and corticosteroids are not only ineffective in relieving chronic soft-tissue inflammation but may actually hinder the healing process. Two studies reported slowed muscle repair in animals treated with an NSAID (Obremsky et al., 1994; Almekinders and Gilbert, 1986). Indomethacin added to repetitively stretched fibroblasts in vitro reduced the secretion of prostaglandins but also inhibited the synthesis of DNA, an effect that may be detrimental in the remodeling phase of repair (Almekinders et al., 1995). Corticosteroids are also notorious for impairing surgical wound healing (Suh et al., 1992). Thus NSAIDs and corticosteroids may actually worsen an already dysfunctional tissue repair response in fibromyalgia.

Manual therapy in fibromyalgia treatment

In 1904 Stockman recognized the potential of manual therapy in treating chronic rheumatism (what is now called fibromyalgia) and noted that 'indurated fibrous tissue can however only be removed by local and well-directed manipulations' (Stockman, 1904). This idea was reiterated recently by a leading fascia researcher, 'Treatments involving direct mechanical stimulation of connective tissue can potentially reverse connective tissue fibrosis' (Langevin, 2008). Myofascial fibrotic changes can theoretically be treated by breaking up excessive collagen adhesions through soft-tissue and myofascial release techniques (Ward, 2003). If there is excess tension in the fascial system in fibromyalgia due to chronic sympathetic nervous dominance, manual therapy may also help reduce that tension.

A randomized controlled pilot study demonstrated that osteopathic manipulative treatment (OMT), in conjunction with medication, was more effective in relieving symptoms of fibromyalgia than medication alone (Gamber et al., 2002). A total of 24 patients were included in the study, and the treatment group received once weekly OMT sessions for 23 weeks. The control group received either moist heat packs at each visit or no additional treatment beyond their usual medications. The osteopathic manipulative techniques used in this study were individualized for each patient, so it is difficult to assess how much treatment directed specifically at the fascia that each patient received. Each patient received Jones strain/counterstrain techniques and other modalities per provider discretion—including myofascial release, muscle energy, soft-tissue treatment and craniosacral manipulation.

A Swedish study on connective tissue massage in fibromyalgia found a pain-relieving benefit of 37% in addition to reduced use of analgesics and positive effects on quality of life. The treatment group consisted of 23 patients who received 15 treatments over 10 weeks, while the control

group participated in weekly discussion groups. The connective tissue massage is described as a 'manual techniques to detach dense connective tissue', but no further description of the technique is provided. Interestingly, this treatment was chosen for the study because 'experienced massage therapists who were surveyed prefer connective tissue massage for the treatment of individuals with fibromyalgia' (Brattberg, 1999).

However, for manual therapies to be effective in fibromyalgia, they must take into account the colloidal properties of fascia, and according to Chaitow and DeLany 'the amount of resistance colloids offer increases proportionally to the velocity of force applied to them. This makes a gentle touch a fundamental requirement … when attempting to produce a change in, or release of restricted fascial structures which are all colloidal in their behavior' (Chaitow and DeLany, 2000). Therefore, only slow and sustained pressure will effect changes in the fascial tissue.

Appropriate manual therapy must allow for the state of reduced growth hormone and thus reduced capacity for tissue repair in fibromyalgia by allowing for sufficient rest between sessions. Utilizing the growing body of knowledge on the properties of fascia can help manual therapists treat fibromyalgia patients with techniques that don't cause further injury and inflammation, but rather gently break apart existing fascial restrictions and adhesions and promote tissue healing.

Conclusion

This paper presents the hypothesis that fascial dysfunction in fibromyalgia leads to widespread pain and central sensitization. Using other known abnormalities in fibromyalgia, a proposed mechanism leading to fascial dysfunction in fibromyalgia is described.

The in vivo microdialysis techniques developed by Shah's group to assess myofascial trigger points could also be used to evaluate the chemical composition of fascial interstitial fluid for evidence of inflammation (Shah et al., 2005). In vitro examination of fibroblasts removed from fascial tissues in fibromyalgia could look for evidence of activation, such as excess secretion of extracellular matrix and inflammatory mediators. Comparing fascial IGF-1 levels in fibromyalgia to controls may also be useful.

Finally, clinical studies of manual therapies that target the fascia, like Rolfing and myofascial release, could help define the role of fascia in producing fibromyalgia pain. Directly comparing a therapy aimed at releasing fascial restriction such as myofascial release to a massage therapy that focuses primarily on muscle relaxation would be informative. If there is clinical improvement with manual therapies targeting the fascia, this could significantly improve our ability to treat fibromyalgia, and guide further research on the peripheral pathology of fibromyalgia towards the fascia.

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