Medical Hypotheses (2007) **68,** 74—80

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Pathophysiological model for chronic low back pain integrating connective tissue and nervous system mechanisms ☆

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Received 21 June 2006; accepted 22 June 2006

Summary Although chronic low back pain (cLBP) is increasingly recognized as a complex syndrome with multifactorial etiology, the pathogenic mechanisms leading to the development of chronic pain in this condition remain poorly understood. This article presents a new, testable pathophysiological model integrating connective tissue plasticity mechanisms with several well-developed areas of research on cLBP (pain psychology, postural control, neuroplasticity). We hypothesize that pain-related fear leads to a cycle of decreased movement, connective tissue remodeling, inflammation, nervous system sensitization and further decreased mobility. In addition to providing a new, testable framework for future mechanistic studies of cLBP, the integration of connective tissue and nervous system plasticity into the model will potentially illuminate the mechanisms of a variety of treatments that may reverse these abnormalities by applying mechanical forces to soft tissues (e.g. physical therapy, massage, chiropractic manipulation, acupuncture), by changing specific movement patterns (e.g. movement therapies, yoga) or more generally by increasing activity levels (e.g. recreational exercise). Non-invasive measures of connective tissue remodeling may eventually become important tools to evaluate and follow patients with cLBP in research and clinical practice. An integrative mechanistic model incorporating behavioral and structural aspects of cLBP will strengthen the rationale for a multidisciplinary treatment approach including direct mechanical tissue stimulation, movement reeducation, psychosocial intervention and pharmacological treatment to address this common and debilitating condition.

Introduction

Despite considerable research efforts, chronic low back pain (cLBP) remains a poorly understood condition causing substantial disability, work absenteeism and health care costs [1—4]. While it is known that many patients with an episode of acute low back pain improve clinically without specific treatment, it is less clear why others progress to develop recurrent or chronic symptoms [5]. It is generally recognized that cLBP is a dynamic, fluctuating condition with multifactorial etiology and complex pathogenesis. Historically,

☆ Supported by NIH NCCAM R01-AT01121.
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0306-9877/$ - see front matter
doi:10.1016/j.mehy.2006.06.033

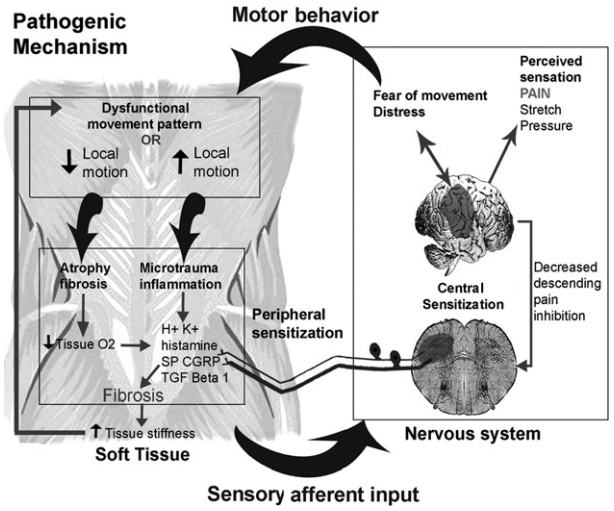

Figure 1 Pathophysiological model for chronic low back pain linking somatic and behavioral components.

mechanistic models for cLBP have tended to focus on musculoskeletal tissues, on the nervous system, or on behavior. In this paper, we propose a new, dynamic and integrative pathophysiological model for cLBP bringing together recent research on movement and neuroplasticity along with well-established connective tissue remodeling mechanisms (Fig. 1). We hypothesize that plasticity in both connective tissue and nervous systems, linked to each other via changes in motor behavior, play a key role in the natural history of cLBP, as well as the response of cLBP to treatments and placebos.

What is already known about mechanistic factors contributing to cLBP?

Tissue structural abnormalities

To date, a considerable amount of research on low back pain has focused on structural abnormalities of spine-associated tissues (e.g. disc herniation, facet joint degeneration) with emphasis on diagnostic imaging (e.g. X-ray, CT scan, MRI). However, the association between symptoms and imaging results has been consistently weak, and up to 85% of patients with low back pain cannot be given a precise pathoanatomical diagnosis using these methods [6]. This, along with the generally poor predictive value of diagnostic imaging in cLBP, and the often disappointing effects of many ''lesion-specific'' treatments such as intra-articular corticosteroid injections [7], has spurred research efforts toward ''non-structural'' psychological and behavioral aspects of cLBP, and away from tissue pathology.

Psychological factors

A number of studies [8—10] have reported that, in patients with acute or subacute low back pain, measures of emotional distress are associated with the future development of chronic pain and disability. Psychosocial factors potentially contributing to emotional distress in patients with cLBP include job dissatisfaction, poor social support and the influence of pain-related behavior on work and family dynamics [11,12]. A key component of pain-related behavior is fear of pain with consequent decrease in physical activity [13,14]. While rest may be initially important in the face of acute low back injury (e.g. disc herniation, muscle sprain), it is increasingly recognized that timely resumption of physical activity is critical to successful rehabilitation [15]. However, after an episode of acute low back pain, patients often remain sedentary because of fear that movement will cause pain. Such behavior is particularly detrimental since decreased recreational activity leads to deconditioning, which further impacts emotional well being [16,17].

Movement pattern abnormalities

A growing body of evidence supports the notion that both pain and fear affect not only how much, but also *how* patients with cLBP actually move. Abnormal trunk muscle activity during postural perturbation, impaired control of trunk and hip during arm movements and abnormal postural compensation for respiration all have been documented in cLBP [18—21]. Several models have been proposed to explain such abnormal movement patterns including the ''pain-spasm-pain'' model (reflex sustained co-contraction of agonists and antagonist muscles) [22] and ''pain adaptation'' (slowing and decreased range of motion due to selective increased activation of antagonists) [23]. Although it has been proposed that altered muscle activation patterns in cLBP can stabilize the spine during movement, thus preventing further injuries, this adaptation comes at the cost of a limited range of motion [24]. Recent experiments in addition suggest that, in normal individuals, fear of pain by itself can cause altered trunk muscle activation patterns during limb movement that resembles those observed in patients with cLBP [25]. Both experimental back pain (painful

cutaneous electrical stimulation) and anticipation of pain (without electrical stimulation) caused increased activity and co-contraction of superficial muscles along with delayed or decreased activation of deep muscles. Thus, patients with cLBP appear to have a constellation of motion-limiting muscle activation patterns that may be initiated or aggravated by emotional factors.

Neuroplasticity and central sensitization

In addition to abnormal movement patterns, patients with cLBP have been shown to have generalized augmented pain sensitivity and cortical activation patterns suggesting abnormal central pain processing [26]. Ongoing pain is associated with widespread neuroplastic changes at multiple levels within the nervous system [27—29] including primary afferent neurons, spinal cord, brainstem, thalamus, limbic system and cortex [30—33]. Recent neuroimaging data have uncovered distinct ''brain networks'' involved in acute vs. chronic pain, with chronic pain specifically involving regions related to cognition and emotions [34]. Recent findings of reduced pre-frontal cortex *N*-acetyl aspartate levels and decreased pre-frontal and thalamic gray matter density also have been described in cLBP, compared with controls, suggesting neuronal or glial loss, possibly due to toxic effects of prolonged excitation [35,36]. At the level of the somatosensory cortex, functional reorganization of somatosensory areas has been documented in chronic pain [37]. In patients with cLBP, magnetoencephalography assessment of cortical activation during painful stimuli showed a shift and expansion of the cortical area representing the low back towards the leg [38]. Pronounced shifts in motor cortical activation patterns during movement in patients with phantom limb pain (but not in pain-free amputees) also suggests that neuroplastic changes during chronic pain may involve motor as well as sensory cortical reorganization [39]. Indeed, current models increasingly view chronic pain as a multisystem output, the ''pain neuromatrix'' including both sensory and motor components [40—42].

Proposed role of connective tissue remodeling in cLBP

We hypothesize that connective tissue remodeling occurs in cLBP as a result of emotional, behavioral and motor dysfunction. We further hypothesize that increased connective tissue stiffness due to fibrosis is an important link in the pathogenic mechanism leading to chronicity of pain, fear-avoidance and further movement impairment.

Effect of mechanical stress on connective tissue

Abnormal movement patterns can have important influences on the connective tissues that surround and infiltrate muscles. A hallmark of connective tissue is its plasticity or ''remodeling'' in response to varying levels of mechanical stress [43]. Both increased stress due to overuse, repetitive movement and/or hypermobility, and decreased stress due to immobilization or hypomobility can cause changes in connective tissue [44,45]. A chronic, local increase in stress can lead to microinjury and inflammation (overuse injury, cumulative trauma disorder) [46—48]. A consistent absence of stress, on the other hand, leads to connective tissue atrophy, architectural disorganization, fibrosis, adhesions and contractures [49—53]. Factors influencing whether atrophy or fibrosis predominates during stress deprivation include the concurrent presence of inflammation, tissue hypo-oxygenation and cytokines such as TGFβ-1 that promote fibrosis [54,55]. Fibrosis therefore can be the direct result of hypomobility or the indirect result of hypermobility via injury and inflammation.

Connective tissue/muscle interactions

In muscle, plasticity of perimuscular and intramuscular connective tissue plays an important role in how muscle responds to mechanical stress. It has been shown, for example, that during the early phase of immobilization, loss of muscle length is primarily due to shortening of muscle-associated connective tissue, which is only later followed by actual shortening of muscle fibers [56]. The poorly understood phenomena of ''myofascial trigger points'', ''taut muscle bands'' and ''muscle spasm'' also may contribute to connective tissue remodeling and fibrosis. Although there is some controversy as to the definition and nature of these entities, and whether or not they are related to each other [57—59], decreased tissue pH and increased levels of inflammatory cytokines were recently reported in myofascial trigger points in the presence of pain [60]. Thus, the presence of painful muscle contraction or tender foci within perimuscular fascia may add to the factors promoting hypomobility and tissue fibrosis. Regardless of its original cause, connective tissue fibrosis is

detrimental, as it leads to increased tissue stiffness and further movement impairment.

Effect of connective tissue pathology on sensory afferent modulation

Tissue microinjury, inflammation and fibrosis not only can change the biomechanics of soft tissue (e.g. increased stiffness) but also can profoundly alter the sensory input arising from the affected tissues. Connective tissue is richly innervated with mechanosensory and nociceptive neurons [61]. Modulation of nociceptor activity has been shown to occur in response to changes in the innervated tissue. Tissue levels of protons, inflammatory mediators (prostaglandins, bradykinin), growth factors (NGFs) and hormones (adrenaline) [30,62,63] all have been shown to influence sensory input to the nervous system. Conversely, nociceptor activation has been shown to modify the innervated tissue. Release of Substance P from sensory C-fibers in the skin can enhance the production of histamine and cytokines from mast cells, monocytes and endothelial cells [64,65]. Increased TGFβ-1 production, stimulated by tissue injury and histamine release, is a powerful driver of fibroblast collagen synthesis and tissue fibrosis [54,66,67]. Thus, activation of nociceptors by itself can contribute to the development or worsening of fibrosis and inflammation, causing even more tissue stiffness and movement impairment.

Connective tissue remodeling and low back pain

We propose that, in patients with cLBP, connective tissue fibrosis can occur in the lower back due to one or several of the following factors: (1) decreased activity, (2) changes in muscle activation patterns causing muscle co-contraction, muscle spasm or tissue microtrauma and (3) neurally-mediated inflammation. To date, there is a paucity of published research devoted to connective tissue in relation to low back pain, reflecting the overall lack of attention to unspecialized ''loose'' connective tissue and fasciae compared with specialized connective tissues such as cartilage. We hypothesize that connective tissue remodeling may play an important role in the pathophysiology of LBP because (1) plasticity in response to changing mechanical loads is one of connective tissue's fundamental properties and (2) pathological remodeling (fibrosis) due to changes in tissue movement is well documented in other types of connective tissues (e.g. ligaments, joint capsules).

Dynamic pathophysiological model linking sensory, motor and emotional components of LBP with connective tissue plasticity

Most episodes of acute low back pain resolve, allowing resumption of normal activities. We propose that, in contrast, patients who develop fear of movement in response to the acute pain episode will be more likely to develop cLBP. In our pathophysiological model, this progression to cLBP first involves changes in the amount and pattern of movements leading to connective tissue remodeling and locally increased tissue stiffness. Peripheral and central nervous system sensitization will then contribute to tissue inflammation, emotional distress, pain-related fear and decreased movement. Additional psychosocial factors such as family dysfunction, secondary gain, job dissatisfaction and litigation can further contribute to decreased physical activity and to the vicious cycle illustrated in Figs. 1 and 2.

In both connective tissue and nervous system, plasticity responses are characterized by changes over time and the potential for reversibility. The mechanism presented in this paper is compatible with the complex natural history of low back pain including temporal variability (i.e. waxing and waning of symptoms and disability in recurrent low back pain) and potential for ''feed-forward'' acute exacerbation of symptoms (i.e. acute flare-up). An acute flare-up of pain may be triggered by any situation causing locally increased inflammatory cytokines, decreased tissue pH or oxygen content. In fibrosed connective tissue and muscle,

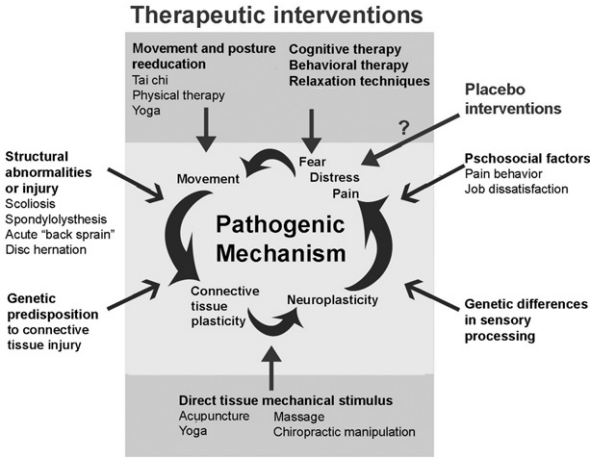

Figure 2 Relationship of proposed chronic low back pain pathogenic mechanism to precipitating factors and non-pharmacological therapeutic interventions.

blood and lymphatic flow may be chronically compromised by the disorganized tissue architecture and thus vulnerable to unusual muscle activity (e.g. beginning a new work activity or sport), or to conditions causing further decrease in perfusion such as prolonged sitting. Once local activation of nociceptors is initiated, peripheral and central nervous system sensitization mechanism amplify both the tissue inflammation (via release of inflammatory neurotransmitters such as Substance P) and the perceived pain, leading to distress, fear of movement etc. Each exacerbation of pain potentially leads to increased movement restriction and fibrosis, setting the patient up for more painful episodes.

The proposed model links several well-developed but separate areas of research into a comprehensive and testable model that plausibly explains why a patient with acute low back pain (e.g. due to acute back sprain) may go on to develop chronic or recurrent low back pain. By explicitly including connective tissue plasticity as part of the mechanism, the model incorporates additional factors that have not been linked mechanistically to the pathogenesis of low back pain. Testing this model will first require confirming the primary hypothesis that connective tissue fibrosis occurs in cLBP, then testing the relationship between movement, connective tissue fibrosis and persistent pain.

Effect of treatments and placebos

In addition to its role in the pathological consequences of immobility and injury, the dynamic and potentially reversible nature of connective tissue plasticity may be key to the beneficial effects of widely used physical therapy techniques as well as ''alternative'' treatments involving external application of mechanical forces (e.g. massage, chiropractic manipulation, acupuncture), changes in specific movement patterns (e.g. movement therapies, tai chi, yoga) or more general changes in activity levels (e.g. increased recreational exercise) (Fig. 2). Connective tissue remodeling also may be important in the therapeutic effect of pharmacological treatments commonly used for cLBP via direct effects on tissues (anti-inflammatories), reduction of muscle spasm (muscle relaxants) and/or pain-induced fear of movement (analgesics, anxiolytics). The effect of placebos in cLBP also may involve decreased fear of pain with consequent increased physical activity and beneficial connective tissue remodeling effects. Improving our understanding of therapeutic mechanisms is key to developing more effective treatment strategies for cLBP with minimal adverse effects. While manual or movement-based treatments have the advantage of not causing drug-induced side effects (e.g. gastritis, sedation), these treatments could conceivably worsen cLBP if applied forces actually cause inflammation due to excessive tissue stretching or pressure. A paradoxical aspect of connective tissue remodeling is that it potentially underlies both beneficial and harmful effects of mechanical forces, including those used therapeutically. It is well known in physical therapy, for example, that application of direct tissue stretch to ligaments and joint capsules needs to be gauged carefully to avoid causing increased tissue inflammation [44]. Indeed, understanding how much force (or movement) is beneficial, and how much can be harmful is one of the challenges of these clinical modalities. The hypothetical model presented in this paper suggests that behavior modification and movement reeducation may be most effective in the early stages of cLBP (before extensive tissue fibrosis has occurred) and that combining these approaches with carefully applied direct tissue stretch may be necessary in cases of long standing hypomobility with pronounced fibrosis and stiffness. Understanding the underlying pathophysiology of cLBP will help optimize the selection of the best treatment or treatment combination.

Future testing of the model and clinical significance

The model presented in this paper predicts that beneficial connective tissue remodeling can result from a variety of therapeutic interventions. The model also suggests that measures of connective tissue remodeling may become useful tools for evaluating the response to pharmacological and non-pharmacological treatments for LBP. Recently developed non-invasive ultrasound based techniques such as ultrasound elastography can be used for evaluation of connective tissue structure and biomechanics in vivo [68–70]. Such techniques may become useful tools to objectively document changes in connective tissue over time and thus measure the effects of various treatments. Eventually, these techniques may be useful to guide treatments in clinical practice.

The development, testing and implementation of effective treatment strategies are highly dependent on understanding the pathophysiological mechanisms of the condition being treated. An integrative model incorporating behavioral and somatic aspects of cLBP will strengthen the rationale for a multidisciplinary treatment approach including

direct mechanical tissue stimulation, movement reeducation and psychosocial intervention. Understanding how these various treatments may work synergistically in cLBP will support efforts to develop appropriate integrative approaches to treat this common and debilitating condition.

Acknowledgements

We thank Drs. Lorimer Moseley, Magdalena R. Naylor, Janet R. Kahn, John J. Triano and Robert W. Hamill for helpful discussions.

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