The Wave
2011

Life Chiropractic College West

A One Hour Look At Mechanics and Health

Dan Murphy, DC

- **Mechanics as whole body non-neurological communication network**
- **Mechanics as it influences body chemistry**
- **Mechanics as neurological controls to the muscle system**
- **Mechanics as influences to visceral neurology**

Mechanics as whole body non-neurological communication network

◆ REVIEW ARTICLE ◆

Taylor&Francis healthsciences

Mechanobiology and diseases of mechanotransduction

Donald E Ingber

The current focus of medicine on molecular genetics ignores the physical basis of disease even though many of the problems that lead to pain and morbidity, and bring patients to the doctor's office, result from changes in tissue structure or mechanics. The main goal of this article is therefore to help integrate mechanics into our understanding of the molecular basis of disease. This article first reviews the key roles that physical forces, extracellular matrix and cell structure play in the control of normal development, as well as in the maintenance of tissue form and function. Recent insights into cellular mechanotransduction – the molecular mechanism by which cells sense and respond to mechanical stress – also are described. Re-evaluation of human pathophysiology in this context reveals that a wide range of diseases included within virtually all fields of medicine and surgery share a common feature: their etiology or clinical presentation results from abnormal mechanotransduction. This process may be altered by changes in cell mechanics, variations in extracellular matrix structure, or by deregulation of the molecular mechanisms by which cells sense mechanical signals and convert them into a chemical or electrical response. Molecules that mediate mechanotransduction, including extracellular matrix molecules, transmembrane integrin receptors, cytoskeletal structures and associated signal transduction components, may therefore represent targets for therapeutic intervention in a variety of diseases. Insights into the mechanical basis of tissue regulation also may lead to development of improved medical devices, engineered tissues, and biologically-inspired materials for tissue repair and reconstruction.

Keywords: cytoskeleton; disease; extracellular matrix; integrin; mechanical forces; mechanotransduction; stress-activated ion channels; tissue engineering

Ann Med 2003; 35: 1–14

From the Vascular Biology Program, Departments of Surgery and Pathology, Children's Hospital and Harvard Medical School, Boston, MA 02115, USA.

Correspondence: Donald E Ingber, MD, PhD, Children's Hospital, Enders 1007, 300 Longwood Avenue, Boston, MA 02115, USA. Fax: 617-232-7914. E-mail: donald.ingber@tch.harvard.edu

Introduction

The molecular biology revolution has led to advances in knowledge and new technologies that are revolutionizing the way in which clinical medicine is practiced. Completion of the Human Genome Project, massively parallel gene and protein profiling techniques, and powerful bioinformatics tools are just a few examples. Yet there is a huge disconnect between these 'genome-age' technologies and the reality of how diseases manifest themselves. From the time the first human looked, listened and felt for what is wrong with a sick friend, caregivers have recognized the undeniable *physical* basis of disease. The thrill in the chest of a patient with aortic valve disease, bounding pulse in the hypertensive and wheeze of the patient with emphysema all ignite reflexive clinical responses in the mind of the skilled physician, and sometimes even lead to immediate diagnoses.

But in the current genome euphoria, there appears to be no place for 'physicality'. This is especially worrisome given that abnormal cell and tissue responses to mechanical stress contribute to the etiology and clinical presentation of many important diseases, including asthma, osteoporosis, atherosclerosis, diabetes, stroke and heart failure. There is also a strong mechanical basis for many generalized medical disabilities, such as lower back pain and irritable bowel syndrome, which are responsible for a major share of healthcare costs world-wide. In fact, surgeons sometimes even use mechanical forces as therapeutics, such as when traction forces are used to accelerate bone healing. However, what is missing is how these physical interventions could influence cell and tissue function, or how altered cell or tissue mechanics may contribute to disease development.

In this article, I first review the fundamental role that physical forces and changes in tissue mechanics play in normal development and physiology. I then describe recent advances in our understanding of cellular mechanotransduction, the molecular mech-

 ISSN 0785-3890
DOI 10.1080/07853890310016333

T&F -:- FULL SGML TEXT -:- Annals of Medicine
N:/SANN/149/149.3D
Page Count: 14 Page Range: 1–14

MS. 149 Op. PGW {F2-PDF}
Produced: 24/07/2003 At: 14:38:57
Page: 1

Key messages

- Mechanical forces are critical regulators of cellular biochemistry and gene expression as well as tissue development.
- Mechanotransduction – the process by which cells sense and respond to mechanical signals – is mediated by extracellular matrix, transmembrane integrin receptors, cytoskeletal structures and associated signaling molecules.
- Many ostensibly unrelated diseases share the common feature that their etiology or clinical presentation results from abnormal mechanotransduction. Mechanotransduction may be altered through changes in cell mechanics, extracellular matrix structure or by deregulation of the molecular mechanisms by which cells sense mechanical signals or convert them into a chemical response.
- Molecules that mediate mechanotransduction may represent future targets for therapeutic intervention in a variety of diseases. Insights into the mechanical basis of tissue regulation also may lead to development of improved medical devices, engineered tissues, and biomimetic materials for tissue repair and reconstruction.

viewed as the end-result of the disease process, recent advances in mechanobiology suggest that abnormal cell and tissue responses to mechanical stress may actively contribute to the development of many diseases and ailments. Thus, it might be wise to search for a physical cause when chemical or molecular forms of investigation do not suffice.

These observations also raise the possibility that the molecules that mediate mechanotransduction, including ECM molecules, cell surface adhesion receptors, cytoskeletal components, and related signal transduction molecules may represent future targets for therapeutic intervention in a variety of diseases. The value of macroscale forces as therapeutics has already been demonstrated by surgeons, however, the potential clinical value of developing approaches to selectively control microscale forces may be even greater. Pursuit of the relation between structure and function at the molecular scale in living cells and tissues also may lead to the development of entirely new biomaterials and microdevices for repair and replacement of injured tissues. Thus, if we are to advance patient care in the twenty first century, we need to do more than delineate the genetic causes of disease; we also must reintegrate mechanics into our understanding of the molecular basis of disease.

by which these cells sense mechanical forces and convert them into biochemical signals are still unknown, some possible mechanisms have been proposed. The ECM–integrin–cytoskeleton pathway is one of the signaling pathways most studied. Cells attach to the ECM via integrins that are linked to the cytoskeleton. This provides a structural connection to transmit mechanical signals from the ECM to the cell (Juliana and Haskill 1993; Maniotis et al. 1997). The major cellular components involved in the mechanotransduction mechanisms are the integrins, cytoskeleton, G proteins, receptor tyrosine kinases (RTKs), mitogen-activated protein kinases (MAPKs), and stretch-activated ion channels (Fig. 1). It should be noted, however, that these components are related in a cell either physically, functionally, or both.

In this section, the role of these cellular components in the mechanotransduction mechanisms is briefly reviewed. Many reviews are available that focus on different types of cells, including dermal fibroblasts (Silver et al. 2003), cardiac fibroblasts (MacKenna et al. 2000), cardiac myocytes (Sadoshima and Izumo 1997), SMCs (Osol 1995), endothelial cells (Davies 1995), and bone cells (Duncan and Turner 1995). In addition, a review that focuses on the mechanotransduction at cell–matrix and cell–cell contacts is also available (Chen et al. 2004). These reviews are excellent references for those who are interested in a more in-depth understanding of cellular mechanotransduction mechanisms.

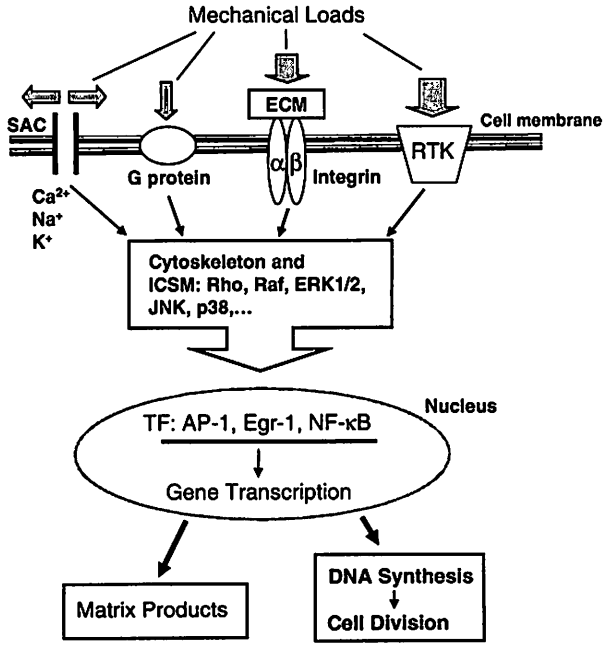


Fig. 1 A conceptual illustration of cellular mechanotransduction mechanisms. (ICSM: Intracellular signaling molecules; TF: Transcriptional factors)

6.1 Integrins

Integrins are the main mechanoreceptors that link the cytoskeleton to the ECM. They contain a large ECM domain responsible for binding to substrates, a single transmembrane domain, and a cytoplasmic domain (Hynes 1992). Serving as both adhesive receptors (Albelda and Buck 1990; Aplin et al. 1999) and mechanotransducers (Ingber 1991; Juliana and Haskill 1993; Giancotti and Ruoslahti 1999; Katsumi et al. 2004), integrin receptors transmit signals across the membrane after binding ECM ligands, thereby regulating various cellular functions, including cell attachment, proliferation, migration, and differentiation (Coppolino and Dedhar 2000). In addition, integrins bind paxillin, caveolin, and focal adhesion kinase and through these binding proteins, integrins are able to recruit kinases to activate pathways that lead ultimately to ERK1/2 and JNK phosphorylation (see below) (Iqbal and Zaidi 2005).

6.2 Cytoskeleton

The fundamental structural unit of the cytoskeleton is a filamentous network of microfilaments, microtubules, and intermediate filaments (Ingber 1998). Microfilaments, comprised of actin monomers attached with small binding proteins (e.g., α-actinin, filamin A, talin, and vinculin), are semi-flexible. Microtubules are rod-like, stiff polymers, whereas intermediate filaments are very flexible, elongated polymers (Oddou et al. 2000). The elastic and flexible nature of the cytoskeletal components provides the mechanical properties required for resistance to deformations, and hence allows the cell to maintain its shape in the presence of mechanical stress. The mechanical properties of the cells also influence how they respond to mechanical stress because how the cell deforms under mechanical forces depends on their mechanical properties (Wang et al. 2002).

Furthermore, mechanical loads that are transferred across the integrins can be transduced into a chemical response through changes in the cytoskeletal structure at the site of receptor binding or at other locations inside the cell (Ingber 1997). It has been shown that mechanical stresses that act on magnetic beads coated with an integrin ligand are transmitted to the cytoskeleton (Wang et al. 1993). Results from many studies with various cell types and model systems have also shown that a mechanical stress applied to integrins can alter cytoskeletal structure and activate signal transduction and gene expression in a stress-dependent manner (Schmidt et al. 1993; Wang et al. 1993; Urbich et al. 2002). In vascular endothelial cells, for example, the connections between integrins and their specific ECM ligands are essential for relaying the signals induced by shear stress to intracellular pathways (Jalali et al. 2001). In rat vascular SMCs, the interactions between integrins and specific matrix proteins are found to be responsible for sensing mechanical strain as well (Wilson et al. 1995). Rho, a member of the Ras superfamily of small GTPases, is implicated in the integrin mediated signal transduction. In particular, Rho plays a major role in regulating

actin stress fiber formation and the focal adhesion assembly (Ridley and Hall 1992; Pavalko et al. 1998).

6.3 G proteins

G proteins are another family of membrane proteins that are involved in modulating the mechanotransduction pathways. G protein subunits are localized at the sites of focal adhesions, which are the sites of mechanotransduction (Hansen et al. 1994). Mechanical forces on a cell bring conformational changes to G proteins, which initiate signaling cascades, thus leading to cell growth. The activation of G proteins by shear stress and cyclic stretching has been demonstrated in cardiac fibroblasts (Gudi et al. 1996, 1998). Furthermore, activation of G proteins has been investigated in endothelial cells by subjecting them to uniaxial strain at various strain magnitudes, rates, and cycle numbers. The results showed a rapid activation of G proteins in a strain-magnitude and strain-rate dependent manner (Clark et al. 2002), confirming the participation of G proteins in the mechanoreception of mechanical strain.

6.4 Receptor tyrosine kinases

The activation of G proteins by mechanical stress triggers a cascade of downstream signaling events which causes a generation of second messengers. RTKs are a diverse group of transmembrane proteins involved in the signal transduction whose activation seems to play a major role in integrin-mediated signaling. Many growth factors, such as EGF and PDGF, bind to cell surface RTKs (Ullrich amd Schlessinger 1990). The binding of the ligand causes receptor dimerization, which results in a cascade of complex signaling events (Cantley et al. 1991; Chao 1992; Karin 1992). RTKs also induce tyrosine phosphorylation and the activation of Raf-1 and ERKs or MAPKs (Boulton et al. 1991; Cobb et al. 1991a,b; Kyriakis et al. 1992).

6.5 Mitogen-activated protein kinases

MAPKs play an important role in cell signaling as well. Signals originating from mechanical forces can lead to gene expression and protein synthesis through the MAPK pathway. The phosphorylation of one of the MAPKs (ERK1 and 2), for instance, leads to the activation of regulatory proteins in the cytoplasm and nucleus. It has been shown that shear stress induced a transient activation of ERK in bovine aortic endothelial cells (Yamazaki et al. 1993; Jo et al. 1997). Mechanical stretching also rapidly activated ERKs in human pulmonary epithelial cells and in fetal lung fibroblasts (Hubmayr et al. 1996; Chess et al. 2000). In addition, p38 MAPK and JNK/SAPK (stress activated protein kinase) are activated by various cellular stresses. In the chondrocytes of articular cartilages, for instance, mechanical compression activates p38 MAPK, SAPK, and ERK1/2 phosphorylation (Fanning et al. 2003). In adult cardiac fibroblasts, both ERK and JNK are activated by a cyclic mechanical load (MacKenna et al. 1998). Both MAPK and JNK are activated in response to static stretching in cardiac fibroblasts (Komuro et al. 1996). Phosphorylation of these second messengers leads to the activation of downstream transcriptional factors such as AP-1, Egr-1, and NF-κB, which subsequently induce the expression of other signaling proteins (Hughes-Fulford 2004; Kakisis et al. 2004).

6.6 Stretch-activated channels

Besides the protein kinase signaling molecules, the activation of mechano-sensitive ion channels has also been proposed as a transduction mechanism (Hamill and Martinac 2001). Stretch-activated ion channels allow the movement of ions like Na^+, K^+, and Ca^{2+} in and out of cells (Sachs 1992; Ruknudin et al. 1993). In particular, changes in intracellular Ca^{2+} levels regulate a wide range of cellular processes, including cell growth, cell motility, contraction, apoptosis, and differentiation.

Mechanical stimulation elevates Ca^{2+} in many types of cells, including SMCs, fibroblasts, osteoblasts, and vascular endothelial cells (Shen et al. 1992; Sigurdson et al. 1992; Mow 1994; Pommerenke et al. 1996; Kirber et al. 2000). The stretching of cultured cardiac endothelial cells increased Ca^{2+} levels via the activation of stretch-activated channels (SACs), since this increase was blocked by SAC blockers such as gadolinium (Naruse and Sokabe 1993; Kohler et al. 1998). ERK1/2 activation by mechanical stretching also requires the activation of the Ca^{2+} -sensitive EGF receptor, mainly via stretch-activated ion channels, leading to vascular smooth muscle growth (Iwasaki et al. 2000). Also, human disc cells respond to fluid shear stresses by increasing intracellular Ca^{2+} concentration (Elder et al. 2001). Therefore, regardless of the cell type, the integrins, cytoskeleton, RTKs, G proteins, MAP kinases, and Ca^{2+} are essential in enabling cellular mechanotransduction.

7 Summary

In this review, we attempted to clarify that various mechanical forces acting on load-sensitive cells in vivo, such as chondrocytes and tendon fibroblasts, regulate cellular functions, including gene expression, protein synthesis, cell growth, and differentiation. These forces balance the cellular synthesis and degradation of various matrix components, thus maintaining tissue homeostasis. However, excessive/abnormal mechanical loads may tilt the equilibrium from cellular anabolism to catabolism, consequently leading to tissue pathophysiological conditions, such as osteoarthritis, tendinopathy, and fibrosis in cartilage, tendon, lung, and skin. In an effort to better understand the causes of tissue disorders and to develop effective protocols for their treatment and prevention, it is necessary to study the effects of various mechani-

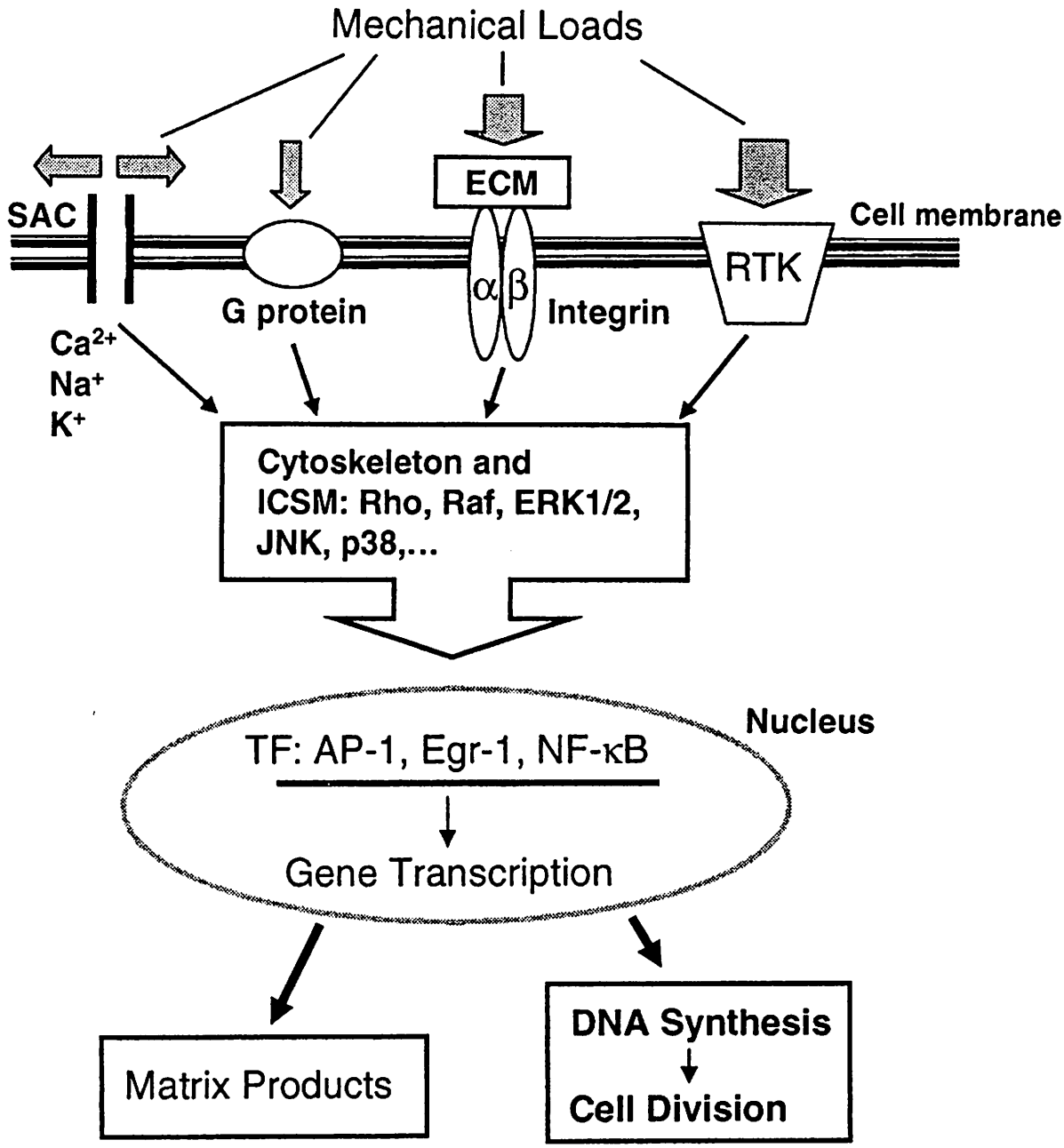


Fig. 1 A conceptual illustration of cellular mechanotransduction mech anisms. (ICSM: Intracellular signaling molecules; TF: Transcriptiona factors)

Wang and Li *Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology* 2010, **2**:16
http://www.smarttjournal.com/content/2/1/16

SMARTT
SPORTS MEDICINE ARTHROSCOPY
REHABILITATION THERAPY TECHNOLOGY

REVIEW Open Access

Mechanics rules cell biology

James HC Wang*[1] and Bin Li[2,3]

Abstract

Cells in the musculoskeletal system are subjected to various mechanical forces *in vivo*. Years of research have shown that these mechanical forces, including tension and compression, greatly influence various cellular functions such as gene expression, cell proliferation and differentiation, and secretion of matrix proteins. Cells also use mechanotransduction mechanisms to convert mechanical signals into a cascade of cellular and molecular events. This mini-review provides an overview of cell mechanobiology to highlight the notion that mechanics, mainly in the form of mechanical forces, dictates cell behaviors in terms of both cellular mechanobiological responses and mechanotransduction.

1. Introduction

Mechanical forces act on humans at different levels, from the body as a whole to individual organs, tissues, and cells. It is well known that appropriate mechanical loads are beneficial to bone and muscle by enhancing their mass and strength. On the other hand, excessive mechanical forces can also be detrimental; for example, excessive mechanical loading of tendons plays a major role in the development of tendinopathy [1,2]. Thus, mechanical forces have a profound effect on tissue homeostasis and pathophysiology. The central players in the human body's response to mechanical forces are various types of mechano-sensitive cells. Examples of such cells include tenocytes in tendons, fibroblasts in ligaments and skin, osteocytes in bone, chondrocytes in articular cartilage, and endothelial cells in blood vessels. Mechanical forces induce a wide range of cellular events, including proliferation, differentiation, and gene and protein expression by both adult differentiated and stem cells [3]. This mini-review provides a concise overview of cellular mechanobiological responses, with a focus on cells from musculoskeletal tissues. In addition, mechanotransduction mechanisms, by which cells "convert" mechanical forces into cellular biochemical events, are also briefly reviewed to emphasize the notion that mechanics, mainly in the form of external and internal mechanical forces, plays a vital role in cell biology. Note that readers who are interested in a more broad and in-depth understanding of the role of mechanics in cell biology should consult relevant papers, which are abundant in the literature.

2. External Mechanical Forces

External mechanical forces are defined as forces, such as tensile, compressive, or shear stresses, that are applied to cells from their environment. Depending on the cell type, the forces can come in one form or a combination of them. For example, fibroblasts in tendons and ligaments are mainly under tensile stress *in vivo*, while chondrocytes and osteocytes are subjected to compression and shear stress due to fluid flow in addition to tensile forces. In blood vessels, endothelial cells lining the vessel surface are subjected to a combination of tensile stress due to vessel expansion, hydrostatic pressure, and fluid shear stress.

Because of the ability to control experimental conditions, *in vitro* model systems have been developed to investigate cellular mechanobiological responses. In many of these systems, tensile forces are applied to the substrate and hence cause substrate deformation, which in turn loads cells that adhere to the underlying substrate. There are two ways to apply tensile mechanical forces to cells: the substrate may be stretched uniaxially or biaxially. Uniaxial stretching is appropriate for application of mechanical forces to cells originating from tendons (e.g., patellar and Achilles tendons) and ligaments (e.g., anterior cruciate ligament and medial collateral ligament), as these cells are aligned with their long axis parallel to the tendon or ligament and are therefore subjected primarily to uniaxial stretching *in vivo* [4-6]. On the other hand,

* Correspondence: wanghc@pitt.edu
[1] MechanoBiology Laboratory, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, 210 Lothrop St, BST E1640, Pittsburgh, PA 15213, USA
Full list of author information is available at the end of the article

molecular events. Such a process is termed cellular mechanotransduction (Fig. 1).

While the mechanisms of cellular mechanotransduction are still not completely understood, it is generally accepted that external mechanical forces acting on ECM have to be transmitted into a cell through integrin-mediated adhesions [73,74]. Integrins, which contain both a large ECM domain responsible for binding substrates and a cytoplasmic domain, are the main adhesive receptors and mechanotransducers that link the cytoskeleton to the ECM [26,75]. Therefore, the ECM-integrin-cytoskeleton pathway plays a major role in the mechano-signaling process. In a "tensegrity" model, mechanical forces applied to the cell membrane are directly and immediately transmitted to the nucleus through the inter-connected cytoskeleton composed of actin filaments, microtubules, and intermediate filaments [76]. Such a model is supported by the finding that application of mechanical stress to integrins altered the cytoskeleton and activated gene expression in a stress-dependent manner [77-79]. Using a FRET-based cytosolic Src reporter in a living cell, local stress was shown to induce rapid activation (< 0.3 sec) of Src at remote cytoplasmic sites; thus, a pre-stressed cytoskeleton can rapidly transduce mechanical signals [80].

In addition to integrins and the cytoskeleton, G proteins also function as mechanotransduction molecules [81,82]. Another important component of cellular mechanotransduction is intracellular Ca^{2+} [83]. Mechanical stretching of fibroblasts and many other types of cells increases the levels of intracellular Ca^{2+}, which serves as a secondary messenger [84,85]. In addition, cellular mechanotransduction also involves stretch-activated ion channels (SACs) [86,87]. In response to applied mechanical stresses, SACs open to allow ions like Ca^{2+}, Na^{+}, and K^{+} to pass through, thus transducing mechanical signals into activation of intracellular signaling molecules [88]. Finally, recent studies have shown that primary cilia also play an important role in cellular mechanotransduction. In bone cells, for example, primary cilia translate fluid flow into cellular responses independent of SACs [89].

In addition to the roles of many cellular components such as integrin and cytoskeleton in cellular mechanotransduction, researchers are also beginning to understand the mechanisms of how mechanical forces are initially sensed by the cell. In adherent cells, force transmission is primarily dependent on the attachment of cells to ECM molecules such as collagen or fibronectin [90]. Therefore, ECM proteins may function as "force sensors." Mechanical stresses acting on ECM may unfold a domain

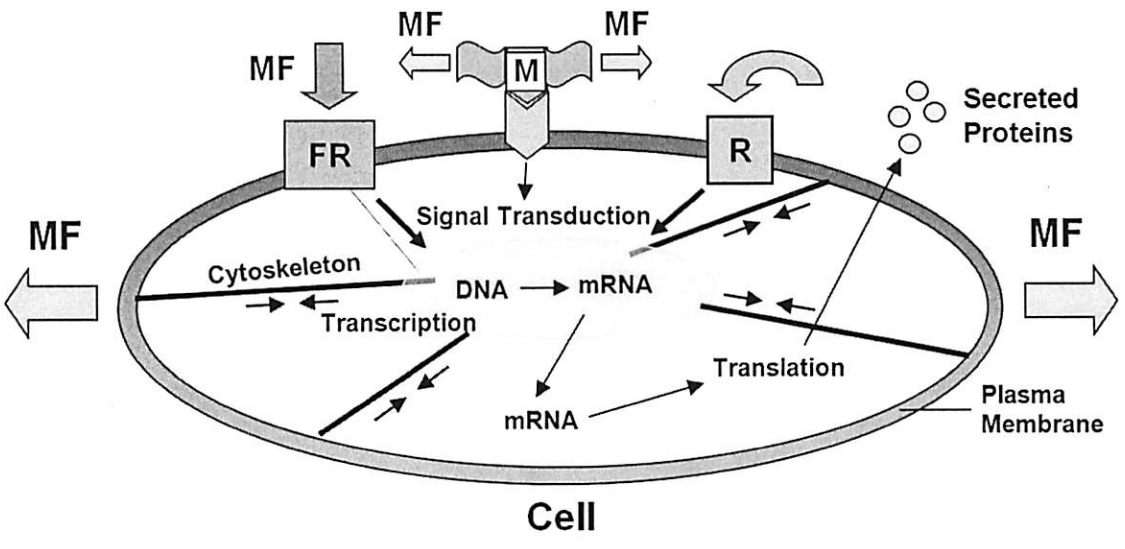


Figure 1 Schematic illustration of the "mechanical nature" of cellular mechanotransduction mechanisms. Mechanical forces (**MF**) can induce mechanotransduction by directly altering conformation of an extracellular matrix (**ECM**) protein and integrin configuration and transmitting forces to the cytoskeleton and nucleus, thus eventually affecting transcription and translation. Also, mechanical forces can unfold a domain of the extracellular protein (**M**) and expose a cryptic site that may serve as an activating ligand for a cell surface receptor, resulting in a series of signaling events. Also, when mechanical forces are applied to "force receptors" (**FR**), such as integrins and G proteins, they initiate signal transduction, resulting in transcription followed by translation. As a result, soluble factors are secreted into the ECM, which act on the receptor (**R**) and then initiate a cascade of signaling events. Note that double arrows indicate intracellular tensions in the actin filaments. (Modified with permission from Wang and Thampatty, **Fig. four** in *Encyclopedia of Biomaterials and Biomedical Engineering*, 2008, p.1783-1793, Taylor & Francis).

of the ECM protein, resulting in exposure of its cryptic site, which may serve as an activating ligand for an adjacent receptor [83]. This potential force-sensing mechanism is supported by the finding that small and large forces unfold the weakest domain and the most stable domain of fibronectin, respectively [91]. Besides the conformation change in an ECM protein due to applied external mechanical forces, the cytoskeletal force, or the internal mechanical force, controls $\alpha_5\beta_1$ integrin switching between relaxed and tensioned states. Such a switch directly controls the strength of $\alpha_5\beta_1$-fibronectin bond by engaging the synergy site in fibronectin [92].

6. Conclusion

Mechanical forces are ubiquitous and are known to greatly influence physiology and pathophysiology in humans. Mechano-responsive cells are responsible for these mechano-effects, as years of intensive mechanobiology research have shown that external mechanical forces influence a wide spectrum of cellular events, including alterations in cell proliferation, differentiation, gene expression, and protein production. It is also now appreciated that internal mechanical forces generated by cells themselves regulate cell biology in terms of metabolic state, cell proliferation and differentiation, etc. Particularly, CTFs, which are the internal mechanical forces transmitted to ECM, regulate many vital cellular functions such as migration and ECM assembly.

The keys to understanding mechanical force-regulated cell biology are cellular mechanotransduction mechanisms by which cells "convert" mechanical force signals into biochemical signals in cells. The role of ECM proteins, integrins, and cytoskeleton in cellular mechanotransduction is now firmly established. Recent studies also point to predominant role of primary cilia in mechanical signal transduction. They also show that mechanical forces may cause mechanotransduction events by altering conformation of signaling molecules, thus affecting their activity and consequently eliciting a cascade of biochemical events such as gene expression.

The fact that mechanics plays a dominant role in cell biology provides a solid foundation and rationale for use of mechanics to improve human health by designing appropriate equipment/instruments, exercise protocols, and rehabilitation regimens. For instance, in sports medicine, such practices will help improve overall performance while reducing and preventing musculoskeletal injuries in athletes. Also, combined use of "bio-interventions" and "mechanics" will further improve the outcome of clinical treatments of musculoskeletal injuries.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
JW and BL drafted and revised the manuscript together. Both authors read and approved the final manuscript.

Acknowledgements
This work is supported in part by NIH AR049921, AR049921S1, and AR049921S2 (JHW).

Author Details
[1]MechanoBiology Laboratory, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, 210 Lothrop St, BST E1640, Pittsburgh, PA 15213, USA, [2]Orthopedic Institute, Soochow University, 708 Renmin Rd, Suzhou, Jiangsu 215007, China and [3]Department of Orthopedics, The First Affiliated Hospital of Soochow University, 188 Shizi St, Suzhou, Jiangsu 215006, China

Received: 27 March 2010 Accepted: 8 July 2010
Published: 8 July 2010

References

1. Fredberg U, Stengaard-Pedersen K: **Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation.** *Scand J Med Sci Sports* 2008, **18(1)**:3-15.
2. Wang JH, Iosifidis MI, Fu FH: **Biomechanical basis for tendinopathy.** *Clin Orthop Relat Res* 2006, **443**:320-332.
3. Wang JH, Thampatty BP: **Mechanobiology of adult and stem cells.** *Int Rev Cell Mol Biol* 2008, **271**:301-346.
4. Archambault J, Tsuzaki M, Herzog W, Banes AJ: **Stretch and interleukin-1beta induce matrix metalloproteinases in rabbit tendon cells in vitro.** *Journal of Orthopaedic Research* 2002, **20(1)**:36-39.
5. Kim SG, Akaike T, Sasagaw T, Atomi Y, Kurosawa H: **Gene expression of type I and type III collagen by mechanical stretch in anterior cruciate ligament cells.** *Cell Structure & Function* 2002, **27(3)**:139-144.
6. Li Z, Yang G, Khan M, Stone D, Woo SL, Wang JH: **Inflammatory response of human tendon fibroblasts to cyclic mechanical stretching.** *American Journal of Sports Medicine* 2004, **32(2)**:435-440.
7. Hung CT, Williams JL: **A Method for Inducing Equi-Biaxial and Uniform Strains in Elastomeric Membranes Used as Cell Substrates.** *Journal of Biomechanics* 1994, **27(2)**:227-232.
8. Lee AA, Delhaas T, Waldman LK, MacKenna DA, Villarreal FJ, McCulloch AD: **An equibiaxial strain system for cultured cells.** *Am J Physiol* 1996, **271(4 Pt 1)**:C1400-1408.
9. Schaffer JL, Rizen M, Litalien GJ, Benbrahim A, Megerman J, Gerstenfeld LC, Gray ML: **Device for the Application of a Dynamic Biaxially Uniform and Isotropic Strain to a Flexible Cell-Culture Membrane.** *Journal of Orthopaedic Research* 1994, **12(5)**:709-719.
10. Sotoudeh M, Jalali S, Usami S, Shyy JY, Chien S: **A strain device imposing dynamic and uniform equi-biaxial strain to cultured cells.** *Ann Biomed Eng* 1998, **26(2)**:181-189.
11. Angele P, Yoo JU, Smith C, Mansour J, Jepsen KJ, Nerlich M, Johnstone B: **Cyclic hydrostatic pressure enhances the chondrogenic phenotype of human mesenchymal progenitor cells differentiated in vitro.** *J Orthop Res* 2003, **21(3)**:451-457.
12. Toyoda T, Seedhom BB, Yao JQ, Kirkham J, Brookes S, Bonass WA: **Hydrostatic pressure modulates proteoglycan metabolism in chondrocytes seeded in agarose.** *Arthritis & Rheumatism* 2003, **48(10)**:2865-2872.
13. Burton-Wurster N, Vernier-Singer M, Farquhar T, Lust G: **Effect of compressive loading and unloading on the synthesis of total protein, proteoglycan, and fibronectin by canine cartilage explants.** *Journal of Orthopaedic Research* 1993, **11(5)**:717-729.
14. Steinmeyer J, Torzilli PA, Burton-Wurster N, Lust G: **A new pressure chamber to study the biosynthetic response of articular cartilage to mechanical loading.** *Res Exp Med (Berl)* 1993, **193(3)**:137-142.
15. Chen AC, Sah RL: **Effect of static compression on proteoglycan biosynthesis by chondrocytes transplanted to articular cartilage in vitro.** *J Orthop Res* 1998, **16(5)**:542-550.
16. Davisson T, Kunig S, Chen A, Sah R, Ratcliffe A: **Static and dynamic compression modulate matrix metabolism in tissue engineered cartilage.** *Journal of Orthopaedic Research* 2002, **20(4)**:842-848.

Connective tissue: A body-wide signaling network?

Medical Hypotheses
Volume 66, Issue 6, June 2006, Pages 1074-1077

Helene M. Langevin
From the Department of Neurology, University of Vermont, College of Medicine

FROM ABSTRACT:

Unspecialized "loose" connective tissue forms an anatomical network throughout the body.

This paper presents the hypothesis that connective tissue also functions as a body-wide mechanosensitive signaling network.

Three categories of signals are discussed: electrical, cellular and tissue remodeling, each potentially responsive to mechanical forces over different time scales.

It is proposed that these types of signals generate dynamic, evolving patterns that interact with one another.

Such connective tissue signaling would be affected by changes in movement and posture, and may be altered in pathological conditions (e.g. local decreased mobility due to injury or pain).

Connective tissue thus may function as a previously unrecognized whole body communication system.

Since connective tissue is intimately associated with all other tissues (e.g. lung, intestine), connective tissue signaling may coherently influence (and be influenced by) the normal or pathological function of a wide variety of organ systems.

Demonstrating the existence of a connective signaling network therefore may profoundly influence our understanding of health and disease.

THIS AUTHOR ALSO NOTES:

Research and consequent medical specialization has broken the human body into systems (e.g. respiratory, digestive, musculoskeletal), and this is unfortunate.

The musculoskeletal system does not physiologically function in isolation from the rest of the body. **[Key Point]**

The musculoskeletal tissues (bones, muscles, cartilage, tendons) are strongly associated with posture and movement.

Pathophysiological Model for Chronic Low Back Pain Integrating Connective Tissue and Nervous System Mechanisms

Medical Hypotheses
Volume 68, Issue 1, January 2007, Pages 74-80

Helene M. Langevin and Karen J. Sherman
The primary author is from the Department of Neurology, University of Vermont, College of Medicine.

FROM ABSTRACT

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.

The integration of connective tissue and nervous system plasticity into the model of cLBP 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.

THESE AUTHORS ALSO NOTE:

"Historically, 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."

These authors propose 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."

Energy Medicine

The Scientific Basis

James L. Oschman PhD
Nature's Own Research Association
Dover
New Hampshire
USA

Foreword by
Candace Pert PhD
Research Professor
Department of Physiology and Biophysics
Georgetown University School of Medicine
Washington, DC
USA

CHURCHILL LIVINGSTONE 2000

EDINBURGH LONDON NEW YORK PHILADELPHIA ST LOUIS SYDNEY TORONTO 2000

Mechanics as it influences body chemistry

Presidential Address
International Society for the Study of the Lumbar Spine
Dallas, 1986
Where Is the Pain Coming From?

VERT MOONEY, MD

WHEN REFERRING TO low-back pain, the answer to the question "Where is the pain coming from?" should be very useful. Throughout the history of medicine, once a clear understanding of pathophysiology was evident, significant changes in treatment and prognosis have occurred. For example, once it was understood that wounds did not necessarily heal by secondary intention and develop "laudable pus," primary wound healing with its diminished scar and morbidity could be expected. Once it was understood that bed sores occurred from excessive pressure and could be prevented by rapid mobilization or various nursing techniques, the problem greatly decreased. Thus, with improved understanding, historically, surgery and rehabilitation of the disabled individual have become much more effective.

In the case of low-back disease, although we all are aware of it, the depth of our ignorance must be emphasized. In the United States in the decade from 1971 to 1981, the numbers of those individuals disabled from low-back pain grew at a rate 14 times that of the population growth.[25] This is a greater growth of medical disability than any other. Yet this growth occurred in the very decade when there was an explosion of ergonomic knowledge, labor-saving mechanical assistance devices, and improved diagnostic equipment. We apparently could not find the source of pain. In 1985, $6 billion in workers' compensation was disbursed for low-back pain, the leading source of work place injury and second only to the common cold in accounting for lost work time.[7] We do not really know the cause of the common cold either. If we understood where the pain was coming from, these statistics would not be possible.

Let us look at various aspects of the clinical history of chronic back problems. Certainly every study that has reviewed the incidence of chronicity recognizes that the sooner the individual is treated with expert care, the sooner he or she is back to work. The corollary to this also is true that the longer the patient declares himself disabled, the less chance he has to return to an active and normal life. Could low-back disease be habituating?

When we analyze various components of the natural history of low-back pain, we should find some clues as to the source of the pain. Is the pain primarily on a mechanical basis? Elsewhere in the body, mechanical overload to motion segments reflects itself as degenerative or proliferative arthritis. Ultimately this is reflected by the skeletal structures responding to increased stress concentration as demonstrated by increased bone density with associated joint space narrowing and reactive changes about the joint edges as they thicken and stiffen. Yet, all studies point to a lack of correspondence of the radiographic changes of arthropathy in the spine to back pain symptoms. While degenerative disease, like grey hair and wrinkled skin, has an onward march of pathologic changes, the incidence of back pain peaks in the middle years and diminishes in the aged. Certainly degenerative arthritis of the spine cannot be defined as the major cause of chronic back pain.

Again, look at mechanical causes of back disability. Are individuals with inherent or posttraumatic instability likely candidates for back pain? Indeed, can we predict pathologic and potentially symptomatic instability by radiographic analysis? At this point it also must be emphasized that no physical examination sign of spine range of motion has ever been demonstrated to be more accurate than radiographic examination. An elegant study from the University of Oklahoma on totally normal males (prior to employment) demonstrates as much as 8 mm translation at the L4–5 segment with an average of 3 mm.[13] In fact, at the most mobile segment there was a range of 2° to 20° with an average of 13° of motion (Figures 1 and 2). Thus, although individuals with back pain may become stiffer, certainly there is no reason to believe that hypermobility is related to the onset of back pain. Except for significant trauma, it is unlikely that purely mechanical factors are the source of chronic back pain. It is also unlikely that the measurement of lumbar range can truly assess impairment.

In the spine, there must be something unique that obeys different rules than the connective tissue found elsewhere. At every other motion segment (joint), from the sprained ankle to the twisted knee, we have learned to expect fairly precise rates of predictable recovery if significant anatomic instability has not been created by the injury. Six weeks to 2 months is usually enough to heal any stretched ligament, muscle tendon, or joint capsule. Yet we know that 10% of back "injuries" do not resolve in 2 months and that they do become chronic. There must be some tissue obeying different rules.

Anatomically the motion segment of the back is made up of two synovial joints and a unique relatively avascular tissue found nowhere else in the body—the intervertebral disc. Is it possible for the disc to obey different rules of damage than the rest of the connective tissue of the musculoskeletal system?

To emphasize the significance of the potential for different injury and repair between facets and disc, we must ask the question whether degenerative change can occur at the synovial joints and not within the disc itself. Yes, indeed it can. In the cadaver studies of Gill, Videman, et al,[9] this occurred about 20% of the time (Figure 3). Certainly the reverse is true, ie, the disc can be damaged without the facet joints. This is usually demonstrated by discography, but more of this later.

From the University of Texas Health Sciences Center, Division of Orthopaedics, Dallas, Texas.

Delivered at the 13th Annual Meeting of the International Society for the Study of the Lumbar Spine, May 29–June 2, 1986, Dallas, Texas.
Submitted for publication June 30, 1986.

Let us look more closely at the pathophysiology of the disc. Chemistry of the disc is based largely on the relationship between mucopolysaccharide production and water content. During the growth period these molecules are large, but once adulthood has been reached, they begin to break down to smaller molecules with mucopolysaccharide production being switched to chondroitin sulfate B and keratosulfate, both of which bind less water.[14] This is a phenomenon of the nucleus material itself, not so much of the annulus fibrosis which does not lose much water. Mechanical activity has a great deal to do with the exchange of water and oxygen concentration. The work of Urban, Holm, and Maroudas[34] has been very informative in this area. An important aspect of disc nutrition and health may be the mechanical aspects of the disc related to the fluid mechanics. A significant example of this is the increase in height of more than 5 cm of an astronaut whose discs are unopposed by gravity.[26] Recent studies by Kraemer et al[21] demonstrated that load has a significant effect on water content. They were even more precise in that their model, which used nonsymmetric loads, demonstrated that there is a limit to which water can be squeezed out of a disc, but with loss of water, higher concentration of electrolytes in the disc increases the osmotic absorption. Thus, after reduction of the pressure, water is quickly reabsorbed and the disc regains height and volume. This pumping action maintains the nutrition and biomechanical function of the intervertebral disc. Thus, this research substantiates the view that unchanging posture, as a result of constant pressure such as standing, sitting or lying, leads to an interruption of pressure-dependent transfer of liquid. Actually the human intervertebral disc lives because of movement.

The fluid content of the disc can be changed by mechanical activity, and the fluid content is largely bound to the proteoglycans, especially of the nucleus. Indeed we are now made aware from dog studies that repair by proteoglycan synthesis is very slow.[13] Can these aggregates be moved about the disc and thus potentially become a source of mechanical irritation. It has been demonstrated by Krag et al[22] that indeed in the case of metal pellets placed within the disc and subjected to repetitive flexion to neutral maneuvers, the pellets will slowly migrate posteriorly. In addition, Adams and Hutton[1] have demonstrated that flexion compression loads of the segments caused disc deterioration with gradual nuclear extrusion. They can demonstrate these maneuvers with initial posterior positioning of the nucleus. Gradually fissures appeared in the posterior annular lamellae with the nuclear pulp migrating into these. Although this was poorly seen in the cadaver lateral discogram, contrast material (a combination of radiopaque fluid and a few drops of blue dye), as seen in the axial projection, showed a gradual migration of fluid posterolaterally, with a gradual disruption of the lamellae of the annulus. These tests were of course done on cadaver specimens but they were cycled under load and at a rate similar to physiologic events. Thus, from experimental models we have examples of fluid exchange, a slow rate of repair of water binding chemicals, a movement of aggregates within the disc, and the potential of these aggregates to create disruption within the disc. Do these laboratory models have anything to do with the living question of where is the pain coming from?

Let's look first to the question of the potential of repetitive activity (mechanical therapy?) changing the position of mucopolysaccharide aggregates within the disc. There is a clinical phenomenon known as centralization of pain, which is used by the advocates of the McKenzie-type exercise program to treat the painful back. By various maneuvers performed by the examining therapists, the maneuver that changes the pain from the lateralized position to the center of the back is chosen as an exercise program. The patient is asked to perform repetitively this exercise in an effort to reduce persistent pain. Usually the exercise is from neutral to extension repetitively, but occasionally it is from neutral to flexion. These individuals are usually not in such severe pain that surgical care is anticipated, and thus the definitive diagnostic study of discography with associated CT scan (which would provide a view as in the Adams and Hutton cadaver study) is not done. Nonetheless, it has been demonstrated that clinically there is a high degree of response to this treatment. In a consecutive series of patients reviewed by Donelson et al,[6] 97 patients with radiating pain were treated with the purpose of centralizing their pain. In this group, three eventually emerged as unresolvable by treatment, and at surgery they were noted to have extruded discs. All of the rest had adequate reduction of their pain so that surgical treatment was not considered. Another study of this type of program compared flexion traction and back school to repeated extension exercises.[36] The repeated exercises had the highest success rate. Extension exercises were somewhat more effective in treating lumbar syndrome than pure back school alone, which did not enforce mechanical activity but rather suggested restful postures and nonmobile spines while lifting.

But do we yet know where the pain is coming from? In the living individual perhaps the most appropriate study of the abnormalities of the disc in current technology is the CT scan of a discogram (again the same perspective as Adams and Hutton). Although the discogram has been maligned in the past, by progressively more discriminating analysis than the techniques of the past, this may yet emerge as a useful diagnostic tool. In a study that used the CT scan discogram compared to reproduction of clinical pain, only 3% of the painful discs could be defined as radiographically normal[32] (Figure 5). Moreover, in another study that analyzed the deterioration of the disc in a more specific manner than merely degeneration, there was a high correlation of disc disruption with exact reproduction of pain.[35] The criterion of disc disruption under these circumstances was the progressive nonsymmetrical invasion of nuclear material into the peripheral annulus (Figure 6). The study gives some suggestion as to the characteristics of the deteriorating disc that separates the symptomatic disc from the degenerating disc (Figures 7 and 8). The implication of these findings is that the gradual symmetric aging process is not painful but the nonsymmetric disruptive process (perhaps with abnormal nutrition due to the asymmetry) is persistently painful.

Where will the future lead us? First we must understand more accurately the chemistry of the painful disc as opposed to the chem-

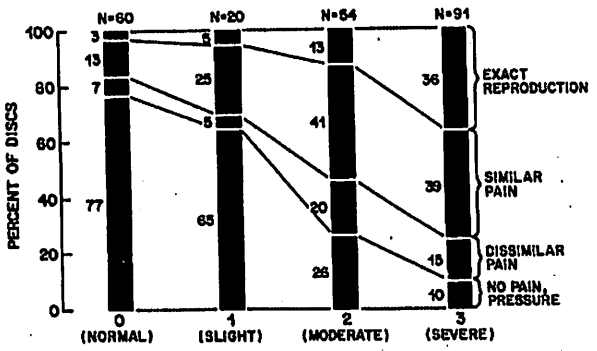


Fig 5. Pain response in discogram in annular disruption levels (225 discs). Comparison of pain response to discographic changes as seen on CT discogram. Results of the more sensitive discographic tests showed that only 3% of the normal discs had exact reproduction of their pain.

with no more morbidity than that of a discogram from the lateral approach. This percutaneous suction discectomy has already demonstrated efficacy in the treatment of the contained herniated disc.[27] Its ultimate role may be the biopsy of the disc, the removal of sufficient material to allow irrigation, and the instillation of prophylactic chemical agents. Can this be a potential treatment of the future?

In summary, what is the answer to the question of where is the pain coming from in the chronic low-back pain patient? I believe its source, ultimately, is in the disc. Basic studies and clinical experience suggest that mechanical therapy is the most rational approach to relief of this painful condition. Avoidance of habituation to pain and inactivity is largely a societal question rather than a medical question. In the future we expect a more precise definition of disc abnormality, best seen by a CT scan discogram—perhaps better with magnetic resonance imaging. Assessment of disc chemistry with ultimate appropriate therapeutic agents instilled in a relatively innocuous manner may be the ultimate treatment for the painful disc unrelieved by mechanical therapy. Prolonged rest and passive physical therapy modalities no longer have a place in the treatment of the chronic problem.

REFERENCES

1. Adams MA, Hutton HC: Gradual disc prolapse. Spine 10:524–531, 1985
2. Bigos SJ, Spengler DM, Martin NA, et al: Back injuries in the industry: A retrospective study: III. Employee-related factors. Spine 11:252–256, 1986
3. Cady LD, Bischoff DP, O'Connell ER, Thomas PC, Allan JH: Strength and fitness and subsequent back injuries in firefighters. J Occup Med 21:269–272, 1979
4. Cohn M, Huntington C, Machado A, Cohn M: Epidural morphine and Depo-Medrol: An Effective Non-Evasive Therapy for Recurrent Low Back Pain. Abstracts of the International Society for the Study of the Lumbar Spine. Dallas, June 1, 1986, p 35
5. Davis GC: Endorphins and pain. Psychiatrists of North America Symposium on Endorphins 6:473–487, 1983
6. Donelson R, Murphy K, Silva G: Centralization phenomenon: Its usefulness in evaluating and treating sciatica. Abstracts for the International Society for the Study of the Lumbar Spine, Dallas, June 1, 1986
7. Frymoyer JW, Mooney V: Current concepts review: Occupational orthopaedics, J Bone Joint Surg 68A:469–473, 1986
8. Frymoyer JW, Pope MW, Costanza MC, et al: Epidemiologic studies of low back pain. Spine 5:419–423, 1980
9. Gill K, Videman T, Shimizu T: Effect of repeated extensions in cadaver spines. Clinical Biomechanics (In press)
10. Gill K, Videman T, Shimizu T: Effect of arteporon in rabbit degenerative disc model. (Nature, submitted for publication)
11. Hadler NM: Medical Management of the Regional Musculoskeletal Diseases. Orlando, Grune & Stratton, 1984
12. Hadler NM: Regional musculoskeletal disease of the low back: Cummulative trauma vs single incident. Clin Orthop 221:33–41, 1987
13. Hayes MA, Howard TC, Gruel CR, Kopta JA: Roentgenographic evaluation of lumbar spine flexion–extension in normal individuals. Abstracts for the Federation of Spinal Association Meeting, New Orleans, February 19, 1986
14. Holm S, Maroudas A, Urban JP: Nutrition of the intervertebral disc: Solutransport and metabolism. Connect Tissue Res 8:101–119, 1981
15. Holm S, Urban J: Sulphate tracer incorporation as an in vivo measure of proteoglycansynthesis rate in the canine intervertebral disc. Abstracts for the International Society for the Study of the Lumbar Spine, Dallas, June 1, 1986
16. Horal J, The clinical appearance of low back disorders in the city of Gothenberg, Sweden: Comparisons in incapacitated probands with matched controls: Acta Orthop Scand [Suppl] 118:1–109, 1969
17. Howe JF, Calvin WH, Loeser JD: Impulses reflected from dorsal root ganglia and from focal nerve injuries. Brain Res 116:139, 1976
18. Howe JF, Loeser JD, Calvin WH: Mechanosensitivity of dorsal root ganglia and chronically injured axones: A physiological basis for the radicular pain of nerve root compression. Pain 3:25, 1977
19. Hult L: Cervical, dorsal, and lumbar spinal syndromes: A field investigation of non-selected material of 1200 workers in different occupations with special reference to disc degeneration and so-called muscular rheumatism. Acta Orthop Scand [Suppl] 17:1–102, 1954
20. Jackson RW, Silver RL: Arthroscopic treatment of degenerative joint diseases of the knee. Abstracts of the American Orthopedic Association Annual Meeting, June 1986
21. Kraemer J, Kolditz D, Gowin R: Water and electrolyte content of human intervetebral discs under variable loads. Spine 10:69–71, 1985
22. Krag M, Seroussi R, Wilder D, Byrne K, Trausch I: Internal displacements from in vitro loading of human spinal motion segments: Experimental results and finite element in model predictions. Abstracts for the International Society for the Study of the Lumbar Spine, Dallas, May 30, 1986
23. Mixter WJ, Barr JS: Rupture of the intervetebral disc with involvement of the spinal canal. N Engl J Med 211:210, 1934
24. Mooney V, Robertson J: The facet syndrome. Clin Orthop 115:149–156, 1976
25. National Center for Health Statistics (Series 10, No. 134): Prevalence of selected impairment, United States—1977. Hyattsville, Maryland, Department of Health and Human Services, 1981
26. Nixon J: Intervertebral disc mechanics: A review. Journal of World Society of Medicine 79:100–104, 1986
27. Onik G, Helms C, Ginsburg L, Hoaglund F, Morris J: Percutaneous lumbar diskectomy using an aspiration probe. AJNR 6:290–293, 1985
28. Ooi Y, Mita F, Satoh Y: Pathophysiological study of intermittent claudication in the lumbar canal stenosis. Abstracts of the International Society for the Study of the Lumbar Spine. Dallas, May 31, 1986
29. Parke WW, Watanabe R: The intrinsic vasculature of the lumbosacral spinal nerve root. Spine 10:508–515, 1985
30. Robertson RS, Keeve JP: Worker injuries: The effects of worker's compensation and OSHA inspections. Journal of Health Politics Policy and Law 8:581, 1983
31. Rydevik D, Holm S, Brown MD, Lundborg H: Nutrition of spinal nerve roots: The role of diffusion from the cerebral spinal fluid. Transactions of the 30th Orthopedic Research Society Meeting 9:276, 1984
32. Sachs B, Spive M, Vanharanta H, et al: Dallas Discogram description: A new classification of CT/Discography. Spine 12:287–294, 1987
33. Snook SH, Campanelli RA, Hard JW: A study of three preventive approaches in low back injury. J Occup Med 20:478, 1978
34. Urban JPG, Holm S, Maroudas A: Nutrition of the intervebral disc. Clin Orthop 129:101–114, 1977
35. Vanharanta H, Sachs V, Spive M: Disc degeneration and leaking of annulus and reproduction of back pain during discography, ACT discographic study. Abstracts of the International Society for the Study of the Lumbar Spine, Dallas, May 1, 1986
36. Vanharanta H, Videman T, Mooney V: McKenzie exercises, back trac and back school in lumbar syndrome. Abstracts of the International Society for the Study of the Lumbar Spine, Dallas, June 1, 1986
37. Wall PD, Gutnick M: Ongoing activity in peripheral nerve: The physiology and pharmacology of impulses arising from a neuroma. Exp Neurol 43:480, 1974
38. Weinstein J: Mechanisms of spinal pain: The dorsal root ganglion and its role as a mediator of low-back pain. Spine 11:999–1001, 1986

Address reprint requests to

Vert Mooney, MD
Professor and Chairman
Division of Orthopaedics
University of Texas Health Sciences Center
5323 Harry Hines Boulevard
Dallas, TX 75235-9031

Accepted for publication June 30, 1986.

Mechanics as neurological controls to the muscle system

Neural Elements in Human Cervical Intervertebral Discs

TUVIA MENDEL, BSc, CAROLE S. WINK, PhD, and MARILYN L. ZIMNY, PhD

This study attempted to characterize neural elements within the human cervical intervertebral disc. Cervical intervertebral discs were obtained from four adult human subjects at autopsy. Discs were stained in bulk with gold chloride, sectioned, and viewed with the light microscope. Nerve fibers appeared to enter the disc in the posterolateral direction and course both parallel and perpendicular to the bundles of the anulus fibrosus. Nerves were seen throughout the anulus but were most numerous in the middle third of the disc. Receptors resembling Pacinian corpuscles and Golgi tendon organs were seen in the posterolateral region of the upper third of the disc. These results provide further evidence that human cervical intervertebral discs are supplied with both nerve fibers and mechanoreceptors. [Key words: cervical intervertebral disc, neural elements]

THE INNERVATION OF the intervertebral disc (IVD) and other tissues of the spine is of considerable clinical importance. Pain and disorders of the vertebral column are common complaints, and although there have been many clinical and experimental studies on the causes of back and neck pain, there is no consensus on the mechanisms responsible.[27] Nerve fibers have been observed in the anterior and posterior longitudinal ligaments in the lumbar region[17,21,23,25] and in the outer third of the anulus fibrosus of the lumbar IVD.[3] Malinsky found encapsulated nerve endings as well as nerve fibers in the outer layers of the anulus fibrosus of the lumbar IVD.[19] Horackova and Malinovsky observed nerve fibers and encapsulated nerve endings in the capsules of intervertebral (apophyseal) joints, including those in the cervical region,[15] and Bogduk et al recently demonstrated the presence of free nerve endings within the anterior half of the C5–6 disc from two operative specimens.[4] The purpose of the present study was to examine the entire cervical IVD from each vertebral level and further characterize neural elements within the disc.

MATERIALS AND METHODS

Fourteen cervical IVDs from all vertebral levels were obtained from four adult human subjects at autopsy and were immediately frozen in saline. Subsequently, seven discs were thawed and cut into anterior and posterior halves, and each half was cut sagittally into three pieces. The six pieces of disc were then sewn into plastic netting to preserve their original orientation and were stained in bulk by the use of a modified gold chloride method.[31] After staining, the pieces were dehydrated in graded alcohols, embedded in paraffin, and serially sectioned at 30 μm.[20] Each disc yielded 40–45 sections. The remaining seven discs were cut into anterior and posterior halves. The halves were frozen and serially sectioned at 100 μm on a sliding microtome. Each disc yielded 15–20 sections. The individual sections were placed in compartmentalized Petri dishes to maintain orientation, fixed with lemon juice and formic acid, and stained with gold chloride, as above.[31] All sections were mounted on slides and viewed with the light microscope. Every section of every disc was studied to assess the presence of nerves and mechanoreceptors. The mechanoreceptors were measured with a millimeter ruler on photomicrographs. Using the paraffin sections and the Bioquant Image Analysis Morphometry Program (R & M Biometrics, Inc., Nashville, TN), the diameters of nerves were measured in the following five regions of the disc: posterior, posterolateral, lateral, anterior, and nerves perpendicular to the anulus.

From the Department of Anatomy, Louisiana State University Medical Center, New Orleans, Louisiana.

Accepted for publication January 1, 1990.

RESULTS

Nerve fibers appeared to enter the disc in the posterolateral direction (Figure 1) and course perpendicular to the fibrocartilaginous bundles in the deep layers of the anulus fibrosus (Figure 2) and parallel to the bundles in the more superficial layers of the anulus fibrosus (Figure 3). Nerves were more numerous in the middle third of the disc. Measurements of nerve diameters in five regions of the disc are shown in Table 1. The average diameters ranged from 1.86 to 2.87 μm. These diameters fall within the range of the diameters of Type III pain fibers, ie, 1–6 μm. No nerves were seen in the nucleus pulposus. Receptors 130 × 80 μm resembling Pacinian corpuscles (Figures 4–5) were found in superficial layers, and receptors 100 × 60 μm resembling Golgi tendon organs (Figure 6) were seen in the deeper layers of the anulus fibrosus. Both types of receptors were most prevalent in the posterolateral regions of the anulus fibrosus. Only three or four mechanoreceptors were identified per disc.

DISCUSSION

The nerve fibers found in the cervical IVD may have been branches from the ventral primary ramus (Figure 1). Bogduk et al dissected cervical spines in adult human cadavers and traced nerves going to the discs from sinuvertebral and vertebral nerves, which are branches of the ventral primary ramus.[4] Although we did not dissect these nerves from the rami, the neural elements we saw in the discs appeared to enter the anulus fibrosus in the posterolateral direction, similar to branches of the sinuvertebral and vertebral nerves described by Bogduk et al.

Malinsky reported seeing encapsulated receptors from 110 × 50 μm to 180 × 80 μm on the surfaces (predominantly the lateral surfaces) of the lumbar IVDs in the adult human.[19] The Pacinian-like receptors (Figures 4–5) seen in the superficial layers of the anulus fibrosus of the cervical IVD in this study were of similar size (130 × 80 μm). The receptors resembling Golgi tendon organs seen in the deeper layers of the anulus fibrosus (Figure 6) were about the same size (100 × 60 μm) as those seen by Zimny et al in the human medial meniscus (125 × 50 μm).[29] Although both large (1,300 × 600 μm) and small (97 × 53 μm) Pacinian-like corpuscles and large (1,400 × 800 μm to 600 × 100 μm) Golgi tendon organs have been found in joint capsules, subsynovial connective tissues, and the connective tissues surrounding musculotendinous junctions,[2,9,11–13] there have been no reports of large receptors within ligaments or menisci.[8,28–30] In the present study, only small receptors (130 × 80 μm to 100 × 60 μm) were seen within the anulus fibrosus of the cervical IVD. The reasons for this are unknown. It may be that large, complex receptors cannot exist among the densely packed fibrous and avascular fibrocartilaginous bundles of ligaments,

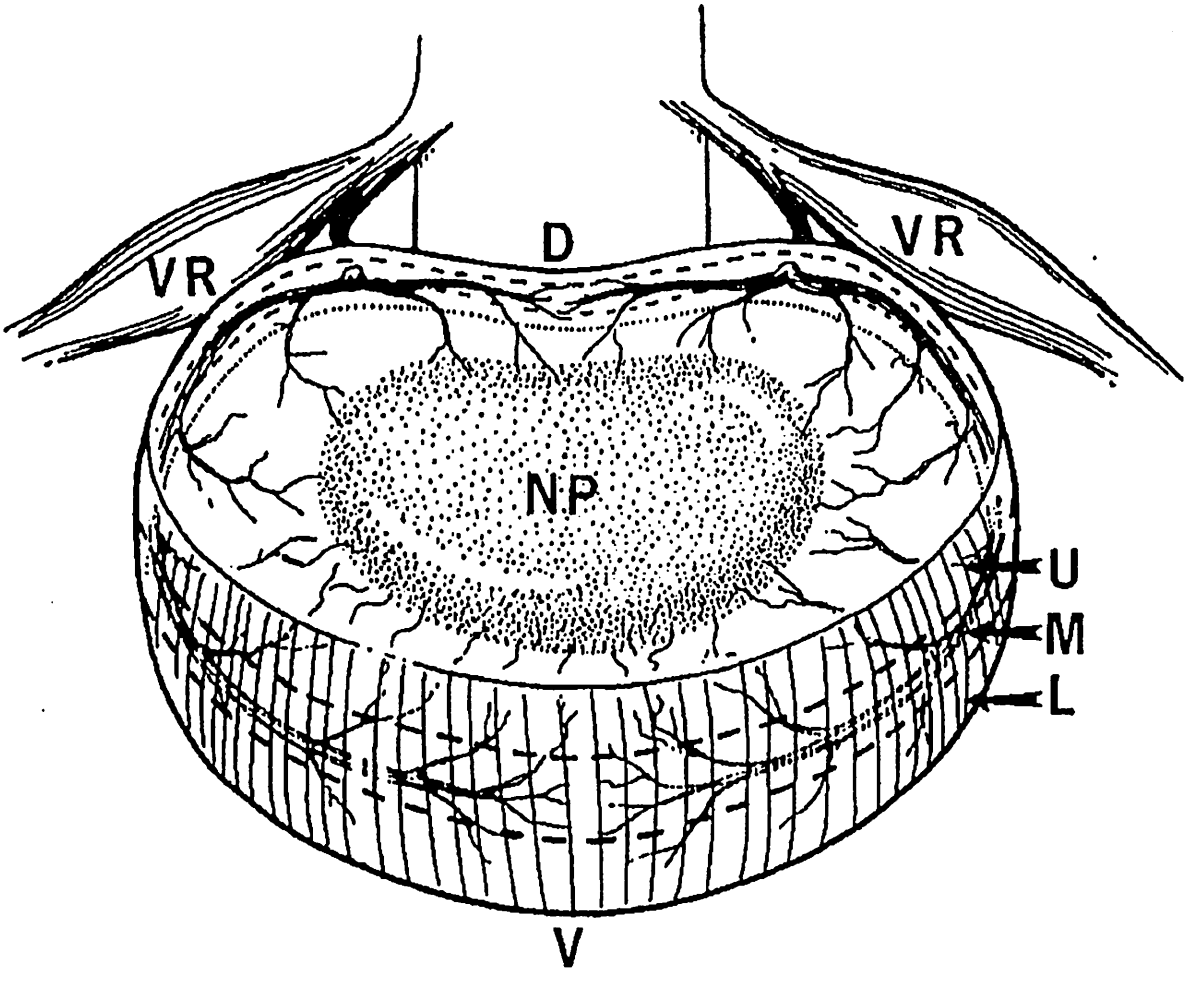


Fig 1. Diagram of cervical IVD showing distribution of nerve fibers. It is hypothesized that these were branches from the ventral primary rami (VR). D = dorsal; V = ventral; NP = nucleus pulposus; U = upper (superior) third of disc; M = middle third of disc; L = lower

Fig 3. N
tion of

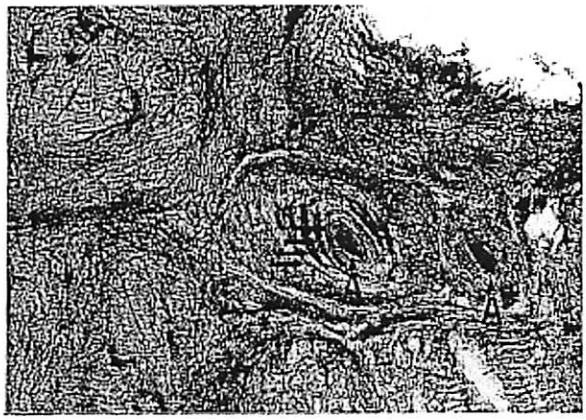


Fig 5. Micrograph of receptors in Figure 4. Note capsule lamellas (arrows) of larger receptor. A = axon terminal. Original magnification ×300.

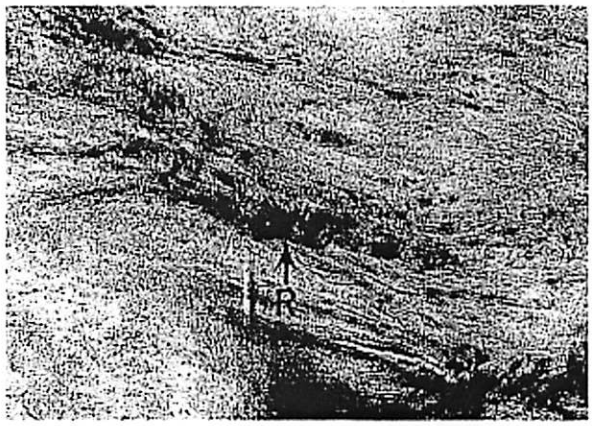


Fig 6. Micrograph of horizontal section through posterolateral aspect of disc (deep). Note receptor (R) resembling Golgi tendon organ. Original magnification ×150.

ones reported by Bogduk et al using a cholinesterase stain,[4] were seen throughout the anulus fibrosus of the cervical IVD in the present study.

Based on the classification of Freeman and Wyke,[9] the Pacinian-like receptors seen in the present study could be classified as Type II receptors. These are described as cylindrical or conical corpuscles, average size 280 × 120 μm, with a thick laminated capsule (up to 10–12 layers) and a single (bifid or trifid) nerve terminal, linked in clusters of two or three corpuscles. They are low-threshold mechanoreceptors and adapt rapidly. The Golgi-like receptors seen could be classified as Type III receptors. These mechanoreceptors are fusiform corpuscles 600 × 100 μm (average size), with high thresholds, and adapt slowly. The other type of encapsulated receptor (Type I—Ruffini), was not seen in the cervical IVD in this study.

Although no definite conclusions can be made from the results of this study as to the functional significance of the neural elements within the cervical IVD, it appears that the disc is supplied with nerve fibers of various sizes and small encapsulated receptors, as suggested by Bogduk et al.[4] The presence of neural elements within the IVD indicates that the mechanical status of the disc is monitored by the central nervous system. If the nonencapsulated nerve endings in the anulus fibrosus are pain receptors, their presence may explain the occurrence of neck or shoulder pain when there is dislocation or trauma to the disc. To what degree the encapsulated receptors (mechanoreceptors) may monitor the deformation and position of the disc is not apparent. Both Pacinian corpuscles and Golgi tendon organs are reportedly active in response to changes in tension.

Recent studies have shown that the IVD has a complex structure and mechanical properties that vary from region to region and change with age.[16,18,24,26] There is evidence that the disc is capable of some regeneration.[6] These findings plus evidence that the disc is innervated suggest that the IVD may be more than a pad that absorbs shock and maintains the spaces between vertebral bodies. The concentration of nerves in the middle third of the disc may be sensing superoinferior compression or deformation. The circumferential arrangement of the nerve bundles about the disc and the superficial-to-deep location of the mechanoreceptors may enable the IVD to sense peripheral compression or deformation as well as alignment.

ACKNOWLEDGMENTS

The authors thank Mrs. Michele St. Onge for her technical assistance, Mrs. Mary Ann Wilde for typing the manuscript, Mr. Garbis Kerimian for the photography, Dr. Richard Whitworth and Dr. Andrew King for their assistance in collecting IVDs, and Mr. Eugene R. New who made the drawing (Figure 1).

REFERENCES

1. Barnett CH, Davies DV, MacConaill MA: Synovial Joints: Their Structure and Mechanics. London, Langmans Press, 1961
2. Bistivens R, Essan A, Awad A: Structure and ultrastructure of mechanoreceptors at the human musculotendinous junction. Arch Phys Med Rehabil 62:74–83, 1981
3. Bogduk N, Wilson AS: The nerve supply to the human lumbar IVD. J Anat 132:39–56, 1981
4. Bogduk N, Windsor N, Inglis A: The innervation of the cervical intervertebral discs. Spine 13:2–8, 1988
5. Boyd IA: The histological structure of the receptors in the knee joint of the cat correlated with their physiological response. J Physiol (Lond) 124:476–488, 1954
6. Bradford DS, Cooper KM, Oegema TR: Chymopapain, chemonucleolysis and nucleus regeneration. J Bone Joint Surg 65A:1220–1230, 1983
7. Crock HV, Goldwasser M: Anatomical studies of the circulation in the region of the vertebral endplate in adult greyhounds. Spine 9:702–706, 1984
8. DeAvila GA, O'Connor BL, Visco DM, Sisk TD: The mechanoreceptor innervation of the human fibula collateral ligament. J Anat 162:1–7, 1989
9. Freeman MAR, Wyke B: The innervation of the knee joint: An anatomical and histological study in the cat. J Anat 101:505–532, 1967
10. Gardner E: The distribution and termination of nerves in the knee joint of the cat. J Comp Neurol 80:11–32, 1944
11. Halata Z: The ultrastructure of the sensory nerve endings in the articular capsule of the knee joint of the domestic cat (Ruffini corpuscles and Pacinian corpuscles). J Anat 124:717–729, 1977
12. Halata Z, Badalomente MA, Dee R, Propper M: Ultrastructure of sensory nerve endings in monkey (Macaca fascicularis) knee joint capsule. J Orthop Res 2:169–176, 1984
13. Halata Z, Rettig T, Schulze W: The ultrastructure of sensory nerve endings in the human knee joint capsule. Anat Embryol 172:265–275, 1985
14. Hassler O: The human IVD: A microangiographical study on its vascular supply at various ages. Acta Orthop Scand 40:765–772, 1969
15. Horackova L, Malinovsky L: Sensory innervation of the intervertebral joints in man. Folia Morphol (Praha), 35:390–397, 1987
16. Humzah MD, Soames RW: Human intervertebral disc: structure and function. Anat Rec 220:337–356, 1988
17. Jackson HC, Winklemann RK, Bickel WH: Nerve endings in the human lumbar spine and related structures. J Bone Joint Surg 48A:1272–1281, 1966
18. Kapandji IA: The Physiology of Joints. Vol. 3, Trunk and Vertebral Column Edinburgh, Churchill-Livingston, 1974
19. Malinsky J: The ontogenetic development of nerve terminals in the IVD of

PubMed

Display Settings: Abstract

Spine (Phila Pa 1976). 1995 Dec 15;20(24):2645-51.

Mechanoreceptors in intervertebral discs. Morphology, distribution, and neuropeptides.

Roberts S, Eisenstein SM, Menage J, Evans EH, Ashton IK.

J.P. O'Brien Laboratory, Centre for Spinal Studies, RJAH Orthopaedic & District Hospital, Oswestry, Shropshire, UK.

Abstract

STUDY DESIGN: The present study investigated the occurrence and morphology of mechanoreceptors in human and bovine intervertebral discs and longitudinal ligaments.

OBJECTIVE: To determine the type and frequency of mechanoreceptors present in intervertebral discs and anterior longitudinal ligaments in two patient groups, those with low back pain and those with scoliosis. Bovine coccygeal discs were examined.

SUMMARY OF BACKGROUND DATA: Nerves have been described in intervertebral tissues, but there is little information on the endings of these nerves and their receptors, stimulation of which can cause a nerve impulse.

METHODS: The presence of mechanoreceptors were investigated by immunolocalization of nerves and neuropeptides. By examining sequential sections, the frequency of receptors was assessed.

RESULTS: Immunoreactivity to neural antigens showed mechanoreceptors in the anulus fibrosus and longitudinal ligaments of bovine and human specimens. Their morphology resembled Pacinian corpuscles, Ruffini endings, and, most frequently, Golgi tendon organs. They were found in 50% of discs investigated from patients with low back pain and in 15% of those with scoliosis.

CONCLUSIONS: Mechanoreceptors were found in the outer 2-3 lamellae of the human intervertebral disc and anterior longitudinal ligament. Physiologic studies in other tissues indicate that these provide the individual with sensation of posture and movement, and in the case of Golgi tendon organs, of nociception. In addition to providing proprioception, mechanoreceptors are thought to have roles in maintaining muscle tone and reflexes. Their presence in the intervertebral disc and longitudinal ligament can have physiologic and clinical implications.

Comment in
Spine (Phila Pa 1976). 1996 Jul 1;21(13):1609-10.

PMID: 8747242 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

Spine (Phila Pa 1976). 1994 Mar 1;19(5):495-501.

Mechanoreceptor endings in human cervical facet joints.

McLain RF.

Source

Department of Orthopaedic Surgery, University of California, Davis, Sacramento.

Abstract

Twenty-one cervical facet capsules, taken from three normal human subjects, were examined to determine the type, density, and distribution of mechanoreceptive nerve endings in these tissues. Clearly identifiable mechanoreceptors were found in 17 of 21 specimens and were classified according to the scheme for encapsulated nerve endings established by Freeman and Wyke. Eleven Type I, 20 Type II, and 5 Type III receptors were identified, as well as a number of small, unencapsulated nerve endings. Type I receptors were small globular structures measuring 25-50 microns in diameter. Type II receptors varied in size and contour, but were characterized by their oblong shape and broad, lamellated capsule. Type III receptors were relatively large oblong structures with an amorphous capsule, within which a reticular meshwork of fine neurites was embedded. Free (nociceptive) nerve endings were found in subsynovial loose areolar and dense capsular tissues. The presence of mechanoreceptive and nociceptive nerve endings in cervical facet capsules proves that these tissues are monitored by the central nervous system and implies that neural input from the facets is important to proprioception and pain sensation in the cervical spine. Previous studies have suggested that protection muscular reflexes modulated by these types of mechanoreceptors are important in preventing joint instability and degeneration. It is suggested that the surgeon take steps to avoid inadvertently damaging these tissues when exposing the cervical spine.

"Encapsulated mecahnoreceptors are a consistent finding in normal human cervical facets."

"The presence of these receptors in the facet capsule indicate that the mechanical state of the capsule (position, tension, pressure, etc.) is under the surveillance of the central nervous system."

PubMed

Display Settings: Abstract

Spine (Phila Pa 1976). 1998 Jan 15;23(2):168-73.

Mechanoreceptor endings in human thoracic and lumbar facet joints.

McLain RF, Pickar JG.

Department of Orthopaedic Surgery, Cleveland Clinic Foundation, Ohio, USA.

Abstract

STUDY DESIGN: Histologic analysis of normal human facet capsules to determine the density and distribution of encapsulated nerve endings in the thoracic and lumbar spine.

OBJECTIVES: To quantify the extent of mechanoreceptor innervation in normal facet tissues and determine the relative distribution of three specific receptor types with respect to thoracic and lumbar segments.

SUMMARY OF BACKGROUND DATA: Ongoing studies of spinal innervation have shown that human facet tissues contain mechanoreceptive endings capable of detecting motion and tissue distortion. The hypothesis has been advanced that spinal proprioception may play a role in modulating protective muscular reflexes that prevent injury or facilitate healing.

METHODS: Whole facet capsules harvested from seven healthy adult patients were processed using a gold chloride staining method and cut into 35-micron sections for histologic analysis. No sampling was performed; all sections were analyzed. Receptor endings were classified by the method of Freeman and Wyke if they met the following three criteria: 1) encapsulation, 2) identifiable morphometry, and 3) consistent morphometry on serial sections.

RESULTS: One Type 1 and four Type 2 endings were identified among 10 thoracic facet capsules. Five Type 1, six Type 2, and one Type 3 ending were identified among 13 lumbar facet capsules. Occasional atypical receptive endings were noted that did not fit the established classification. Unencapsulated free nerve endings were seen in every specimen, but were not quantified.

CONCLUSIONS: Encapsulated nerve endings are believed to be primarily mechanosensitive and may provide proprioceptive and protective information to the central nervous system regarding joint function and position. A consistent, but small population of receptors has been found previously in cervical facets, but innervation of the thoracic and lumbar levels is less consistent. This suggests that proprioceptive function in the thoracic and lumbar spine is less refined and, perhaps, less critical than in the cervical spine.

PMID: 9474721 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms

LinkOut - more resources

Mechanics as influences to visceral neurology

N Engl J Med. **1994** Apr 14;330(15):1047-50.

Lack of effect of intraarticular corticosteroids for chronic pain in the cervical zygapophyseal joints.

Barnsley L, Lord SM, Wallis BJ, Bogduk N.

Source

Cervical Spine Research Unit, Faculty of Medicine, University of Newcastle, Callaghan, NSW, Australia.

Abstract

BACKGROUND:

Chronic pain in the cervical zygapophyseal joints is a common problem after a whiplash injury. Treatment with intraarticular injections of corticosteroid preparations has been advocated, but the value of this approach has not been established. We compared the efficacy of a depot injection of a corticosteroid preparation with the efficacy of an injection of a local anesthetic agent in patients with painful cervical zygapophyseal joints.

METHODS:

Sixteen men and 25 women with pain in one or more cervical zygapophyseal joints after automobile accidents (mean age, 43 years; median duration of pain, 39 months) were randomly assigned to receive an intraarticular injection of either bupivacaine (0.5 percent) or betamethasone (5.7 mg) under double-blind conditions. The patients were followed by means of regular telephone contact and clinic visits until they reported a return to a level of pain equivalent to 50 percent of the preinjection level. The time from treatment to a 50 percent return of pain was compared in the two groups with the use of a survival analysis.

RESULTS:

Less than half the patients reported relief of pain for more than one week, and less than one in five patients reported relief for more than one month, irrespective of the treatment received. The median time to a return of 50 percent of the preinjection level of pain was 3 days in the 21 patients in the corticosteroid group and 3.5 days in the 20 patients in the local-anesthetic group ($P = 0.42$).

CONCLUSIONS:

Intraarticular injection of betamethasone is not effective therapy for pain in the cervical zygapophyseal joints after a whiplash injury.

"Alternatively, the patients who derived a benefit from either treatment may have had a condition that was improved by the stretching of the joint capsule during intraarticular injection, irrespective of what was injected."

Spine (Phila Pa 1976). 1995 Apr 15;20(8):869-76.

The nature and distribution of the innervation of human supraspinal and interspinal ligaments.

Jiang H, Russell G, Raso VJ, Moreau MJ, Hill DL, Bagnall KM.

RESULTS:

The ligaments were found to be well innervated. Innervation was equally distributed along the ligament, symmetrically distributed between left and right sides, and more densely distributed in the periphery. Pacinian corpuscles were scattered randomly, close to blood vessels, whereas Ruffini corpuscles were in the periphery, close to the collagen bundles.

CONCLUSIONS:

Human supraspinal and interspinal ligaments are well innervated. This innervation might form the basis of neurologic feedback mechanisms for the protection and stability of the spine. These mechanisms might also be important in the development of diseases such as scoliosis.

Traditional staining techniques that identify nerves and nerve endings are based on gold chloride or silver nitrate. Antibodies against neural filament proteins, as used in this study, are more specific.

"The results presented in this study show the SSL/ISL to be richly innervated, but the actual, total innervation of the ligament was probably underestimated."

"Pacinian corpuscles are fast adaptive corpuscles and have been reported to be capable of sensing fast motion and acceleration."

"Pacinian corpuscles were observed throughout the SSL/ISL complex. They were always found in close association with blood vessels and were not associated or correlated with the collagen bundles."

This suggests that "Pacinian corpuscles function as sympathetic afferent endings that initiate reflexes concerned with the local control of blood flow." The "distribution of Pacinian corpuscles and their close association with blood vessels also strongly suggests a vascular function for these end organs."

[WOW!: This is quite important for chiropractors: a somatic nerve ending found in a spinal ligament initiating a sympathetic efferent reflex that controls blood supplies.]

Spine (Phila Pa 1976). 1995 Nov 15;20(22):2379-85.

Responses of mechanosensitive afferents to manipulation of the lumbar facet in the cat.

Pickar JG, McLain RF.

Source

Department of Anatomy and Physiology, Kansas State University, Manhattan, USA.

Abstract

STUDY DESIGN:

The response of mechanosensitive afferent nerve endings in the lumbar spine to manipulation of a lumbar facet isolated using a unique surgical approach was studied in anesthetized adult cats.

OBJECTIVES:

To characterize sensory nerve endings in the lumbar spine with respect to their receptive field and conduction velocity and to assess their response to facet joint motion.

SUMMARY OF BACKGROUND DATA:

Previous studies have identified the presence of encapsulated endings in normal human facet capsules and have documented the presence of mechanosensitive units responsive to spinal loading. Previous neurophysiologic studies have used preparations that stripped all paraspinous musculature away from the field to expose the facets and lamina.

METHODS:

A unique hemilaminectomy approach was developed that permitted physiologic loading of the lumbar facet without disturbing its overlying musculature. Recordings of single unit afferent activity were made from fine filaments teased from the L6 dorsal root. Response to L5-L6 facet motion was studied by applying cranial, craniomedial, and medial distractive forces and lateral compressive forces to the facet joint.

RESULTS:

Single unit recordings were obtained from 16 afferents with receptive fields in the lumbar spine. Seven of 16 afferents had receptive fields in or near the facet, and the remaining nine afferents had receptive fields in paraspinal tissues some distance from the facet joint. There were nine Group II afferents, three Group IV, and four unclassified afferents. The majority of endings responded in a graded fashion relative to the direction of force applied.

CONCLUSIONS:

Mechanosensitive endings in the lumbar spine show graded sensitivity to the direction of facet manipulation. These Group III and IV afferents can reside some distance from the facet joint and remain sensitive to facet motion.

PubMed

Display Settings: Abstract

Spine (Phila Pa 1976). 1995 Dec 15;20(24):2652-8.

Electromyographic response of the porcine multifidus musculature after nerve stimulation.

Indahl A, Kaigle A, Reikerås O, Holm S.

Spine Clinic, Ostfold Central Hospital, Fredrikstad, Norway.

Abstract

STUDY DESIGN: In this study, a porcine model was used to study whether a nerve reaction in the anulus fibrosus of a lumbar disc or in a **facet** joint capsule could cause a muscular response in the **multifidus** musculature.

OBJECTIVES: To determine if there is an interrelationship between the intervertebral disc and **facet** joint innervation and the **multifidus** musculature as a possible pain mechanism.

SUMMARY OF BACKGROUND DATA: The innervation of the anulus fibrosus of the intervertebral disc and the capsule of the **facet** joint is well described in the literature, although the functions of these nerves are poorly understood. An interrelationship between this innervation and the paraspinal musculature has not been previously described.

METHODS: Fifteen adult pigs were used to measure the electromyographic response in the **multifidus** musculature to electrical stimulation of the lateral region of the disc anulus and the **facet** joint capsule in the L1-L2 motion segment. Motor unit action potentials were recorded using three sets of bipolar needle electrodes placed into the deepest fascicles of the **multifidus**, bilateral to the L2, L3, and L4 spinous processes. The effect of lidocaine **injection** into the **facet** joint and subperiosteal muscle detachment on the electromyographic response were studied.

RESULTS: Stimulation of the disc anulus fibrosus induced reactions in the **multifidus** on multiple levels and on the contralateral side, whereas stimulation of the **facet** joint capsule induced reactions predominantly on the same side and segmental level as the stimulation. Introduction of lidocaine into the **facet** joint resulted in a significantly reduced electromyographic response to either stimulation, with the most drastic reduction seen when stimulating the **facet** joint capsule. Subperiosteal detachment of the paraspinal muscles prevented any muscular response.

CONCLUSIONS: Stimulation of the disc and the **facet** joint capsule produced contractions in **multifidus** fascicles. The clinical implications are that there may be interactive responses between injured or diseased structures, i.e., disc or **facet** joints, and the paraspinal musculature. Activation of the **multifidus** muscles may have a stabilizing effect, constraining the motion of the lumbar spine. Longstanding muscular contraction may produce ischemic conditions and may be a potential source of pain.

PMID: 8747243 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms

LinkOut - more resources

PubMed

Display Settings: Abstract

Spine (Phila Pa 1976). 1997 Dec 15;22(24):2834-40.

Interaction between the porcine lumbar intervertebral disc, zygapophysial joints, and paraspinal muscles.

Indahl A, Kaigle AM, Reikeräs O, Holm SH.

Spine Clinic, Ostfold Central Hospital, Fredrikstad, Norway.

Abstract

STUDY DESIGN: A porcine model was used to study whether muscular activation in the paraspinal muscles caused by nerve stimulation in the anulus fibrosus of a lumbar intervertebral disc could be altered by saline **injection** into the zygapophysial (**facet**) joint.

OBJECTIVES: To elucidate possible mechanisms regarding the nerve pathways and interactions between the intervertebral disc, zygapophysial joints, and the paraspinal musculature.

SUMMARY OF BACKGROUND DATA: The physiologic basis for chronic low back pain, including muscular spasm, is uncertain. Although extensive research involving the lumbar motion segments and the surrounding tissues has been performed, the neuromuscular connection has not been sufficiently investigated.

MATERIALS AND METHODS: Twenty-three adolescent pigs were used to measure the electromyographic response in the paraspinal musculature to electrical stimulation of the posterolateral L3-L4 anulus fibrosus, before and after introduction of physiologic saline into the zygapophysial joint. Motor unit action potentials were recorded using three sets of needle electrodes placed into the deepest fascicles of the **multifidus**, bilateral to the L4 and L5 spinous processes, and into the central longissimus musculature, bilateral to the L4 spinous process.

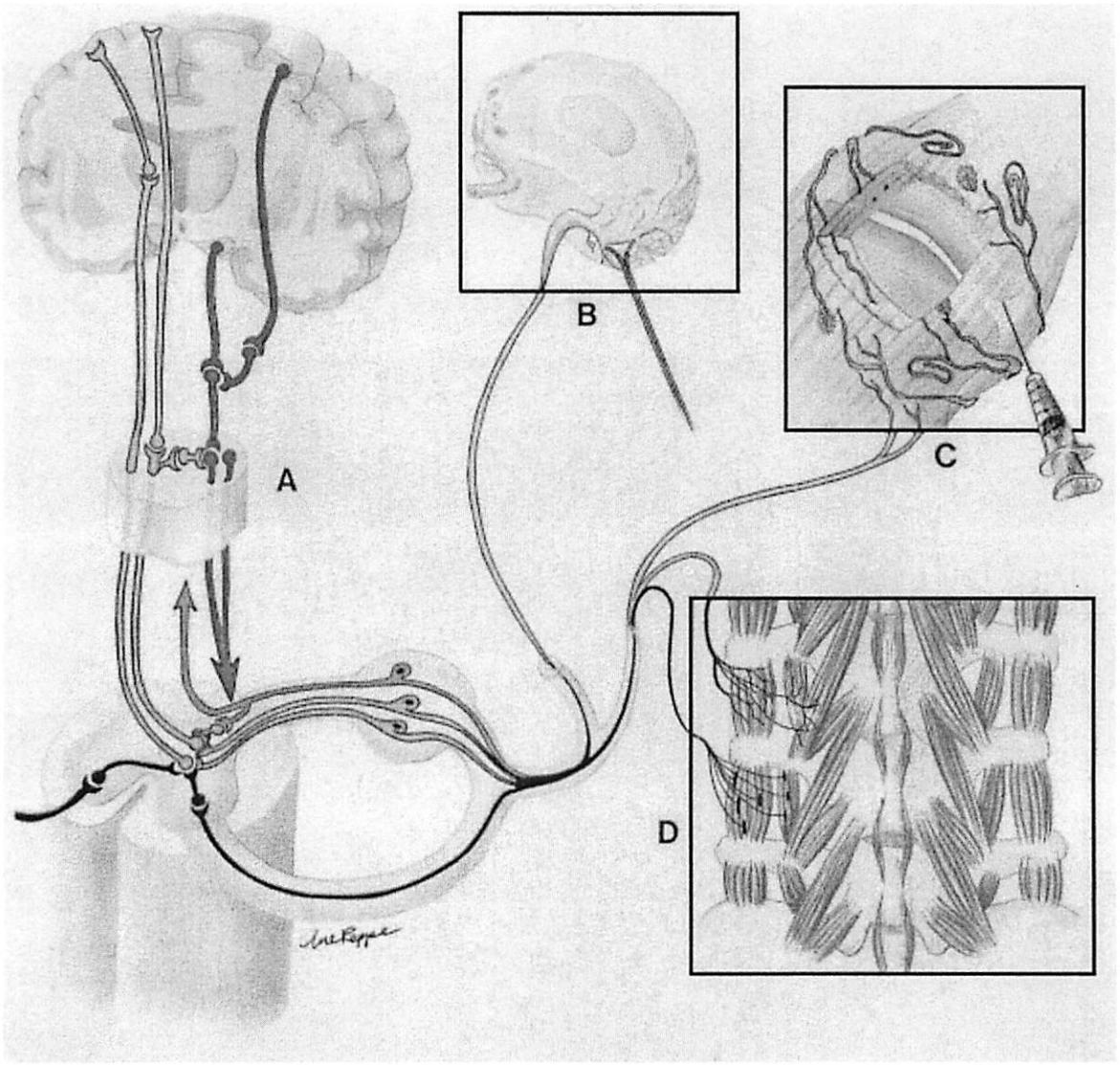
RESULTS: Stimulation of the nerves within the posterolateral anulus of the disc elicited reactions in the paraspinal muscles, namely the lumbar **multifidus** and longissimus. Introduction of physiologic saline into the zygapophysial joint resulted in a reduction in the motor unit action potential amplitude. This reduction was manifested as an immediate and constant reduction, a graded reduction, or a delayed reaction, during which the reduction occurred an average of 5 minutes after the saline **injection**.

CONCLUSIONS: Introduction of physiologic saline into the zygapophysial joint reduced the stimulation pathway from the intervertebral disc to the paraspinal musculature. The zygapophysial joints may therefore have a regulating function, controlling the intricate neuromuscular balance in the lumbar motion segment.

PMID: 9431619 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources


A
B
C
D

PubMed

Display Settings: Abstract

Spine (Phila Pa 1976). 1997 Jan 1;22(1):17-25.

Identification of the location, extent, and pathway of sensory neurologic feedback after mechanical stimulation of a lateral spinal ligament in chickens.

Jiang H, Moreau M, Raso J, Russell G, Bagnall K.

Department of Surgery, University of Alberta, Edmonton, Canada.

Abstract

STUDY DESIGN: This study traced the location, extent, and pathway of sensory feedback after the mechanical stretching of a lateral spinal ligament in young chickens. The pathway was traced by locating the sites of Fos protein production in neuronal cell bodies at various sites in the nervous system.

OBJECTIVES: To trace the location, extent, and pathway of sensory feedback after the mechanical stretching of a lateral spinal ligament in young chickens.

SUMMARY OF BACKGROUND DATA: The innervation of ligaments is thought to form part of a protective feedback mechanism to provide stability for joints. The precise pathway and extent of the feedback for spinal ligaments is currently unknown. Such information would provide a clear focus for future studies, especially for diseases such as scoliosis where it has been suggested that there is abnormality in perception of sensory feedback.

METHODS: The intertransverse ligament on the right side at T3-T4 in 4-week-old chickens was exposed by blunt dissection. After Fos production resulting from the surgery had been stopped, the ligament was stretched mechanically and repeatedly for 60 minutes using a 300-g weight. Various areas of the nervous system then were sectioned and processed immunohistochemically to identify areas of Fos production in nerve cell bodies. The presence of Fos indicated neurons that had been stimulated by the stretching the ligament, including interneurons along the feedback pathway.

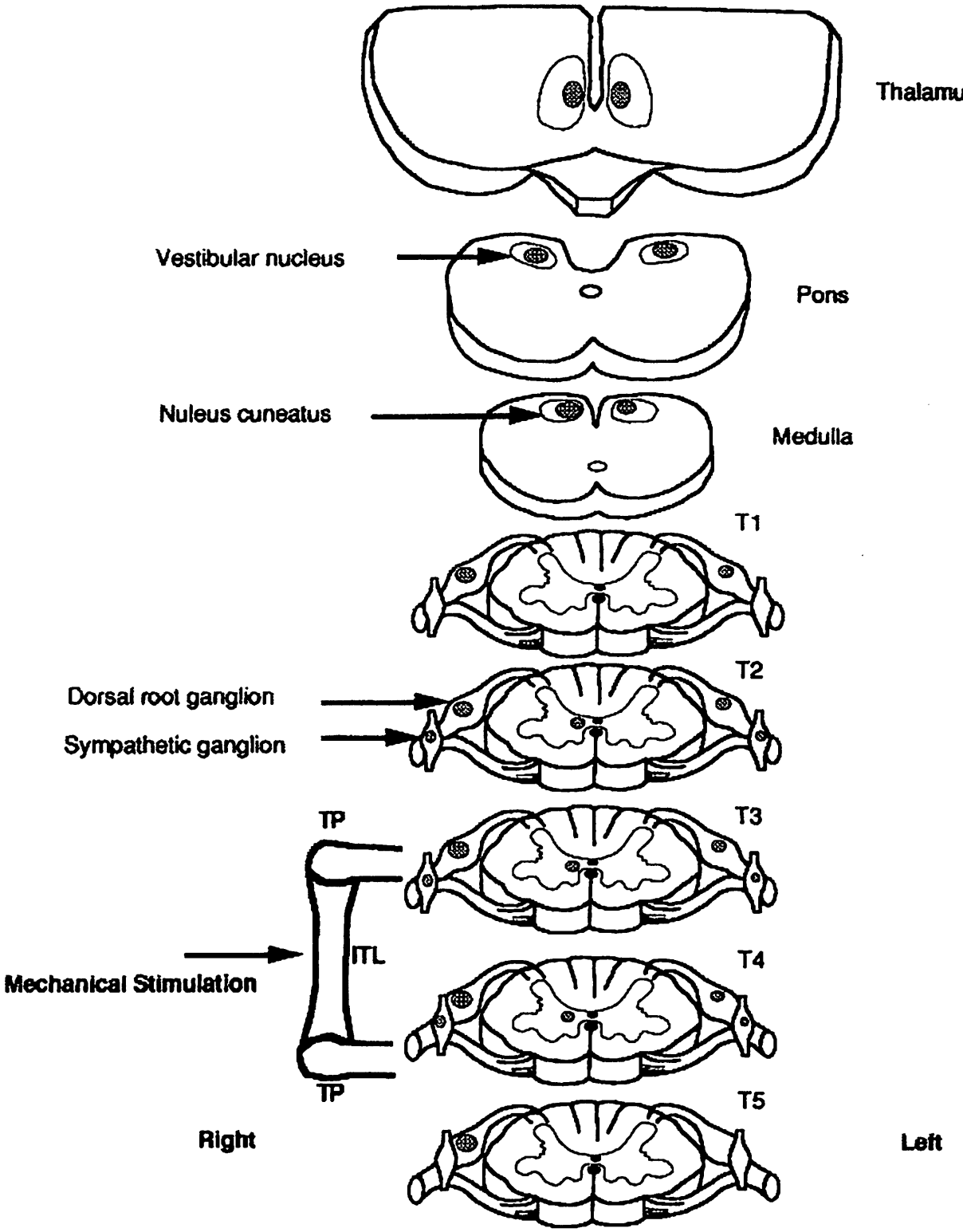
RESULTS: Fos protein was identified in nerve cell bodies in the dorsal root ganglia and intermediate gray matter of the spinal cord at the level of stimulation as well as at several spinal cord levels above and below the site of stimulation. Identification was made on the ipsilateral and the contralateral sides, although the extent of Fos production was less on the contralateral side. Fos presence also was identified in sympathetic ganglia at these sites. Nerve cell bodies in the combined nucleus cuneatus and gracilis in the medulla oblongata, the vestibular nuclei, and the thalamus also contained Fos-positive particles.

CONCLUSIONS: Stretching a single lateral ligament of the spine produces a barrage of sensory feedback from several spinal cord levels on both sides of the spinal cord. This sensory information also is transferred to higher levels in the brain, including the nucleus gracilis and cuneatus, the vestibular nuclei, and the thalamus. These sites of Fos production suggest the locations of pathways for this sensory information, which include the dorsal columns and the spinocerebellar tracts. The information obtained from this study provides a clear focus for future studies in this area, particularly for diseases such as scoliosis where it is thought that incorrect perception of sensory information from the ligaments might be a major contributing factor.

PMID: 9122777 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources



TP = transverse process ITL = intertransverse ligament

= Area of positive reaction

Did You Know?

- Spinal stiffness was linked to visceral pathology with nearly 100% accuracy based upon sympathetic innervation. (*Medical Times*, 1921)
- 1,000 capsules of Tylenol in a lifetime doubles the risk of end stage renal disease. (*New England Journal of Medicine*, 1994)
- The average time for a whiplash-injured patient to achieve maximum improvement is 7 months 1 week. (*Spine*, 1994)
- 93% of patients with chronic whiplash pain who have failed medical and physical therapy care improve with chiropractic adjustments. (*Injury*, 1996)
- Taking the correct drug for the correct diagnoses in the correct dose will kill about 106,000 Americans per year, making it the 4th most common cause of death in the US. (*Journal of the American Medical Association*, 1998)
- Nonsteroidal anti-inflammatory drugs for rheumatoid and/or osteoarthritis conservatively cause 16,500 Americans to bleed to death each year, making that the 15th most common cause of death in the US. (*New England Journal of Medicine*, 1999)
- Glutamate and aspartame can cause chronic pain sensitization, and removing them from the diet for 4 consecutive months can eliminate all chronic pain symptoms. (*Annals of Pharmacotherapy*, 2002)
- Chiropractic spinal adjusting has been shown to be better than 5 times more effective than the NSAIDs pain drugs Celebrex and Vioxx in the treatment of chronic neck and low back pain. (*Spine*, 2003)
- In patients suffering from chronic pain subsequent to degenerative spinal disease, 59% can eliminate the need for pain drugs by consuming adequate levels of omega-3 essential fatty acids. (*Surgical Neurology*, 2006)
- Chiropractic adjustments have been shown to significantly lower blood pressure. (*Journal of Human Hypertension*, 2007)
- The estimated incidence of chronic pain from whiplash trauma is 15-40%. (*Jour of the Am Academy of Ortho Surg*, 2007)
- Meniere's Disease has been linked to a disorder of the upper cervical spine facet joints. (*International Tinnitus Jour*, 2007)
- Supplementing with vitamin D3 has the potential to reduce cancer deaths in America by 75%. (*Ann of Epidemiology*, 2009)
- Potentially, the largest exposure of Americans to the neurotoxin mercury is through the consumption of products containing High Fructose Corn Syrup. (*Environmental Health*, 2009)
- Those who consumed the highest amounts of nonsteroidal anti-inflammatory pain drugs increased their risk of dementia, including Alzheimer's dementia, by 66%. (*Neurology*, 2009)
- The newest estimate for the incidence of autism is 1 in 91 US children. (*Pediatrics*, 2009)

These published facts and hundreds more are available through my Article Review Service, now in its 11th year. Reviews are detailed, thorough, timely and cutting-edge, with KEY POINTS summary and chiropractic practical applications. The Reviews are in PDF format for easy printing. They are excellent for educating the chiropractor, staff, patients and for lecture preparation.
Easy sign-up through the website with a credit card using PayPal. $100.00 per year. The Archives (past years) are also available.

Website: **www.danmurphydc.com**
Assistant: **Phyllis (925) 420-6564** **Michelle Schaer, DC (602) 826-2277**

SUBSCRIBER COMMENTS
Dr. Dan,
Any chiropractor that truly cares about his patients and not about just making a buck needs to be subscribing to your Article Review Updates. I certainly am going to do my part to see that each chiro I come in contact with knows what an absolutely invaluable resource it is. I sat in amazement at the last two articles you sent regarding antibiotic overuse and atopic disorders. What crucial information to pass on to my practice members. Thanks and keep up the awesome work. Dr. G.M.; August 1, 2002
Dear Dan,
I hope you can continue providing this information for many years to come. I have been in practice for 18 years and find these citations to be the most informative, chiropractically relevant information that I have received in my career. I would be willing to pay more for this information to make sure that it keeps coming. Again, thank you!! JR, DC; January 8, 2005