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Effects of Mechanical Loading on Intervertebral Disc Metabolism In Vivo

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Abstract

The overall goal of this work is to define more clearly which mechanical loading conditions are associated with accelerated disc degeneration. This article briefly reviews recent studies describing the effects of mechanical loading on the metabolism of intervertebral disc cells and defines hypothetical models that provide a framework for quantitative relationships between mechanical loading and disc-cell metabolism.

Disc cells respond to mechanical loading in a manner that depends on loading magnitude, frequency, and duration. On the basis of the current data, four models have been proposed to describe the effects of continuous loading on cellular metabolism: (1) on/off response, in which messenger ribonucleic acid (mRNA) transcription remains altered for the duration of loading; (2) maintenance, characterized by an initial change in mRNA levels with return to baseline levels; (3) adaptation, in which mRNA transcription is altered and remains at a new steady state; and (4) no response. In addition, five hypothetical mechanisms that describe the long-term consequences of these metabolic changes on disc-remodeling are presented.

The transient nature of gene expression along with enzyme activation/inhibition is associated with changes at the protein level. The hypothetical models presented provide a framework for obtaining quantitative relationships between mechanical loading, gene expression, and changes at the compositional level; however, additional factors, such as regulatory mechanisms, must also be considered when describing disc-remodeling.

A more quantitative relationship between mechanical loading effects and the metabolic response of the disc will contribute to injury prevention, facilitate more effective rehabilitation treatments, and help realize the potential of biologic and tissue engineering approaches toward disc repair.

Pathology of the spine and back are associated with, or aggravated by, mechanical factors. Despite the growth in knowledge of the pathologic processes and micromechanical disorders that give rise to low-back pain, the links between biomechanics, disc degeneration, and back pain are still poorly defined. An understanding of the relationship between disc mechanics and biology is a priority. A more precise definition of damaging loading would enable improved injury prevention, for example, while an improved understanding of healthy loading would facilitate more effective rehabilitation treatments. Furthermore, mechanobiologic studies on the intervertebral disc are necessary to provide baseline information against which effective biologic treatments and tissue-engineering treatments may be adequately judged.

The first goal of this article is to review the recent studies that have described the effects of mechanical loading on intervertebral disc-cell metabolism, focusing on which mechanical loading conditions are associated with accelerated disc degeneration. The second goal is to define hypothetical models that provide a framework for quantitative relationships between mechanical loading and disc-cell metabolism. The third and final goal of this article is to describe several factors that are required to provide a link between joint-loading and altered metabolic responses.

Effects of Disc Degeneration on Disc Material Properties

Substantial alterations in the properties of disc material are associated with intervertebral disc degeneration and aging. The most striking alterations occur in the nucleus pulposus, with an eightfold increase in shear modulus and substantial loss of swelling pressure¹. Alterations in the annulus with disc degeneration are less dramatic than in the nucleus yet still substantial, with consequences that are potentially more harmful than nucleus changes. With intervertebral disc degeneration and aging, the compressive modulus of the annulus approximately doubles, the shear modulus increases slightly, and some alterations in tensile properties take place^{1,2}. Structural alterations in the disc annulus are associated with significant decreases in the Poisson ratio as well as decreased radial permeability and increased axial and circumferential permeability¹. Altered structural properties are likely associated with altered molecular interactions and microfailure of the disc annulus that can occur through fiber rupture and separation of layers (delamination). However, the causative question relating to mechanically accelerated disc degeneration remains unclear. A mechanobiologic view of the spine suggests that alterations in intervertebral joint-loading conditions affect physical signals on the disc tissue and cells. Both mechanical factors and biologic factors then interact to define whether the disc tissue remains in homeostasis, accumulates damage, or otherwise remodels in response to loading conditions.

Mechanically Accelerated Disc Degeneration

Competing hypotheses on mechanical involvement in disc degeneration include wear and tear (or overloading) and hypomobility¹. In the overload hypothesis, a demanding mechanical environment produces localized trauma such that accumulation of tissue injury and microdamage outpaces the ability of the disc to repair itself due to the slow rate of turnover and biologic repair by its cells. Hypomobility also produces adaptive changes that may be related to a lack of mechanical stimulus or reduced transport. Overloading and immobilization together have been proposed in the progression of disc degeneration, in which increased flexibility and/or range of motion (hypermobility) occurs in early degeneration followed by painful limitation of motion, tissue stiffening, and hypomobility in late degeneration^{1,2}.

In reviewing recent epidemiology studies, Battié et al.³ found that physical exposures played relatively small roles in disc degeneration and concluded that genetic influences were the largest factor. This is in contrast to most, but not all, of the early epidemiology studies, which found an association between heavy physical loading and radiographic signs of disc degeneration. The effect (beneficial or harmful) of physical activity depends on factors such as recovery times, the level of adaptation, and the stage of degeneration, which complicates the quantification and definition of damaging mechanical loading. Although genetics may indeed be the largest factor in explaining the variance associated with the progression of disc degeneration, genetics may influence the quality of the tissue material as well as anthropometry, which have direct mechanical consequences. Furthermore, quantifying the precise loading history that may result in microdamage remains a daunting task; this may account for the large percentage (25% to 50%)³ of overall variance in lumbar degeneration

that remains unexplained. A comprehensive mechanobiologic understanding is required in order to provide more precise definitions of healthy and damaging loads while also revealing more clearly the capacity of the disc to remodel in response to load.

Mechanical Effects on Intervertebral Disc Metabolism

Rodent-tail models of disc degeneration have been popular in recent years because they enable researchers to directly address mechanical loading effects on disc metabolism. Static loading models have demonstrated that excessive compression-loading on rat and mouse tails induces alterations that are similar to disc degeneration⁴. In particular, sustained static compression results in altered water and proteoglycan contents as well as changes in the structure of motion segments and the architecture of the annulus fibrosus. High magnitudes of static loading also result in altered biosynthesis and cellular apoptosis^{4,5}.

These models apply the overall concept that alterations in mechanical loading (the experiments have most often applied compression loading) on the caudal intervertebral joints result in alterations in disc metabolism with specific changes in messenger ribonucleic acid (mRNA) expression and enzyme activation. Variations in mRNA expression and enzyme activation lead to changes at the protein level and eventually to compositional and structural changes. With the current state of knowledge, the most direct method of understanding the mechanisms for in vivo remodeling is to develop a quantitative relationship between joint-loading conditions and the biosynthetic response that leads to functional changes in the intervertebral disc. Analysis of gene expression and enzyme activation represents the best characterization of the short-term intervertebral disc-remodeling response, especially in light of the long half-lives of proteoglycans and collagens in the disc⁶. Once this quantitative relationship is established at the message level, it is important to determine how alterations in gene expression correspond to changes at the protein level.

Recent studies investigating cyclic compression-loading on rodent-tail models have been important to distinguish between overloading and immobilization responses and to more precisely quantify the relationships between cyclic compression and cellular metabolism by analyzing gene expression responses. Several important conclusions can be drawn from these dynamic loading studies:

1. Immobilization and high magnitudes of cyclic compression have distinct effects on mRNA expression, with immobilization causing a more general downregulation in mRNA levels. Furthermore, the mRNA response to cyclic compression is distinctly different depending on whether loading follows immobilization or is initiated on discs that have been freely mobile.
2. Thresholds of mechanical loading exist where too little stimulus and too much stimulus both result in altered disc metabolism. In the rat tail, loading near the load magnitude threshold (approximately 0.2 MPa) or near the load frequency threshold (approximately 0.2 Hz) results in gene expression responses that are very similar to those in the unloaded group; however, increasing the load magnitude (approximately 1.0 MPa) and both increasing and decreasing the frequency (0.01 and 1 Hz) results in appreciable changes in disc metabolism.
3. Best and worst-case loading conditions can be defined in which best combination loads refer to a predominantly anabolic response (upregulation of proteins and downregulation of enzymes) and worst combination loads refer to a predominantly catabolic response (downregulation of proteins and up-regulation of enzymes). In the rat tail, cyclic loading at 1 MPa and 1 Hz for two hours results in predominantly upregulated catabolic gene responses in both the nucleus and annulus. Compression

following immobilization, on the other hand, has a more highly catabolic response, with downregulation of several matrix proteins in addition to upregulation of enzymes. Furthermore, two hours of cyclic loading at 1 MPa and 0.01 Hz for two hours results in a predominantly anabolic response in the nucleus, with upregulation of all anabolic genes and a relatively modest upregulation of catabolic genes^{7,8}.

A view of remodeling as anabolic and catabolic remodeling alone does not take into consideration alterations in disc structure that may take weeks or months to accumulate. This study of the short-term effect of mechanical loading is a reasonable starting point in describing the complex disc mechanobiologic responses, although one must also consider the long-term consequences of these effects on disc-matrix structure, in which a predominantly anabolic response could, for example, lead to increased fiber content in the nucleus. In addition, in some cases, a balanced change in both anabolic and catabolic gene-expression responses complicates the prediction of the long-term consequences on matrix structure and composition.

4. Increasing compression-loading duration (from 0.5 to four hours) has been demonstrated to lead to two general responses. First, annulus cells had a pattern of mRNA expression that was continuously upregulated with continued loading (particularly related to collagen metabolism), whereas nucleus cells had a pattern of mRNA expression with an initial increase in mRNA levels followed by a decrease (particularly related to aggrecan metabolism). The nucleus response was representative of a decrease in message level, probably due in some part to diminished gene expression unrelated to translation, as the reduction in message level occurred prior to its expected half-life⁹.

General Hypotheses for Gene Expression and Remodeling Response to Mechanical Loading

We hypothesize that gene expression of proteins and matrix proteases in the intervertebral disc is a quantitative function of intervertebral joint forces and is dependent on loading mode, magnitude, frequency, and duration. We propose that for each gene, in each disc region (i.e., annulus versus nucleus), the general shape of the transient gene-expression response may be defined by an initial amplitude, a final amplitude, and the time it takes gene production to obtain a new steady-state level. The steady-state level of gene expression response may be equal to 1 (homeostasis), greater than 1 (i.e., upregulation), or less than 1 (i.e., downregulation), provided that measurements are taken at times greater than the half-life of the mRNA being measured.

Potential gene expression responses to continuous loading may occur in the following fashion, as proposed on the basis of experimental observations of mRNA levels following compression loading in vivo (Fig. 1). First, an on/off response to mechanical loading could be represented as a gene-expression response that increases to a maximum rate and stays upregulated as long as the mechanical stimulus is continued, as was observed by the annulus cells in response to continued mechanical loading at 1 MPa and 1 Hz⁶. Second, a maintenance-type response could be characterized by an initial upregulation followed by a return to control levels, as demonstrated by the nucleus pulposus cells in response to 1 MPa and 1 Hz loading⁹. Third, there could be an adaptation, which would entail an upregulation to a peak level followed by equilibrium at a new steady state that would be different than the gene-expression levels required to maintain homeostasis. Fourth, the effects of mechanical loading could result in no response from the cells and therefore no change in mRNA levels.

Any of the first three aforementioned changes in mRNA levels could manifest as a downregulation of genes (instead of the upregulations shown in Figure 1).

We further propose that five distinct outcomes in protein levels exist as a consequence of alterations in gene expression and enzyme activity (Fig. 2): (1) turnover/repair—conditions promoting increases in message that result in turnover of proteins without a change in protein levels, (2) anabolic remodeling—conditions promoting increases in the message for proteins that may result in increased protein levels, (3) catabolic remodeling—increased message levels for enzymes that may result in increased enzyme activity and a loss in proteins, (4) homeostasis—no notable changes in message or protein levels relative to baseline, and (5) injury—an upregulation in both anabolic and catabolic genes that is maintained for an extended duration and may or may not modulate protein levels. Previous studies have found that mechanically induced alterations in mRNA levels of cartilaginous tissues correlate to alterations in synthesis as measured with radiolabeled tracers⁹. While changes in the protein synthesis of matrix molecules generally follow changes in mRNA levels, the same is not necessarily true of the enzymes, in which the concentration of active proteolytic enzyme has been observed to change in response to loading⁴. As a result, we hypothesize that enzyme activation, in addition to the changes in gene expression of anabolic and catabolic genes described in Figure 2, is responsible for biologic remodeling of intervertebral disc tissue. Therefore, any of the five changes in protein level described above may be either enhanced or suppressed as the result of changes in enzyme activation.

Patterns of turnover and remodeling are specific to each structural component as observed in previous studies, where loading changed collagen expression in the disc but had no effect on aggrecan (i.e., two hours at 1 MPa and 1 Hz in the annulus)⁷. It is also important to interpret changes in protein levels relative to the region of the disc where these changes occur (i.e., annulus versus nucleus). For example, an increase in collagen production in the annulus of discs subjected to compression joint-loading may be considered a desirable anabolic remodeling response working to maintain the strength of the annulus, whereas an increase in collagen fiber production in the nucleus, although still an anabolic remodeling response, may be more characteristic of an undesirable degenerative change.

Mechanisms for Mechanotransduction

Mechanical loading clearly can induce highly specific metabolic responses. Our hypothetical model is based on phenomenological relationships between joint-loading conditions and cellular biosynthetic responses *in vivo*. The mechanistic relationships between the mechanical stress and altered biosynthetic responses may follow several pathways of mechanotransduction, as outlined in Figure 3. Specifically, intervertebral joint-loading will result in mechanical stresses within the tissue that may affect disc cells through direct and indirect mechanotransduction mechanisms. Those direct mechanotransduction mechanisms will influence cell shape, size, and/or pressure on the cell, while indirect mechanotransduction mechanisms may lead to alterations in localized fixed-charge density, nutrient transport, and pH. All of these factors, as well as autocrine/paracrine effects, may result in altered biosynthesis and/or the loss of cell viability and eventually matrix remodeling.

Much of the experimental evidence driving our hypothetical model of intervertebral disc mechanobiology is derived from studies that made use of rodent tails. The intervertebral joints of the tail offer many similarities to lumbar or other spinal intervertebral joints, yet their relevance to the human condition must be put in context with limitations of the model (e.g., differences in size, geometry, and the presence of notochordal cells). Nevertheless, the ability to have precise control over the mechanical boundary conditions *in vivo* makes this

model highly appealing. Furthermore, familial genetics has been identified as a primary predictor of human disc degeneration. Although familial genetics is not explicitly considered within these models, it is likely that its influence on disc integrity is related to the way in which the specific biomechanical thresholds of an individual affect the initiation and progression of biologic changes.

Although the majority of the factors that are outlined in Figure 3 have not been characterized, a few of the direct mechanotransduction mechanisms have been explored in the rat-tail model. First, the resting stress and disc height of rat caudal discs were reported to be between 0.1 and 0.2 MPa and 0.81 ± 0.05 mm, respectively, based on a refined radiographic measurement technique of tail disc space in vivo while under compression loading⁹. Dynamic in vivo deformations have demonstrated changes in disc height on the order of 0.45 mm in vivo with 1.0 MPa cyclic loading at 1 Hz for two hours. However, it is important to consider that deformations of the caudal motion segments occur not only as a result of disc deformations but also as a result of vertebral and end-plate deformations¹⁰. Despite the increasing volume of information relating external loading conditions to specific biosynthetic responses, a large gap remains in the understanding of which extracellular (and also intracellular) mechanotransduction pathways are involved in mediating these changes.

Conclusions

Several hypotheses have been offered regarding the gene-expression response to sustained loading. The transient nature of gene expression along with enzyme activation will define changes on the protein level. Understanding the relationship between mechanics and cell metabolism is a priority not only for distinguishing healthy loading from damaging loading but also for providing a baseline understanding required for tissue engineering and gene therapy. Our hypothetical models describe mechanical effects on disc metabolism and provide a framework for obtaining quantitative relationships between mechanical loading, gene expression, and changes on the protein level. A more quantitative relationship between mechanical loading on the disc and gene-expression responses will contribute to injury prevention, facilitate more effective rehabilitation treatments, and help realize the potential of biologic and tissue-engineering approaches toward disc repair.

Although important work on intervertebral disc mechanobiology has been undertaken, there are many areas in which knowledge is lacking. These areas include a refined understanding of remodeling changes with an appreciation of not only anabolic versus catabolic responses but also phenotypic changes, an improved understanding of the interaction between damage in disc tissue and associated inflammatory and remodeling responses, an improved understanding of the relationships between complex (e.g., bending and compression) and/or compound (e.g., compression following immobilization) loading on disc mechanobiology, and, finally, a more comprehensive understanding of the relationship between animal models and human discs with attention to size scale, biomechanics, matrix structure, notochordal cells, and end-plate differences.

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Fig. 1. Schematic representation of the cellular response of the intervertebral disc to continuous loading characterized by four distinct mRNA expression responses—on/off response, adaptation, maintenance, and no response. These responses are based on experimental observations.

Fig. 2. Hypothetical mechanisms for biologic remodeling and repair of the intervertebral disc. Following a finite loading event, these combinations of changes in anabolic and catabolic mRNA production may result in one of the five outcomes in the composition/structure, indicated here as a change in protein level. Additional factors, such as enzyme activation, may either enhance or suppress the long-term outcome of these changes.

Fig. 3. Flowchart of some of the direct and indirect extracellular pathways for mechanotransduction, demonstrating the complexity of interactions between joint-loading and biologic remodeling. ECM = extracellular matrix; FCD = fixed-charge density.