CHAPTER 6

Effects of Exogenous Mechanical Forces on Cells

6.1 Biological Effects of Strain on Cells: Clinical Examples (Disuse Atrophy and Overuse Hypertrophy)

6.2 Concept of Mechanical Strain

6.3 Characteristics of Strain Acting on Cells
- **a. Magnitude**
- **b. Duty cycle**
- **c. Frequency**
- **d. Uniformity**
- **e. Direction**

6.4 Effects of Exogenous Forces on Cells *In Vitro* (Table 6.1)

6.5 Effects of Exogenous Forces on Tissue *In Vitro* and *In Vivo*

6.6 Mechanisms by Which Mechanical Strain Affects Cell Biology (Transduction Mechanisms)

6.4 EFFECTS OF EXOGENOUS MECHANICAL FORCES ON CELLS *IN VITRO*

TABLE 6.1

CELL TYPE (%ε)*	MITOSIS	SYNTHESIS	REGULATOR	2nd MESS.	YR.(REF.)
Connective Tissue					
Osteoblasts	**DNA Syn.**	**ND**	**PGE_2**	**cAMP**	**1980** [15]
Osteoblasts	**NA**	**ND**	**PGE_2**	**ND**	**1984** [18]
Osteoblasts	**NA**	**ND**	**PLA_2**	**ND**	**1988** [2]
Osteoblasts (0.7-2.8)	**NA**	**ND**	**PGE_2**	**ND**	**1990** [12]
Osteoblasts (.04)	**DNA Syn.**	**dec. Collagen dec. NC Protein dec. Alk. Phos.**	**PGE_2**	**no cAMP**	**1991** [4]
Osteoblasts (0.3) (Periosteal)	**Prolif.**	**Collagen Collagenase**	**PKC, PLC ic^+ PGE_2 no ec PGE_2**	**Ca**	**1991** [10]
Osteoblasts (1) (Haversian)	**Prolif.**	**Collagen**	**no PKC no PLC no ic PGE_2 no ec PGE_2**	**ND**	**1991** [10]
Osteoblasts (1-8)	**Prolif. (@1) no Prolif. (>1)**	**ND (no alk. phos.)**	**ND**	**ND**	**1994** [13]
Fibroblasts (+) and (-) IL-1	**ND**	**ND**	**PGE_2**	**cAMP**	**1990** [14]
Fibroblasts (1)	**Prolif.**	**Collagen**	**ND**	**ND**	**1991** [10]
Fibroblasts (14) Human dermal and scar	**dec. DNA**	**ND**	**ND with scar**	**ND**	**1988** [9]
Fibroblasts (13) Rat ligament	**2.7x inc.**	**1.4x inc. Collagen**	**ND**	**ND**	**1990** [17]

ND, not done.
*** Maximum strain in the substrate **NC, noncollagenous $^+$ic, intracellular; ec, extracellular**

Cartilage	**ND**	**ND**	**ND**	**dec. cAMP**	**1976** [3]
Chondrocytes	**DNA Syn.**	**ND**	**no PGE_2**	**cAMP**	**1984** [1]
Macrophages (4&8) ("Activated")	**ND**	**ND**	**PGE_2 release**	**NA**	**1996** [8]
<u>Muscle</u>					
Smooth Muscle (Arterial)	**ND**	**Collagen NC** Protein**	**ND**	**ND**	**1976** [11]
<u>Epithelia</u>					
Epithelial	**DNA Syn.**	**ND**	**ND**	**ND**	**1984** [5]
Endothelial (10) (Aorta)	**Prolif.**	**ND**	**ND**	**ND**	**1987** [16]
Endothelial (4.9) (Pulmonary artery)	**No effect**	**dec. Fibronectin**	**ND**	**ND**	**1989** [7]

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6.5 EFFECTS OF EXOGENOUS MECHANICAL FORCES ON TISSUE *IN VITRO* AND *IN VIVO*

TABLE 6.2

CELL(%ε)	MITOSIS	SYNTHESIS	REGULATOR	2nd MESS.	YR./REF.
In Vitro					
Bone (Tibia)	**DNA Syn.**	**ND**	**ND**	**dec. cAMP**	**1975**
Fibroblasts	**ND**	**Metalloproteinase**	**ND**	**ND**	**1980**
Art. Cartilage	**ND**	**Protein, GAGs**	**ND**	**ND**	**1989**
In Vivo					
Fibroblasts	**ND**	**Collagen Collagenase**	**ND**	**ND**	**1976**
Osteoblasts	**Prolif.**	**Matrix**	**ND**	**ND**	**1984**

6.6 MECHANISMS BY WHICH MECHANICAL STRAIN AFFECTS CELL BIOLOGY (TRANSDUCTION MECHANISMS)

6.6.1 Direct Effects on Cells (Fig. 6.1)

6.6.1.1 Cell Membrane Strain-Related Mechanisms

6.6.1.1.1 Cell Wounding

Fracture of cell membrane (high strain); "cell wounding." Allows a) release of stored molecules that can have autocrine and paracrine action and b) entry of soluble extracellular agents into the cell.

6.6.1.1.2 Receptors

Change in membrane receptor configuration and orientation.

6.6.1.1.3 Ion Channels

Strain-sensitive (stretch-activated) ion channels.

6.6.1.1.4 Membrane-Bound Enzymes

Strain-sensitive membrane-bound proteins (enzymes, e.g., phospholipases, adenylate cyclase, and protein kinases)

1) Adenylate cyclase (from Molecular Cell Biology)

Activation leads to production of the second message cAMP.

2) Phospolipase

Hydrolyzes phospholipids in the membrane. This produces inositol 1,4,5-triphosphate which releases calcium ions from the endoplasmic reticulum into the cytoplasm to act as second messenger. Another second messenger, 12, diacylglycerol, is also produced by the PLC hydrolysis of phospholipids. PL also produces arachidonic acid (from breakdown of phospholipid), the substance from which eicosa synthesized.

3) Protein Kinase

Normally an inactive, soluble cytosolic protein. Calcium ions cause it to be bound to the cell membrane. Might play an important role in cell proliferation. Activation of PKC in different cells results in varied cellular responses.

6.6.1.1.5. Cytoskeleton

Alteration of the protein complex at the junction of cytoskeletal elements and the cell membrane.

6.6.1.2 Deformation of the Cytoskeleton (Actin Network)

6.6.2 Indirect Effects on Cells (Tissue-Level Effects)

6.6.2.1 Compression and Hydrostatic Pressure

6.6.2.1.1 Physicochemical changes in the micromovement of the cell (e.g., due to the pressure-dependent change in the activity coefficient of ions; colligative properties of the fluid).

6.6.2.1.2 Change in tissue permeability to soluble autocrine, paracrine, and endocrine factors.

6.6.2.2 Fluid Flow (Electrokinetic)

6.6.2.2.1 Alteration in concentration of nutrients and soluble regulators in the microenvironment of the cell.

6.6.2.2.1.1 Electroosmosis: Electrical Current-Generated Mechanical Strain (*viz*., Articular Cartilage)
(From E. H. Frank and A. J. Grodzinsky, J. Biomech., 20, 615-627, 1987)

Electroosmosis is an electrokinetic effect (the converse to streaming potential) resulting in current-generated strain. In articular cartilage an applied electrical potential (voltage) produces a force on mobile counterions in the interstitial fluid and an oppositely directed force on the ionized ECM. If this was the classical case of a rigid, charged membrane (not the case of articular cartilage) electroosmotic flow of fluid would be produced across the membrane. In the case of articular cartilage fluid is electroosmotically redistributed within the ECM while the charged solid matrix is simultaneously translated eletctrophoretically in the opposite direction. This electrophoretic translation of matrix results in strain of the tissue. Another component of strain is the tissue deformation associated with the frictional force of the tissue fluid acting on the solid matrix as the fluid is redistributed electroosmotically.

6.6.2.2.2 Streaming potential.

6.6.2.2.3 Strain-Related Potentials (Piezoelectric)

6.6 MECHANISMS BY WHICH MECHANICAL STRAIN AFFECTS CELL BIOLOGY (TRANSDUCTION MECHANISMS)

6.6.3 Second Messengers (from Molecular Cell Biology, J. Darnell, *et al*.)

Binding of certain ligands (*e.g*., certain hormones) to their cell surface receptors leads to the activation of an enzyme that results in the increased concentration of an intracellular signaling compound (the *second messenger*). The second messenger triggers an alteration in the activity of one or more proteins that control certain cell functions. Removal or degradation of the ligand reduces the level of the second messenger and terminates the metabolic response.

The following are second messengers:

1) 3',5' - cyclic adenosine monophosphate (cAMP)

2) 3',5' - cyclic guanosine monophosphate (cGMP)

3) 1,2 - diacylglycerol

4) inositol 1,4,5 - triphosphate

5) Ca^{2+}