Mechanotransduction and strain amplification in bone cell processes

Y Han,* S Cowin,* M Schaffler,• S Weinbaum*

*Departments of Biomedical and Mechanical Engineering and CUNY Graduate School, New York, NY 10031, •Leni and Peter May Department of Orthopedics, Mt Sinai School of Medicine, New York, NY 10029

Introduction

A paradox in bone tissue is that tissue-level strains due to animal and human locomotion are too small to initiate intracellular chemical responses directly. A model was recently proposed in You et al. (2001) J. Biomech. **34,** 1375-1386 to resolve this paradox, which predicts that the fluid flow through the pericellular matrix in the lacunar-canalicular porosity due to mechanical loading can induce strains in the actin filament bundles of the cytoskeleton that are more than an order of magnitude larger than tissue level strains. In this study, we greatly refine this model by using the latest ultrastructural data for the cell process cytoskeleton, the tethering elements that attach the process to the canalicular wall (You et al. (2004) Anat. Rec. **278A,** 505-513), and their finite flexural rigidity EI predicted in Weinbaum et al. (2003) PNAS, **100,** 7988-7995.

Methods

We have constructed a much more realistic 3-D model for the osteocytic process and have used large deformation "elastica" theory for finite EI to predict the deformed shape of the tethering elements and the hoop strain on the actin filament bundle. The model for the actin filament bundle is based on a 19 filament central bundle that is cross-linked by fimbrin and surrounded by a double helical coil of brush border myosin I which advances 37.5 nm in each revolution. In the model the tethering fibers in the pericellular matrix, when subject to hydrodynamic drag, transmit a tensile force across the cell process membrane via membrane proteins that are directly linked to the myosin I helices. A detailed analysis of the stress distribution in this complicated structure is presented and the strains induced on the outer filaments of the actin filament bundle are calculated.

Results

Our model predicts a cell process that is three times stiffer than in the previous study by You et al. (2001) and that the effective Young's modulus of the cell process is 600 times greater than the cell body. Despite its stiffness the model predicts hoop strains on the cell process which are one to two orders of magnitude greater than whole tissue strains. These cellular level strains are > 0.5 percent for tissue level strains > 1000 microstrain at 1 Hz and > 250 microstrain at frequencies > 10 Hz. This suggests that only rather large tissue strains in the physiological range can produce a stimulatory response and that without the strain amplification mechanism bone cells would not be able to detect the small whole tissue strains that are produced by mechanical loading *in vivo.*

Discussion

The foregoing results provide a reasonable explanation of the results of You et al. (2000) J. Biomech. Eng. **122,** 387-393 and other investigators who have shown *in vitro* that cells grown on elastic substrates do not elicit chemical signals when subject to strains of < 0.5 percent, whole tissue stains that would cause bone fracture. Furthermore, it would appear, in view of the large difference in the elastic modulus of the cell process and the cell body, that when cells are subject to fluid shear stress *in vitro* it is the cell body that is producing the observed chemical responses such as the release of Ca ions, PGE_2 and other second messengers. In contrast, *in vivo* one anticipates that the cell process is the sensing element of the cell. Therefore, we propose that this strain amplification model provides a more likely hypothesis for the excitation of osteocytes than the fluid shear hypothesis previously proposed in Weinbaum et al. (1994), J. Biomech. **27,** 339-360.