served which was dose dependent of the mean peak amplitude of the response on shear stress magnitude applied to bone cell.[50,52] El-Haj et al. measured cyclic adenosine monophosphate (cAMP) levels by means of a radioimmunoassay. They found a cAMP response in the endosteal lining cells and osteocytes when these cells were subjected to mechanical shear stress.[53] The amount of intracellular cAMP is also dose dependent on the strain rate and the magnitude of loading.[54]

Insulin-like growth factor I (IGF-I) can stimulate cellular DNA in periosteal cells resulting in an increased rate of bone remodeling and proliferation. It is an important regulator of skeletal growth. By testing the expression of the gene for IGF, Bikle et al. found that during development, rat bone changes its capability to produce and respond to IGFs with a progressive trend toward the dominance of IGF-I.[55] Results obtained from in situ hybridization analysis also show that IGF-I mRNA expression in rat osteocytes can increase in response to mechanical stimulation.[56,57]

Pathway of Mechanotransduction

According to the above studies, mechanisms involved in the conversion of mechanical stimuli into biological responses by means of signal transduction in bone cells have been proposed by several scholars.[58-62] A well-known pathway is the inositol phosphate cascade.[60,61] As shown in Fig. 3, fluid flow in the lacunocanalicular system can cause a shear force on the surface of osteocytes resulting in changes of the shape of the cell. This deformation can induce ligand release by the cell. Then, binding of a ligand to a receptor activates membrane-bound enzyme phospholipase C (PLC) which hydrolyzes phosphatidyl inositol 4,5-bisphosphate (PIP_2) into inositol 1,4,5-triphospate (IP_3) and diacylglycerol (DG).[63] The interaction of IP_3 with the endoplasmic reticulum (ER) causes the rapid release of calcium from the ER. As shown in Fig. 4, protein kinase C (PKC), a membrane-bound calcium-dependent enzyme, is also involved in cell proliferation. Jones et al. observed that activation of PLA_2, which is essential for the synthesis of PGE_2, is related to PLC.[59] On the other hand, when a bone cell is subjected to a shear force, G-protein can activates ade-

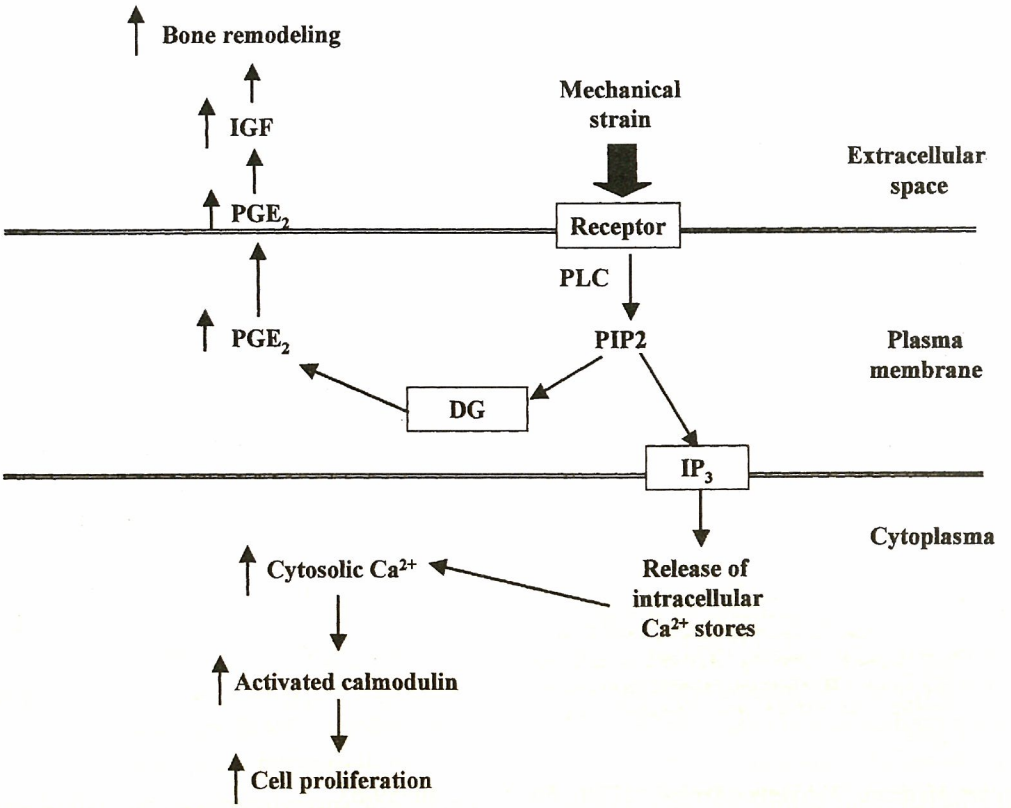

Fig. 4. Signal cascade pathway of mechanotransduction in bone remodeling.