J Musculoskelet Neuronal Interact 2008; 8(1):15-17

Hylonome

Black Forest Forum
May 10-13, 2007
Castle Bad Liebenzell, Germany

Describing force-induced bone growth and adaptation by a mathematical model

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Abstract

This work proposes a mathematical model that qualitative describes the process of mechanically force-induced bone growth and adaptation. The mathematical model includes osteocytes as the key interfacing layer connecting tissue, cellular and molecular signaling levels. Specifically, in the presence of an increase in the mechanical stimuli, osteocytes respond by mechano-transduction releasing the local factors nitric oxide (NO) and prostaglandin E_2 (PGE_2). These local factors act as the signaling recruitment signals for bone cells progenitors and influence the coupling activity among osteoblasts and osteoclasts during the process of bone remodeling. The model is in agreement with qualitative observations found in the literature concerning the process of bone adaptation and the cellular interactions during a local bone remodeling cycle induced by mechanical stimulation.

Keywords: Mathematical Modeling, Bone Cells, Osteocytes, NO, PGE_2, Mechano-transduction, Bone Adaptation

Mechanical stimulation has been recognized as a potential regulatory factor involved in development, growth, maintenance and function of the skeletal system[1]. Bone constitutes the basic unit of the skeletal system. It is a highly organized structure designed and developed to allow locomotion; to give structural support to the body; to serve as an internal reservoir for minerals[2] and to supply location for the immune system[3].

Bone is a living tissue continuously undergoing renewal and building up of the bone matrix, by adapting its shape and structure according to mechanical and biophysical demands. These dynamic characteristics are orchestrated by a highly active cellular activity, mainly involving osteoclasts, osteoblasts, and osteocytes. Osteoclasts are multinucleated cells coming from hematopoietic precursors of the mononuclear-phagocytic lineage, and their role is to resorb the bone matrix[4-6]. Osteoblasts, the bone-forming cells, are of mesenchymal origin. They produce and deposit the extracellular organic matrix, called osteoid, which undergoes mineralization[1,7,8]. On the other hand, during the mineralization process, some osteoblasts are embedded in lacunae and differentiate into osteocytes. Osteocytes possess long extensions entering into the lacuno-canalicular network, and allowing them to communicate with cells in the bone surface or in the vasculature[8,9].

In the literature, bone is hypothesized as a regulated system[7], which tunes its strength by changing the amount and the material properties of bone tissue, in places where mechanical or biophysical demands require it. This regulation process provides the mechanisms leading to functional adaptation in the local microenvironment, while keeping the bone tissue strong enough to support eventual higher functional loads or new biophysical demands[2]. Up to now, several attempts have been made to understand and mathematically model the bone dynamics in order to describe the complex phenomena behind the bone regulation process[10-14].

Based on the Mechanostat Theory proposed by Frost[7], as a general conceptual framework for bone growth, development, maintenance and functional adaptation[15], we propose a mathematical model of bone dynamics encompassing from signaling pathways for intercellular communication at the cellular level up to a rough description of the mechanical

The authors have no conflict of interest.

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Accepted 1 June 2007

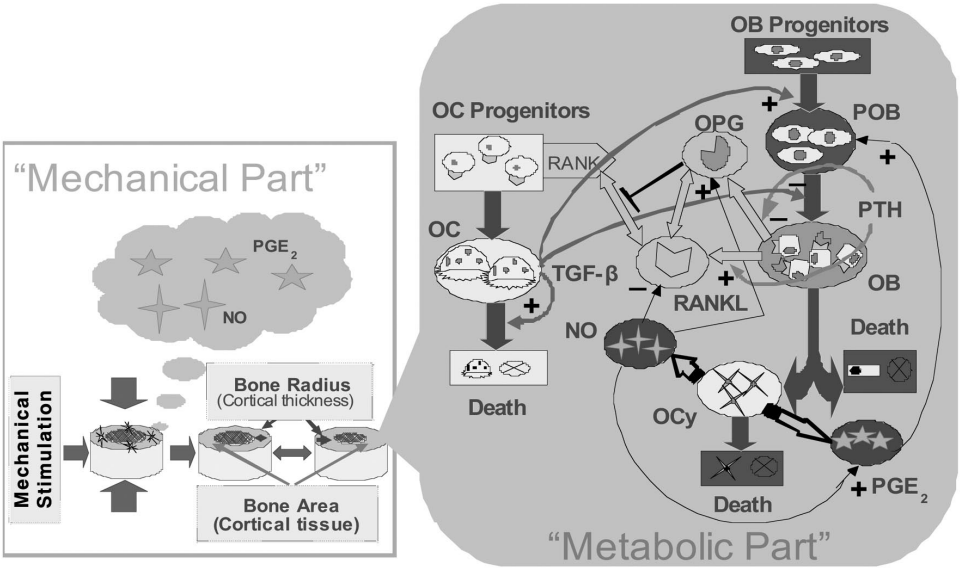

Figure 1. Scheme of The Proposed Model[16,17]. The scheme shows the interactions considered in the model. In the diagram, ellipses represent states and boxes represent cell differentiation phases not included in the mathematical description. Arrows with a positive (+) sign represent a stimulation influence, and with a negative (-) sign correspond to an inhibition influence.

force influence at the tissue level. Figure 1 shows a scheme of the model with the considered interactions[16]. The dynamics at the cellular level is based on the model proposed by Lemaire et al.[12]. The key difference in the mathematical model proposed[16,17] when compared to previously published ones[10-14], it is the ability of the model to describe the bone dynamics, during a bone remodeling cycle, occurring at the tissue, at the cellular and at the molecular level. The mathematical description includes the osteocytes as the key mechano-transducers[9,18-22]. Specifically, osteocytes act as an interface layer between the bone cells, the inter-cellular communication via signaling pathways, and the mechanical stimulation at the tissue level.

The mechanotransduction process is assumed to be carried out by osteocytes. Osteocytes detect changes in the mechanical force demands and respond to these stimuli by releasing the local factors Nitric Oxide (NO) and Prostaglandin E_2 (PGE_2). These local factors have an influence on the cellular activity via the RANKL-RANK-OPG cytokine system, altering the microenvironment where the highly coupled activity among bone cells takes place.

In the model, the bone *thickness* at the tissue level grows as a result of an adaptation process stimulated by an increase in the average mechanical demands. The force-induced bone growth and adaptation process itself is considered as a positive balance between the formation and resorption activities at the cellular level.

The resulting model[16,17] is nonlinear, of 9th order and has a total of 38 parameters. The achieved results capture qualitatively very well the bone adaptation response and the cell interactions during bone remodeling. The model potential power of prediction enables one to examine the effect of metabolic changes together with the influence of physical activity. Overall, the model provides a theoretical framework to study and to analyze the multiple and simultaneous interplay among the factors involved in each level of abstraction. Specifically, the model offers a conceptual framework to explore the study and development of new therapeutic treatments to pathological conditions and bone disorders such as Osteoporosis.

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