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Fluid flow induced calcium response in osteoblasts: Mathematical modeling

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ABSTRACT

Fluid flow in the bone lacuno–canalicular network can induce dynamic fluctuation of intracellular calcium concentration ($[Ca^{2+}]_i$) in osteoblasts, which plays an important role in bone remodeling. There has been limited progress in the mathematical modeling of this process probably due to its complexity, which is controlled by various factors such as Ca^{2+} channels and extracellular messengers. In this study we developed a mathematical model to describe $[Ca^{2+}]_i$ response induced by fluid shear stress (SS) by integrating the major factors involved and analyzed the effects of different experimental setups (e.g. $[Ca^{2+}]_i$ baseline, pretreatment with ATP). In this model we considered the ATP release process and the activities of multiple ion channels and purinergic receptors. The model was further verified quantitatively by comparing the simulation results with experimental data reported in literature. The results showed that: (i) extracellular ATP concentration has more significant effect on $[Ca^{2+}]_i$ baseline (73% increase in $[Ca^{2+}]_i$ with extracellular ATP concentration varying between 0 and 10 μM), as compared to that induced by SS (25% variation in $[Ca^{2+}]_i$ with SS varying from 0 to 3.5 Pa); (ii) Pretreatment with ATP-medium results in different $[Ca^{2+}]_i$ response as compared to the control group (ATP-free medium) under SS; (iii) Relative $[Ca^{2+}]_i$ fluctuation over baseline is more reliable to show the $[Ca^{2+}]_i$ response process than the absolute $[Ca^{2+}]_i$ response peak. The developed model may improve the experimental design and facilitate our understanding of the mechanotransduction process in osteoblasts.

1. Introduction

Osteoblasts can sense the mechanical signals generated by physical activities such as bone deformation during walking and jumping, and translate these signals into biological responses. These mechanically induced biological responses (i.e. mechanotransduction) include intracellular calcium concentration ($[Ca^{2+}]_i$) fluctuation, cell membrane potential variation, gene expression, and release of bio-factors (e.g. prostaglandin E_2, nitric oxide, and ATP) (Genetos et al., 2005; Liu et al., 2008; Riddle et al., 2007). These mechanotransduction processes play a critical role in the in vivo bone remodeling process. Fluctuation of $[Ca^{2+}]_i$ is one of the earliest responses in osteoblasts to mechanical stimulation, e.g. shear stress (SS) induced by fluid flow in lacuno–canalicular system (Allen et al., 2000; Hung et al., 1995). Ca^{2+} is also an essential messenger throughout the entire lifespan of osteoblasts (Karaki et al., 1997). Therefore, it is important to study the fluctuation of $[Ca^{2+}]_i$ in osteoblasts during mechanical stimulation to better understand the bone remodeling process.

The calcium response induced by fluid flow in osteoblasts (SS-induced $[Ca^{2+}]_i$ response) and the underlying pathways have been extensively investigated in recent years (Allen et al., 2000; Batra et al., 2005; Donahue et al., 2003a; Hung et al., 1995; Huo et al., 2008; Ponik et al., 2007). Various pathways in SS-induced $[Ca^{2+}]_i$ response have been identified, such as ATP, ion channels, and purinergic receptors. The ATP release through plasma membrane is critical for the spatial-temporal characteristics of $[Ca^{2+}]_i$ waves in osteoblasts and osteocytes (Genetos et al., 2005; Riddle et al., 2007). P2X receptors, a type of ligand gated ion channels, can respond to the binding of extracellular ATP by opening and introducing calcium influx into cytosol that results in increased $[Ca^{2+}]_i$ (Burnstock, 2006; Erb et al., 2006). G-protein coupled P2Y receptors on membrane can also respond to ATP resulting in the formation of IP_3 in cytosol which further activates IP_3 receptor on endoplasmic reticulum (ER) and induces Ca^{2+} release of ER calcium store (Erb et al., 2006; Gallagher and Buckley, 2002; Hoebertz et al., 2002; Katz et al., 2006; You et al., 2002). The decrease of calcium concentration in ER, the major intracellular calcium store (Hung et al., 1996; Liu et al., 2008), can activate the store-operated calcium channels on membrane which is also responsible for the $[Ca^{2+}]_i$ fluctuation (Francis et al., 2002;

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