Food Engineering Progress
Vol. 17, No. 1. pp. 48~54 (2013.02)

산업식품공학
Food Engineering Progress

Mechanistic Modeling in Biosystem Engineering: A Review on Mechanistic Models of Calcium Metabolism

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Abstract

Calcium is an essential nutrient generally obtained from dietary foods. However, its metabolism is a complex biological network requiring an effective analytical tool. In this review, a few notable calcium mechanistic models are assessed, emphasizing the power of mechanistic modeling in analyzing biological systems because no publication has reviewed them in a single place. Reviewed models are categorized by target systems: calcium absorption, calcium excretion, bone turnover, and whole calcium homeostasis. In the calcium absorption model, two transport systems carrying calcium from intestine to blood have been mechanistically described. Since urine calcium excretion is poorly understood, its model has not been explicitly developed although it is modeled as a part of the whole calcium metabolic system. Cell-based bone turnover model has been conceived to describe the mechanism under bone cell regulation. Finally, whole calcium metabolism has been a target to explain the metabolic control of calcium homeostasis that is linked to the endocrine system. Reviewed models focus on explaining how the calcium metabolic system behaves in response to conditional perturbations by involving effective factors such as endocrine system. We expect that not only will this study provide comprehensive information for future studies in calcium metabolism, but also that it will suggest what the concepts of biosystem modeling are and how they can be used for assessing the target system.

Key words: biosystem modeling, calcium metabolism, mathematical modeling, mechanism, mechanistic modeling

Introduction

Biosystem operates various metabolisms that involve complex interactions among effective factors in order to maintain its biological functions, limiting the direct analytical approach such as experiments. For this reason, to effectively analyze the biosystems and to help experiments, the field of biosystems engineering has applied mathematical modeling to solve questions caused by the complex mechanisms (Kang et al., 2001; Kim et al., 2012).

Calcium is an essential nutrient in human health. Most of required calcium for human health is provided from dietary food. Consequently, calcium metabolic process after calcium intake from food source has been a main issue in foods and nutritional studies, and even in the field of engineering because of its analytical ability.

Serum calcium concentration is maintained within very narrow ranges (around 10 mg/dL) to prevent malfunction of cells and tissues. A deviation of more than 10% from normal serum calcium concentration may result in disease (Weaver and Heaney, 1999). Since abnormal serum calcium concentration results in severe health problems, calcium is metabolized to maintain serum calcium concentration by balancing absorption, excretion, and bone turnover which involves bone resorption and formation, called as calcium homeostasis (Fig. 1).

Not only do hormonal systems regulate calcium metabolic pathways, but also physiological conditions including genetics and nutritional status significantly affect calcium metabolism. Particularly, parathyroid hormone (PTH) and vitamin D are the main regulators, acting on calcium metabolic pathways which bridge the subsystems (bone, kidney and intestine) (Hurwitz et al., 1983; Raposo et al., 2002). The actions of PTH and vitamin D in calcium homeostasis have been addressed during the past few (Nordin, 1990). Table 1 shortly summarizes the factors that influence calcium metabolism. Calcium metabolism and its effective factors are well-summarized in elsewhere (Weaver & Heaney, 2006; Weaver, 2008).

As calcium metabolism involves many interactions among regulating factors, the mechanistic modeling has been applied to analyze the regulating mechanism in calcium metabolism either focusing on partial calcium metabolic pathways or

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Received October 12, 2012; revised January 3, 2013; accepted February 12, 2013

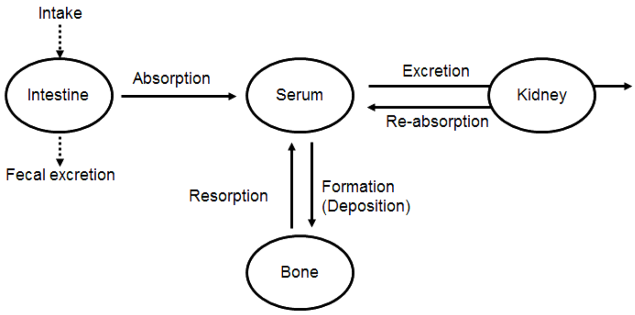

Fig. 1. Calcium intake is either excreted via feces or metabolized to maintain serum calcium concentration. Calcium metabolism involves 4 major organs and 3 main routes which are absorption occurring in the intestine, excretion with reabsorption through renal action, and bone turnover consisted of bone resorption and formation.

whole calcium homeostasis. Unfortunately, no publication has reviewed and summarized the models for calcium metabolism in a single place. Therefore, it is worthwhile to review the developed mechanistic models of calcium metabolism. In this study, we are aimed to review a few notable mechanistic models by target metabolic system; 1) absorption, 2) urine excretion, 3) bone turnover, and 4) whole calcium homeostasis so that this study can be a platform in the future model-based studies in calcium metabolism.

Calcium absorption modeling

Calcium is absorbed through two different transport systems; active and passive transport. The proportion of each transport depends on the calcium load. Active transport dominates at low calcium loads, whereas the proportion of calcium transported passively increases as the calcium load increases.

In 1986, Bronner et al. (1986) confirmed that two transport processes coexisted in the rat intestine and analyzed the three component steps, i.e., calcium entry, intracellular diffusion and calcium extrusion. They used the simplest function (M-M equation) to quantitatively analyze the rat experimental data and showed that active calcium transport was proportionate to the content of calcium binding protein. Their calculated rate of intracellular calcium diffusion was 70 times faster with calcium binding protein than in the absence of it. The three component steps were then further investigated by Feher et al. (1992) and Slepchenko & Bronner (Slepchenko & Bronner, 2001). Feher et al. (1992) developed a mathematical model for 3 steps in active calcium absorption to examine the role of facilitated diffusion based on animal (chicks) data. They simulated calcium absorptive fluxes as a function of the calcium binding protein and showed that active calcium transport was linearly dependent on calbindinD_{9k}, an intestinal calcium binding protein, concentration. They also tested the affinity of calcium and calbindinD_{9k} on calcium absorption and showed that physiological affinity is optimally programmed. Slepchenko and Bronner (Slepchenko and Bronner, 2001) developed a mechanistic model to prove the coexistence of two mechanisms of calcium entry in the rat duodenum. The model was able to fit experimental data of calcium absorption that varied with calcium load and proposed the coexistence of two calcium channels: carrier mediated flux at low luminal calcium concentrations and channel like flux at high luminal calcium concentrations. Moreover, the linear dependence of maximum calcium transport on calbindinD_{9K} content was simulated using the model, which is in line with experimental data.

Even though the above models are notable achievements in calcium absorption modeling, there are some limitations. The above models did not explicitly include the action of vitamin D although its effect was literally considered. As vitamin D is known to influence all 3 steps in calcium absorption (Perez et al., 2008), formulating the explicit function for vitamin D can be our next aim. Also, the above model assumed that intracellular diffusion was the rate-limiting step in active calcium transport. However, it is now believed that calcium entry is the rate-limiting step (Hoenderop et al., 2005). Finally, the above

Table 1. Factors that influence calcium metabolism.

Systems	Regulating factors	References
Endocrine system	PTH	(Cioffi et al., 2000; Shrestha et al., 2010)
	Vitamin D	(Bouillon et al., 2003; Dawson-Hughes, 1996)
	Sex steroid hormone	(Compston, 2001; Syed & Khosla, 2005)
	Insulin-like growth factor-1	(Hill et al., 2008)
Genetics	Age	(Wastney et al., 1996; Weaver et al., 1995)
	Gender	(Wu et al., 2010)
	Race	(Wigertz et al., 2005)
Environment	Diet (Nutrient)	(Heaney et al., 1999; Weaver, 2008)
	Exercise	(Doty & Seagrave, 2000)
	Disease (ex. Obesity)	(Shapses & Riedt, 2006)

models may not be useful when modeling whole calcium homeostasis because of the differences in time frame. For example, intracellular diffusion is on a microsecond time frame, while calcium homeostasis is modeled on an hourly-basis. Thus, as modeled in the study by Raposo et al. (2002), it is effective to use a function that integrates the 3 steps into one and includes the regulatory action of vitamin D.

Urine calcium excretion modeling

Renal calcium excretion is the important calcium excretion route. Although the models that study whole calcium homeostasis include a function for urine calcium excretion (Hurwitz et al., 1987; Peterson & Riggs, 2010; Raposo et al., 2002), it has been less frequently modeled compared to other calcium metabolic processes because the mechanism is still poorly understood.

In 1979, Allen et al. (Allen et al., 1979) estimated re-absorbed calcium as filtered calcium minus measured urine calcium, and used glomerular filtration rate (GFR) to estimate filtered calcium. This suggests that urine calcium excretion can be modeled as a function of GFR, ionized serum calcium and urine calcium. In whole calcium homeostatic models (Hurwitz et al., 1987; Raposo et al., 2002) a term that denoted renal threshold was employed to model urine calcium excretion and was designed to be controlled by regulators (PTH). In the most recent model by Peterson & Riggs (Peterson & Riggs, 2010), both concepts were combined to evaluate the calcium homeostatic response arising from altered GFR conditions.

Recently, researchers suggest that the mechanism of renal calcium re-absorption is very similar to intestinal absorption because both processes involve epithelial cells (Hoenderop et al., 2005). Also, urine calcium excretion is determined by the feedback action of serum calcium through PTH (acting on renal threshold) and vitamin D (affecting re-absorption). Therefore, it is logical to combine renal calcium filtration (controlled by GFR, threshold and PTH), and re-absorption (using the same type of function used in calcium absorption modeling) in order to develop a model for urine calcium excretion.

Bone turnover modeling

Calcium homeostasis involves bone as the major source of calcium. Consequently, bone turnover (or remodeling) is closely associated with calcium metabolism. Herein, we introduce a few selected mechanistic models for bone metabolism in terms of study objectives, dynamic functions and main regulatory systems. We focus on the model that is capable of explaining bone remodeling in terms of cellular interactions and regulations.

Because bone formation and resorption are the results of osteoclasts (OC) and osteoblasts (OB), their cellular interactions have been a target for mechanistic modeling (Kroll, 2000; Komarova et al., 2003; Rattanakul et al., 2003; Lemaire et al., 2004; Komarova, 2005). Largely, two types of dynamic functions have been used in cell-level models for bone remodeling; 1) power function (Komarova et al., 2003; Komarova, 2005; Ayati et al., 2010) and 2) mechanistic equations (Kroll, 2000; Lemaire et al., 2004; Pivonka et al., 2008, 2010; Rattanakul et al., 2003). Power function is relatively simple, and well predicts the cyclic nature of bone remodeling. However, as regulators are lumped into power terms the model cannot explain the effect of a specific regulator. In contrast, mechanistic equations are able to account for the specific regulatory action (e.g., the effect of PTH on OB and OC). However, this demands the model to have a complex structure and is computationally expensive.

We found 3 notable power function-models for bone cell dynamics. Komarova (2005) and Komaorva et al. (2003) constructed a model of OB and OC dynamics using power law approximation. Power terms were representatives of autocrine and paracrine actions by regulators such as RANKL, OPG, TGF-β and IGF-1. The model simulated different modes of cellular dynamics with respect to autocrine and paracrine factors, and predicted a change in bone mass in response to OB and OC population dynamics. They showed that the regulation of OC by autocrine factors is the largest determinant of the dynamic behavior (Komarova et al., 2003), and the PTH effect on bone varied with type of PTH administration (amplitude and duration) (Komarova, 2005). In 2010, Ayati et al (2010) used the model by Komarova to investigate the dynamic patterns of model simulation in normal and myeloma bone disease. The model predicted stable oscillation in OB and OC population in normal bones, while unstable oscillation was shown in those with myeloma disease. They applied the model to propose the optimal therapeutic scheme in the myeloma case.

Alternatively, there are a few notable attempts that use mechanistic equations to model bone cell dynamics. In 2000, Kroll (2000) developed a mathematical model for OB and OC differentiation in bone, which accounted for the temporal effect of PTH in bone turnover. The model calculated the ratio of OB to OC, determining net bone formation or resorption, with respect to the type of PTH administration (constant infusion vs.

pulse) and frequency of PTH pulse. The model simulation agreed to the paradoxical effect of PTH on bone; net bone loss with continuous administration, and net bone formation with intermittent administration. Rattanakul et al. (2003) developed a simpler model than that by Kroll, and explained the same patterns in PTH action, i.e., the paradoxical effects according to type of administration. They further predicted that OB and OC population varied with duration and length of interval of estrogen treatment (i.e., pulsatile administration). They used parametric changes to represent different regulatory status for PTH and estrogen. Regarding the complex network of cellular control of bone remodeling, Lemaire et al. (2004) proposed a mathematical model to explain the interactions between OB and OC. The basis of this model is that the stages of cellular differentiation control cell population. This model integrated the most important aspects of bone remodeling including tight coupling between OB and OC, the catabolic effect induced by PTH, and the action of RANK-RANKL-OPG system and TGF-β on regulating bone differentiation. The model simulation agreed well with experimental results from literature. Ultimately, the model was used in simulating metabolic diseases and in evaluating possible routes for therapeutic regimes. Pivonka et al. (2008) improved the above model by Lemaire et al. (2004). They used the model to propose the optimal model structure with emphasis on expression of OPG and RANKL on osteoblastic cell lines. Relative changes in bone volume were predicted by the developed model as a function of RANKL/OPG expression profiles. They further investigated the role of RANK-RANKL-OPG system as it is essential in simulating bone remodeling (Pivonka et al., 2010). The model predicted that catabolic bone disease (e.g., osteoporosis) was most affected through the RANK-RANKL-OPG system. They used the model in indentifying virtual therapeutic strategies for catabolic bone diseases associated with defects in the RANK–RANKL–OPG system.

The above introduced studies are the most cited studies which have established the mechanistic models of bone cell dynamics and bone turnover (remodeling). Beside the models introduced, there are alternative models for bone metabolism. For example, Wimpenny & Moroz (2007) recently proposed a model explaining the bone turnover cycle with an osteocyte feedback control loop & Martin (1994) modeled calcium diffusion and precipitation in bone mineralization. However, few models have combined calcium metabolism and bone turnover predicted by bone cell population. Therefore, it is worthwhile to develop a model that predicts bone resorption and formation as a result of cell-level regulation of bone.

Whole calcium homeostasis modeling

Calcium homeostasis is an essential mechanism for human health. It involves effective mechanisms to regulate calcium metabolism in response to physiological perturbations so that humans maintain normal serum calcium levels. Several models have modeled calcium homeostasis to predict calcium metabolism with respect to disturbance, to explain its regulatory mechanisms, to apply the model in a clinical setting to evaluate calcium and bone metabolic diseases.

In the early 70s, Powell (1972), and Powell & Valentinuzzi (1974) presented a theoretical quasi-linear model of calcium homeostasis based on qualitative physiological information. They used the dual-feedback regulatory loop of PTH and calcitonin as a functional module in controlling plasma calcium. The model aimed at describing variations in plasma calcium, PTH and calcitonin in response to input stimuli and suggested some experiments to validate the model. Hurwitz et al. (1983) developed a mathematical model of calcium homeostasis in chickens, which was explained by a feedback control loop of plasma calcium, 3 control subsystems (bone, kidney, and intestine) and 2 main regulators (PTH, and vitamin D). They used either their own experiments or published data to estimate model parameters. They used the model to simulate changes in serum calcium and regulators, and calcium flow in subsystems at different calcium intakes. They imposed growth to the model and predicted oscillations in plasma calcium concentration and regulators in response to the rate of growth (Hurwitz et al., 1987a; Hurwitz et al., 1987b). El-Samad et al. (2002) showed that integral feedback control well explained dynamics in calcium homeostatic response in dairy cows and used it to develop a dynamic model. The model successfully simulated the tight maintenance of serum calcium concentration even when extreme perturbation occurred to the calcium homeostasis system. The model was then applied to examine parturient hypocalcemia in dairy cows, demonstrating that loss of modulation (e.g., abnormal model parameter values) caused a disruption in maintaining plasma calcium concentration. In 2002, a minimal but completed mathematical model for calcium homeostasis was developed by Raposo et al. (2002). This study exhibited an example of the standard model developing procedure; starting stepwise from the kinetic description of calcium metabolism, and then adding feedback/feedforward regulatory branches by calcium, PTH and vitamin D. Model parameters and variables were adjusted to literature values or accepted biochemical patterns in calcium homeostasis so that the model simulation fit published data. This model was able to predict the response of the calcium homeostasis system to

various perturbations such as infusion of calcium, PTH and vitamin D. Then, the model was used to simulate extreme cases (e.g., renal failure and hypo/hyper-calcemia), suggesting that models can be a useful tool to examine calcium metabolic diseases. A study by Wastney et al. (2005) proposed a dynamic model of short-term calcium homeostasis in healthy men. They inserted dynamic functions of calcium and PTH metabolism into a previous calcium kinetic model and fit the previous citrate experimental data (Grant et al., 1990) to develop a dynamic model. As a result, the model predicted a dynamic change in serum calcium and PTH in response to citrate infusion. In 2009, a pharmacokinetics/pharmcodynamics (PK/PD) approach was used in developing a mechanistic model of calcium homeostasis in rats and humans (Abraham et al., 2009). This PK/PD model focused on PTH metabolism and its regulatory action on calcium turnover in plasma, and fit actual data sets obtained either by literature or pharmacokinetic experiments in rats. This model demonstrated the interspecies difference of sensitivity to PTH stimulation in rats and humans, and proposed a model-based tool to suggest clinical experiments for the development of new therapeutic drugs targeting this system. Another model-based study also focused on PTH response in calcium homeostasis in humans based on a specifically designed experiment (Shrestha et al., 2010). The developed model included mathematical formulations for PTH metabolism in order to explain the response of plasma PTH with respect to acute changes (in minute) in plasma calcium levels. They demonstrated that two pools of PTH (PTH in plasma and parathyroid gland) are necessary for fast dynamics of the Ca-PTH axis and asymmetric nature of PTH secretion function. Despite that the above 2 models do not model calcium metabolic pathways, they provide information of the dynamics in Ca-PTH regulation, which is useful in whole calcium homeostasis modeling. Most recently, a complete model that includes both calcium homeostasis and bone biology has been proposed for humans (Peterson & Riggs, 2010) based on two previous notable models (Lemaire et al., 2004; Raposo et al., 2002). The same types of mathematical functions (Hill-type function, with different parameter values obtained from various literatures) were iteratively used to describe components (e.g., calcium metabolic pathways and regulators) in calcium/phosphate metabolism associated with PTH, vitamin D and bone remodeling markers. As a result, a complex and large-volumetric model was developed. This model was able to quantify changes in calcium homeostasis and bone remodeling in response to physiological perturbations (e.g., PTH infusion) depending on timescale (how fast and long) and magnitude (how much). The authors highlighted the use of model-based analyses in predicting disease progression and/or therapeutic intervention.

The above introduced models attempt to fuse mechanistic modeling with physiological phenomena related to calcium homeostasis/metabolism. The unique characteristics of the models provide an opportunity to apply them to calcium metabolism research according to the purpose of study and target systems. For example, we can use them to develop a new model to differentiate adolescent and adult calcium metabolism, which has never been reported.

Mechanistic modeling has proposed a new window to study biosystems including calcium metabolism. In this study, a few notable mechanistic models for calcium metabolism were selected and shortly reviewed to provide the minimal guideline for future model-based study. The models in this review propose possibilities of using the model-based approach to examine calcium metabolism, e.g., uncovering unknown mechanisms, to facilitate design of experiments, and to utilize the model in testing dietary source of calcium. For example, a comprehensive model which integrates published models may be used to uncover poorly understood mechanisms, such as the regulatory system of calcium metabolism in adolescents, and to design clinical experiments to characterize calcium related diseases for population and individuals. This may become possible when more experimental data is obtainable with progressions in experimental approaches. In addition, since calcium is mainly obtained from dietary food, functional food or dietary supplement has been studied for past decades. With this point of view, developed models or future modeling work may be an effective tool for testing food system as a calcium provider. Besides the prospective studies on calcium metabolism, this review illustrates how the modeling is used to analyze the non-engineering biosystem so that the modeling is further applicable to various agricultural and food systems.

Acknowledgments

This study was financially supported by research fund of Chungnam National University in 2012. Thank you for Dr. Connie Weaver and Dr. Meryl Wastney in Purdue University for their great guidance and review of this study.

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