HOSTED BY

ELSEVIER

CrossMark

Available online at www.sciencedirect.com

ScienceDirect

Food Science and Human Wellness 5 (2016) 8–16

Food Science and Human Wellness

www.elsevier.com/locate/fshw

Calcium intake, calcium homeostasis and health

Fan Pu [a], Ning Chen [b,**], Shenghui Xue [a,*]

[a] *La Jolla Institute of Allergy & Immunology, La Jolla, CA 92037, USA*

[b] *Hubei Exercise Training and Monitoring Key Laboratory, Hubei Provincial Collaborative Innovation Center for Exercise and Health Promotion, College of Health Science, Wuhan Sports University, Wuhan 430079, China*

Received 10 January 2016; received in revised form 24 January 2016; accepted 24 January 2016

Available online 1 February 2016

Abstract

Calcium, as the most abundant mineral in human body, is involved in many physiological and pathological processes. Here, we reviewed the key mechanisms of calcium homeostasis, including calcium sensing receptor regulation, intestinal calcium absorption, renal calcium reabsorption and bone calcium resorption. We further discussed the roles of dietary calcium and vitamin D in diseases associated with dysfunctional regulation of calcium. However, the over-dosed consumption of calcium could increase the risks for a series of diseases, such as kidney stone, myocardial infarction and stroke.

Keywords: Calcium; Homeostasis; Calcium sensing receptor; Dietary calcium; Vitamin D

1. Introduction

Calcium is the 5th of the most abundant elements in the earth crust and is also the most abundant mineral in human body. The human body contains approximately 1 kg of calcium with more than 99% deposit in the bone in the form of calcium phosphate [1]. Through interacting with numerous proteins distributed in different cellular compartments, calcium is involved in a large amount of aspects of life, such as muscle contraction, enzyme activation, cell differentiation, immune response, programmed cell death and neuronal activity [1–11]. Such broad functions are maintained by tightly controlled calcium concentration in extracellular fluid and cellular compartments. The concentrations of calcium in blood and extracellular fluid are usually maintained at 1–2 mmol/L, while the concentration of intracellular calcium at resting state is maintained at 100 nmol/L or less by calcium ATPase, channels, and exchangers located in plasma membrane and endoplasmic reticulum (ER) membrane [2,12]. During the signaling process of calcium, the concentration of intracellular calcium is increased to approximately 100 μM, which triggers calcium signaling through the activation or deactivation of an array of calcium-binding proteins. In addition, pathogens, such as bacteria and viruses, can hijack calcium signaling to benefit their own life cycles including invasion, replication and proliferation [13,14].

Due to the regulation by calcium sensing receptor (CaSR) located in the parathyroid gland, the concentration of extracellular calcium is dedicatedly maintained by intestinal absorption, kidney reabsorption and bone resorption/formation. The miscommunication of these processes is responsible for calcium-related diseases, such as osteomalacia [15,16]. Americans at all ages, however, do not consume enough dietary calcium compared with the recommendations by the Institute of Medicine [17]. The deficiency of calcium could cause various diseases, such as osteoporosis. In this paper, we will review the key factors controlling calcium homeostasis and further discuss the diseases associated with the dysfunctional regulation of calcium and vitamin D.

* Corresponding author at: La Jolla Institute of Allergy & Immunology, La Jolla, CA 92037, USA. Tel.: +1 404 4837052.

** Corresponding author at: Hubei Exercise Training and Monitoring Key Laboratory, Hubei Provincial Collaborative Innovation Center for Exercise and Health Promotion, College of Health Science, Wuhan Sports University, Wuhan 430079, China.

E-mail addresses: nchen510@gmail.com (N. Chen), xuesh15@hotmail.com (S. Xue).

Peer review under responsibility of Beijing Academy of Food Sciences.

http://dx.doi.org/10.1016/j.fshw.2016.01.001

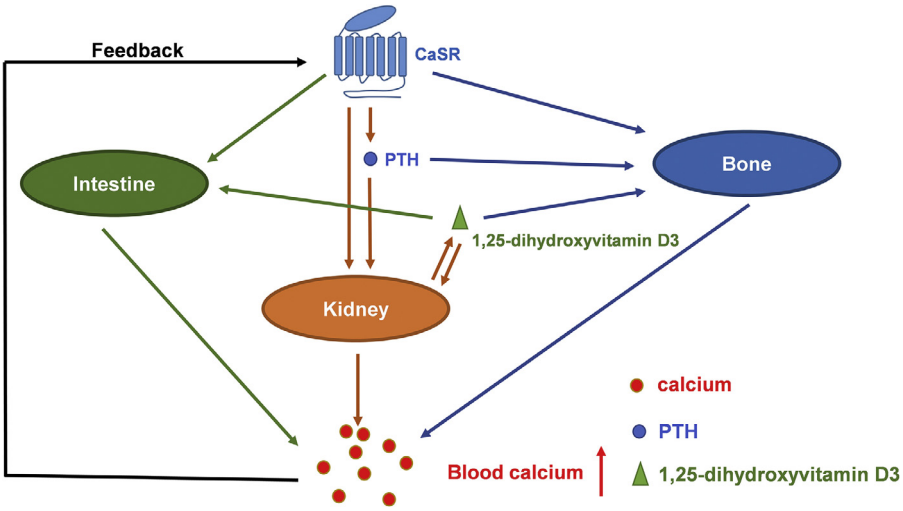

Fig. 1. Regulation of calcium homeostasis by CaSR. The decrease of blood calcium level activates CaSR in parathyroid gland, which further promotes the secretion of PTH. PHT increases blood calcium level by the direct activation of calcium reabsorption in kidney and calcium release in bone. PHT also promotes the production and secretion of 1,25-dihydroxyvitamin D3 in kidney cells. 1,25-Dihydroxyvitamin D3 regulates the intestinal calcium absorption, kidney calcium reabsorption and bone calcium release. CaSR expressed in bone, kidney and intestine cells are also involved in the regulation of calcium homeostasis.

2. Molecular mechanism of extracellular calcium homeostasis

Extracellular calcium homeostasis is mainly controlled by three physiological modes, including intestinal calcium absorption, renal calcium reabsorption, and bone formation/resorption [18], which is mainly regulated by CaSR through the modulation of parathyroid hormone (PTH), calcitonin and 1,25-dihydroxyvitamin D3 secretion (Fig. 1) [19–21].

2.1. Calcium uptake in intestine

Intestine is the major organ responsible for calcium uptake. In general, calcium from diets is absorbed by intestine through two pathways including transcellular absorption and paracellular transport of calcium (Fig. 2). In duodenum of intestine, transcellular absorption is responsible for 80% calcium uptake in low-calcium diets and less than 10% calcium uptake in high-calcium diets [22]. Certain calcium channels, intracellular calcium-binding proteins and calcium pumps are responsible for transcellular absorption of calcium. This process is initiated by transient receptor potential vanilloid type 6 (TRPV6) channel, a transmembrane calcium selective channel located in the brush border side membrane responsible for calcium entry [23,24]. After calcium enters the cell through TRPV6 channel, calcium-buffering proteins bind to calcium and transport calcium inside the cell. At last, calcium is excluded out of the cell to blood vessels through plasma membrane ATPase 1b (PMCA1b) located in the basolateral membrane [25].

TRPV6 channel belongs to the transient receptor potential (TRP) super family that contains 6 different proteins. TRPV1-4 are non-selective cation channels activated by protons, lipids, and the changes of temperature, pressure and osmolarity. TRPV5 and TRPV6 are calcium selective channels involved in renal calcium reabsorption and intestinal calcium absorption, respectively [18,23,24]. TRPV6 is located in many types of cells, including the cells from intestine, prostate cancer and breast cancer [26–28]. The activation of TRPV6 in the brush border membrane of intestine is the first step of calcium entry. This protein contains long intracellular N-terminal and C-terminal domains and 6 putative transmembrane domains. TRPV6 is also modified through N-linked glycosylation [29]. Different from TRPV1-4, TRPV5 and TRPV6 are constitutively activated [24,30]. The functional TRPV5 and TRPV6 channels are tetramers. The expression levels of TRPV6 in intestine and many types of cancer cells are regulated by vitamin D. TRPV6 is also induced by low calcium diets or at the time of weaning [31,32]. Transgenic mice with TRPV6 overexpression can result in hypercalcemia

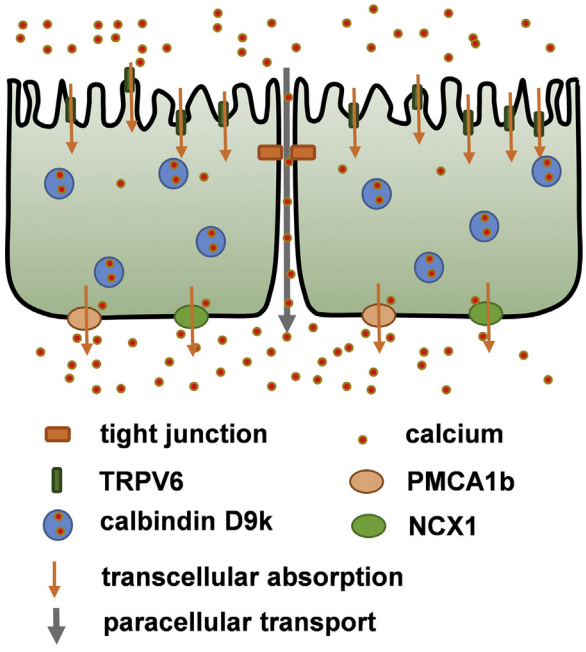

Fig. 2. Intestinal calcium absorption by transcellular absorption and paracellular transport.