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Review article

Calcium and anti-aging medicine.

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Abstract

Calcium (Ca) plays a significant role in human cells and tissues. However, the intake of Ca and vitamin D is not fully sufficient in Japan and a large number of Japanese people are found not to meet the dietary reference intakes. Ca is a major component of bones and teeth. Ca deficiency is a causative risk factor for bone aging, such as decline of bone mineral density and osteoporosis. Intracellular and extracellular concentrations of Ca ions (Ca^{2+}) are properly controlled and there exists an extracellular concentration gradient of Ca^{2+} ten thousand times greater than intracellular. Intracellular Ca is stored in the endoplasmic reticulum and sarcoplasmic reticulum and is released by stimulation, such as when muscular contraction, release of neurotransmitters, and exocytosis of hormones are performed. Furthermore, Ca plays an important role in skin homeostasis. Ca concentration gradient also exists in the epidermis and is in the greatest concentration immediately below the stratum corneum. This contributes to the formation of a skin barrier. Keratinocytes, which are produced in the stratum basale, traverse to the surface layer of the skin via calcium gradient in the process of differentiation and maturation. Thermosensitive transient receptor potential (TRP) channel is involved in sensibility of the skin. The concentration of Ca^{2+} is regulated by Ca^{2+} channel, and the sensibility for stimuli alters. Age-related biological changes considerably influence these systems. The attenuation of Ca absorption ability induces chronic Ca deficiency. The loss of Ca in bones and the increase of parathormone (PTH) secretion in parathyroid gland cause ectopic calcification. Structural changes in component protein of channels, which are induced by aging and glycative stress, trigger Ca leak. Consequently, Ca^{2+} concentration gradient is attenuated and intracellular Ca^{2+} concentration is increased. The following measures are required to maintain homeostasis of the body with a stable Ca^{2+} concentration gradient: 1. Avoidance of deficient Ca intake. 2. Prevention of structural protein modification in Ca^{2+} channels such as countermeasures for glycative stress.

KEY WORDS: Ca^{2+} concentration gradient, Ca^{2+} channels, parathormone, skin barrier, transient receptor potential (TRP) channels, Ca deficiency

Introduction

Inadequate calcium intake is frequently found in Japanese dietary habits. Calcium, which is ingested with food, is taken into the body via the process of digestion and absorption through the intestine. Calcium, which is dissolved as calcium ion (Ca^{2+}) in extracellular fluid and also exists in cytoplasm and cell organella, plays a significant role in all cells in the body [1]. Functions of calcium in cells are diversified as follows: Signal transmission, the regulation of enzyme activity, the control of apoptosis, the exocytosis of neurotransmitters and hormones, and the contraction of muscle fibers. These calcium metabolisms influence lifestyle such as exercise and eating habits, and age-related physical changes. Contrarily, age-related calcium metabolic disorders appear as a phenotype such as osteoporosis, blood vessel calcification and decreased muscular contraction power. This paper describes the effects of calcium diabolism on the whole body and discusses the prevention separately with three items in the degrees of aging, risk factors of body aging and skin aging.

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Ingestion and absorption of calcium

Calcium, which is necessary for physical activities, is provided by food ingestion and intestinal Ca^{2+} absorption occurs through the small intestinnal mucosal membrane as calcium changes into Ca^{2+} under the effects of gastric acid. Calcium absorption is reduced due to the infection of *Helicobacter pylori*, atrophic gastritis, ingestion of gastric secretion inhibitor, and decline of gastric acid secretion, hypoacidity or achlorhydria which are induced by aging. Therefore, calcium reference intake per day has been stipulated by the Ministry of Health, Labour and Welfare as the amount of calcium intake is larger in the elderly than in the young [2]; 650 mg between 30 – 49 years old, 700 mg between 50 – 69 years old and 750 mg over 70 years old. The average amount of calcium intake in Japan is 500 – 600 mg and a large number of people do not meet the desired value. The allowable upper limit value is 2,500 mg and risk factors of excessive ingestion increase for arrhythmia, calculus and other conditions.

The measurement of calcium urine collection is the most effective index marker to assess calcium intake. The content of calcium in hair decreases along with aging [3] and there is a possibility that it reflects on the age-related reduction of calcium intake or absorption ratio.

For calcium absorption, vitamin D plays an essential role [4]. Vitamin D is either food derived or biosynthetic. Food sources that provide Vitamin D are lipid-rich meat, fish and eggs as well as mushrooms. Recommended dietary allowance for Vitamin D is 600 IU for adults between 51 – 70 years old and 800 IU over 71 years old, which indicates that the elderly are prone to vitamin D deficiency. Synthesis of vitamin D occurs as follows: 7-dehydrocholesterol is converted into previtamin D3 in the skin due to ultraviolet light. In the liver, 25-OH vitamin D is produced. This is metabolized to active type $1\alpha,25(OH)_2$ vitamin D in the kidney. This active vitamin D promotes the absorption of calcium in the intestine. Previtamin D3 formation is decreased in the skin along with aging and active type vitamin D formation is decreased due to the age-related reduction of renal function or chronic kidney disease (CKD).

Ca^{2+} concentration gradient via cell membrane

Ca^{2+} concentration in the body is elaborately regulated in large part by the parathormone (PTH) and vitamin D so that Ca^{2+} signaling plays a diversified role for vital phenomena (***Fig. 1***). Ca^{2+} concentration gradient exists via cell membrane, where extracellular Ca^{2+} concentration is 10^{-4} – 10^{-3} M and intracellular Ca^{2+} concentration is as low as 10^{-8} – 10^{-7} M (***Fig. 2***) [5]. Ca^{2+} channel [6] and Ca^{2+} pump [7], which are proteins, play a vital role in maintaining the homeostasis of the organism, regulating dynamics of intracellular Ca^{2+}.

Voltage-dependent calcium channel (VDCC) is distributed in various cells such as the nerve and the muscle and is involved in the contraction of skeletal muscle, smooth muscle and cardiac muscle, the sinus rhythm of cardiac pacemaker, and the release of neurotransmitters. Ion channel receptors are as follows: Inositol trisphosphate (IP3) receptor exists in endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR). Ryanodine receptor exists in T tube. Capacitative Ca^{2+} channel exists in cell membrane. Ca^{2+} channels consist of several subunits. When subunit proteins have structural changes such as glycative modification or bonding becomes loose, a Ca^{2+} leak is induced (***Fig. 3***) [8, 9]. Consequently, intracellular Ca^{2+} concentration increases and Ca^{2+} concentration gradient decreases, which lowers cell functions.

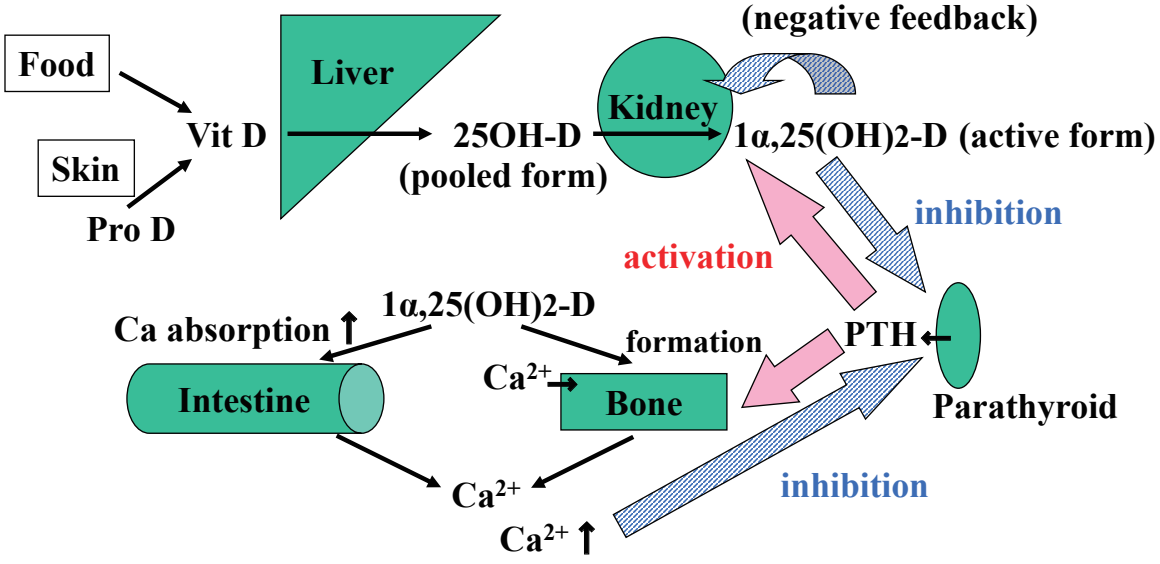

Fig. 1. **Calcium metabolism regulated by vitamin D and parathormone.**

Ca, calcium; Vit, vitamin; PTH, parathormone.

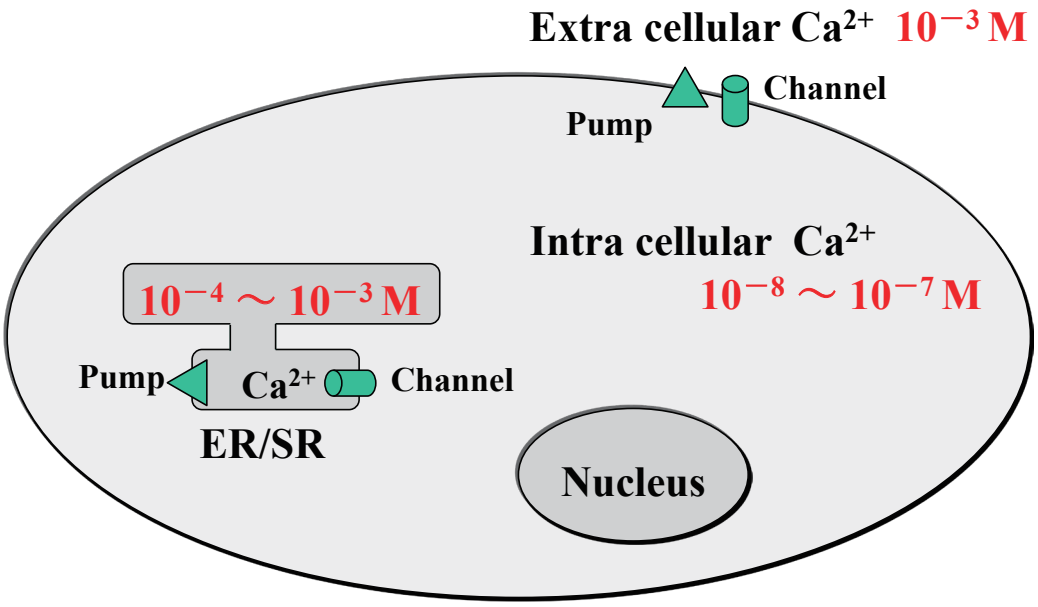

Fig. 2. **Calcium concentration gradient in the cells.**
ER, endoplasmic reticulum; SR, sarcoplasmic reticulum; Ca, calcium.

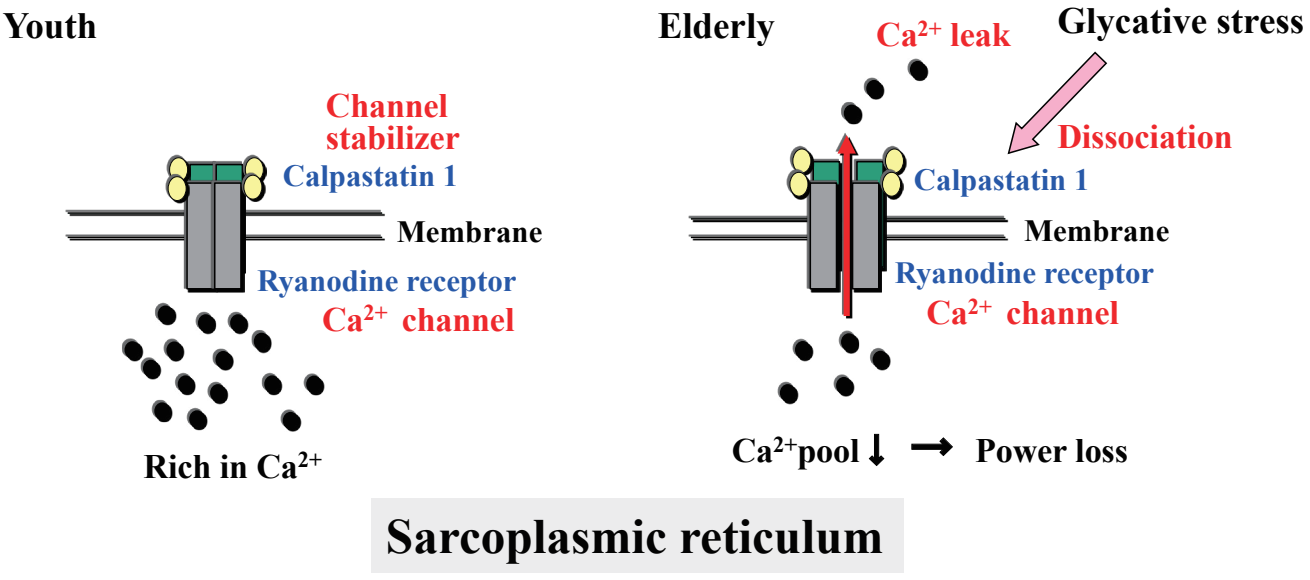

Fig. 3. **Calcium leak from Ca^{2+} channels in the elderly.**
Ca, calcium.

Ca^{2+} pump is a protein that is responsible for the active transport of calcium utilizing ATP energy against the concentration gradient. Ca^{2+} pump in SR consists of one peptide chain with approximately 110 k of molecular weight, where 994 amino acid residues are connected [7]. Conjugated protein, in which the α-klotho gene is involved, exists for active Ca^{2+} transport. The α-klotho gene was identified as a gene of a mutant mouse that had similar phenotype to human aging symptoms; the gene notably decreased in expression [10]. The α-klotho protein functions as a control factor for electrolyte metabolism and immediately responds to the decline of Ca^{2+} concentration. Subsequently, the α-klotho protein accelerates the recruitment of Na^+ and K^+-ATPase to the cell surface. The changes in the generated Na^+ concentration gradient and changes in membrane potential induce calcium reabsorption in the kidney, Ca^{2+} transport of liquor cerebrospinalis via the vascular tunic, and PTH secretion in the parathyroid [10]. Accordingly, an α-Klotho gene knockout mouse shows osteoporosis and ectopic calcification due to the calcium loss and secondary PTH supersecretion.

Chronic calcium deficiency stimulates PTH secretion in the parathyroid. Ca^{2+} mobilization from bone is increased (accelerated bone turnover) and Ca^{2+} concentration in ER is increased (decreased concentration gradient). Consequently, cell activities are adversely affected (***Fig. 4***) [11, 12]. Excessive calcium mobilization leads to calcium deposition in nerve or vessel walls rather than in bones. Excessive PTH adversely affects not only bones but also kidney, cranial nervous system, cardiovascular system, lungs, muscle, skin, lymphocyte, genitalia, and endocrine system.

The control system of intracellular Ca^{2+} activity is deteriorated in aged cells. For instance, aged egg cells have altered calcium oscillation; calcium oscillation is referred to as repetitive Ca^{2+} increases at fertilization with Ca^{2+} release from ER of the egg cell. For an aged egg cell, in comparison with a young egg cell, the amplitude of calcium oscillation is small and high-frequency abnormal calcium oscillation occurs. This tends to induce disorders in fertilization and when an egg is fertilized, embryonic development tends to deteriorate [13]. We assume the reason is that Ca^{2+} in ER decreases in aged cells. In addition, the number of mitochondria decreases in aged egg cells. The mitochondrion, which is a cell organelle that is contained in a eukaryotic cell, plays prominent roles for biological activities such as energy production, ATP production, production of reactive oxygen species (ROS), control of apoptosis and regulation of intracellular Ca^{2+} concentration [14].

Degree of aging and calcium

a) Bone age

After the growth period, bone mineral density is reduced, and bone trabeculae is deteriorated. The progress of these symptoms leads to osteoporosis [11]. This is bone aging. In the body, 99% of calcium is stored in bones and teeth. Bone mineral is comprised mainly of calcium (Ca) and phosphorus (P). Bones are maintained by the mechanism

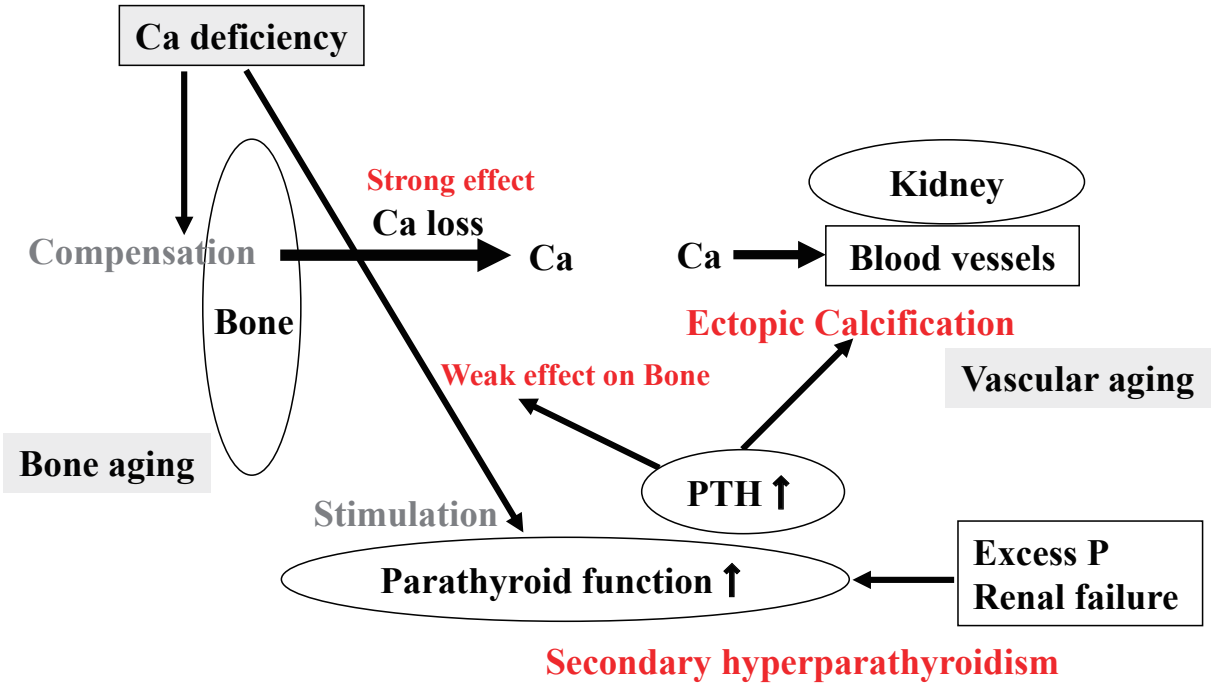

Fig. 4. **Influence by chronic calcium deficiency.**

Calcium deficiency causes Ca loss from the bone as compensation and stimulates parathyroid. PTH causes ectpic calcification while the bone calcification effect is weak under the chronic Ca deficiency condition. Ca, calcium; PTH, parathormone.

of bone remodeling; bone formation by osteoblasts and bone resorption by osteoclasts. For bone formation, calcium is deposited in bones and for bone resorption, calcium is lost from bones. Bones function as a reservoir for calcium. Chronic calcium deficiency induces calcium mobilization from bones (accelerated bone turnover). Consequently, bone mineral density is reduced. Furthermore, Calcium deficiency stimulates PTH secretion from the parathyroid. PTH promotes vitamin D activation and increases the quantity of calcium absorption in intestine. Chronic calcium and vitamin D deficiency is a great risk factor for bone aging [15].

There has been increasing attention on a newly discovered function of bones lately. Fibroblast growth factor 23 (FGF23), which is produced in bones, regulates the blood concentration of phosphorous [10]. It has been recognized until now that P is altered passively by the active alternation of calcium. However, FGF23, with the action on receptor Klotho-FGF receptor complex, inhibits P resorption in the renal proximal tubule and inhibits intestine P absorption via decreased blood $1\alpha,25\text{-}(OH)_2$ vitamin D. Therefore, blood P concentration is lowered by FGF23. Failure of FGF23 activity causes high-phosphorous blood disease accompanied by acceleration of P resorption, and acceleration of FGF23 activity causes hypophosphatemia. In chronic kidney disease (CKD), hyperphosphatemia is caused by failure of P discharge, and hypocalcemia is caused by failure of vitamin D activity.

b) Hormone age

Typical hormones that decrease along with aging are growth hormone (GH) / insulin-like growth factor-I (IGF-I) [16, 17], dehydroepiandrosterone-sulfate (DHEA-s) [18], melatonin [19], and sex hormones such as estrogen. IGF-I, as the second messenger of GH, is involved in cellular proliferation, protein synthesis, glycolipid metabolism and central nerve activity. The secretion of GH / IGF-I is reduced, when glycative stress is severe [20]. Research results of one-year GH administration to aged patients with osteoporosis, which is accompanied by the condition with low serum IGF-I, indicated that the bone density was significantly improved. Judging from this, it is recognized that GH promotes calcium deposition in bones [21].

IGF-I produces IP3 signaling molecules at the cell level, in cardiac muscle cells. IGF-I stimulates Ca^{2+} sensor proteins, which is designated as neuronal calcium sensor 1 (NCS-1), and IP3 receptor, which is an intracellular Ca^{2+} channel. Subsequently, intracellular Ca^{2+} concentration is increased. Excessive IGF-I stimulation contributes to gene expressions such as cardiac hypertrophy [22].

Exocytosis of peptide hormones such as GH is triggered by Ca^{2+} release from Ca^{2+} store in ER and successive intracellular Ca^{2+} elevation [23-25]. Accordingly, an extremely deficient state of calcium hinders hormone secretions. Pubertal females with deficient calcium intake are recognized to have the decrease in adrenal androgen secretion, which can lead to the decline of bone density and retardation of pubertal development.

DHEA-s decreases with aging and is involved in varied age-related regressive changes [13]. DHEA-s, which is adrenal androgen, contributes to the increase of bone mass via the conversion to estrogen and testosterone in the peripheral tissues (intracrine regulation) [26]. In bone remodeling of climacteric females, estrogen secretion from the ovary decreases and control of osteoclasts is removed. Therefore, bone absorption is activated, and calcium is lost in bones. Climacteric females, in large part, have blood estradiol concentration under the value for sensitivity of detection (10 pg/mL). However, some estradiol has been detected in climacteric females, as it is converted from adrenal-gland-derived DHEA-s.

Furthermore, secretion of melatonin, which is related to sleep, also decreases with aging [19]. Melatonin is deeply involved in bone metabolism. This is shown in chickens with removal of the pineal gland, where scoliosis is induced. Melatonin receptors are also distributed in the bone tissues and show the inhibition of bone absorption. However, this is not a direct action on osteoclasts but an indirect action via osteoblasts. Careful attention to hormone balance is required to maintain proper calcium metabolism.

c) Vascular age

Vascular aging induces regressive changes and results in arteriosclerosis, which is characterized by the loss of elasticity and degradation of the arterial walls. There are three main pathological forms of arteriosclerosis: atherosclerosis, Mönckeberg's arteriosclerosis, and vascular fibrosis or arteriolosclerosis (***Fig. 5***).

Depending on vascular location, blood vessel diameter, and individual risk factors, lesion location and morphology of arteriosclerosis differ. The above-mentioned pathological forms have complex interactions in arteriosclerosis in large part. Atherosclerosis is induced due to atheroma. An atheromatous plaque, which consists of cholesterol, inflammatory cells and others, is deposited in the tunica intima. LDL cholesterol is modified due to oxidation and glycation, and macrophage excessively takes it in with phagocytic function via scavenger receptors. In this manner, foam cells are formed. Dead foam cells are attached to the arterial wall, which results in a core of atheroma [27, 28].

Mönckeberg's arteriosclerosis, where calcium deposits are in the muscular middle layer of the walls of arteries, are found frequently in the aged. Arteriolosclerosis, where excess fibrous connective tissues are formed (fibrosis), is characterized by the narrowing lumen, and is a cause of high blood pressure and cerebral hemorrhage. In the large artery, aorta thoracica, the fragmentation, redistribution and minimization of elastic fibers occurs, the elastic layer is notably thickened, and calcium binding capacity with elastin from elastic fiber protein increases.

Vascular wall calcification is a major factor of arteriosclerosis. The rise in calcium-phosphate product value affects calcium metabolism in bones and blood vessels, as P rise induces hyperparathyroidism and calcium rise induces low turnover of ossification. Vascular wall calcification is not merely a passive mineral deposit. Phosphorus (P) directly acts on the vascular wall cells via Na-dependent P transport mechanism, and induces the calcification of vascular wall, promoting apoptosis and differentiation of bones and cartilage cells [29, 30].

Hypercontraction of smooth muscles, which is induced by abnormal Ca^{2+} regulation in smooth muscles, is involved in disease states of hypertension. Excretion of Ca^{2+} into urine increases in patients with essential hypertension and a negative calcium balance is induced (hypercalciuria).

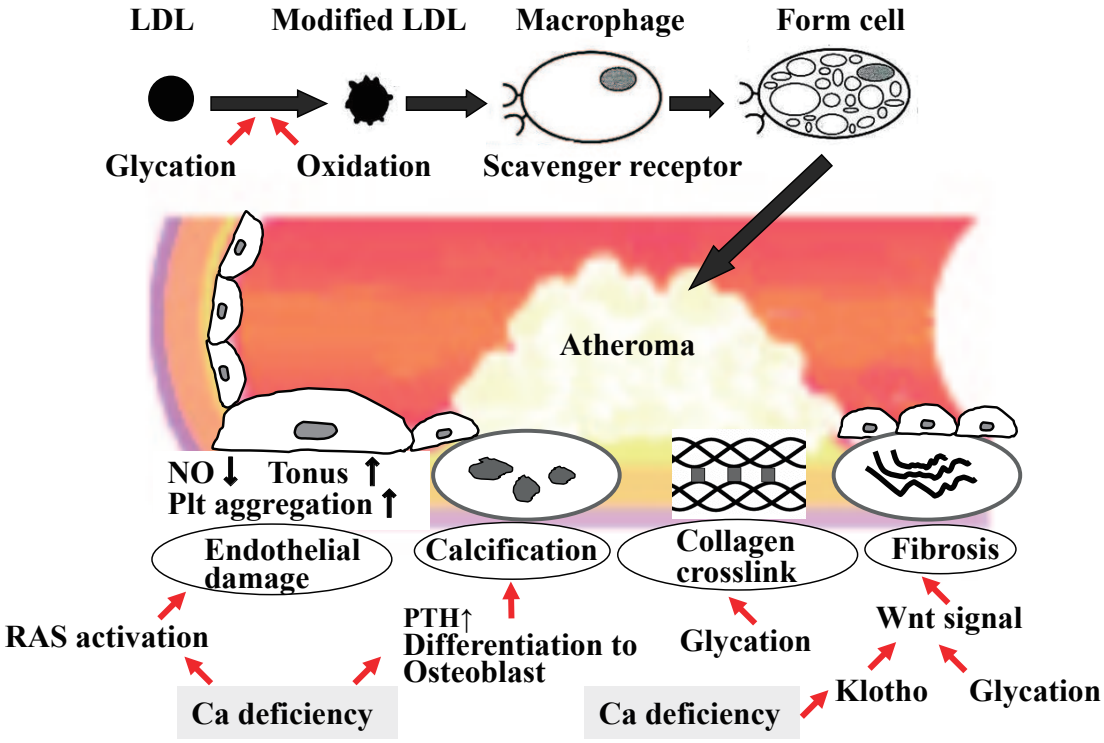

Fig. 5. **Arteriosclerosis and chronic calcium deficiency.**

LDL, low-density lipoprotein; NO, nitric oxide; Plt, platelet; RAS, renin angiotensin system; Ca, calcium; PTH, parathormone.

Thus, the patients with essential hypertension have a higher risk for urinary concrement. Furthermore, secondary promoted PTH secretion accelerates ectopic calcification. Paradoxically, chronic deficient intake of calcium contributes to calcification of blood vessels [31-33].

d) Neural age

Calcium metabolism is deeply involved in neural activity such as neural transmission. According to research results of food factors related to the onset of Alzheimer's disease, nutrient status of patients indicated that there is often significantly low intake of calcium and other nutrients such as omega-3 polyunsaturated fatty acid, vitamin C and carotene [34]. Hyperparathyroidism, which is accompanied by calcium dysbolism, presents myriad neurological symptoms in psychosomatic manifestations such as obsessive-compulsive neurosis, depressive psychosis, anxiety, phantasms and others [35]. As causative factors of cyclic psychosis (bipolar disorder), changes in intracellular information transmission as well as involvement of mitochondriagenetic polymorphism are mentioned [36]. Failures in calcium regulation due to abnormal mitochondria are causes of bipolar disorder.

Neural transmission is an elementary reaction of varied neural activities such as behaviors, learning and mental activities. The release of neurotransmitters is induced by the following: voltage-dependent calcium channel (VDCC) is activated by action potential, which reaches presynapse. Ca^{2+} dependent synaptic vesicle, which enters via the VDCC, is integrated with cell membranes [37, 38]. Efficient neural transmission requires functions of SNARE protein conjugate binding Ca^{2+} channel, and Ca^{2+} binding protein [39, 40]. It is indicated that due to Alzheimer's diseaseor aging, Ca^{2+} leaks occur from Ca^{2+} channels in nerve endings [9].

Alzheimer's disease is characterized by deposition of aggregates whose components are amyloid β (Aβ) and tau protein in the brain. In dendrites, which is a part of nerve cells, Aβ promotes the aggregation of metabotropic glutamate receptor 5 (mGluR5) in the synapse, and tau heightens the phosphorylation of N-methyl-D-aspartate (NMDA) receptor, as is recognized. As a result of these changes, binding of mGluR and NMDA is strengthened and calcium flows into nerve cells. Consequently, intracellular Ca^{2+}concentration rises [41]. The relationship between neural age and calcium is a key issue.

e) Muscle age

Along with aging, muscle mass decreases, muscular contraction power declines, and frequency of discomforts such as muscle cramps increase. Muscle fiber consists of slow twitch fibers and fast twitch fibers. With aging, mainly the fast twitch fibers decrease. Quantitative decline in muscle fiber is a major cause for muscular contraction power declines. There is, however, a possibility that muscular contraction mechanism is altered due to aging.

When skeletal muscle is stimulated by the motor nerve, muscle contraction occurs as follows: Ca^{2+} is released from SR via ryanodine receptor, which is an intracellular Ca^{2+} release channel. Ca^{2+} binds troponin. Conformational

alternation of tropomyosin occurs. ATP binding to myosin is induced. Myosin and actin interact, using sliding. This is a mechanism of muscle contraction. Normal muscle contraction must be performed in conditions where intracellular Ca^{2+} is maintained as low, and Ca^{2+} are stored in SR so that functions of Ca^{2+} pump and Ca^{2+} channel play a vital role. When the activities of Ca^{2+} channels in SR and Ca^{2+} pumps are inhibited, muscle contraction does not occur, although action potential remains [42]. It is indicated that Ca^{2+} leaks from Ca^{2+} channels in SR, and Ca^{2+} concentration gradient decreases [10].

Calcium deficiency induces the decline in muscle contractions, and leg cramps are induced. Extreme calcium deficiency causes the convulsion and tetany of muscle [43]. Deficiency of vitamin D also induces the decline of muscle contraction. In hyperparathyroidism, excessive PTH causes myalgia [44]. Judging from the above, calcium also plays a significant role in muscles.

2. Risk factors of aging

a) Immune stress

Calcium metabolism is related to activities of immunocompetent cells in diversified manners. For the synthesis, proliferation and activation of DNA in lymphocyte, Ca^{2+} in extracellular fluid is necessary and the decrease of Ca^{2+} concentration in extracellular fluid inhibits the formation of immunoglobulin G (IgG) in plasma cells [45]. In the process of T lymphocyte activation and the viral infection of B lymphocyte, intracellular Ca^{2+} increases [46]. There is a possibility that the calcium deficiency induces the deterioration of immune functions.

When histamines are released from mast cells in an allergic reaction, extracellular calcium is brought into cells [47]. Chronic calcium deficiency or excessive P intake promotes allergic reactions, inducing the acceleration of PTH secretion, and increasing Ca^{2+} of mast cells.

Atrophic gastritis is induced due to prolonged infection of *Helicobacter pylori*. The number of gastric parietal cells are significantly reduced and consequently, hypoacidity or achlorhydria occurs. Calcium absorption quantity is reduced in the conditions of hypoacidity and achlorhydria and subsequently, the chronic intake deficiency of calcium habitually occurs.

According to an epidemiologic study of National Cancer Center, dietary deficiency of calcium increases risk factors for the onset of colorectal cancer [48, 49]. Its mechanism has not been thoroughly clarified. It is, however, assumed that bile-acid-derived carcinogen alleviation via calcium and catabolite repression inhibition of the intestinal mucosa cells are related to this.

b) Oxidative stress

Regulations of vascular tonus are performed by sustaining two pathways of vascular smooth muscle; one pathway is to increase or decrease the level of phosphorylation in myosin light chain (MLC), reacting to intracellular Ca^{2+} concentration, and the other pathway is to increase or decrease Ca^{2+} sensibility, changing MLC phosphorylation level Ca^{2+}-independently [50, 51]. Nitric oxide (NO)/cGMP signaling decreases Ca^{2+} and reduces Ca^{2+} sensibility due to antagonism with Rho/Rho-kinase signaling, which induce the attenuation of tonus. Because of oxidative stress, failures of signal transductions occur including the acceleration of Rho/Rho-kinase or the decline of NO/cGMP signaling, and consequently, abnormal vascular contraction and twitches are induced [52].

Endoplasmic reticulum (ER) in nerve cells functions as a reservoir of calcium. Calcium-activated potassium channels of cell membranes open via Ca^{2+} release, and membrane potential is maintained. Oxidative stress not only damages cells but also changes intracellular Ca concentration and excitability is altered [53, 54]. In cardiac muscle cells, Ca^{2+} intake to SR depends on balance of Ca^{2+}-ATPase and Ca^{2+} release channel activities. Oxidative stress promotes Ca^{2+} release, decreasing quantity of calmodulin in ER [55-57].

Consequently, oxidative stress and calcium metabolism are cooperatively related to essential activities for the body such as vascular expansion and contraction, excitation of nerve cells, cardiac muscle and skeletal muscle. The human body utilizes a small quantity of free radicals, but excessive oxidative stress can ruin these mechanisms.

c) Physical and mental stress

Stress symptoms such as a feelings of irritation frequently occur in a state of hypercalcemia or hypocalcemia. It is not simple, however, to assess physical and mental stress medically and quantitively. Excessive loads of physical and mental stress, and excessive secretion of cortisol due to the accelerated actions of hypothalamus-hypophysis-adrenal system affects calcium metabolism [58, 59]. Brain-derived nutrition factor (BDNF) is a key molecule for mood disorders such as depressive symptoms. It is possible that a genetic type of BDNF and its low-affinity receptor, p75 neurotrophin receptor (p75NTR), are related to mood disorders [60, 61]. Cortisol decreases the release of BDNF-induced glutamic acid and attenuates intracellular Ca^{2+} rise after the addition of BDNF. Calcium supplement sare used for mitigation of premenstrual tension symptoms [62, 63].

The excessive secretion of cortisol, which is a stress hormone, and the administration of adrenocorticosteroid induce the decline of short-time intensive bone strength and also causesecondary steroid-induced osteoporosis, which is accompanied by severe fragility fractures [64, 65]. Its mechanism is as follows: bone formation is inhibited due to the inhibition of osteoblast differentiation and the increase of apoptosis. Osteoporosis is promoted via the prolonged life span of osteoclasts, the inhibition of intestinal calcium absorption, the inhibition of reabsorption of calcium in renal tubules and the decrease of GH formation. In steroid-induced osteoporosis, bone density decreases in both cancellous bone and cortical bone. Furthermore, not only bone mass but also bone quality as well as microstructures are attenuated. Therefore, the ratio of fragility fractures is high.

d) Glycative stress

Glycative stress represents a condition attributed to the excessive formation of reducing glucose, lipids and diverse alcohol-derived aldehydes in the body. These aldehydes react with biological materials to form carbonyl-modified proteins and/or advanced glycation end products (AGEs) [66, 67]. All proteins that exist in a living body must submit to post-translational modification due to glycative stress. Ca^{2+} channels and Ca^{2+} pumps are required to maintain Ca^{2+} concentration gradient intercellularly and extracellularly, or inside or outside of ER/SR. The proteins of channels

and pumps are, however, also inevitably affected by glycative stress. It has been reported that Ca^{2+} leaks from Ca^{2+} channels due to aging [8,9]. It is assumed that structural alternations due to modifications by glycation greatly affect the calcium leak as its causative factor. The calcium leak from channels attenuates Ca^{2+} concentration gradient, increases intracellular Ca^{2+} concentration and deteriorates cell functions.

The following disorders in carbohydrate metabolism, which are induced by type II diabetes mellitus or metabolic syndrome, decrease PTH secretion from parathyroid [68-70]: hyperglycemia, the increase of insulin resistance and relative insulin deficiency, and the increase of advanced glycation endproducts (AGEs). Furthermore, Calcium dysbolism is induced via the decrease in the number of vitamin D receptors in the kidney and the intestine, and the inhibition of vitamin D activation in the kidney [71-73]. Diabetes mellitus presents symptoms polydipsia and polyuria, which is related to osmotic diuresis. Calcium deficiency tends to occur due to the increase in quantity of Ca discharge from renal tubules.

Ca^{2+} channels in pancreatic β cell ER are ryanodine receptors and Ca^{2+} is released from ER by stimulation. This triggers the insulin secretion. Cyclic ADP-ribose (cADPR), as an intracellular messenger transmitting Ca^{2+} signal (allostericmolecule), affects ryanodine receptors and increases the sensitivity to stimuli (***Fig. 6***) [74]. Cyclic ADP-ribose (cADPR) is synthesized by an enzyme of the CD38 family, cADP ribosesynthetic enzyme. Prolonged calcium deficiency induces the decrease in Ca^{2+} storage in ER and the insulin secretion decreases. Furthermore, glycative stress is strengthed.

Chronic renal failure causes hypocalcemia and hyperphosphatemia and secondary hyperparathyroidism is induced due to continuous stimuli to parathyroid [75, 76]. High PTH blood disease promotes regressive changes of bones, cardiac muscle, skeletal muscle, cranial nervous system and the vascular system [77, 78]. Risk factors of aging increase glycative stress such as impaired secretion of insulin, glycometabolism and lipometabolism [79-81].

e) Lifestyle habits

Lifestyle choices such as eating habits and exercise significantly affects calcium metabolism. An unbalanced diet such as deficiency of calcium and vitamin D induces acceleration of PTH secretion, and balance of calcium in bones shifts to the negative [11, 12, 15]. Severe deficiency of calcium induces tetany and cramp of muscles [82], and ventricular arrhythmia in cardiac muscles [83]. Mechanical stimulation to epiphysis exerts favorable effects on calcium metabolism. Contrarily, for reduced mechanical stress, such as bedridden condition or a microgravity environment, immobility-induced osteoporosis is induced via the inhibition of bone formation and the promotion of bone absorption.

Alcohol intake stimulates bone absorption and promotes calcium loss [84, 85]. In chronic alcoholic females, estrogen secretion is reduced along with decreased ovarian function and bone metabolism is exacerbated [86]. Chronic alcohol intake induces the decline in urinary volume, the rise in urinary osmolality and a decline in excretion of urine citric acid. Thus, this is a risk factor of urolithiasis. [87, 88]. Alcohol intake can lead to tetany via the promotion of hypocalcemia [89].

Toxic substances contained in cigarette smoke such as nicotine, tar, carbon monoxide, formaldehyde, benzopyrene,

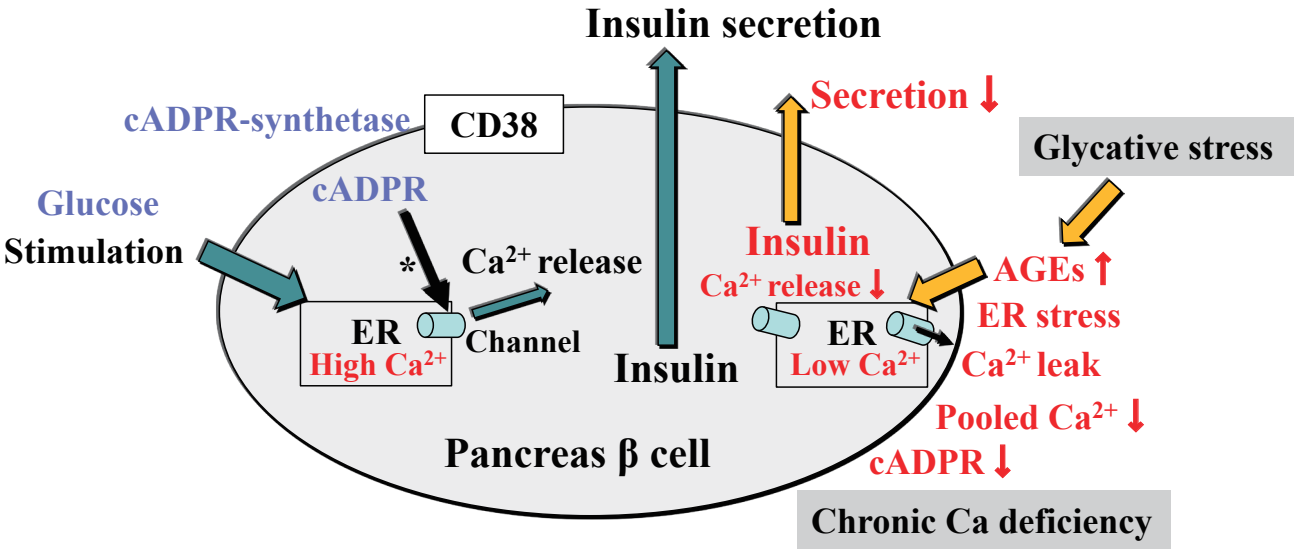

Fig. 6. **Calcium metabolism and insulin secretion in the pancreatic β cell.**

Once pooled Ca^{2+} in ER are decreased, insulin secretion reduces. * cADPR acts on Ca^{2+} channels (Ryanodine receptor) as an allosteric modulator. Ca, calcium; ER, endoplasmic reticulum; cADPR, cyclic adenosine diphosphate ribose; cADPR-synthetase belongs CD38 family; AGEs, advanced glycation end products.

nitrosoamine, lower activities of osteoblasts [90, 91]. As a result, calcium precipitation in bones is reduced.

Skin aging and calcium

Regressive alternations in the skin are diversified, which occur along with aging. To assess degrees of skin aging, five types of characteristics are *shiwa-nenrei*, wrinkle age (increase of wrinkles), *shimi-nenrei*, skin spot age (skin spots and alternations in skin tone and complexion), *uruoi-nenrei*, rich moisture age (decline in moisturizing capacity), *mochihada-nenrei*, soft and smooth age (decline in skin elasticity) and glycation age (increase in AGEs accumulation). It has been recognized that photoaging (oxidative stress) accounts for 70% of skin aging factors [92, 93]. Countermeasures for oxidative stress have been being established including ultraviolet (UV) care and usage of antioxidant. Other skin aging risk factors are glycative stress, the reduced secretion of estrogen, intestinal dysbiosis, physical and mental stress, lifestyle habits such as smoking, alcohol intake, low quality of sleep, calcium deficiency and constipation. There is a possibility that chronic calcium deficiency impairs skin homeostasis and promotes skin aging.

The epidermis primarily consists of keratinocyte, which comprises more than 90% of the epidermis, and contains Langerhans cells, which is related to immunity, chromocytes, which produces melanin pigment, and Merkel cells, which is related to the nerve system (***Fig. 7***) [92, 93].

Located on the outermost layer covering a living body, skin plays the role of barrier to protect the underlying body from varied stimuli of the external environment. Calcium plays a significant role for homeostasis of skin barrier function. When calcium metabolism is impaired, the barrier function is damaged. Consequently, rich moisture is impaired, in other words, the aging process is accelerated in "rich moisture age". Ca^{2+} concentration in keratinocytes of basal layer is sustained in low amounts due to the regulations of Ca^{2+} channels and Ca^{2+} pumps. Ca^{2+} concentration gradually increases from the basal layer to the surface layer and a Ca^{2+} concentration gradient is formed [94-96]. Ca^{2+} concentration is the highest immediately under stratum corneum in stratum granulosum (the top part of surface layer). Keratinocytes are divided and proliferated in the basal layer and travel to the surface layer via Ca^{2+} concentration gradient. In this process, Ca^{2+} concentration and keratin content in keratinocytes increase, and cells lose their nucleus. Keratinocytes, which are divided by the stimulation of Ca^{2+} concentration rise, produce lipids such as acylceramide [97]. These lipids are filled up in the intercellular space and firm skin barriers are formed [98].

Ca^{2+} gradient decreases along with aging. Furthermore, Ca^{2+} gradient decreases or disappears due to atopic dermatitis, psoriasis and dry skin [99]. Dry skin is too sensitive as a stimulus. This is the reason that the itch sensation is notably found during dry season of winter.

Transient receptor potential (TRP) channels are involved in the perceptions of the skin such as pain and itch. Ion channels and receptors are expressed in the nerve end of nociceptors. Stimuli are related to the following: ion channels such as piezo1and acid-sensing ion channels (ASICs) are responsible for mechanical stimuli. TRPV1–4

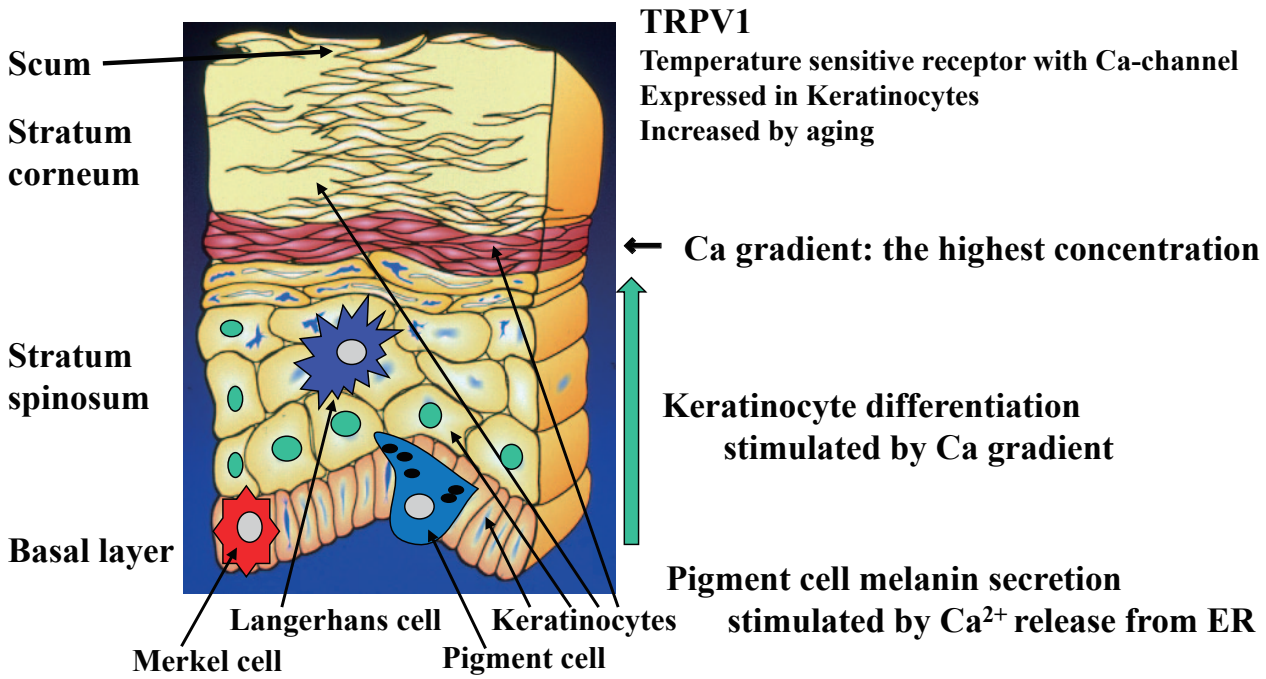

Fig. 7. **The role of calcium in skin function.**

TRPV1 is activated by temperature, acids, capsaicin, oxidative stress, glycative stress and Ca^{2+} depletion in ER. TRPV1, transient receptor potential cation channel subfamily V member 1; Ca, calcium; ER, endoplasmic reticulum.

channels for heat stimuli, TRPM8 and TRPA1 channels for cold stimuli, ASICs,TRPV1,TRPV3,TRPM8 and TRPA1 channels, ATP receptors and B2 receptors for chemical stimuli [100, 101]. Four channels, TRPV1–TRPV4 channels, which are Ca^{2+}-permeable ion channels in the skin, sense the temperature and open the filter gate. TRPV1 is a capsaicin receptor and TRPA1 is a wasabi receptor. TRPV3 and TRPV4 are recognized to be highly expressed in the epidermal keratinocytes. These channels are activated by oxidative stress, the rise in intracellular Ca^{2+} concentration, temperature changes, PH changes, mechanical stimuli and osmotic pressure changes. Skin becomes too sensitive when Ca^{2+} concentration gradient via cell membranes decreases due to the chronic calcium deficiency or the aging-related regressive alternations. For this reason, pruritus is caused in the elderly. Ca^{2+} channels consist of multiple subunits. When protein structures alter, being modified by glycation, a Ca^{2+} leak is induced, Ca^{2+} concentration gradient decreases, and intracellular Ca^{2+} concentration increases.

It is suspected that partially, calcium is involved in the formation of skin spots, which is related to skin spot age. Quantity of melanin formation in pigment cells due to ultraviolet irradiation increases locally, and the melanin transport to basal layer (peripheral keratinocytes) is accelerated. Skin spots are formed as follows: Solar ultraviolet radiation impairs DNA, which is not repaired properly. This induces mutations in genes relating to melanin formation and gene groups relating to cellular proliferation. Ultraviolet stimulates epidermis keratinocytes, and cytokines are released, including basic fibroblast growth factor (bFGF), α-melanocyte-stimulating hormone (α-MSH) and endothelin-1 (ET-1). Thus, melanin synthesis is accelareted [92, 93]. Alpha-MSH exacerbates tyrosinases activities via cyclic AMP, promotes melanin synthesis, and further, activates genes relating to melanin synthesis. ET-1 induces intracellular Ca^{2+} mobilization, increases gene transcriptive activities via intracellular signal transduction system, and consequently, promotes melanin synthesis. Accordingly, Ca^{2+} gradient via cell membranes of pigment cells decreases, cellular Ca^{2+} concentration increases, and melanin synthesis increases. There is a possibility that skin spot formation is promoted. Intracellular Ca^{2+} regulation by SERCA2b, which is a Ca^{2+} channel, has the regulation action of melanin synthesis [102]. There is a possibility that by controlling this mechanism, skin pigmentation can be regulated.

Conclusion

Calcium metabolism is regulated in a strict manner so that Ca^{2+} concentration gradient is maintained intercellularly and extracellularly, or inside or outside of ER/SR. Calcium plays a significant role for function maintenance in human cells and tissues. For this reason, Ca^{2+} leaks from Ca^{2+} channels are a growing concern. These induce the attenuation of Ca^{2+} concentration gradient and the rise in cellular Ca^{2+} concentration. Muscle contraction, neurotransmitter release, and decline in functions of hormone exocytosis are induced. Problems occur in skin barrier functions and perception sensitivity, as is recognized. Therefore, it is essential for maintenance and promotion of health to avoid the deficiency of calcium and vitamin D and prevent functional proteins such as Ca^{2+} channels from modification by glycation.

Conflict of Interest Statement

The author states that the performance of this study entailed no issues representing a conflict of interest.

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