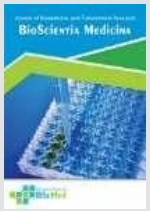
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Role of Calcium in the Skin Barrier

Nopriyati[1*], Ahmad Ligar Suherman[1], Yulia Farida Yahya[1], Mutia Devi[1]

[1] Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

ARTICLE INFO

Keywords:
Calcium
Intake
Skin barrier
Calcium gradient

***Corresponding author:**
Nopriyati

E-mail address:
nopriyati@fk.unsri.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v6i7.543

A B S T R A C T

Calcium is a macromineral that is an important part of the body. Bones and teeth contain more than 99% of the human body's calcium. Calcium is also found in other tissues, such as the skin. The concentration of calcium in the body tends to decrease with age because released from the body through sweat, skin cells, and faeces. Calcium intake varies worldwide, with an average of 175-1233 mg/day. Many countries in Asia have an average calcium intake of less than 500 mg/day. The skin barrier function is in the epidermis. The formation of the epidermal barrier and the maintenance of homeostasis is important to protect the individual from the external environment and organisms. Epidermal calcium gradient, endoplasmic reticulum (ER) calcium homeostasis, and calcium influx through calcium channels play important roles in keratinocyte differentiation, barrier formation, and barrier homeostasis. Understanding the mechanism of regulation and function of calcium related to skin barrier homeostasis is aimed at improving understanding of calcium in the skin barrier

1. Introduction

Calcium is a macromineral that is an important part of the body. Bones and teeth contain more than 99% of the calcium in the human body. Calcium can be found in the blood, muscles, and other tissues, such as the skin. Calcium in the bones can be used as a reserve that the body can use as needed. The concentration of calcium in the body tends to decrease with age because it is removed from the body through sweat, skin, and feces.[1]

Based on research, there are differences in the level of calcium intake in the diet in each country. The average intake of calcium in the human diet is 175-1233 mg/day. Many countries in Asia have an average calcium intake of less than 500 mg/day. Countries in Africa and South America mostly have low calcium intakes between 400-700 mg/day. In contrast to Northern European countries that have a calcium intake of more than 1000 mg/day.[2]

The skin barrier function is in the epidermis, especially in the stratum corneum (SC). The stratum corneum consists of corneocytes, which are the end products of keratinocyte differentiation.[3] Calcium ions serve as universal signals to modulate various aspects of keratinocyte cellular function. The distribution and dynamics of calcium ions in the skin play an important role in epidermal homeostasis. In the mammalian epidermis, there is a calcium gradient between the lower and upper epidermal layers, with low levels in

the basal and spinosum layers, increasing towards the stratum granulosum, and decreasing again in the stratum corneum. The calcium gradient along the epidermis plays an important role in the differentiation of keratinocytes and the formation of the permeability barrier of the epidermis, and this allows dynamic changes of calcium ions to generate calcium signals. Recent studies have shown that the release of calcium ions from intracellular stores and the influx of extracellular calcium ions are important for regulating the structure and function of the epidermis.[4]

This literature review aims to improve understanding of calcium metabolism, including absorption, regulation of body calcium homeostasis, excretion, and calcium at the skin barrier.

Calcium metabolism

Intake

Based on the Minister of Health Regulation No. 28 of 2019 concerning the recommended dietary allowances (RDA) for the Indonesian people, the daily calcium requirement for adult men and women averages in the range of 1000-1200 mg per day.[5] Calcium intake in the average human diet is 175-1233 mg/day.[2] Calcium deficiency causes impaired releasing of the neurotransmitter, muscle contraction, hormone-releasing, blood clotting, and enzyme regulation.[6] Excess calcium intake causes side effects, including the formation of kidney stones.[7]

Absorption

Calcium is absorbed in the small intestine through the intestinal membrane through two mechanisms, namely active transport (transcellular) and passive transport (paracellular). Active transport of calcium occurs mainly in the duodenum and proximal jejunum, while passive transport occurs along with segments of the intestine.[8]

Active transport of calcium depends on the calcitriol and the vitamin D receptor/VDR intestinum. Calcitriol is an active hormone that acts on intestinal cells and functions to increase calcium absorption. This transcellular mechanism is activated by calcitriol and occurs at low and moderate levels of calcium absorption. Transcellular transport occurs in the duodenum, where VDR is expressed at the highest concentration (Figure 1).[7] The duodenum is the most efficient because the absorption of calcium can take calcium even under very low calcium diet circumstances through the active mechanism, but it has all the components of duodenal calcium transport through the transcellular and paracellular.[8]

Passive diffusion or paracellular transport involves the movement of calcium between mucosal cells and depends on the electrochemical gradient of the serous lumen. The energy for paracellular transport comes from the free energy generated by the transepithelial calcium gradient (5 mM in the lumen and 1.25 mM in the plasma). Passive diffusion generally occurs during high calcium intake (high concentrations in the lumen) and occurs along with segments of the intestine. The permeability of each segment of the intestine determines the rate of passive diffusion. The highest passive diffusion occurs in the duodenum, jejunum, and ileum.[7]

In several controlled metabolic research series United States Department of Agriculture/USDA, the average absorption fraction of calcium (percentage of calcium absorbed from a given dose) in nonpregnant men and women is 25% of intake, and an average loss of calcium through urine is 22%, faeces 75%, slightly through the skin, sweat and hair.[7]

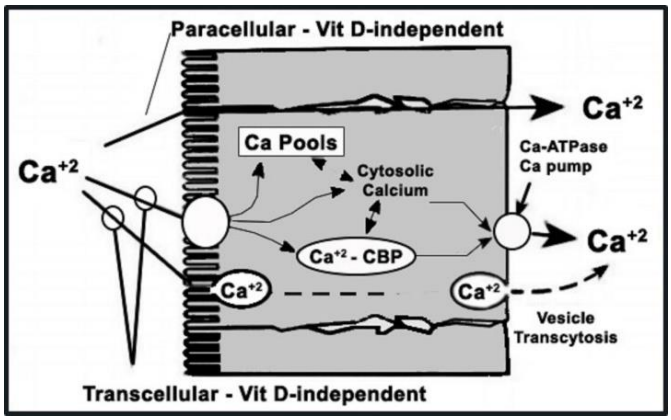


Figure 1. Schematic illustration of calcium absorption in the intestine.[7]

In transcellular transport, calcium enters enterocytes through calcium transport protein/transient receptor potential cation channel/vanilloid family member 6/transient receptor potential V6 (TRPV6), a calcium channel on the brush border. Calbindin is a calcium-binding protein that facilitates uptake through TRPV6 and transport through enterocytes. The function of Ca^{2+}ATPase is to pump calcium out of enterocytes into circulation. Paracellular transport depends on active sodium transport, which creates an osmotic gradient in the paracellular space and a transepithelial potential difference across the epithelial layer.[7]

Regulation of calcium homeostasis in the body

Serum calcium consists of ionic components (50%), bound to protein (40%), mainly albumin, and a small fraction bound to organic and inorganic acids such as citric, lactate, bicarbonate, and sulfate. Calcium balance is maintained by 3 main organs, namely: the gastrointestinal system, bones, and kidneys. The concentration of calcium in the blood and extracellular fluid was maintained at a concentration of 2.5 mM. Calcium sensing receptor (CaSR), a member of the G protein-coupled receptor superfamily of parathyroid, kidney, gut, lung, brain, skin, bone marrow, osteoblast, breast, and other cells, acts as a cell surface sensor for extracellular calcium levels.[7]

The body's calcium homeostasis involves various organs, including the intestines, parathyroid glands, kidneys, and bones.[9] Maintenance of circulating calcium ion levels within physiological ranges essential for maintaining normal body function. Serum calcium levels are controlled by the endocrine system, which involves the metabolites of vitamin D/vitamin D-related endocrine system/VDRES, calcitriol, and parathyroid hormone (PTH).[7]

The vitamin D metabolic system forms the basic mechanism of calcium homeostasis in mammals. Total serum calcium levels were maintained in the normal range between 8.5-10.5 mg/dL. If these levels change slightly, the CaSR of the parathyroid glands signals to secrete PTH (Figure 2). Parathyroid hormone stimulates the kidneys to produce calcitriol by activating bone resorption, thereby increasing extracellular calcium levels. Calcitriol acts through endocrine forms in the intestines, bones, and kidneys to increase serum calcium levels.[7]

Calcitriol, through its receptors, provides relative feedback to suppress PTH production and release (PTH suppression). When serum calcium levels increase, feedback mechanisms cause CaSR to be inactivated, and PTH secretion falls dramatically. If there is an increase in serum calcium levels, parafollicular c cells of the thyroid gland secrete calcitonin which blocks bone calcium resorption, and this helps maintain serum calcium levels within normal limits. High serum phosphorus levels suppress calcitriol formation.[7]

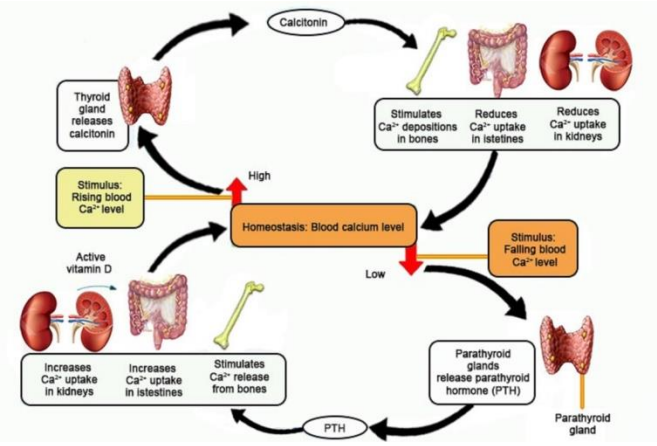


Figure 2. Schematic overview of calcium homeostasis.[7]

An increase or decrease in blood calcium levels is a signal for the thyroid and parathyroid glands to release hormones that play a role in maintaining calcium levels in the blood.[7]

Excretion

Calcium is excreted by the body through urine, feces, and sweat. Calcium is mostly excreted in the urine (20-300 mg/day) and a small part through sweat (35 mg/day). The amount of calcium excreted in the urine reflects the amount of calcium absorbed. Urinary calcium excretion is a function of the balance between the amount of calcium filtered by the kidneys and the efficiency of renal tubular reabsorption. Nearly 98% of filtered calcium is reabsorbed through active and passive mechanisms at 4 sites in the kidney, each site keeping the calcium balance in balance. As much as 70% of filtered calcium is passively reabsorbed in the proximal tubule.[7]

Active calcium transport is regulated by CaSR in the ascending loop of Henle. When serum calcium levels are high in the extracellular fluid, active reabsorption of Henle is stopped through CaSR. When the filtered calcium level is low, CaSR is activated, and a large fraction of the calcium is reabsorbed. In the distal tubule, the ion channel transient receptor potential cation channel, vanilloid family member 5 or TRPV5, plays a role in controlling the active transport of calcium. This is regulated by calcitriol and estradiol. The collecting ducts play a role in passive transport, although the relative percentage of total calcium reabsorbed by the collecting ducts is low. Overall, the daily excretion of calcium in healthy men and women through the kidneys is about 5 mmol/day.[7]

Skin barrier

Skin is a barrier to the environment, protecting it from mechanically and chemically harm, against microorganisms, and preventing transepidermal water loss (TEWL). This is mainly associated with the epidermal barrier, which is a defense system consisting of 3 components: (1) forming cornified protein envelope (CE); (2) lipids that fill the extracellular space; and (3) skin pH range of 5 protects from microbes.[3,10] Inflammation of the epidermis can reduce barrier function, characterized by impaired barrier function of dry skin, itching, redness, and rough texture.[11]

The skin barrier is located in the stratum corneum (SC) and consists of protein-enriched cells (corneocytes with sheath corneum and cytoskeletal elements, and desmosomes corneum) and enriched intercellular lipid domains (figure 3).[3,12] Corneocytes as bricks, intercellular lipids as mortar (cement). Corneum desmosomes are analogous to spikes that maintain corneocytes until desquamation occurs on the skin surface.[13]

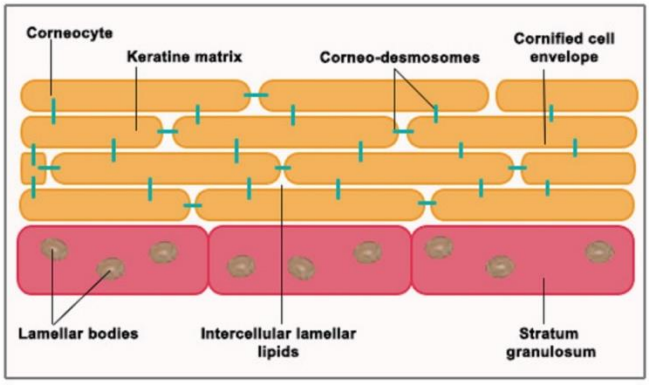


Figure 3. Schematic depiction of the stratum corneum like a brick wall.[13]

The epidermis is composed of keratinocytes, melanocytes, Langerhans cells, and Merkel cells. Keratinocytes are cells that have the ability to proliferate and contain keratin which is needed as a support for the internal structure of the epidermis. Keratinocytes mature and have differentiated, and their shape gets flattered until, finally, the cell nucleus disappears. Finally, the result of this differentiation process is the formation of the stratum corneum. The formation of the stratum corneum is an important function of the epidermis. The stratum corneum or often called the horn layer prevents water loss and absorption of infectious substances/agents that are harmful to the body. The structure of the epidermis can be analogous to the arrangement of bricks and cement mixture, with corneocytes as the bricks and the lipid barrier as the cement mixture.[3,12]

Corneocytes are arranged in the upper part of the epidermis and contain protein. Beneath the SC lies the stratum granulosum, containing basophilic structures called keratohyalin granules. The granules contain the inactive precursor protein profilaggrin. Through dephosphorylation and proteolysis, profilaggrin is converted into filaggrin which has a glue-like function that attaches keratin filaments to form microfibrils. Filaggrin degradation produces free amino acids that play a role in protection against ultraviolet radiation and skin hydration. Keratohyalin granules also contain various other protein precursors, such as involucrin, loricrin, elafin, envoplakin, cystatin A and other proteins that play a role in the formation of the cornified cell sheath. In addition to keratohyalin granules, cells in the stratum granulosum contain lamellar granules, which are organelles bound to cell membranes that contain glycolipids, glycoproteins, and phospholipids. The molecules contained in the lamellar granules are secreted between the granular layer and the SC to form a mortar/cement mixture that binds to the corneocytes in the SC.[3,12]

The nuclear epidermis, tight junctions, gap junctions, adherent junctions, desmosomes, and cytoskeletal elements contribute to the skin barrier. Lipids are synthesized in keratinocytes during the differentiation process of the epidermis, then released into the extracellular domain, where the lipid-rich extracellular layer is formed. The corneum sheath, a strong protein/lipid polymer structure, is located beneath the cytoplasmic membrane on the outside of the corneocyte. Ceramides A and B form the ceramides backbone (for the addition of free fatty acids and cholesterol SC), covalently bound to corneum sheath proteins. Filaggrin crosslinks with the corneum sheath and aggregates the keratin filaments into macro fibrils. Cytokines, 3',5′cyclic adenosine monophosphate (cAMP), and calcium influence the formation and maintenance of barrier function.[3,12]

The skin barrier is acquired through the final differentiation process during the conversion of keratinocytes to corneocytes. The corneocyte matrix is arranged in the form of a lamellar membrane derived

from lipid precursors, then secreted from the lamellar body (LB) and became a permeability barrier mediator in the outer stratum corneum. The lipids that play an important role are cholesterol, free fatty acids, and ceramides, with lipid synthesis de novo in the epidermis. Epidermal lipid biochemistry causes changes in lipid composition. Changes in lipid composition accompanied by abnormalities of epidermal differentiation cause skin barrier disruption. This allows the entry of environmental allergens and immunological and inflammatory reactions in atopic dermatitis.[12,14] An increasing number of skin diseases are generally caused by disruption of the skin barrier. When the skin barrier performs a physiological function as a skin barrier, it interferes with drug delivery into the skin. Penetration enhancers can be chemical and physical used to increase the penetration of topical drugs and patches transdermal.[13]

Impaired differentiation of keratinocytes and skin barrier dysfunction is the main causes or aggravating factors for many inflammatory skin diseases, including atopic dermatitis, psoriasis, and ichthyosis.[4,11,12,8,15] Disruption of the barrier triggers inflammation, as well as inflammation, can interfere with the function of the skin barrier. In atopic dermatitis, inflammation decreases the expression of tight junctions and antimicrobial peptides. Therefore, understanding the mechanisms regulating keratinocyte differentiation and skin barrier homeostasis is important for understanding various skin disorders and their therapeutic regimen.[4]

Calcium in skin barrier

Calcium homeostasis in skin barrier

The skin barrier function is in the epidermis, especially in the SC, the outermost cornified layer. The stratum corneum consists of corneocytes, which are the end products of keratinocyte differentiation. Intercellular lipid SC, a lamellar double layer consisting of ceramides, cholesterol, and free fatty acids. The lamellar body (LB), a specialized organelle in the skin, plays a central role in the formation of lipids SC, proteins, and antimicrobial barriers. Studies have shown that levels of BL secretion, lipid synthesis, and barrier permeability homeostasis are regulated by changes in the extracellular calcium ion concentration of the upper epidermis triggered by impaired barrier permeability.[4]

The formation of the epidermal barrier is highly dependent on calcium ions. The integrity of the epidermal barrier depends on the formation of the sheath of the corneum, a protein coat that is synthesized by keratinocytes. The differentiation of keratinocytes into corneocytes, which form the corneum sheath, is induced by high concentrations of calcium. Calcium ions are required in several steps of the formation of the corneum sheath. Calcium induces specific genes for the corneum sheath and is a prerequisite for the activity of various enzymes in the differentiation process.[4]

Endoplasmic reticulum calcium homeostasis is critical in the regulation of keratinocyte differentiation, formation of intercellular junctions, antimicrobial barriers, and barrier permeability homeostasis. Thus, the release of calcium ions from intracellular stores, such as the ER, and the mechanism of calcium ion influx are important in the skin barrier. Recent studies have identified the role of various types of calcium channels, mediators of calcium entry and exit in keratinocytes (Table 1).[4]

Table 1. Calcium channels in the plasma membrane of various cells in the body.[16]

Type	Gate	Location
Type L	High voltage-activated (HVA)	Skeletal muscle, myocytes, dendrites, neurons cortex
Type P	HVA	Nerve Purkinje
Type N	HVA	Brain and peripheral nervous system
Type R	Intermediate voltage-activated (IVA)	Granule cells cerebellar
Type T	Low voltage-activated (LVA)	Nerve cells, osteocytes, thalamus
Receptor inositol 1,4,5 triphosphate (IP_3)	IP_3	ER / sarcoplasmic
Receptor ryanodine	Receptors dihydropyridine in tubules T	The endoplasmic reticulum / sarcoplasmic
Two-pore channel	Nicotinic acid adenine dinucleotide phosphate (NAADP)	Lysosomal / endosomal membrane
Cation channels of sperm	Calcium-induced calcium release (CICR)	Sperm
Transient receptor potential (TRP)	TRPA TRPC TRPM TRPML TRPP TRPV	The central nervous system, peripheral nervous system, intestinum, kidney, human sperm, skin, lung, lymph, placenta

In the stratum spinosum, involucrin, evoplakin, and periplakin are bound to each other at the plasma membrane by Nε-(γ glutamyl) lysine (isopeptide bonds). Binding to membranes or crosslinking between proteins all depends on calcium. Calcium is a mediator of lamellar body formation and secretor. Lamellar bodies act as suppliers of lipids. Mortar epidermis is formed in the epidermal layer and replaces membrane phospholipids with ω-OH-ceramide.[10]

In the granular layer and stratum corneum, a process continued from adding and the next protein crosslinking e.g., loricrin, filaggrin, small proline-enriched proteins repeatedly, and protein sheathing corneum, which depend on calcium. Lipids, desmosomcorneum, proteases, protease inhibitors, antimicrobial peptides, and skin pH affect the skin barrier. Loss of the epidermal calcium gradient and decreased stratum granulosum calcium concentration induces dramatic changes in the composition of the corneum sheath. The most abundant protein in the corneum sheath in healthy skin is loricrin (80% of the total mass of the corneum sheath). With age, the amount of loricrin decreases to below 50%. The reduced protein filaggrin and its expression contribute to dry skin. All of these changes contribute to the reduced effectiveness of the epidermal barrier.[10]

Acute disruption of the barrier due to topical solvents or tape stripping induces an immediate depletion of extracellular calcium ions in the epidermis, especially the upper stratum granulosum, and results in loss of the normal epidermal calcium gradient. Upper epidermal calcium levels progressively recover over 6-24 hours as the barrier restores. Inhibition of extracellular calcium loss in the upper epidermis by high calcium solutions or occlusion with a membrane vapor impermeable impairs barrier restoration. These findings suggest that the acute loss of stratum granulosum calcium concentration following barrier disruption is an important regulatory signal initiating the immediate release of pre-stored LB contents into the SC gap. Acceleration of epidermal LB synthesis leads to barrier repair.[4]

Celli et al. proved that most of the calcium ions measured in the epidermis are derived from intracellular stores in the ER, and ER calcium depletion is an important signal for terminal differentiation and epidermal barrier homeostasis.

This study demonstrated that most of the stratum granulosum calcium ion depletion following barrier disruption originates from intracellular RE calcium stores, triggering ER stress. The same study showed that the induction of ER stress in the skin stimulates BL secretion as well as caspase 14 and loricrin expression. The results of this study emphasize the important role of intracellular calcium release, especially from the ER, in the regulation of keratinocyte differentiation and barrier homeostasis (Figure 4).[4]

In addition to the extracellular calcium content, the entry of calcium into keratinocytes also regulates barrier restoration. The mechanism of increasing intracellular calcium ions in the stratum granulosum in response to the current increase in extracellular calcium can be explained through the role of the calcium-sensing receptor (CaSR), which is expressed in the stratum granulosum. The calcium-sensing receptor, a subfamily of G protein-coupled receptors in the plasma membrane, senses elevated extracellular calcium levels and activates phospholipase C through Gaq, which produces inositol triphosphate (IP3), thereby causing the release of calcium from intracellular stores such as the ER and Golgi and stimulating influx calcium ion through store-operated calcium channel.[4]

Lee et al. demonstrated that the L-type calcium ion channel inhibitor, verapamil, abolished the barrier recovery barrier induced by high extracellular calcium ions. Both extracellular calcium and calcium influx through calcium channels regulate the homeostasis of the permeability of the epidermal barrier. Choi et al. demonstrated that high-frequency sonophoresis or iontophoresis that did not cause changes in skin barrier function could trigger LB secretion and cytokine expression through mechanisms that trigger changes in the epidermal calcium gradient. These observations indicate that changes in the calcium levels of the outermost epidermis without affecting the skin barrier function are a strategy to increase the permeability barrier function.[4]

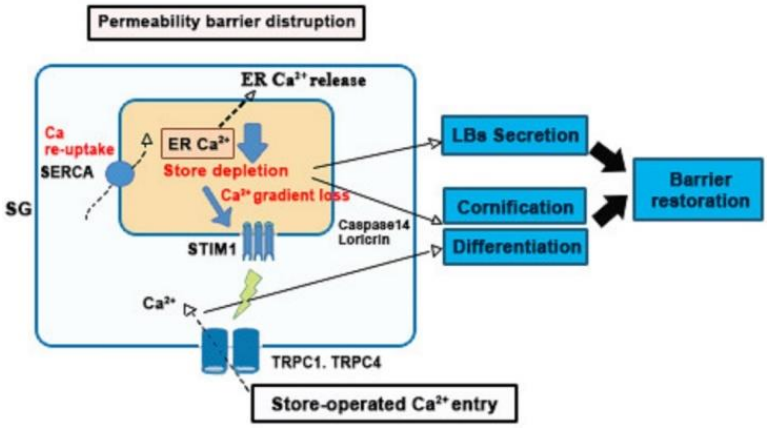


Figure 4. Schematic overview of the role of endoplasmic reticulum (ER) calcium signaling in barrier permeability homeostasis. SERCA: Sarco/endoplasmic reticulum Ca^{2+} ATPase isoform.[4]

Recent studies have shown that intracellular calcium stores in the ER are the main compartment, forming the epidermal calcium gradient. Impaired barrier permeability stimulates the release of ER Ca^{2+} in stratum granulosum (SG) keratinocytes, leading to the depletion of ER Ca^{2+} and loss of the epidermal calcium gradient. Depletion of ER Ca^{2+} stimulates lamellar body (LB) secretion, caspase 14, and loricrin expression indicating that changes in ER Ca^{2+} are important signals for initiating two major metabolic responses (lipid and protein barrier restoration) leading to barrier restoration. The next physiological response to the depletion of ER Ca^{2+} is a rapid increase in store-operated Ca^{2+}, a mechanism involved in

recharging ER Ca^{2+} deposits. The stromal interaction molecule 1 (STIM1) is the ER Ca^{2+} sensor that triggers the entry of store-operated Ca^{2+}. In SG, the inclusion of store-operated Ca^{2+} is mediated by TRPC1 and TRPC4. The entry of this calcium through TRPC1 and TRPC4 further stimulates keratinocyte differentiation.[4]

Epidermal calcium gradient

The epidermal calcium gradient is the difference in the concentration of calcium ions in each stratum in the epidermis. Extracellular calcium is a major component of the epidermal calcium gradient and is a signal for barrier repair due to barrier disruption.[4]. The formation of the epidermal barrier starts from the stratum basalis. In this layer, there are stem cells that will grow and develop. These cells continue to replace the desquamated dead corneocytes. The concentration of calcium ions is relatively low in the stratum basale because calcium is required for keratinocyte differentiation and corneocyte formation. In the stratum spinosum, calcium concentrations increase, reaching a peak in the stratum granulosum followed by a sharp decrease in SC, where keratinocytes reach the end of differentiation into corneocytes (figure 5).[10]

The epidermal calcium gradient is formed to overcome the differences in calcium requirements of keratinocytes. Low calcium concentration for proliferation and high calcium for differentiation.[10] Calcium ions and their concentration gradients in the epidermis are important in regulating keratinocyte differentiation, skin barrier formation, and barrier permeability homeostasis. Recent studies have shown that intracellular calcium ion storage in the endoplasmic reticulum (ER) is a major component of the epidermal calcium gradient.[4]

The calcium gradient is formed by the relative concentrations of calcium ions in the extracellular and intracellular spaces, which form the basis of skin function. The epidermal calcium gradient is generated by several mechanisms, including changes in the calcium ion gradient after acute SC barrier disruption (fading rapidly and reappearing after 6 hours with barrier repair) and evidence that the reappearance of the calcium ion gradient after barrier disruption is accelerated by barrier repair, and delayed by inhibition of recovery barrier.[1] Loss of the normal extracellular calcium gradient stimulates LB secretion and barrier repair.[17]

Elias et al. suggested that sustained low levels of TEWL accompanied by restriction of ion movement in the intact epidermis led to the formation of an epidermal calcium ion gradient.[18] Recent studies have shown that the passive diffusion of calcium ions is sufficient to produce a calcium ion gradient. These findings suggest that ER calcium stores play a role in the epidermal calcium gradient. Calcium gradients and calcium signaling are important in regulating many skin functions. It has been demonstrated that asymmetric distribution of calcium concentrations regulates polarity and cell migration through a signaling mechanism that controls cell migration.[4]

The increase in intracellular calcium ions in response to the increase in extracellular calcium ions controls the differentiation process of keratinocytes and epidermis, the synthesis of differentiation-specific proteins, the formation of cell adhesion, and the inhibition of LB secretion of the stratum granulosum. The absence of a calcium ion gradient in some diseases is characterized by impaired differentiation. The calcium gradient is important for normal growth and differentiation. The components involved in the formation of a calcium ion gradient include the permeability of the epidermal barrier, endogenous calcium ion stores in the ER, and the Golgi. A calcium gradient is formed in the later stages of fetal development in the fetus.[19]

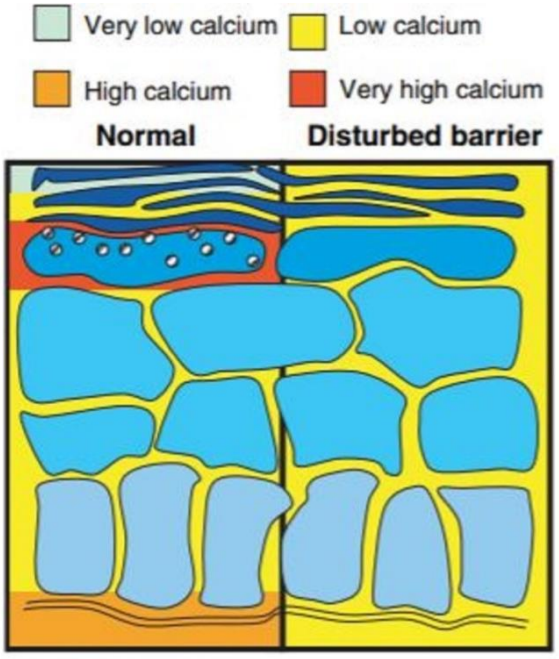


Figure 5. Schematic illustration of calcium gradient in the normal skin barrier and disturbed skin barrier.[19]

In the normal skin barrier, there are differences in calcium levels in each layer of the epidermis. High calcium levels are found in the stratum basalis, decreased in the stratum spinosum, then increased again in the stratum granulosum, and decreased again in the stratum corneum. This creates a calcium gradient. In the disturbed barrier, there is no difference in calcium levels in each layer of the epidermis.[19]

Calcium in keratinocyte differentiation

The skin is characterized by vertical differentiation from the basal layer to the SC. Calcium ions are the main regulators of keratinocyte differentiation and proliferation. The basal layer contains proliferative cells. As differentiation progresses, the keratinocytes progress upward through each layer of the epidermis, along with specific changes at different stages of differentiation, and eventually become the final differentiated corneocytes in SC (figure 6). Calcium plays an important role in all processes of keratinocyte differentiation, from differentiation in the basal layer and spinosum to the final differentiation in the stratum granulosum. Calcium regulates the transcription of all genes encoding keratinocyte differentiation-specific proteins.[4]

In addition to extracellular calcium ions, CaSR causes keratinocyte differentiation. Protein kinase C Activated (PKC) increases diacylglycerol and intracellular calcium, inducing markers of differentiation of stratum granulosum keratinocytes, including transglutaminase, involucrin, loricrine, cytokeratin 1, cytokeratin 10, and filaggrin. Among isozymes, PKC alpha and delta are activated by calcium ions in the human epidermis and regulate extracellular calcium-induced transcription of differentiated genes.[4]

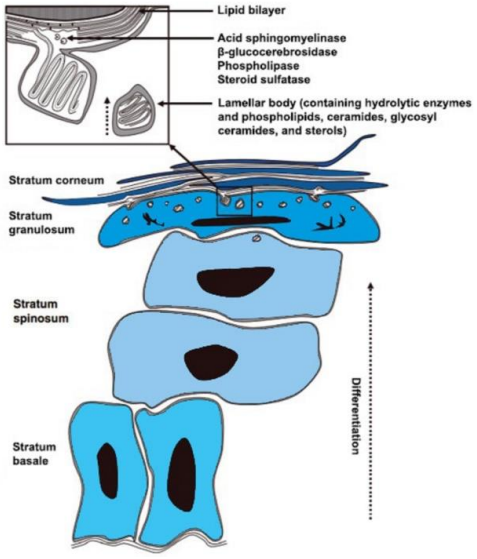


Figure 6. Schematic illustration of keratinocyte differentiation.[20]

Calcium in cell apoptosis

Apoptosis is a programmed cell death that normally occurs during the development and aging process of all body tissues. Apoptosis is a cell homeostatic mechanism to maintain cell populations in body tissues and in the body's defense mechanism.[21]

Apoptosis in mammals has 1 of 2 initiation phases: death receptor pathway (extrinsic apoptotic pathway) and mitochondrial pathway (intrinsic apoptotic pathway) for the pathway chosen depends on the nature of the signal to be integrated. Mitochondrial intermembrane cleft contains many apoptotic factors such as cytochrome c, apoptosis-inducing factor (AIF), procaspase 9, Smac/Diablo, and endonuclease. These factors are released into the cytosol in response to apoptotic signals, such as DNA damage, oxidative stress, energetic catastrophe, viral infection, ER stress, or intoxication xenobiotic. The release of apoptotic factors is preceded by permeabilization of the outer mitochondrial membrane (Figure 7).[21]

The endoplasmic reticulum is an important organelle for calcium ion storage, maintaining ion concentrations in the 0.1-1mM range compared to 100 nM in the cytosol and mitochondrial matrix. The release of stored calcium ions and uptake by mitochondria is a mechanism that triggers apoptosis. Mitochondria are the key decoding of the apoptotic process. Various apoptotic stimuli lead to the release of mitochondria-specific pro-apoptotic factors. Overloading mitochondrial calcium ions is one of the pro-apoptotic pathways, which induces mitochondrial swelling with disruption or rupture of the outer membrane and, ultimately, the release of mitochondrial apoptotic factors into the cytosol.[21]

If the release of ER calcium ions is prevented, the cell is protected from apoptosis. Many proteins play a role in mitochondrial calcium ion homeostasis. In addition to apoptosis, increased mitochondrial calcium ion uptake is essential for increasing mitochondrial aerobic metabolic requirements, which are required for efficient mitochondrial respiration and maintaining normal cell bioenergetics. Overloading mitochondrial calcium ions causes controlled apoptosis, and a transient increase in calcium ions is required for cells to survive.[21]

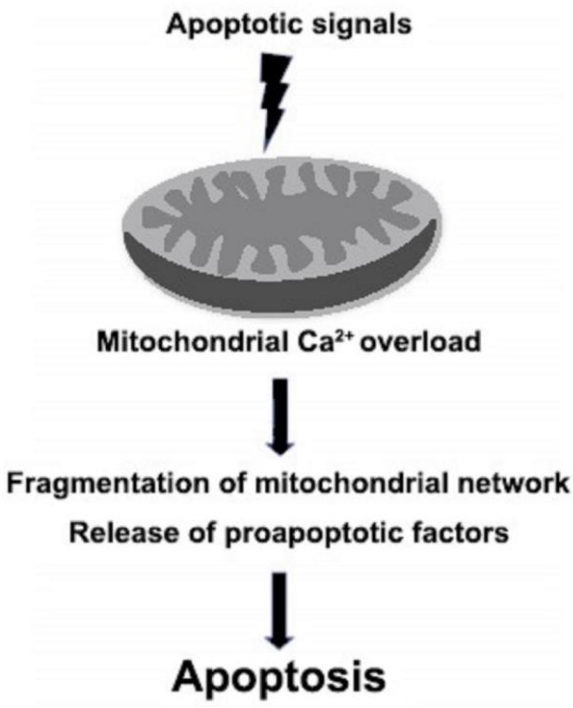


Figure 7. Schematic overview apoptosis initiated apoptotic signal in the form of the release of calcium ions ER savings and increased uptake by the mitochondria.[21]

2. Conclusion

Epidermal calcium gradient, ER calcium homeostasis, and calcium influx through calcium channels play important roles in skin barrier homeostasis, epidermal barrier formation, keratinocyte differentiation, and apoptosis. Understanding the mechanism of regulation and function of calcium-related to skin barrier homeostasis can add insight into the role of calcium in the skin barrier.

3. References

1. Titchenal A, Hara S, Caacbay NA, Lau WM, Yang YY, et al. Calcium. In: Human Nutrition. University of Hawai at Manoa Food Science and Human Nutrition Program. 2020; 613–631.
2. Balk EM, Adam GP, Langberg VN, Earley A, Clark P, et al. Global dietary calcium intake among adults: a systematic review. Osteoporos Int. 2017; 28(12): 3315–3324.
3. Kubo A AMSB. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ OJ, editor. Fitzpatrick's Dermatology. 9th ed. McGraw Hill Education. 2019; 206–31.
4. Lee SE LS. Skin barrier and calcium. Ann Dermatol. 2018; 30(3): 265–75.
5. Permenkes RI. Regulation of the Minister of Health of the Republic of Indonesia Number 28 of 2019 concerning The Number of Recommended Nutritional Adequacy for the People of Indonesia 2019. 2019.
6. Jellum L, Hitzeman J, Knauss M, Henderson S, Harnden T, et al. Blood, Bones & Teeth Micronutrients. In: Principles of Nutrition. 2nd ed. Galileo: Georgia Highlands College; 2018; 360–1.
7. Catharine RA, Taylor CL, Yaktine AL DVH. Calcium metabolism. DRI Dietary Reference Intakes Calcium Vitamin D. Washington DC: The National Academic Press; 2011; 38–42.
8. James WD, Elston DM, Treat JR RM. Eczema, Atopic Dermatitis and Noninfectious

immunodeficiency disorder. In: Andrew' disease of the skin clinical dermatology. 13th ed. Elsevier; 2019; 69.
9. Moe SM. Calcium homeostasis in health and in kidney disease. Compr Physiol. 2016; 6(4): 1781–1800.
10. Rinnerthaler M RK. The influence of calcium on the skin pH and epidermal barrier during aging. Curr Probl Dermatol. 2018; 54: 86–79.
11. Yosipovitch G, Misery L, Proksch E, Metz M, Stander S SM. Skin barrier damage and itch: Review of Mechanisms, Topical Management and Future Directions. Acta Derm Venereol. 2019; 99: 1201–1209.
12. Proksch E JJ. The skin's barrier. Gournale d Ital dermatolo venereolo. 2009; 144(6): 689–700.
13. Elias PM, Franz TJ, Tsai JC, Menan GK, Feingold KR SM. Skin Barrier. In: Bolognia JL, Schaffer JV CL, editor. Dermatology. 4th ed. Wiley; 2018. p. 2176–9.
14. Asmara A, Daili SF, Noegrohowati T ZI. Vehiculum in Topical Dermattherapy. MDVI. 2012; 39(1): 25–35.
15. Sutiari NK. Macro Mineral Calcium. Denpasar: Faculty of Public Health Udayana University. 2017.
16. Samanta A, Hughes, TET M-BVY. Transient Receptor Potential (TRP) Channels. Membrane Protein Complexes: Structure and Function. 2018; 141–165.
17. White JML. Irritant contact dermatitis. In: Griffiths C, Barker J, Bleiker TO, Chalmers R CD, editor. Rook's Textbook of dermatology. 9th ed. Wiley. 2017; 129.1-129.8.
18. Requena CN, Amodio PS, Castaño O EE. Wound healing-promoting effects stimulated by extracellular calcium and calcium-releasing nanoparticles on dermal fibroblasts. Nanotechnology. 2018; 29(39): 395102.
19. Celli A, Sanchez S, Behne M, Hazlett T, Gratton, E MT. The epidermal Ca2+ Gradient: Measurement Using the Phasor Representation of Fluorescent Lifetime Imaging. Biophys J. 2010; 98(5): 911–21.
20. Proksch E, Brandner JM JJ. The skin: an indispensable barrier. Exp Dermatol. 2008; 17(12): 1063–72.
21. Giorgi C, Baldassari F, Bononi A, Bonora M, De Marchi E, Marchi S PP. Mitochondrial Ca2+ and apoptosis. Cell Calcium. 2012; 52(1): 36–43.