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Importance of Calcium

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Abstract: Calcium is the most abundant mineral in the body. Calcium regulates many cellular processes and has important structural roles in living organisms. Skeletal muscle structure and function, polymerisation of fibrin and the conduction of impulses in the nervous system are regulated by calcium. Calcium is an important intracellular messenger in protozoa, plants, and animals. Calcium-transporting systems which are located in the plasma membrane and in the organelles, regulate the ionic concentration of calcium in various compartments according to the different demands of the physiological cycle and these systems upregulate calcium entry by the action of several hormones and calcium binding proteins. Opening of calcium influx channels increases the cytosolic calcium concentrations but high calcium concentrations are toxic to the cell. Because of this toxicity; calcium is rapidly removed from the cytosol by calcium pumps and exchangers. Changes in cytosolic calcium concentrations cause a wide range of cellular responses. Cellular calcium is known to play an important role in apoptosis and the accumulation of calcium can induce various apoptotic pathways in the cell. Maintenance of the cellular calcium homeostasis has various benefil's for human health and the deficiency of calcium causes many pathological conditions.

Key Words: Calcium, apoptosis, signalling, calcium binding proteins

Introduction

Cytoplasmic calcium (Ca^{2+}) concentration modulates various cellular functions, such as gene expression, metabolism, proliferation, secretion, neural excitation and fertilization (1, 2). The recommended intake of calcium is approximately 1000 mg/day, this requirement increases during childhood growth, lactation and pregnancy (3). The intracellular Ca^{2+} is sequestered into intracellular organelles; mitochondria, endoplasmic/sarcoplasmic reticulum (ER/SR), nucleus, lysosomes, and Golgi apparatus (4). These structures provide both an internal Ca^{2+} regulation and distribution system, and a scaffold for the synthesis, targeting, and insertion of channels and receptors (5).

Parathyroid hormone, calcitonin and 1, 25 dihydroxyvitamin D, and some systemic (thyroid, sex steroid, glucocorticoid) hormones or humoral factors (cytokines, growth factors) are involved in the regulation of the Ca^{2+} level in blood and in bone metabolism (6).

Ca^{2+} homeostasis is also very important in the aging process, cancer, heart disease, and muscle and neurodegenerative diseases (7), as well as descent of the testis (8, 9).

Calcium signalling

Ca^{2+} signalling plays an important role in exocrine and hormonal secretion, muscular and non-muscular motility, and the activity and regulation of several metabolic pathways (10). The majority of intracellular Ca^{2+} is stored in the ER and once Ca^{2+} is released from the ER, specific plasma membrane Ca^{2+} channels are activated, resulting in a 10-100 fold increase in intracellular Ca^{2+} concentration of (3, 11). Stimulation of cell surface receptors that increase phosphatidylinositol 4, 5-bisphosphate hydrolysis leads to intracellular Ca^{2+} release and activation of plasma membrane Ca^{2+}entry channels (12). The Ca^{2+}-binding protein, calmodulin, activates protein kinase C (PKC) by phosphorylation, analogous to cAMP and diacylglycerol activating protein kinases, and

protein kinase C may activate cytoplasmic enzymes or affect gene transcription by phosphorylating the kinases in the MEK-MAPK signalling pathway (3).

Brain aging is associated with a dysregulation of intracellular Ca^{2+} homeostasis, which leads to deficits in Ca^{2+}-dependent signalling pathways (13). Associative learning behaviours of living animals have been correlated with changes of neuronal voltage-dependent K^+ currents, PKC-mediated phosphorylation and synthesis of the Ca^{2+} and GTP-binding proteins. Some of these molecular events have been found to be dysfunctional in Alzheimer's disease (14).

Ca^{2+} is also an important intracellular messenger in plants. Free Ca^{2+} concentration in the cytoplasm is influenced by extracellular signals such as light, gravity, and hormones, various physiological processes such as cell elongation, abscission, senescence, tuberization, stomatal control, chloroplast movement, and secretion (15). Calcium signalling and Ca^{2+}-dependent protein kinases play pivotal roles in some protozoa, including the malaria parasites and in algal species (16, 17). Ciliary and flagellar motility is regulated by changes in intraflagellar Ca^{2+} (18). Also Ca^{2+} may be an appropriate candidate as a second messenger during the morphogenetic transformation of *Leishmenia donovani* (19).

Calcium pumps

Cells use both active and passive mechanisms to maintain Ca^{2+} within a narrow range for intracellular signalling and other metabolic processes. Active mechanisms include plasma membrane and ER/SR-Ca^{2+}-ATPases, Na^+/ Ca^{2+}exchangers (NCX), while the passive mechanisms include Ca^{2+} channels (4, 10).

Changes in the transport activity of the plasma membrane calcium ATPase (PMCA) occur during aging (7). PMCA is regulated by calmodulin, which stimulates PMCA activity by binding to an autoinhibitory domain of PMCA (20). Sarcoplasmic reticulum Ca^{2+} ATPases (SERCA) are encoded by three genes. SERCA1 is expressed largely in skeletal muscle and SERCA2a is expressed largely in cardiac muscle. SERCA2b is ubiquitous and functions to maintain the ER stores loaded with Ca^{2+}. The expression pattern and specialized function of SERCA3 are not fully understood (21).

Secretory pathway calcium ATPase (SPCA) activities from a number of tissues have been studied and shown to be particularly high in the brain, aorta, heart, fat pads and testis (22). SPCA supplies the Golgi apparatus, and possibly other more distal compartments of the secretory pathway, with the Ca^{2+} and Mn^{2+} necessary for the production and processing of secretory proteins. (23), SPCA1 is induced in lactating mammary tissue (24). It could also play a role in detoxification of cells overloaded with Mn^{2+} (25).

The Ca^{2+} channel mediates the penetration of Ca^{2+} into cells. They are not completely selective and transport Ba^{2+} and Sr^{2+} in preference to Ca^{2+} (10). There are Ca^{2+} channels in the plasma membrane and also the SR membrane (26).

The Na^+/Ca^{2+} exchanger is expressed in the plasma membrane of virtually all animal cells especially in the excitable cells. As a reversible transporter, it also mediates Ca^{2+} entry in parallel with various ion channels. In cardiac myocytes, and probably other cell types, the exchanger serves a housekeeping role by maintaining a low intracellular Ca^{2+} concentration (27).

Calcium in apoptosis

Calcium and Ca^{2+} binding proteins induce apoptosis via extrinsic and intrinsic pathways. An extrinsic pathway, activated through cell death receptors such as Fas, proceeds via initiator caspases 8 or 10 (28), which in turn convert the major executioner enzyme, caspase 3 (29). In some cases the extrinsic pathway can intersect with an intrinsic mitochondrial apoptotic pathway. In this intrinsic pathway, an apoptosome complex is formed when direct or indirect cell death signals cause the release of mitochondrial cytochrome c (30), which then complexes with apaf-1 and pro-caspase 9 in the presence of dATP (31). Caspase 9 is activated in the complex and then triggers caspase 3, cleaving target proteins, and apoptosis ensues (28, 32).

Mitochondria contain several proteins that are liberated through the outer membrane in order to participate in the degradation phase of apoptosis (33). Soluble proteins are released from the intermembrane space such as the proapoptotic cytochrome c (34), procaspase 2, 3 and 9, the apoptosis inducing factor (AIF) (33) and Smac/Diablo (35, 36) initiating the caspase cascade leading to the cleavage of a large quantity of proteins and eventually to the ordered disassembly of the cell. Irreversible opening of the mitochondrial permeability transition pore and the collapse of the mitochondria membrane potential is controlled by

members of the Bcl-2 family and induction of uncoupling protein-3 (33, 37, 38). A second intrinsic pathway does not involve the formation of an apoptosome complex. This pathway requires the formation of an ER complex involving caspases 7, 9, and 12 (39). ALG-2 appears to mediate ER stress-induced apoptosis as a member of the ER complex in response to aberrant concentrations of intracellular Ca^{2+} (28). The ER also contains several Bcl-2 binding proteins, and Bcl-2 has been reported to exert part of its cytoprotective effect within the ER. Overexpression of Bcl-2 in HeLa cells reduces the Ca^{2+} concentration in the ER by increasing passive Ca^{2+} leak from the organelle. Bcl-2-dependent reduction of Ca^{2+} is an important component of the anti-apoptotic program controlled by this oncogene (40).

The dysregulation of mitochondrial Ca^{2+} homeostasis is now recognized to play a key role in several pathologies that enhance generation of reactive oxygen species, triggering of the permeability transition pore, and cytochrome c release, leading to apoptosis (41). Inhibition of caspase activity in the hippocampus blocked long-term, but not short-term, spatial memory. These results suggest that caspase-mediated cellular events in hippocampal neurons are critical for long-term spatial memory storage (42).

Clinical importance

Osteoporosis is a significant problem in women and men. Ca^{2+} and vitamin D have a good safety profile and may actually have benefits far beyond osteoporosis therapy. Ca^{2+} may increase high-density lipoprotein, prevent colon polyps, reduce blood pressure and may promote weight loss (43). Symptoms of Ca^{2+} deficiency include rickets, tetany, and hypertension (44-46). During angiogenesis, endothelial cells react to stimulation with finely tuned signalling responses and Ca^{2+} plays a role in the regulation of angiogenesis (47).

Mutations or functional abnormalities in the various Ca^{2+} transporters often lead to a plethora of diseases. Skeletal-muscle pathology can be caused by mutations in ryanodine receptors (malignant hyperthermia, porcine stress syndrome, and central core disease), dihydropyridine receptors (familial hypokalemic periodic paralysis, malignant hyperthermia, muscular dysgenesis) or Ca^{2+} pumps (Brody disease). Hemiplegic migraine, episodic ataxia and some forms of epilepsy can be due to mutations in PMCA (48). Darier's disease is a high penetrance, autosomal dominant mutation in the ATP2A2 gene, which encodes the SERCA2 Ca^{2+} pump (49).

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