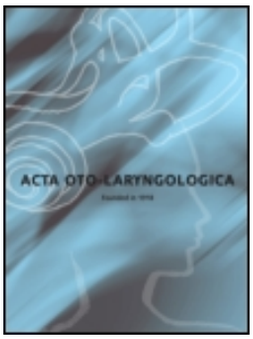

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Basic Mechanisms of Cellular Calcium Homeostasis

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This contribution summarizes some basic principles of calcium distribution and calcium movements in eukaryotic cells. Emphasis is placed upon modes of calcium entry into cells, routes of calcium extrusion from cells, subcellular distribution of calcium, and the regulatory role of calcium for the control of membrane permeability to calcium itself and to other ions.

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INTRODUCTION

It is essential for a eukaryotic cell at rest to maintain the cytosolic free, i.e. ionized, calcium concentration well below 10^{-7} M, which means 10000 times lower than the extracellular calcium-ion concentration. Yet the overall calcium content of cells containing mitochondria and sarcoplasmic reticulum ranges in the order of 1 mmole/g wet weight, which indicates that from subcellular organelles towards the cytosol there exists a 'theoretical' gradient of 10000 as well (Fig. 1). Upon a physiological stimulus, calcium in the cytosol becomes ionized so that the free concentration increases for a limited period up to values around 10×10^{-6} M, i.e. about 100-fold the resting concentration, in order to induce physiological activity. Even under these conditions there remains a gradient of about 100 from extra- to intracellular space and from intracellular binding sites to the cytosol, respectively (Fig. 2).

It is obvious that such a distribution pattern, reflecting a situation far from equilibrium, requires mechanisms to effectively separate different compartments (such as extra- and intracellular space, intra- and extrasarcoplasmatic reticular space), in order to extrude calcium from cytosol to extracellular fluid, to buffer calcium which is in excess of physiological needs intracellularly and to warrant adequate entry or release of calcium to the cytosol.

Under normal physiological conditions this system has in fact the capacity to always keep the calcium-ion concentration in the cytosol well below toxic values. However, under conditions of lack of oxygen, the system may rapidly fail, allowing undue entry and inadequate sequestration of calcium which leads to calcium overload, functional abnormalities and eventually to cell death.

Mechanisms underlying calcium entry into cells

1. The lipid bilayer raises several barriers to the diffusion of ions (Fig. 3). The core formed by interaction of fatty acids forms a strongly lipophilic barrier, while at the internal and external lipid–water interfaces, water molecules become structured, thus 'cementing' the phospholipid head groups together. Charged carboxylic- and phosphate groups as well as charged glycopeptides cause electrostatic repulsion and attraction for ions, which should result in delayed diffusion under certain conditions. Since the energy required to translocate ions through the lipid bilayer is proportional mainly to the charges of the respective

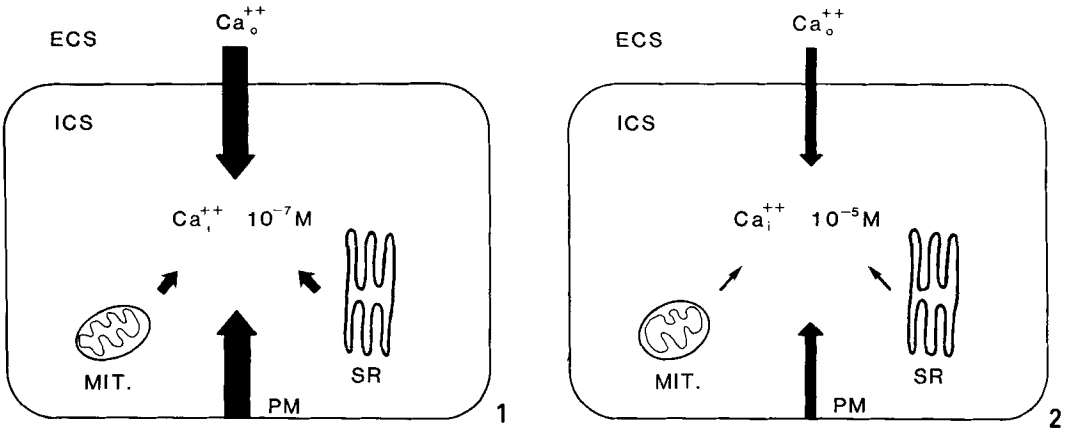

Fig. 1. Gradients for calcium-ions under resting conditions.

Fig. 2. Gradients for calcium-ions under stimulation.

ion, it is conceivable that permeability for calcium is much lower than for sodium and potassium. For theoretical reasons the barrier function of membranes should be strengthened by the existence of a transmembrane electric field which is the consequence of a transmembrane potential. Along with depolarization, the aggregation of water molecules and therewith part of the external and internal barrier dissipates, and in consequence membrane permeability should increase (12, 13, 15).

2. Insertion of protein molecules into a lipid bilayer increases permeability markedly (the interested reader is referred to refs. 2 and 24). It is speculated that due to protein–lipid interactions an increased permeability is created around a membrane-integrated protein (Fig. 4). According to what has been stated before, such a 'permease' molecule should be able to change its structure and thus the quality of interaction with the lipid environment upon, e.g., different degrees of membrane polarization. A phenomenon of this type would therefore explain the basic properties ascribed to ion channels.

3. It has been demonstrated in a number of cell types that some physiological stimuli open up 'channels' through which calcium can enter cells according to the concentration gradient from the extra- to the intracellular space (for details, see e.g. ref. 4). These channels can be operated by drug receptor interactions, e.g. by catecholamines, or they

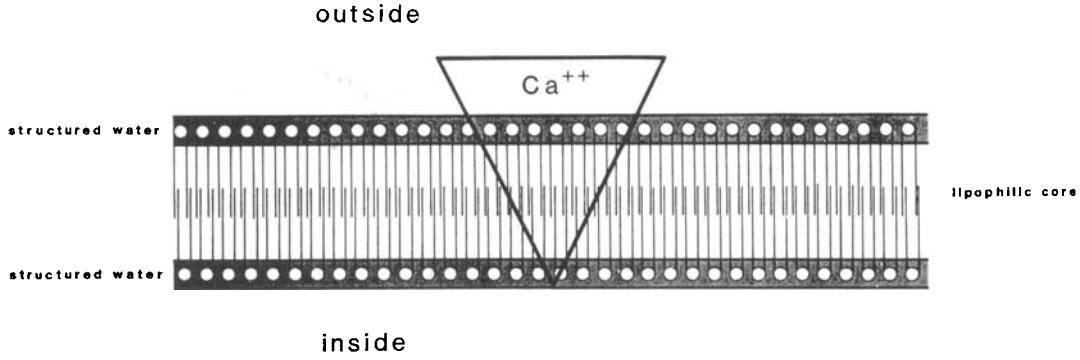

Fig. 3. Permeability of a lipid bilayer for calcium-ions.

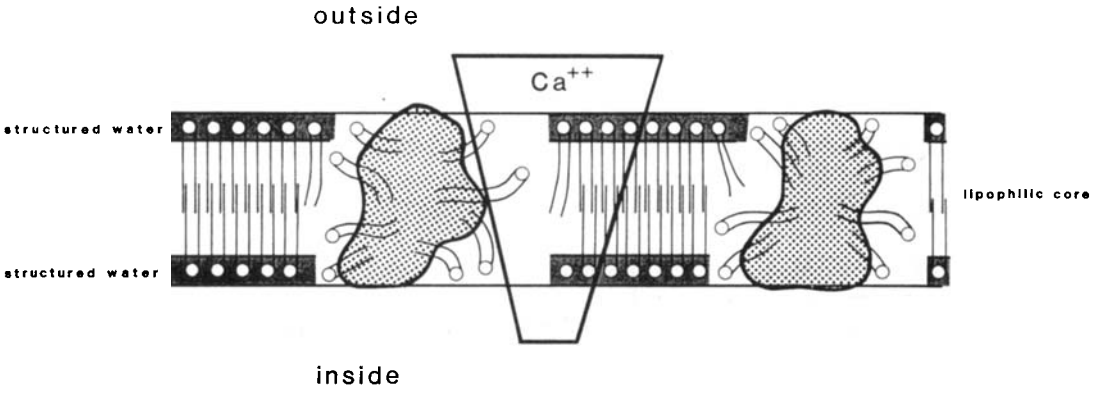

Fig. 4. Formation of "pores" due to protein insertion into liquid bilayer membranes. "Permease"-activity of proteins in membranes.

are activated by a breakdown of the membrane potential (Fig. 5). Accordingly, they are termed 'receptor-operated channels' and 'voltage-operated channels'. Moreover, both types of channel have to be subclassified because they can be opened by a variety of different agonists and they display different thresholds with respect to the membrane potential at which they become activated. Additional differences result from the fact that both the distribution and the selectivity for certain agonists as well as the activation thresholds are variable in different tissues, e.g. heart muscle, smooth muscle, neurons, etc. Furthermore, species-related variations in channel characteristics have to be taken into account. Finally, it is evident that the characteristics of calcium channels are strongly influenced by the experimental approaches which sometimes require rather unphysiological conditions (such as voltage clamping or patch clamping).

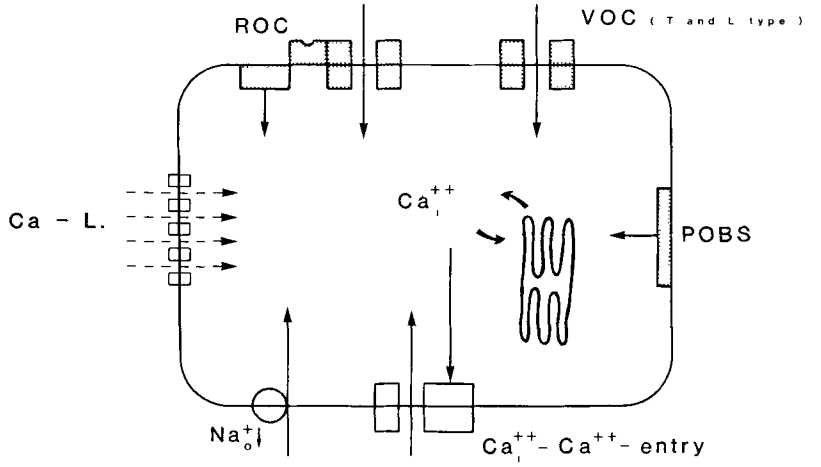

Fig. 5. Mechanisms of calcium increase in the cytosol. ROC = receptor operated channel; VOC = voltage operated channel; POBS = potential operated binding sites; SR = sarcoplasmic reticulum; Ca_i^{++}–Ca^{++}entry = calcium entry induced by increased intracellular calcium; $Na_o^+ \downarrow$ = Na–Ca exchange; Ca-L. = calcium leaks.

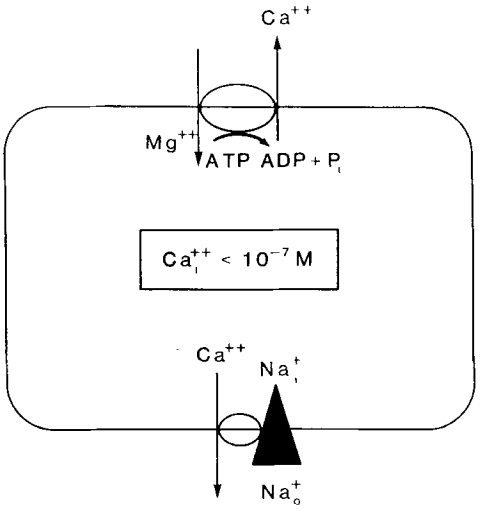

Fig. 6. Outward directed transports of calcium: Na–Ca exchange (lower part) which is driven by the Na gradient. Ca–Mg adenosinetriphosphatase which is driven by phosphorylation through ATP.

Mechanisms underlying intracellular release of calcium

Within the cell, calcium can either be bound to lipids and proteins or can be stored in subcellular organelles like the sarcoplasmic reticulum and mitochondria (Fig. 5). At present it is not known whether storage and release of calcium by the sarcoplasmic reticulum or by mitochondria is of general physiological importance in different cell types, or whether these events are more related to pathological conditions.

The actual contribution of all these processes depends on their respective affinity for calcium and on their absolute capacity to bind or to store this cation (14). While most of the research work is focused upon the contribution of the sarcoplasmic reticulum and of mitochondria to intracellular sequestration and release of calcium, some investigators have put more emphasis on the role of plasmalemmal lipids for calcium handling.

Several investigators suggested that plasmalemmal lipids, preferentially acidic lipids of the phosphatidyl-serine and -inositol class, which seem to be exclusively located at the internal surface of the sarcolemma (11, 13, 16, 25), may contribute considerably to calcium binding and release under both physiological and pathological conditions. The binding capacity of these types of lipids is high (in the mmolar range) and the affinity for calcium is variable, depending on the respective phospholipid and on the actual membrane potential (12).

Phosphatidyl-serine was proposed to be a candidate for high affinity binding of calcium under conditions where the membrane is polarized, while having low affinity in the depolarized state (12, 13).

However, the contribution of calcium–lipid interaction remains theoretical at present, since no clear-cut experimental proof is yet available.

A variety of intracellular proteins have been shown to bind calcium, e.g. tropomyosin in muscle or calmodulin, a related protein, in other cell types (for details, see e.g. ref. 4). The capacity of the latter type of protein to bind calcium under physiological or pathological conditions is still under debate.

With the exception of skeletal muscle cells the contribution of the sarcoplasmic reticulum to regulation of intracellular calcium undulations is not clear and needs further investigation, especially in neuronal cells (4). Mitochondria are definitely involved in sequestration of calcium, however, most probably under pathological conditions such as ischemia-induced calcium overload. Further experiments are required to determine their

affinity for calcium under in vivo conditions, since the results available so far are conflicting.

Cell-outward directed calcium movements

In principle, two major mechanisms have been experimentally verified (Fig. 6) which serve to reduce intracellular calcium or to maintain calcium homeostasis: the ATP-driven sarcolemmal calcium–magnesium ATPase (5, 6, 10, 11, 17, 19, 22) and the sodium-gradient driven Na-Ca exchange process (1, 3, 7, 9, 18, 21).

Both processes are directly or indirectly ATP-dependent, since the sodium gradient can only be maintained as long as the sodium–potassium–ATPase is able to extrude Na from the intra- to the extracellular space. The relative contribution of either process under physiological and pathological conditions is not clear, as yet.

Control of membrane permeability by the intracellular ionized calcium concentration

A regulatory influence of intracellular calcium ions on potassium permeability is well documented for many different cell types, such as neurons, different muscle fibres and conducting tissues, mammalian red blood cells (for review, see (10)). This calcium-induced increase in potassium conductance may result, depending upon the duration of elevated intracellular calcium-ion concentration, in hyperpolarization or, if increased permeability leads to critical loss of cellular potassium, in depolarization. Recently, evidence has accumulated that prolonged increases in cytosolic calcium-ion concentrations not only allow an efflux of potassium with the consequence of membrane depolarization, but also an entry of sodium and calcium through a non-selective cation channel and there is first evidence that this channel can be blocked by a new class of pharmacological agents which belong to the class of para-fluor-phenoxyalkylpiperidinyl-benzthiazolamines (8, 20, 23). It is not clear whether this non-selective cation channel is a converted selective channel, or a pre-existing channel, which is only activated under pathological conditions accompanied by an elevated cytosolic calcium ion concentration or by sustained membrane depolarization, or whether a non-selective permeability originates from lipid reorganization (lipid vesiculation or micellation). Whatever the case, it seems clear that augmented cytosolic calcium-ion concentrations influence membrane properties by inducing increased permeabilities, not only for calcium itself but also for other cations.

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