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CHANGES IN THE TRANSPORT OF Ca^{2+} IN THE LIVER MITOCHONDRIA IN HEPATITIS WITH HELIOTRIN

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Abstract: It is very important to maintain a low level of Ca^{2+} for the normal functioning of the cell, because an increase in the amount of Ca^{2+}, even for a short time, can directly express the effect of various factors: hormones, neuromediators, growth factors and antigens in the cellular response. Eukaryotic cells maintain a Ca^{2+} transport system in the plasma membrane, mitochondria, and endoplasmic reticulum.

Key words: ion, cell, nerve synapses, neurotransmitter, muscle fiber, adrenaline, glycogen, plasma membrane, cytoplasm.

Аннотация: Для нормального функционирования клетки очень важно поддерживать низкий уровень Ca^{2+}, поскольку увеличение количества Ca^{2+} даже на короткое время может напрямую выражать действие различных факторов: гормонов, нейромедиаторов, роста. Факторы и антигены в клеточном ответе. Эукариотические клетки поддерживают систему транспорта Ca^{2+} в плазматической мембране, митохондриях и эндоплазматическом ретикулуме.

Ключевые слова: ион, клетка, нервные синапсы, нейромедиатор, мышечное волокно, адреналин, гликоген, плазматическая мембрана, цитоплазма.

Аннотация: Ҳужайранинг меъёрда фаолият кўрсатиши учун Ca^{2+} ни паст миқдорда ушлаб турилишини аҳамияти жуда муҳим, чунки қисқа вақтга бўлса ҳам Ca^{2+} ни миқдорини ошиши ҳилма хил омиллар: гормонлар, нейромедиа-торлар, ўсиш омили ва антигенлар таъсирини ҳужайра реакциясида бевосита ифодалаши мумкин. Эукариот ҳужайраларнинг плазматик мембранасида, митохондриясида ва эндоплазматик ретикулумида Ca^{2+} ташилиш тизимини сақлайди.

Калит сўз: ион, ҳужайра, нерв синапслар, нейромедиатор, мушак толаси, адреналин, гликоген, плазматик мембрана, цитоплазма.

Ca^{2+} ion plays an important role in cellular reactions, for example, the release of neurotransmitters in nerve synapses, the breakdown of glycogen under the action of adrenaline on muscle cells, the contractile activity of muscle fibers, etc. But the long-term increase in the amount of Ca^{2+} in the cytosol leads to cell death - apoptosis.

While intracellular ionized Ca^{2+} of 10-7 - 10-6 M controls most processes controlled by Ca^{2+}, the amount of Ca^{2+} between tissues is much higher, around 10-3 M. Normally, the plasma membrane maintains three systems that control Ca^{2+} channels, specific ATF-ase, and $Na+/Ca^{2+}$ exchange.

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The entry of Ca^{2+} into the cell according to the amount of the gradient is carried out mainly through the Ca^{2+} channel in the plasma membrane. Ca^{2+} is released from there by plasma membrane Ca^{2+} ATF-ase and $Na+/Ca^{2+}$ exchange. A small amount of Ca^{2+} in the cell is maintained by the activity of the Ca^{2+} transport system in the endoplasmic reticulum and mitochondria with ATF-ase140. The difference between Mg^{2+} ion and Ca^{2+} is that it is present in millimolar amounts in the cytoplasm and does not go outside.

One hypothesis explaining this selectivity towards these ions is that Ca^{2+} forms insoluble phosphate salts with phosphates, including ATF, the cell's main energy currency. Thus, the primary evolutionary strategy, according to the scientist, was to remove excess Ca^{2+} from the cytoplasm to the surface of the element.

Later, after the formation of a gradient of Ca^{2+} in the cell, the increase in the amount of this ion for a short period of time is used by the cell as a kind of signal that activates a number of enzymes and controls proteins.

Ca^{2+} enters the mitochondria electrophoretically through the Ca^{2+} uniporter, which is formed in the respiratory chain of the inner membrane and holds the electrical component that drives the proton. Other ions are also transported through the uniporter, including Sr^{2+}, Mn^{2+}, and Ba^{2+}-like ions.

Hemicationruten red effectively inhibits the entry of Ca^{2+} into mitochondria through the uniporter. Electroneutral $2Na^{2+}/Ca^{2+}$ exchange or Na+-dependent mechanism is the main mechanism of Ca^{2+} release from mitochondria. Sr^{2+} ions can also be transported by the same mechanism.

There are many inhibitors of the Na+-dependent Ca^{2+} release mechanism, but dithiazem and tetraphenylphosphoryl are the most commonly used. The Na+-dependent mechanism is supported by Na+/H+ exchange with a proton-mobility gradient, similar to the work of the Ca^{2+} uniporter.

The participation of these mechanisms in metabolic reactions sensitive to Ca^{2+} in the matrix of mitochondria is thought to be their role in controlling the quantitative fluctuations and changes of Ca^{2+} in the cytosol and in triggering the mechanism of switching the induction of mitochondrial permeability through apoptosis.

The Na+-dependent mechanism of Ca^{2+} release is predominant in liver and kidney mitochondria.

It also transports Sr^{2+} and Mn^{2+} ions, but this process is slower than the transport of Sa^{2+}. This mechanism is considered non-electrogenic and is used to explain the low activity of Na^{+}/Ca^{2+} exchange in the Ca^{2+} cycle of Ca^{2+} into two N^{+} ions and sometimes mitochondria. In addition to the uniporter and Na^{+}/Ca^{2+} exchange mechanisms of Ca^{2+} transport, ligand-inducible Na^{+}-dependent Ca^{2+} efflux is activated by high-speed coupling to Ca^{2+}-dependent domains and, as expected, mechanisms that block specific Ca^{2+} efflux transporters.

On the other hand, Na^{+}-dependent release of Ca^{2+} is also inhibited in the separation of oxidation from phosphorylation, assuming the existence of an active transport system in mitochondria. This transporter system, together with the Na+/H+ antiporter, provides a transport cycle that ensures

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continuous circulation of Ca^{2+} across the inner membrane when Ca^{2+} is low in mitochondria under physiological conditions.

In addition to the physiological transport of Ca^{2+}, there is a completely different mechanism in which the amount of Ca^{2+} in the cytosol is gradually and significantly increased during ischemia and oxidative stress and is associated with increased Ca^{2+} uptake in the mitochondria. In this case, in the absence of exogenous nucleotides in mitochondria and in the presence of inorganic phosphate or peroxides, the increase of Ca^{2+} changes the permeability of mitochondria due to the opening of "pores" sensitive to cyclosporin A.

Antiporter inhibitors that bind the membrane on all sides have opposite effects: "cytoplasmic" inhibitors (in which ADF/ATF binds to the antiporter in the σ conformation) atractylate, carboxyatractylate and acyl CoA stimulate the induction of "pores", while the "matrix" inhibitor (i.e. binding to the antiporter in m conformation) acid prevents its opening.

It is believed that the diameter of "pores" sensitive to cyclosporin A is equal to 2.0 - 2.6 nm. "Pora" exists in two conformations in the open state: low and high conductivity. Cyclosporin A-sensitive pores in the low-permeability state allow compounds with molecular weights up to 300 daltons, including ions such as N^{+}, Ca^{2+}, or K^{+}.

In this case, the "pore" of the mitochondrial membrane is not damaged, and there is no change in its activity, i.e., matrix volume control and membrane potential, and the matrix rN change that occurs with the entry of Ca^{2+} into the mitochondria is controlled, and the Ca^{2+} signaling network allows the cell to transport Ca^{2+} through a channel in the mitochondria during the normal life of the cell. participates in entering.

The "pores" opened in this conformation completely and permanently reduce the transmembrane proton gradient in vitro, allow the release of various ions (similar to Ca^{2+}) and small molecules (similar to pyrimidine and adenine nucleotides), as well as some components from the measuring medium to the matrix (similar to sucrose). provides diffusion.

In the hyperconductance state, Ca^{2+} potential and pH-dependent channel signatures appear, and redox and phosphate potentials are modulated. The opening of the "pore" controls the binding of mitochondria to the cyclophilin matrix domain, explaining the inhibitory effect of cyclosporine A.

The openness of the "pore" is also controlled by the reactive form of oxygen produced by the work of the respiratory chain and the rate of electron transport through the complex in the mitochondrial respiratory chain.

Ca^{2+} inside the mitochondria activates the "pore" by binding to the low-affinity domain (KD + 25 μM). It has been shown that Ca^{2+} ion induces pore opening at higher than physiological levels (>10 μM), but at lower levels it only alleviates the induction of the "pore" by other stimuli.

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A sudden influx of large amounts of Ca^{2+} into the mitochondria can cause the opening of the "pore" even in the pH-dependent low-conductance conformation, while a gentle influx of Ca^{2+} causes the channel to open in the high-conductance state.

In isolated mitochondria, adenine nucleotides inhibit the opening of the "pore" induced by Ca^{2+} and inorganic phosphate or Ca^{2+} and oxidative stress. ADF has the effect of significantly closing the "bribery" that has already been opened. On the other hand, it was found that ATF was the most effective when adenine nucleotides were used to prevent the induction of "pora".

The difference in the effect of adenine nucleotides on this induction process is not related to the affinity of ADF and ATF to adenine nucleotide-translocase.

It can be assumed that different mechanisms underlie the effect of adenine nucleotides on these "pore" components. Extimol, the effect of ATF on the opening of the "pore" depends on the interaction with the kinase on the outer membrane of mitochondria, the closing of the "pore" opened due to the effect of ADF, i.e., its inhibition, can be due to its direct connection with the adenine nucleotide translocase in the inner membrane of mitochondria.

Along with Ca^{2+}, oxidative stress is one of the main inducers of "pore". The opening of "Pora" under conditions of oxidative stress in vivo or in vitro may also involve the oxidation of glutathione, NADF.N and NAD.N. In addition, under conditions of oxidative stress, endogenous phospholipases are activated, and their reaction products include inducers of "pora".

Currently, the biochemical and physiological activity of cyclosporin A-sensitive "pores" in controlling various cellular responses is widely discussed. Under the influence of hormones that enhance the transport of Ca^{2+}, a wave of single and sequentially reversible Ca^{2+} signals appears in the cytosol.

Mitochondria also sense periodic intense and short changes in the amount of Ca^{2+}. In this case, the mitochondria take up a high local amount of Ca^{2+} at a sufficiently high rate, resulting in the activation of the Ca^{2+} uniporter in the mitochondria. Due to the significantly higher rate of Ca^{2+} entry into the mitochondria, the matrix pH changes, opening "pores" in the low-conductance state in the mitochondria, which act as channels for the release of Ca^{2+}. In this case, the release of Ca^{2+} from the mitochondria to the cytosol is observed.

A completely different picture is observed when the amount of Ca^{2+} in the cytosol is gently increased. Under these conditions, the entry of Ca^{2+} into the mitochondria due to the uniporter is significantly slower. In this case, during the absorption of Ca^{2+} into the mitochondria, the matrix pH i practically does not change, as a result, it prevents the opening of the "pore" in conditions of low conductivity.

Excessive uptake of Ca^{2+} in the hyperpermeability state opens "pores", resulting in mitochondrial dysfunction, a significant decrease in membrane potential, and high-amplitude swelling of the mitochondria.

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As a result of these processes, the cell undergoes destruction: necrosis or apoptosis.

The Ca^{2+} ion controls many processes within the cell, including energy production. Such control is carried out directly by the allosteric effect of the Ca^{2+} ion on the target enzyme or by the activation/inhibition of various protein kinases and protein phosphatases that catalyze the phosphorylation/dephosphorylation of the target enzyme.

Currently, it is believed that the Ca^{2+} ion controls the synthesis of ATF in the mitochondria by increasing the activity of several dehydrogenases in the tricarbonic acid cycle.

Summary: It was found that the maximum synthesis and hydrolysis of ATF in mitochondrial respiration is observed when 5•10-7M Sa2+ is added. It was found that a decrease in the amount of Ca^{2+} added to mitochondria to 10-8 M or an increase to 5•10-6 M leads to a decrease in phosphorylated oxidation and ATF hydrolysis.

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