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THE ROLE OF CALCIUM AND CALCIUM REGULATING HORMONAL SYSTEM IN THE MECHANISMS OF COVID-19 CONTAGIOUSNESS AND SEVERITY

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Abstract

Calcium is involved in all vital processes of the body: synaptic transmission, memory development, immunity, blood clotting, heart contractions, etc. In this regard, it is important to understand the involvement of calcium in the development of SARS-CoV-2 virus infection and COVID-19 disease.

We have studied the existing scientific literature, looking for the involvement of both calcium and calcium-regulating hormones (parathyroid hormone, calcitonin, vitamin D) in COVID contagiousness and severity of disease.

Separately, both hypocalcemia and vitamin D deficiency have been identified in a number of large clinical trials as a predictor of mortality in patients hospitalized with COVID-19. Angiotensin-converting enzyme-2 plays a key role in contagiousness with the SARS-CoV-2 virus, and its formation is a calcium-calmodulin-dependent process. In our opinion, in order to prevent the penetration and spreading of the virus in the body, this link should be targeted with the usage of drugs that activate the calcium calmodulin system. Calcium blockers used parallel with hypocalcemia, to some extent, reduce the spreading of the virus in the body in the acute phase of the disease, but it is possible that in the future they lead to deeper and long-term complications - cognitive dysfunction.

However, we did not find any study in the literature that aimed to identify calcium-dependent mechanisms in a complex, dynamic study of the same patients. Therefore, this question is still open in science, because without understanding how the amount of calcium-regulating hormones changes during the disease, without understanding how much phosphorus changes in parallel with calcium, it is impossible to get a complete picture of the disease on the role of calcium-dependent mechanisms in development. Only a summary of such combined data will allow us to reach a scientifically based conclusion, to explain the mechanisms by which hypocalcemia occurs, and by what possible mechanisms it can be prevented.

Keywords: *SARS-CoV-2, calcium, hypocalcemia, calcium regulating hormonal system.*

In December 2019, a new coronavirus disease was discovered, which led to a pandemic in March 2020. The International Committee on Taxonomy of Viruses named this virus SARS-CoV-2 severe acute respiratory syndrome coronavirus 2 [*ICTV, 2020*].

The SARS-CoV-2 virus till continues to mutate, infecting the world's population also today. To date, it has claimed the lives of 5.5 million people [*WHO, 2022*] and is the focus of both healthcare and the scientific community. Every day, new scientific works are published in different high impact journals, aimed at revealing the various mechanisms of infection with COVID-19.

SARS-CoV-2 affects a number of organs,

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causing respiratory, cardiovascular, renal, hepatic and central nervous system disorders [*Zaim S et al., 2020*].

Calcium is directly involved in almost all functions of the body: synaptic transmission, blood clotting, development of immune responses, is a secondary messenger of a number of hormones [*Hasratyan H, 1999; Khudaverdyan D, 2000*]. This suggests that both contagion of SARS-CoV-2, and the course and outcome of the disease, may be calcium-dependent.

The purpose of this article is to summarize the existing literature on the study of calcium related mechanisms participation in the risk of contagion with COVID and desease severity in the last 2 years, which will allow to identify the open scientific problems. Studies of quantitative changes in calcium alone may not be sufficient to determine the causal link, so we will also review the existing literature on calcium-regulating hormonal mechanisms, in particular the role of parathyroid hormone, calcitonin and vitamin D.

SARS CoV-2 causes hypocalcemia: Numerous studies have shown a decrease in serum calcium in patients with hospitalization [*Marazuela M et al., 2020; Martha J et al., 2021*]. Clinical trials of Martha J involved 2032 hospitalized patients, 26% of whom died. Hypocalcemia of different degrees was reported in all deaths, with an average concentration of 0.173 *mmol/L* Ca^{2+} in blood plasma. Hypocalcemia has been recognized by the authors as a predictor factor of death from COVID [*Martha J et al., 2021*]. Hypocalcemia disrupts blood coagulation in several calcium-dependent circuits at the same time: platelet adhesion, activation of damaged tissue, activation of key coagulation factors II, VII, IX, X, synthesis of C and S proteins [*Filippo L et al., 2021*]. Hypocalcemia increases the amount of D-dimer in the body, which is a fibrin-degenarating factor, and the amount of prothrombin, which is a blood-clotting factor. The combined increase of these 2 leads to serious blood clotting disorders, which are the main reason of disorders in patients' different tissues [*Alemzadeh E et al., 2021*]. Hypocalcemia also plays a key role in inflammatory processes. It increases the levels of C-reactive protein, procalcitonin, IL-6. Unfortunately, we have not been able to find any research that could identify the mechanisms underlying COVID caused hypocalcemia.

Calculation of calcium concantration alone does not provide an idea of the reason of the problem and, consequently, the choice of methods to eliminate hypocalcemia, especially since it is known mechanism by which the SARS-CoV-2 infects tissues and leads to problems of organ systems during the disease.

The role of calcium ions in the production of soluble angiotensin converting receptor (ACE-2). The coronavirus is known to have four structural proteins: envelope, membrane, nucleocapsid, and spike proteins. Spike protein has 2 subunits S_1 □ S_2, through which the virus binds to ACE-2 and penetrates into cells. Tissue penetration is facilitated by the trans-membrane protease serine 2 (TMPRSS-2) proteolytic protein [*Bilinska K et al., 2020*], which cleaves the S protein into its subunits, after which only the S_1 protein binds to the ACE-2 receptor [*Hoffmann M et al., 2020*], and the S_2 subunit transmits the virus through the cell membrane [*Shang J et al., 2020*]. Tissues rich in ACE-2 receptors are target for the virus (Fig. 1). There is a point of view that the virus causes a multi-organ infection in the body by the polyamine-dependent mechanisms [*Zilfyan A et al., 2021*].

Angiotensin converting receptor-2 is a protein composed of 805 amino acids, which has 2 domains [*Tipnis S et al., 2000*], transmembrane: 741-763 amino acids [*Donoghue M et al., 2000*] and extracellular ectodomene, 1-740 amino acids [*Towler P et al., 2004*]. The ectodomene is cleaved from the cell membrane by an ADAM-17 protein called TNF-alpha convertase. As a result soluble ACE-2 is produced (Fig. 2). Thus, there are two types of ACE-2 receptors in the body: membrane-bound and free, which is found in blood plasma and tissue fluid [*Tipnis S et al., 2000*]. Moreover, the soluble ACE-2 amount in the plasma of healthy people is so small that it is almost undetectable [*Rice G et al., 2006*], in the plasma of patients with COVID, on the contrary, the amount of free receptor increases sharply [*Lundström A et al., 2021; Vassiliou A et al., 2021*]. Nagy and co-authors, through monitoring, found a positive high correlation between disease severity and amount of free ACE-2 receptors

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

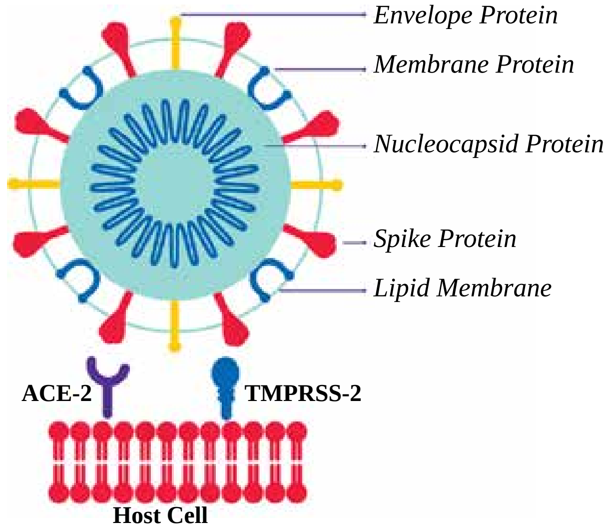

FIGURE 1. Mechanism of SARS-CoV-2 virus cell infection using angiotensin receptors [Sigmaaldrich, 2020]

[*Nagy B et al., 2021*]. The production of free ACE-2 is a calcium-dependent process regulated by calmodulin [*Iwata M et al., 2009; García-Escobar A et al., 2022*]. Calmodulin is activated by binding to calcium ions that have penetrated the cell, then binds to the transmembrane domain of ACE-2, inhibiting the binding of ADAM-17 to the receptor ectodomain and free ACE-2 producing [*Lambert D et al., 2008*].

Lambert significantly stimulated the production of free ACE-2 by blocking calmodulin by means of its antagonists trifluoperazine and calmidazolium. ACE-2 activity is completely suppressed by ethylenediaminetetraacetic acid, EDTA, a calcium binding substence [*Tipnis S et al., 2000*]. It turns out that the calcium calmodulin system can control the production of free ACE-2, which is a key link in the course of the SARS-CoV-2 virus and disease.

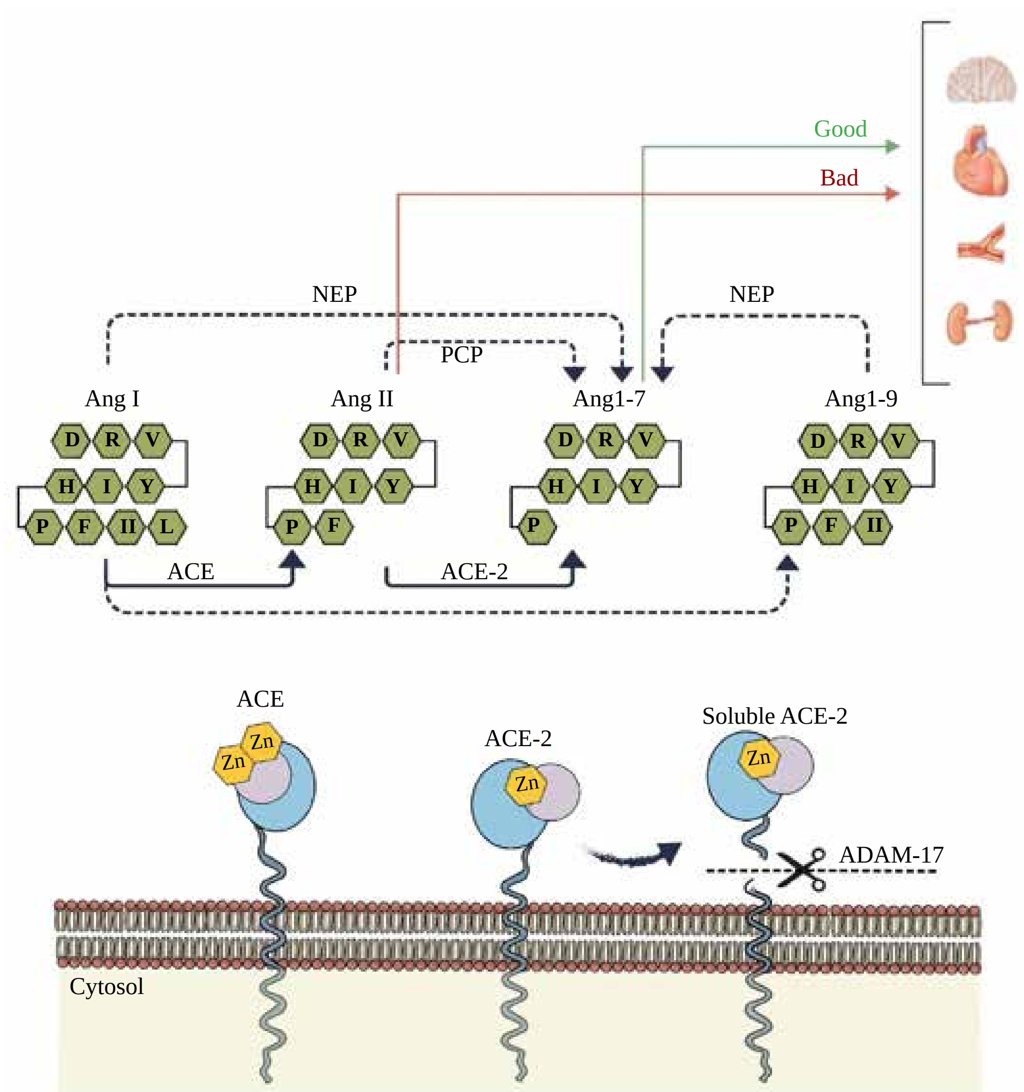

FIGURE 2. ACE-2 pathway [García-Escobar A et al., 2022]

Wang and Zhao's research suggests that the SARS-CoV-2 virus binds to soluble receptors in plasma and penetrates various tissues, infecting cells [*Wang et al., 2021; Yeung M et al., 2021*].

According to Rahman and his teammates, the presence of the receptor in the plasma leads to the spread of the receptor-virus complexes in the bloodstream, which explains the simultaneous damage of tissues in different organ systems during the disease [*Rahman M et al., 2021*].

Early in the development of COVID, there was a 180-degree opposite scientific claim that free receptors, on the contrary, protect the body from infection because the virus-receptor complex, being large in size, does not penetrate new tissues, as if these receptors are a trap for the virus and isolate them [*Krishnamurthy S et al., 2021*]. Examining the material published especially in recent months, we tend to refute this hypothesis, accepting the idea that the soluble ACE-2 is the link between the virus and the virus-receptor complex, circulating in the blood and infecting new tissues.

Thus, dissolved ACE-2 plays a key role in contagiousness with the SARS-CoV-2 virus, and its formation is a calcium-calmodulin-dependent process. In our opinion, in order to prevent the penetration and spreading of the virus in the body, this link should be targeted with the use of drugs that activate the calcium calmodulin system.

It should be noted, however, that ACE-2 recombinant [*Wang K et al., 2020*] is injected into severely hospitalized patients with COVID-19 infection who have cardiovascular problems and hypertension. This is due to the dual function of the receptor. On the one hand, it promotes angiotensin-1 to a strong vasoconstrictor, angiotensin-2, but at the same time, it converts angiotensin-1 into angiotensin 1-7, a vasodilutive protein. For blood pressure, the AT1-7/AT2 ratio must be in the range of 0.5-1 [*Wang K et al., 2020*], as ACE-2 decreases, this ratio decreases, leading to hypertension, as ACE- 2 synthesizes AT1-7 faster than AT-2 [*García-Escobar A et al.,2021*].

The role of calcium ions in the mechanism of virus reproduction. According to the existing scientific literature, calcium ions, in addition to penetrating tissues into the SARS-CoV-2 virus, may also be involved in the life cycle of the virus in target cells. Significant expression of transient receptor potential (TRP) channels genes is observed in virus-infected cells [*Jaffal S, Abbas M, 2021*]. These are cationic pathways, mainly with high permeability to calcium ions [*Julius D, 2013*], that participate in several stages of the virus life cycle [*Jaffal S, Abbas M, 2021*]. Transient receptor potential pathways are classified into several subgroups depending on the amino acid fractions: TRPM (melastatin), TRPML (mucolipin), TRPA (ankyrin), TRPV (vanilloid), TRPP (polycystin), and TRPC (canonical or classical). When the virus is already in the cell, its envelope proteins bind to these receptors, after which the virus assimilates into the endolysosomal membrane of the cell, in particular, the TRPML2 pathways perform this function [*Rinkenberger N, Schoggins J, 2018; Zhao Z, 2021*].

Calcium blockers and Covid-19. Calcium blockers are used in acute treatment of COVID-19: diltiazem, verapamil, amiadarone, nifedipine [*Crespi B, Alcock J, 2020*]. Although calcium channel blockers are widely used in disease treatment regimens, their usefulness is not unequivocally acknowledged in the scientific world. It turns out that hypocalcemia is recognized as a contributing factor to mortality from COVID, but on the other hand, the same patient is given a calcium blocker, which in itself leads to hypocalcemia. Calcium blockers were originally used in medicine as antihypertensive drugs. They block the calcium channels needed to constrict the peripheral arteries, weakening smooth muscles and lowering arterial pressure by dilating blood vessels. Calcium blockers are of two groups: dihydropyridine and non-dihydropyridine, in which there is a structural and functional difference. Almost all dihydropyridines, such as amplodipine, nifedipine, and other dipines [*Solaimanzadeh I, 2020*], are used in the COVID treatment clinics, as are the two non-dihydropyridines, diltiazem and verapamil. All calcium channel blockers reduce the amount of intracellular calcium [*Navarese E et al., 2020*], while intracellular calcium is required for a number of metabolic processes. Thus: Intracellular calcium regulates the activation of mitochondria, the cell's energy factory, on the cell's endoplasmic reticulum. Quantitative fluctuations in calcium in central neurons have been shown to cause mitochondria to swell and die because they are unable to bind to the endoplasmic reticulum and become active, resulting in neuronal apoptosis. This process underlies a number of neurodegenerative diseases [*Godoy J et al., 2021*]. Parkinson's disease is known to be caused by a structural change in alpha-synuclein, but why does this change selectively affect different areas of the brain? Studies have shown that altered alpha-synuclein interacts with dopamine, which is why dopaminergic neurons are particularly affected by the disease. Intracellular calcium deficiency contributes to both alpha-synuclein dysfunction and its interaction with dopamine, and is therefore a risk factor for Parkinson's disease [*Post M et al., 2018*]. Human cognitive functions, especially concentration and memory formation, are high energy-dependent processes. Thus, at the time of concentration the brain, being 1.5-2% of body mass, consumes 20% of all glucose spent by the body. The primary source of glucose here is glycogen accumulated in astrocytes from glial cells. The interaction of astrocytes with activated neurons is regulated by calcium. When intracellular calcium is deficient in neurons and astroglia, this leads to impaired concentration and memory [*Vardjan N et al., 2017*]. The unit of memory is the engram, which describes the magnitude of the structural, dynamic connection of the ensemble consisting mainly of hippocampal neurons [*Tanaka K, McHugh T, 2018*], so the memory generator is the hippocampus. This is where short-term memory is formed, and in order for it to become long-term, engrams need to be created through the hippocampus [*Haubrich J, Nader K, 2018*]. The hippocampus must receive signals from the cortex each time the existing memory is reproduced. For spatial memory, synapses arising and/or activating between the CA1-CA3 sections of the hippocampus's medial-lateral segments of the entorhinal cortex are very important [*Tanaka K, McHugh T, 2018*]. Moreover, their main neurotransmitters are Ca dependent [*Temido-Ferreira et al., 2019*]. Calcium ions, on the other hand, must penetrate the cytoplasm of a neuron in order to activate memory synapses. More than 10 types of calcium channels have been found in CA1-CA3 segment pyramidal cell membranes involved in memory reproduction [*Matthews W, Meck W, 2016*].

COVID-19 virus infects the nervous system, causing encephalopathy, encephalitis, meningitis, ischemic-hemorrhagic stroke, Guillain-Barre syndrome [*Koralnik I, Tyler K, 2020*] in some patients. The long-term effects of COVID-19 are mainly on the nervous system [*Iadecola C et al., 2020*]. The most common of the long-term disorders are olfactory and taste disorders, decreased cognitive function, in particular, difficulty concentrating and developing memory [*Koralnik I, Tyler K, 2020*]. The stimulant effect of COVID-19 virus on neurodegeneration has been confirmed, in particular, the virus accelerates the development of diseases such as Alzheimer's, Parkinson's disease, multiple sclerosis [*Rodriguez M et al., 2020*]. There is ample evidence that the virus causes neurological problems both by directly affecting the nervous system by disrupting synaptic transmission, by neurotransmitters [*Zecca L et al., 2020*], and indirectly, in particular, by problems with the blood clotting immune response origin in the brain [*Wang J et al., 2020*]. Deterioration of memory □ concentration is currently widely discussed as a long-standing post-COVID problem. The virus enters the brain mainly through the olfactory epithelium, passing through the olfactory trunk [*Huang J et al., 2020*], and there are paths directly from the olfactory trunk to the entorhinal cortex and hippocampus [*Leung C et al., 2018*]. Postmortem studies have shown that cerebral accumulations of the SARS-CoV-2 virus occur mainly in the hippocampus, entorhial-frontal cortex [*Matschke J et al., 2020*].

Based on the data presented in the literature, we conclude that the parts of the brain rich in calcium channels are particularly affected, as they are targeted for the life cycle of the virus. It can not be ruled out that long-term cognitive impairment, which lasts for months after an acute period of COVID, is associated with the use of calcium blockers in treatment regimens.

The role of the calcium-regulating hormone system in the mechanisms of COVID-19 disease.

Vitamin D: A study by Radujkovic A. and coauthors (2020) on 185 hospitalized patients with COVID found that 41 of them (22%) were deficient in vitamin D (<12 *ng/ml*). Of all those hospitalized, 28 patients underwent artificial respiration, of which 16% died. The study found a direct high correlation between the need for artificial respiration, mortality and vitamin C deficiency.

Annweiler's team conducted preclinical studies, theoretically hypothesizing that vitamin D could prevent COVID infection through three mechanisms: regulation of the renin-angiotensin system, stimulation of specific immunity, and strengthening of physical barriers [*Annweiler C et al., 2020*]. Covid-19 virus lowers the number of angiotensin-2 receptors by binding to them. This leads to a cascading chain of inflammatory processes, which in turn leads to a cytokine storm, which is the synthesis of a large number of inflammatory cytokines at the same time. Vitamin D activates the genes responsible for the synthesis of angiotensin-2 receptors, thereby correcting this problem [*Mahdavi A, 2020*].

In another investigation 218,372 patients were periodically tested for vitamin D levels for about 12 months from the first days of illness. The authors concluded that there was an inversely proportional correlation between the amount of vitamin C in a patient's contagiousness by SARS-CO-2 virus, and that the majority of deaths in critically ill patients were due to vitamin D deficiency [*Kaufman H et al., 2020*].

Thus, we can state that in the literature there are data from clinical studies published in different journals with a high impact factor of more than 200, which show that vitamin D deficiency several times increases the risk of infection with COVID, as well as predisposes to artificial respiration need and high mortality, but in all the studied mechanisms the protective function of the vitamin D is not related to its regulation of calcium. We believe that in these circumstances, when both vitamin D deficiency and hypocalcemia are considered to be predictors of mortality from COVID, it is at least necessary to determine the correlation between these two indicators, which has not been studied, which is a serious omission for science.

Parathyroid hormone. Although there is a lot of information in the literature on how to treat COVID in patients, who before infection already had high levels of parathyroid hormone, however, there are insufficient studies on the quantitative variations of parathyroid hormone in those who did not initially have hormone problems. On the other hand, it is obvious that the parathyroid glands cannot be inactivated against the background of general hypocalcemia, as there is a negative feedback-regulating mechanism of hormone production and secretion due calcium.

A review of the available literature allows us to conclude that although there are articles recording individual variations in the levels of calcium, vitamin D, and parathyroid hormone in patients with COVID, however, there are no combined studies designed to simultaneously assess calcium and plasma levels in the same patient. Changes in neurons in the brain, such as calcium-regulating hormones such as parathyroid hormone, calcitonin, and vitamin D, and thus the role of COVID infection in the course of the disease. We only managed to find one such article, where Alex Pizzini and his co-authors presented only the numbers: Patients with vitamin D deficiency had hypocalcemia, a significant increase in parathyroid hormone [*Pizzini A et al., 2020*], which does not fit into the concept of calcium channel regulators.

It can be concluded that the possible role of calcium as well as calcium regulatory hormone system, in the contagion with SARS-CoV-2 and severity of the disease has not yet been fully investigated. Calcium blockers used parallel with hypocalcemia, to some extent, reduce the spreading of the virus in the body in the acute phase of the disease, but it is possible that in the future they lead to deeper and long-term complications - cognitive dysfunction. We believe that it is necessary and very actual to investigate in large-scale dynamic quantitative fluctuations of calcium, phosphorus, parathyroid hormone, vitamin D and calcitonin in the blood plasma of people infected with COVID-19, depending on the stage of the disease. Only a summary of such combined data will allow us to reach a scientifically based conclusion, to explain the mechanisms by which hypocalcemia occurs, and by what possible mechanisms it can be prevented.

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I sincerely congratulate our nice scientific and pedagogical staff of the Yerevan State Medical University after M. Heratsi, with the significant day of the entire medical community of our republic - with the date of the 15th anniversary of the founding of the New Armenian Medical Journal.

I am glad that, as a member of the editorial board, I also contributed to the creation of this journal, the international significance of which is worthy of appreciation by the medical community in many developed and developing countries of the world.

Member of the editorial board of NAMJ,
Head of the Department of Normal Physiology of YSMU,
Honored Scientist of the Republic of Armenia,
professor **Khudaverdyan D.N.**

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