The role of calcium in the mechanisms of pathogenesis and pharmacotherapy of mental disorders: a brief review

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ABSTRACT

It is widely accepted that mental disorders cause significant damage to human health. The mechanisms of their pathogenesis have not yet been fully clarified. Hereditary, environmental, metabolic, and other factors are important in these mechanisms. Calcium is considered a possible participant in the mechanisms of pathogenesis. Its serum level is controlled by hormonal regulation. Thyroid and other disorders lead to calcium levels disturbances (hypocalcemia and hypercalcemia). Various physical and mental symptoms accompany these conditions. To clarify the pathogenetic mechanisms of mental disorders and to develop new drug interventions, it is essential to clarify the role of various participants in them, including calcium. The medications that regulate the calcium level, particularly calcium channel blockers, can help develop new treatment methods for mental disorders. It is necessary to study the mentioned drugs' mechanisms of action on mental disorders and the possible ways of their improvement and practical application.

Keywords: *mental disorders, pathogenesis, psychopharmacotherapy, calcium channel blockers, new drugs*

CALCIUM AND NERVOUS SYSTEM

Despite the rapid development of cognitive neuroscience and medicine, the pathogenic mechanisms of mental disorders remain poorly identified, resulting in the therapeutic arsenal of a psychiatrist not being sufficient to address mental health problems fully.

Many factors are involved in the pathogenesis of mental disorders, some of which are heredity, environmental impact [1], and metabolism [2], including calcium metabolism disorders [3,4].

The free ion calcium in the human body participates in various processes, some of which provide the functions of the nervous system, in particular, higher nervous activity [5-7]. Extracellular calcium level abnormalities can cause several psychiatric symptoms, including anxiety, mania, depression, delirium, and psychosis [8]. Intracellular calcium is located in the cytoplasm stored in the endoplasmic reticulum and mitochondria. Its level in the cytoplasm is under strict control.

Calcium is a universal secondary messenger that regulates many essential processes in the cell, such as growth, gene expression, cell plasmatic membrane excitability, apoptosis, and is involved in the activation of enzymes, proteins, and in the regulation of the neurotransmitter vesicles exocytosis [9,10].

Calcium levels in nerve cells must be constantly regulated to ensure their proper functioning. Inside the neuron is a complex calcium signaling system that includes calcium channels, calcium-dependent proteins such as kinases, phosphatases, transcription factors, and neurotransmitter exocytosis [11,12]. There are proteins in the cell membrane that ensure the transport of calcium between extracellular and intracellular media and between the plasma and membrane organelles of the cell. These proteins are voltage-gated calcium channels (VGCC), calcium transporter α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, transient receptor potential channels, and calcium release-dependent pathways. As mentioned, one of the calcium storage sites is the endoplasmic reticulum, which also contains calcium ryanodine and 1,4,5-triphosphate receptors [13].

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In nerve cells, the endoplasmic reticulum is located in the body and protrusions of the cell. It is thought that thanks to this kind of organization, the neuron has united, uninterrupted calcium storage, which is needed to integrate and coordinate the activity of spatially differentiated sites of neurons [14].

Under the influence of the action potential, the potential-dependent calcium channels open in this part, the extracellular calcium ions penetrate the axoplasm of the neuron. Here they bind and modify the molecules of calmodulin proteins in plasma, and the resulting calcium-calmodulin complex activates several enzymes [15]. Activated enzymes, including protein kinases, participate in the release of neurotransmitters in the synaptic transmission, which in turn underlies mental processes. In addition to flowing from the extracellular fluid into the axon, a certain amount of calcium can enter the axoplasm from the endoplasmic reticulum [16].

Synaptic plasticity is the changes that occur in the interneuron connections, due to which the interneuronal interaction is modified and developed [17]. Deviations from this process can lead to disorganizations of mental processes and cause mental disorders [18]. In the presynaptic and postsynaptic mechanisms of neurotransmission and synaptic plasticity, the ratio of intracellular and extracellular calcium is important [19].

CALCIUM HOMEOSTASIS

In the human body, calcium homeostasis is maintained via hormonal regulation by parathyroid hormone (PTH), thyroid calcitonin, and calcitriol. Low blood plasma calcium is regulated by PTH, the high level by calcitonin [20].

In hypoparathyroidism, the production of PTH by the parathyroid glands is insufficient. The cause can be autoimmune, metastatic, radiation, and idiopathic lesions or surgical removal [21]. In another pathology, pseudohypoparathyroidism, PTH synthesis is normal, but the receptors are affected, and there is no response to the hormone by cells [22]. As a result, the regulation of calcium metabolism is disturbed, its level in the blood decreases. Hypoparathyroidism is manifested by an increase in muscle excitability, demonstrated by convulsions, respiratory distress, and stimulation of the motility of the gastrointestinal tract. In addition to somatic symptoms, acute hypocalcemia evokes mental disorders, such as delirium, cognitive disorders [23], irritability, depression, anxiety [24]; psychoses are not seen often [25]. In the case of chronic hypoparathyroidism, the risk of depression and bipolar disorder (BD) is doubled [26].

In hyperparathyroidism, there is excess production of PTH by the parathyroid glands. As a result, plasma calcium levels rise due to its loss in the bones. Mental disorders are also observed, particularly anxiety, cognitive impairment, insomnia, depression, and changes in personality traits [27]. The pathogenic mechanisms of the development of mental disorders in hyperparathyroidism remain undetected. It is assumed that calcium may be involved in these mechanisms, as the disturbed metabolism of calcium leads to disruption of neurotransmission and cognitive processes in the central nervous system (CNS) [28].

CALCIUM AND MOOD

On the other hand, calcium in the brain is involved in mood regulation [29]. Unlike stress, there are no known neurohormonal or physiological mechanisms for mood, and the underlying processes of different moods are not fully understood. Various neural and cognitive complexes are involved in the formation of emotions, in particular, when an emotion is triggered by an external stimulus or remembrance of a previous event, the sensory and memory systems are involved in the formation of emotions. The autonomic nervous system participates in the bodily manifestations arising during the experience of various emotions [30].

Among some people with mood disorders, increased calcium levels in platelets and lymphoblasts have been found [31,32]. According to other studies, during the manic episode of BD, calcium level decrease is seen in cerebrospinal fluid [33], while during the depressive episode, elevated calcium levels are registered in the cerebrospinal fluid and blood plasma [34,35].

Lithium is widely and successfully used as a mood stabilizer medication [36]. This property of lithium may be related to its influence on calcium signaling systems, as lithium has been shown to indirectly inhibit the inositol triphosphate receptor [37], which plays a significant role in the releasing of calcium from intracellular stores [38].

Among individuals with BD, magnetic resonance imaging has shown disturbances in mitochondrial activity [39]. These organoids are involved in the storage and release of intracellular calcium. Interestingly, both lithium and another mood stabilizer, valproic acid, stimulate the production of mitochondrial Bcl-2 protein, which promotes calcium storage in mitochondria [40].

There is also evidence of calcium involvement in mood disorders in animal models. The VGCC blockers, particularly those in the dihydropyri-

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dine group, showed antidepressant effects and enhanced the influence of antidepressants in murine forced swimming models [41,42]. In addition, VGCC-activating compounds in the same models induced depressive-like manifestations [43]. Various experiments on learned helplessness models had shown that when dihydropyridine VGCC blockers were added to an antidepressant that did not work alone at a given dose, the former enhanced the antidepressants' effectiveness [44]. However, these properties have been found in dihydropyridine receptor antagonists; other groups of VGCC blockers have not had this effect or have shown the opposite [45,46].

CALCIUM AND SCHIZOPHRENIA

In the pathogenesis of schizophrenia, along with many other factors, attention is paid to synaptic transmission and neuronal plasticity [47]. The molecular mechanisms of the disease have been extensively studied but remain incompletely elucidated. The possible role of disorders of calcium metabolism in the pathogenic mechanisms of the disease is suggested by the results of observations of calcium metabolism during the disease. So, the observations showed that during remission of psychotic episodes, the amount of calcium in the cerebrospinal fluid increases [34]. In addition, mental state disorders occur when calcium level is changed by some pharmacological agents, which advocates the role of calcium in mental processes. In particular, it has been shown that the usage of VGCC blocker verapamil exacerbates the psychotic manifestations of schizophrenia [48]. Another study showed that in the platelets of people with schizophrenia, in response to receptor stimulation, the mobilization of calcium from the intracellular stores elevated [49]. Based on these and other studies, it has been suggested that high cytoplasmic calcium levels may be the main molecular disorder in schizophrenia [50]. Calcium is known to play a role in the growth and branching of nerve cell dendrites [51], at the same time, schizophrenia is thought to be associated with the decrease in the density of dendritic spines in the prefrontal cortex neurons [52]. Structural and functional changes in dendritic spines are mainly regulated by the influx of calcium from the extracellular environment, so the spines are subject to affection by calcium metabolism disorders [53]. Hence, this mechanism is also a possible way of the calcium role in the development of schizophrenia. Another mechanism that may link calcium to schizophrenia is the formation of synaptic contacts. Calcium ions are involved in the formation of synaptic connections [54], at the same time, in schizophrenia, these connections are known to be reduced or altered [55].

CALCIUM CHANNELS AND THEIR BLOCKERS

L-type calcium channels (LCC) are widely distributed in the nervous tissue [56]. They participate in the excitability of neurons, neurotransmitter release, and other more complex functions, such as memory and learning [57]. Traditionally, these calcium channels served as targets for treating cardiovascular system diseases. Calcium channel blockers (CCB) have long been widely used as antihypertensive, antianginal, and vasodilating medications [58]. After some research, interest in the possible use of these drugs in psychiatric practice decreased in the 2000s [59]. However, the fact that calcium is involved in many mental processes keeps the question of whether drugs that affect calcium metabolism may have a therapeutic effect in the treatment of mental disorders. Recent research works, and the development of methods of biological, particularly molecular psychiatry, encourage the researchers not to abandon this idea and to continue the research.

T-type calcium channels (TCC) are activated by low-voltage potentials. In the brain, these channels are found in the thalamus, nucleus accumbens, ventral tegmental area, and prefrontal cortex. These loci are thought to function pathologically in schizophrenia [60]. A number of antipsychotics, in particular, clozapine, penfluridol, fluspirilene, and haloperidol, have TCC-antagonist effects [61,62].

Calcium channel blockers are drugs that interfere with the influx of calcium to the cell via VGCCs and have as main targets LCCs. Groups of currently used CCBs are phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), dihydropyridines (e.g., nifedipine), and diaminopropanol ethers (e.g., bepridil) [63]. All CCBs bind to TCCs, reduce calcium influx, and via this property, lead to muscle relaxation, vasodilatation, hormones, and neurotransmitter release and participate in neuronal plasticity [64,65].

To manage the channels, it is important to take into account the diversity of channels' molecules, their location, and their affinity to the agonists. Particularly, the CaV1.2 subtype of TCCs is located in the cardiovascular system and is blocked by low doses of dihydropyridine, whilst the CaV1.3 subtype is located in the CNS and is blocked by higher doses; hence for blocking LCCs in the brain, higher doses of drugs are needed than used in cardiovascular diseases [29]. As a result, even if doses are

raised to achieve the ones required to block LCCs in the CNS, peripheral adverse effects will prevail. For this reason, it is required to find ways to make more specific blockers that would be able to specifically bind only or at least mainly to the LCCs of CNS. Approaches to this problem lie in the synthesis of molecules that have a more specific structure or are more lipophilic so that they can cross the blood-brain barrier more readily [60-62].

SUMMARY

There is plenty of data in the literature about the role of calcium in the mechanisms of functioning of various organ systems, including the nervous system. However, there are very little data on the role of this macroelement in the mechanisms of mental processes and their disorders. The literature also describes psychiatric symptoms observed in various disorders of calcium metabolism. It is also known that some calcium channel-related drugs affect psychiatric symptoms. However, the molecular mechanisms of this property remain unknown. Further research is needed to study the role of calcium in the mechanisms of various mental disorders, as well as to explore and develop new ways to adapt calcium channel blockers to psychiatric practice.

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Կալցիումի դերը հոգեկան խանգարումների ախտածնության մեխանիզմներում և ֆարմակոթերապիայում. համառոտ ակնարկ

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ԱՄՓՈՓԱԳԻՐ

Հայտնի է, որ հոգեկան խանգարումները զգալի վնաս են հասցնում մարդու առողջությանը: Դրանց ախտածնության մեխանիզմները դեռևս լիովին պարզաբանված չեն: Այս մեխանիզմներում կարևոր են ժառանգական, շրջակա միջավայրի, նյութափոխանակության և այլ գործոններ: Կալցիումը համարվում է ախտածնության մեխանիզմների հնարավոր մասնակից: Վերջինիս մակարդակն օրգանիզմում վերահսկվում է հորմոնալ կարգավորմամբ: Վահանաձև գեղձի և այլ օրգանների խանգարումների դեպքում օրգանիզմում հանգեցնում են կալցիումի մակարդակի խանգարումների (հիպոկալցեմիա և հիպերկալցեմիա): Այս վիճակներն ուղեկցվում են զանազան մարմնական և հոգեկան ախտանիշներով: Հոգեկան խանգարումների ախտածնական մեխանիզմները պարզաբանելու և դեղորայքային նոր միջամտություններ մշակելու համար անհրաժեշտ է հստակեցնել դրանցում տարբեր մասնակիցների, այդ թվում՝ կալցիումի դերը: Կալցիումի մակարդակը կարգավորող դեղամիջոցները, մասնավորապես կալցիումական անցուղիների պաշարիչները, կարող են օգնել մշակել հոգեկան խանգարումների բուժման նոր մեթոդներ: Անհրաժեշտ է ուսումնասիրել հոգեկան խանգարումների դեպքում նշված դեղորայքի գործողության մեխանիզմները և դրանց բարելավման ու գործնական կիրառման հնարավոր ուղիները:

Հիմնաբառեր. *հոգեկան խանգարումներ, ախտածնություն, հոգեդեղաբուժություն, կալցիումական անցուղիների պաշարիչներ, նոր դեղամիջոցներ*

Роль кальция в механизмах патогенеза и фармакотерапии психических расстройств: краткий обзор

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АБСТРАКТ

Общепризнано, что психические расстройства наносят значительный ущерб здоровью человека. Механизмы их патогенеза до конца не выяснены. В этих механизмах важны наследственные, экологические, метаболические и другие факторы. Кальций считается возможным участником механизмов патогенеза. Уровень последнего в организме контролируется гормональной регуляцией. При заболеваниях щитовидной железы и других заболеваниях в организме наблюдаются нарушения уровня кальция (гипокальциемия и гиперкальциемия). Эти состояния сопровождаются различными физическими и психическими симптомами. Чтобы прояснить патогенетические механизмы психических расстройств и разработать новые лекарственные вмешательства, важно выяснить роль в них различных участников, включая кальций. Лекарства, регулирующие уровень кальция, особенно блокаторы кальциевых каналов, могут помочь в разработке новых методов лечения психических расстройств. Необходимо изучить механизмы действия указанных препаратов на психические расстройства и возможные пути их улучшения и практического применения.

Ключевые слова: *психические расстройства, патогенез, психофармакотерапия, блокаторы кальциевых каналов, новые лекарства*