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Analysis Of Calcium-Dependent Processes In Nerve Cells

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ABSTRACT

This article analyzes the processes associated with calcium in nerve cells. Pathological changes in the nerve cells negatively affect the natural physiological processes in the human organism. Elevated intracellular Ca^{2+} concentrations are involved in neurotransmitter release, synapse plasticity, enzyme activation, and gene expression. Of great importance is the question of studying the mechanisms of pharmacological correction using biologically active substances in pathological conditions in the brain in the synaptosomes, Ca^{2+} transport.

KEYWORDS

Neurons, calcium, Ca^{2+} channels, synapses, polyphenolic compounds.

INTRODUCTION

As the number of older people grows around the world, neurodegenerative dementia and Alzheimer's disease (AD) are on the rise, with the primary economic and social burden on society. In 2015, 46.8 million people were diagnosed with neurodegenerative disease. According to research, these results are expected to double globally every 20 years,

reaching 74.7 million in 2030 and 131.5 million in 2050 (Prince et al., 2015).

There is a steady increase in the number of socially significant neurodegenerative diseases resulting from a violation of Ca^{2+} homeostasis in nerve cells. Pathological changes in nerve cells negatively affect the natural physiological processes in the body.

Synaptic dysfunction is considered to be one of the main causes of neurological disease. Such diseases include Alzheimer's disease, Parkinson's disease, and schizophrenia. The accumulation of amyloid beta-peptide (A β) in mitochondria, especially in synaptic mitochondria, exacerbates synaptic damage and synaptic cleft rupture, resulting in synaptic failure. Thus, the determination of the presence and level of A β in synaptic mitochondria associated with amyloid pathology is important for studying mitochondrial amyloid pathology (Berridge et al., 1997; Zhou et al., 2007; Yan et al., 2018;).

The development of visualization and isolation of synapses has changed the direction of neurophysiological research. An important role in this was played by the fact that synapses play a key role in development, plasticity, heredity, learning, memory, or any other area of brain function (Murphy et al., 2018).

Ca²⁺ transport is a central component in the regulation of signaling and excitation / inhibition of reflexes in nerve cells, and dysfunction of [Ca²⁺] homeostasis in cerebral synaptosomes has been reported to cause serious pathological conditions (Hardingham et al., 2010; Marambaud et al., 2009;). In this regard, it is of great importance to study the mechanisms of pharmacological correction of Ca²⁺ transport of biologically active substances in the synaptosomes of the brain in pathological conditions.

Herbal remedies have traditionally been used to improve memory and cognitive performance in humans, many of which have been extensively studied in recent years for the therapeutic correction of neurodegenerative diseases.

MAIN PART

In the central nervous system, Ca²⁺ is considered a cellular messenger involved in the

regulation of neurotransmitter secretion and nerve excitability, and is inextricably linked with differentiation and transport of various cells, synaptic plasticity, neuronal growth, and neuronal apoptosis (Bucurenciu et al., 2010).

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The presynaptic nerve endings in the central nervous system contain about 100 to 200 synaptic vesicles filled with a neurotransmitter. In order to stimulate synaptic vesicles into the synaptic cleft, the potential stimulus are relative to Ca²⁺.

In the central nervous system, Ca²⁺ is considered a cellular messenger involved in the regulation of neurotransmitter secretion and nerve excitability and is inextricably linked with differentiation and transport of various cells, synaptic plasticity, neuronal growth, and neuronal apoptosis (Györfy et al., 2020; Zhou et al., 2016;).

Subcellular centers of regulation of calcium homeostasis involved in plasticity and physiological vitality of neurons

Ca²⁺ regulates metabolism, proliferation, and cell differentiation. The concentration of calcium in the cytoplasm [Ca²⁺] is regulated by the complex physiological functions of calcium channels and carrier proteins in the plasma membrane, ER, and mitochondria. (fig. 1). Calcium regulates the expression of various genes and regulates the protein phosphorylation function of various proteins. Calcium is an important regulator of synaptic plasticity, neurite growth, and cell life. Changes in calcium regulation in one or more organelles can disrupt synaptic function and, if severe and

stable, can lead to neuronal death (Mattson et al., 2003).

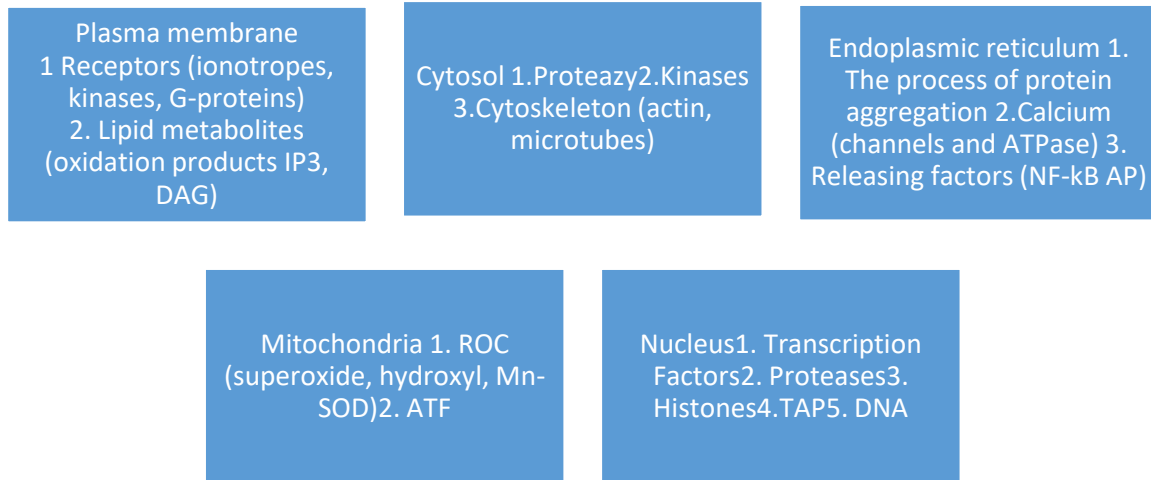


Fig.1

Ca²⁺ homeostasis is essential for cell activity and survival. Mitochondria promote Ca²⁺ buffering and prevent physiological pathology caused by Ca²⁺ overload in cells. Mito- Ca²⁺ is also required for the optimal functioning of some essential mitochondrial functions, such as oxidative phosphorylation and metabolism. Thus, mito- Ca²⁺ homeostasis plays a central role in the physiology of nerve cells.

The endoplasmic reticulum (ER) and mitochondria form tight bonds and exchange molecules such as Ca²⁺ and lipids. Mitochondrial homeostasis Ca²⁺ plays a regulatory role in the transport of Ca²⁺ EP mitochondria, and the role of mitochondrial proteins Miro has been studied in this (Fig. 2). Kyu-Sun Lee and others have studied mito- Ca²⁺ homeostasis disorders in neurodegenerative disease models and their therapeutic correction (Lee et al., 2018).

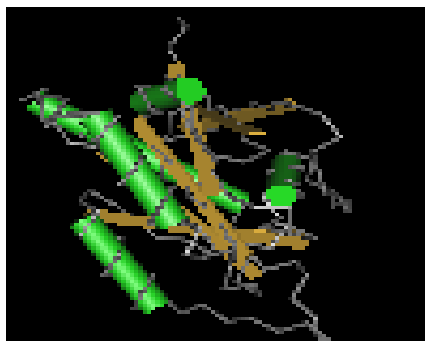


Fig. 2.(41)

Mitochondrial Rho proteins (Miro-1 and Miro-2), atypical Rho GTPases (Fig. 2). There are unique domain organizations with tandem GTP-binding domains and two hand EF domains that can bind calcium. They are also larger than the classic small GTPases. It has been suggested that they are associated with mitochondrial homeostasis and apoptosis.

The exchange of intracellular Ca^{2+} for free calcium acts as a trigger or modulator of many important nervous processes. Such change processes can occur as a result of penetration of Ca^{2+} into the cytoplasm from the extracellular medium of stem cells or currents associated with the ligand or release from intracellular stores.

Thus, an increase in the intracellular concentration of Ca^{2+} plays an important role in transmitter secretion, synapse plasticity, enzyme activation, and gene expression. As for astrocytes, the changes activated by Ca^{2+} neurotransmitters are also of great functional importance. Indeed, as a result of an increase in Ca^{2+} in the cytosol, the structure and function of astrocytes change during a number of slow, intermediate, and long-term periods.

It can be shown that calcium channels play an important and varied role in neural functions. It has been known for many years that calcium channels are a target for various organic and inorganic toxicants. The activity of Ca^{2+} channels is controlled by a wide range of intracellular signaling pathways. These pathways not only modulate the activity of Ca^{2+} -channels in different ways, they not only modulate calcium ions, entering them through calcium channels, but also interact with each other.

Thus, there are important feedback mechanisms between Ca^{2+} channels and intracellular signaling, which can lead to genetic damage as well as environmental damage (Audesirk et al., 2000; Kiryushko et al., 2006;).

Pathological conditions (stroke, ischemia, AIDS, etc.) and toxic poisoning (for example, methylsimob, lead) disrupt calcium homeostasis, which can lead to neuronal death (Denny et al., 1996; Nikonenko et al., 2005;).

Calcium signaling process in neurons.

As the number of older people grows around the world, so does the number of neurodegenerative diseases, which primarily impose economic and social burden on society. Data obtained in the study of synapses in neurons, suggest that synaptic dysfunction leads to neurological and psychotic disease (Südhof et al., 2013;).

Since pathophysiological processes underlie neurological diseases, it is important to study them separately. Analysis of the data shows that α -synuclein is a central factor in Parkinson's disease, along with many neurodegenerative diseases (Burré et al., 2010). Saitsu and others have studied that the most commonly mutated SM protein in Oxstaxara syndrome is Munc18-1. Also in 2008 Südhof T.S. studied that mutations in many "synaptic" genes can lead to autism and schizophrenia (Burré et al., 2010).

Neuronal chemical synapses are part of the basic communication processes between neurons. In the human brain, each of the approximately 86 billion neurons can form more than 105 synaptic connections (Napper et al., 1988; Azevedo et al., 2009;).

If we analyze the physiological processes associated with synapses, having studied the literature, According to Mayford M, neurotransmitters released through synaptic vesicles spread along the synaptic cleft, the distribution of the action potential is provided by interaction with certain postsynaptic ionotropic and metabotropic receptors (Mayford et al., 2012). Controlling this process, examining changes in synaptic strength, is the

molecular basis for memory and cognitive processes.

In the central nervous system, the presynaptic nerve terminal contains synaptic vesicles filled with approximately 100 to 200 neurotransmitters. To move the synaptic into the vesicle, potential stimulation is transmitted from Ca^{2+} to the synaptic cleft (Mayford et al., 2012).

In the nervous system, Ca^{2+} is believed to be a messenger cell involved in the regulation of neurotransmitter secretion and nervous excitability and is inextricably linked to various cell differentiation and transport, synaptic plasticity, neuronal growth, and neuronal apoptosis (Györfy et al., 2020; Jhou et al., 2017;) Calcium (Ca^{2+}) is an important messenger that works everywhere. Eukaryotic cells use Ca^{2+} as a signal carrier for regulation. In particular, it is very important for neurons, it is involved in the transmission

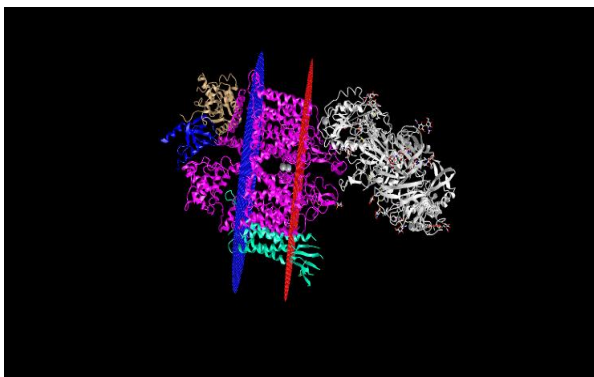
of the depolarizing signal and contributes to synaptic activity. In neurons, complex Ca^{2+} signaling works as follows: Ca^{2+} penetrates

neurons through plasma membrane receptors and ion channels (depending on voltage). The release of Ca^{2+} into the intercellular spaces occurs due to a change in the amount of cytosolic Ca^{2+} from the endoplasmic reticulum through the intracellular channels (Brini et al., 2014;).

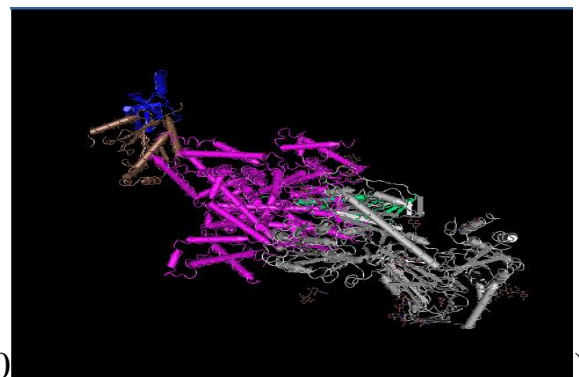
Ca^{2+} channels of the plasma membrane.

The Ca^{2+} channels of the plasma membrane are divided into 3 main groups, depending on the opening mechanism (Prakriya et al., 2006).

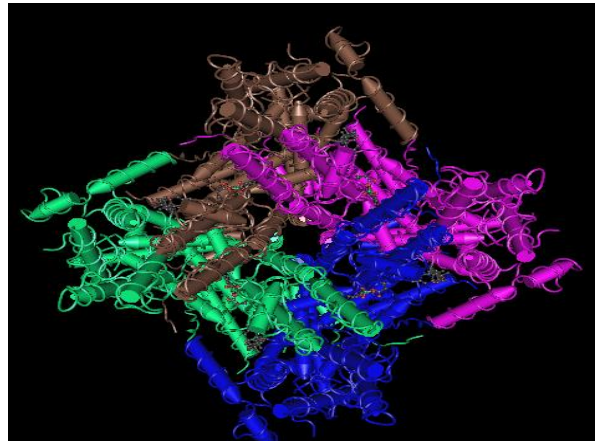
1. VOC (voltage-gated Ca^{2+} channels)
2. ROC (receptor-operated Ca^{2+} channels)
3. SOC (store-operated Ca^{2+} channels)



a)



b) (Wu J. et al., 2016)



c)

Fig. 3.

1.a-b - VOC (voltage-gated Ca^{2+} channels) L-type ion channel
2.c- SOC (store-operated Ca^{2+} channels) TRPC4 ion channel (Vinayagam et al., 2018)

VOC transmits electrical signals that occur on the cell surface membrane due to an increase in local concentration of intracellular Ca^{2+} . In neurons, VOC plays a role in the formation and propagation of nerve impulses and cell homeostasis. VOC consists of 5 separate subunits (α_1 , α_2 , β , γ , δ). Structurally, the α_1 subunit is divided into 3 subfamilies: Ca_v1 , Ca_v2 and Ca_v3 . The α_1 subunit is divided into 6 additional classes depending on the physiological and pharmacological properties of the type of flow carried: L, N, P, Q, R and T (Brini M. et al., 2014).

L-type channels of the Ca_v1 subfamily connect excitatory-contraction processes in skeletal and cardiac muscles. The activity of neuronal cells induces Ca^{2+} permeability in cell bodies and dendrites, which in turn regulates processes such as gene secretion and expression.

The Ca_v2 channels produce currents of the N, P/Q and R types and are mainly responsible for the onset of synaptic transmission, neurotransmitter secretion, and the Ca^{2+} dendritic junction.

The Ca_v3 subfamily is responsible for type T current, is important for cardiac potential in cardiac myocytes and thalamic neurons, and is important for cardiac rhythmic activity (Catterall et al., 2011).

Visualization, isolation and correction of synapses.

The development of visualization and isolation of synapses has changed the direction of neurophysiological research. An important role in this was played by the fact that synapses play a key role in development, plasticity, heredity, learning, memory, or any other area of brain activity (Murphy et al., 2018).

In the scientific study of the nervous system, synaptosomes have become an important system for studying the molecular mechanisms of synaptic function in the brain. Ketrin Xebb and Whittaker in 1957, using isolated acetylcholine (ACh) and choline acetyltransferase (CHAT) as markers, were the first to isolate synaptosomes. Separation of synaptosomes plays an important role in the study of synaptic structure and identification of functional synapse components, including identifiers of key neurotransmitters and the mechanisms by which they are retained.

RESULTS AND DISCUSSION

The scope of this research is to present a comparative study between ion channels and receptors. We use movie review data set from twitter source as input for this experimental study.

In our future studies, we plan to study the effects of new polyphenolic compounds isolated from native plants in the study of calcium transport through the synaptosome membranes of the rat brain. First, we screen several polyphenol compounds and select the one with the highest effect.

It has been shown that organohalogen compounds have biological activity, correcting the functions of homeostasis of nerve cells using various substances. It has been reported that the chalcogen compound has glutathione peroxidase mimetic activity. This compound, like a natural enzyme, is involved in the oxidation-phosphorylation of selenium or tellurium (Parnham et al., 2000). Ebselen, an organic compound with selenium, plays a protective role against cerebral ischemia and stroke (Yamaguchi et al., 1998).

In addition, similar effects have been observed in experimental models from the excitotoxicity of glutamate (Porciúncula et al., 2001; Rossato et al., 2002;) and from the effects of methylsimob (Moretto et al., 2005).

Recent studies have shown that diphenyldielenide has neuroprotective and anti-inflammatory effects (Ghisleni et al., 2003; Nogueira et al., 2004;). A selenium-containing compound, diphenylditelluride, has been shown to be highly toxic to rodents and has demonstrated a pronounced neurotoxic effect in mice upon acute or prolonged exposure (Stangherlin et al., 2005).

CONCLUSIONS

As a result of the analysis of the literature above, it can be concluded that as the number

of neurodegenerative diseases increases worldwide, the study of neuronal Ca^{2+} with various pharmacological agents is gaining in importance. Since Ca^{2+} transport is one of the central components in the regulation of reflex conduction and signaling in nerve cells, dysfunction of $[\text{Ca}^{2+}]$ homeostasis in brain synaptosomes has been studied as a cause of serious pathological conditions. The issue of pharmacological correction of Ca^{2+} transport with the use of biologically active substances in the brain synaptosomes in pathological conditions is topical. Herbal remedies have traditionally been used to improve memory and cognitive performance in humans, many of which have been extensively studied in recent years for the therapeutic correction of neurodegenerative diseases. Based on the analysis of the above literature, our subsequent articles will discuss the effect of plant substances on the permeability of the synaptosomal membrane in vitro.

ACKNOWLEDGMENT

The authors want to thank those who read the article for their valuable comments. Their constructive feedback further enhances the research and their advice is greatly appreciated.

ETHICS

The author confirm that they have thoroughly seen the content of the paper and do not find any conflict of interest and ethical issues.

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