

The Role of Calcium in Auditory Cell

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Abstract

Bekesy's traveling wave theory, published in 1928 and awarded the Nobel Prize in 1961, does not satisfactorily explain all the problems associated with the reception and processing of auditory information [1]

Keywords: intracellular; neuron; auditory signal

Introduction

Bekesy's traveling wave theory, published in 1928 and awarded the Nobel Prize in 1961, does not satisfactorily explain all the problems associated with the reception and processing of auditory information [1]. Comments on this theory have been presented in several published papers [2,3,4]. This paper focusses on important processes related to hearing, which take place at molecular and ionic level. Calcium has many significant and diverse functions in the body. It is very important in ensuring the impermeability of membranes, acts as an intracellular signal and enables the transmission of signals between cells, regulates cytoskeletal functions, contraction of muscle and non-muscle cells, cell division and exocytosis, as well as gene transcription. It plays an essential role in both types of cell death: necrosis and apoptosis. This plays a role in hearing damage by destroying hair cells. Calcium acts as a secondary messenger, regulating the activity of numerous enzymes, ion channels, the expression of rapid response genes. It is involved in energy transformations in the cell (5). Changes in the activity of individual types of calcium channels in the early stages of ontogenesis may regulate phenomena such as natural neuron death and synapse formation.

Importance of Calcium:

The metabolic machinery is diverse, inducing changes in intracellular calcium levels and responding to changes. In the cytosol of hair cells, the calcium concentration is very low, it is 10-7M (Mol), while the concentration in the intercellular space is 10,000 times higher. It is 10-3 M. The existence of such a high concentration gradient causes the constant entry of calcium through various routes into the hair cell and the need for its effective removal. The optimal level of calcium in the cell is 10-6M. Higher levels of calcium in the cell are toxic. However, this situation of changing levels in the cell has been exploited by evolution, which has acquired calcium as an effective intracellular signal and, in some cases, intercellular signal. Calcium is especially predestined to play the role of intracellular signal. Some calcium salts are easily soluble and the calcium ion is small (calcium atom diameter 0.144 nm), and therefore quickly diffuses in the cytoplasm. Its level is strictly controlled, and its excess is almost immediately eliminated. This enables rapid repetition of the auditory signal. Calcium, combining with proteins, like phosphate ions, changes their conformation, and thus can be used to

activate numerous cellular enzymes. The mechanism of the mediator exocytosis cycle is always based on an increase in the calcium level in the cytoplasm of the presynaptic element after depolarization. The level of calcium in the auditory cell increases over time up to 1 msec. causing exocytosis. Exocytosis is interrupted by rapid reduction of calcium levels by calmodulin, calcium transport out of the cell by ATPases, and co-transport dependent on sodium ions. Some of the calcium moves to the endoplasmic reticulum, mitochondria and the nucleus. The ability of calcium to bind to various proteins, changing their properties is the basis for the amplification of the intracellular signal in the auditory cell and thus the amplification of the auditory signal on the way from the receptor to the brain. The calcium signal is energetically cheap - there is no need to synthesize a signal transmitter and its removal is rather difficult. Calcium enters the hair cell by passing through various types of channels. Approximately 106 calcium ions pass through specific calcium channels in 1 ms. Non-specific entry of calcium ions into the cell involves the use of sodium or potassium channels through which one calcium ion is smuggled into the cell for every 100 Na⁺ or K⁺ ions. Calcium introduced in this way does not play the role of a signal. Hence, a much more important role is played by specific channels through which calcium ions enter the cell in a legal, controlled manner. The selectivity of the ion channel depends on selectivity filter in the channel wall and sensors sensitive to changes in membrane potential. These channels can be split into two large groups: channels controlled by changes in membrane voltage, and channels controlled by the attachment of a specific ligand, which is a neurotransmitter (in muscles, in the heart).

In the hair cells there are potential-dependent calcium channels. Recently, mechano-dependent calcium channels have been described in the hairs of hair cells. There are some doubts here, since the role of mechano-dependent channels is fulfilled by potassium channels. A high level of potassium in the endolymph is produced with a significant expenditure of energy. It is difficult to assume that two different mechanisms play the same role. A more probable thesis is that calcium ions play an extremely important role in the cell itself. An important role is played by the cell membrane of the auditory cell. It is a tight barrier for ions, including Ca⁺⁺ ions, trying to enter the cell from the extracellular space and endolymph. The influx of calcium ions into the cell must be precisely regulated. When the cell membrane is unable to

counteract the influx of calcium ions for various reasons (trauma, noise, toxins, etc.), the inflowing calcium ions activate proteolytic and lipolytic enzymes, causing the destruction of intracellular mechanisms, which ultimately leads to cell death. These are disorders at the molecular level that, to a lesser extent, are the cause of tinnitus. Determining these changes is not easy, because the conductivity of calcium current passing through the cell membrane is of an order of picoamperes and the conductivity of the channel is of an order of picosiemens. A very low level of calcium in the cell 10,000 times lower than outside the cell means that the influx of calcium into the cell can raise the Ca^{++} level in the cell up to 100 times, but in a limited space. The level of calcium in the cell regulates transport and secretion of the transmitter. Depolarization of the cell causes, in picoseconds, the opening of calcium channels, the fusion of synaptic vesicles with the presynaptic membrane and the release of the transmitter into the synaptic cleft. This presynaptic area acts as a nanoprocessor that regulates the flow of information. The neurotransmitter is released within 0.2 msec. after the start of the influx of calcium ions. The distance from the site of calcium ion influx to the site of exocytosis is less than 100 nm. The level of calcium must be marked by a substantial increase - up to 20 μM . The ion channel at the channel exit site produces a calcium ion concentration of 100 μM , but over 30 nm this concentration drops to 10 μM . The channel has a binding site for synaptic vesicles, and calcium ions, through specific proteins, cause the vesicle to connect to the presynaptic membrane. The vesicle is emptied during contraction, followed by its separation from the presynaptic membrane and retrograde transport to the Golgi apparatus. All of these procedures can be disrupted, leading to tinnitus or hearing impairment and eventually to cell death and deafness. The release of the neurotransmitter is caused by an increase in the level of calcium ions in the presynaptic area in less than milliseconds, over a nanometer-sized space, which corresponds to the size of ion channels. The translation of changes in calcium levels into cell activity, i.e. transmitter exocytosis, is mediated by sensor proteins - which are calcium level sensors. They are capable of a selective response, proportional to a specific signal level dependent on the energy of the auditory signal. These proteins have a high affinity for calcium ions and the ability for conformational changes of these proteins after combining with calcium. Therefore, the rapid release of the neurotransmitter is associated with the presence of calcium-binding proteins on the membrane of synaptic vesicles. Anterograde and retrograde transport is regulated, as well as the processing of used, emptied vesicles in the cell. An increase in the level of calcium ions in the cell causes the release of calcium from the endoplasmic reticulum. IP3 (inositol 1-4-5 triphosphate) is involved in the release of calcium from intracellular stores. Calcium waves propagate at a speed of 30 micrometers/s. The level of calcium in the cell nucleus increases, which leads to the

activation of the transcription factor CREB (cAMP response element binding protein). CREB activation occurs as a result of phosphorylation with the participation of calmodulin-related calcium-dependent kinase IV located in the cell nucleus (Ca^{++} calmodulin-dependent kinase IV). This affects the transcription of all proteins associated with exocytosis and proteins associated with cell life. The ability of the auditory cell to transmit information depends on several factors: Efficient transmission of auditory information is also dependent on the proper functioning of the synapses. The functioning of the synapses is dependent on:

1. The number and density of the synapses on the hair cell
2. The efficiency of each individual synapse depends on:
 - a) the production and transport of vesicles and their exocytosis
 - b) the amount of transmitter in the vesicles
 - c) the size of the postsynaptic membrane surface
 - d) the density of ion channels
 - e) the rate of decay and reabsorption of the transmitter
 - f) temporal and spatial summation
 - g) production of the mediator itself, so that synaptic fatigue does not occur due to the depletion of the mediator supply.

Spatial summation involves many synapses on the cell, the information transmitted to nerve cell adds up.

Temporal summation applies to a single synapse. If the impulses coming from the dendrite to the nerve cell are more frequent but weaker than those capable of triggering a spike potential, the impulses add up.

The description of processes at the level of nanostructures and nanoprocesses occurring in the auditory cell brings us closer to understanding the mechanism

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