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Integrative Medicine Research

journal homepage: www.imr-journal.com

Review Article

The direct modulatory activity of zinc toward ion channels

Sujin Noh[1], *Sung Ryul Lee*[1], *Yu Jeong Jeong*, *Kyung Soo Ko*, *Byoung Doo Rhee*, *Nari Kim*, *Jin Han*[*]

National Research Laboratory for Mitochondrial Signaling, Department of Physiology, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

ARTICLE INFO

Article history:
Received 22 June 2015
Accepted 8 July 2015
Available online 15 July 2015

Keywords:
conformational change
ion channel
zinc
zinc binding

ABSTRACT

The divalent zinc ion is a cation that plays an indispensable role as a structural constituent of numerous proteins, including enzymes and transcription factors. Recently, it has been suggested that zinc also plays a dynamic role in extracellular and intracellular signaling as well. Ion channels are pore-forming proteins that control the flow of specific ions across the membrane, which is important to maintain ion gradients. In this review, we outline the modulatory effect of zinc on the activities of several ion channels through direct binding of zinc into histidine, cysteine, aspartate, and glutamate moieties of channel proteins. The binding of zinc to ion channels results in the activation or inhibition of the channel due to conformational changes. These novel aspects of ion-channel activity modulation by zinc provide new insights into the physiological regulation of ion channels.

1. Introduction

Zinc is the 24th most abundant element in the Earth's crust and is considered an essential biometal.[1] Apart from zinc's role as a building block for proteins or enzymes, recent studies highlight its dynamic activity as an intracellular signaling molecule. Zinc plays a role in cell–cell communication, signal transduction from extracellular stimuli to intracellular signals, and control of intracellular events.[2–9] Moreover, many human diseases including cancer, diabetes, osteoporosis, dermatitis, and autoimmune and neurodegenerative disorders are associated with dysregulation of zinc homeostasis. Zinc compounds are normally colorless, and in its natural status, zinc is stable as a divalent cation, unlike other bioactive metals such as iron and copper. Recently, zinc ions have attracted a lot of attention as physiological and pathophysiological mediators. Zinc is found in almost every tissue in the body; however, free zinc ions cannot cross the plasma membrane by simple diffusion. Therefore, cellular and whole-body zinc homoeostasis is maintained through the regulation of the expression of genes involved in zinc trafficking: transporters regulating the influx and efflux of zinc (solute-linked carriers SLC39/ZIPs and SLC30/ZnTs, respectively) and the intracellular zinc-binding protein metallothionein.[10] In certain cases, however,

* *Corresponding author*. National Research Laboratory for Mitochondrial Signaling, Department of Physiology, College of Medicine, Cardiovascular and Metabolic Disease Center, Inje University, Bokji-ro 75, Busanjin-gu, Busan 47392, Korea.
E-mail address: phyhanj@inje.ac.kr (J. Han).
[1] These authors contributed equally to this work

http://dx.doi.org/10.1016/j.imr.2015.07.004

intracellular entry of zinc can also be induced by Ca^{2+}-conducting channels that take part in the transport of zinc across the plasma membrane.[11]

Ion channels are protein pores located in the membrane of nearly all cells and many intracellular organelles, where they regulate the selective movement of ions via filter and gating mechanisms.[12] Divalent cations, including calcium, magnesium, and zinc, act as second messengers in the regulation of intracellular signaling pathways, whereas monovalent cations, such as sodium and potassium, mainly regulate the membrane potential and thereby indirectly control the influx of calcium.[8] Based on their channel-opening properties, ion channels can be broadly classified as either voltage-gated, ligand-gated, second messengers-gated, light-gated, or mechanosensitive channels.[13] These ion channels play a pivotal role, not only in the generation of a membrane potential, but also in numerous other cellular processes, including signal transduction, hormone secretion, neurotransmitter release, muscle contraction, volume regulation, growth, motility, and apoptosis.[12,14,15] Channel activities can be modified by mutations in ion channel genes, drugs, or many natural products derived from animals and plants.[12]

Over the past 3 decades, researchers have sought to determine the effect of zinc through electrophysiology studies[12] since divalent metal cations are able to modify the gating of ion channels.[16] While calcium binds almost exclusively to oxygen donors, zinc displays broad selectivity with regard to coordination environments, as it employs oxygen, nitrogen, and sulfur donors from its ligands. Protein function is controlled by its structure and status of charge.[17] The biological effects of zinc occur at much lower concentrations than calcium and manifest as protein inhibition, redox-switches, or protein-interface stabilization.[18] Zinc ions bind with a high affinity to aspartate, cysteine, glutamate, and histidine residues of proteins compared with other amino acids, and hence their dissociation rates are slow, resulting in long-lasting biological effects.[19] For example, the activity of an enzyme can be directly inhibited by chelation of zinc to the catalytic cysteine residue, but allosteric inhibition can be attributed to zinc binding at a cysteine distal to the active site of the enzyme.[18,20] The availability of zinc in the cell influences protein function, most evidently via direct interaction with proteins. Histidine (imidazole group, $(CH)_2N(NH)CH$), cysteine (thiol group, –C–SH or R–SH), aspartate, and glutamate (carbonyl oxygen, C=O) have potential binding regions with an electrical charge for coordination with zinc.[21,22] Thus, these flexible coordination geometries within proteins allow zinc to cause a rapid conformational shift and consequent biological reactions.[23]

Based on the chemical characteristics of zinc, ion channels that possess amino acids with a high affinity to zinc could be influenced by both the extracellular and intracellular zinc pools. Ion channel regulation by zinc may result in the activation or inhibition of the ion current, depending on the zinc concentration and/or the extracellular or intracellular action site (Table 1). A comprehensive summary of all ion channels affected by zinc is beyond the scope of our short review. Instead, we will briefly summarize the current findings on the effects of zinc on some major ion channels, including potassium (K^+), calcium (Ca^{2+}), sodium (Na^+), ligand-gated, and acid-sensing channels. This will lead to a better understanding of the interplay between zinc and ion channels and will expand our knowledge on the (patho)physiological activity of other ion channels that are likely to be affected by zinc.

2. Ion channel activity and its modulation by zinc

Cellular ion channel activity is determined by the total number of channel proteins present at the membrane and by their individual activity and/or kinetics, which is controlled by post-translational and oxidative modifications.[24] Many clinical drugs and natural toxins affect the activity of numerous channels.[12] It has also been suggested that metal ions, including zinc, could affect ion channels either by blocking the current or by modifying the gating through screening of fixed surface charges, metal binding to fixed charges, or nonelectrostatic effects on the gating.[25]

2.1. *Potassium channels and zinc*

Potassium ion (K^+) channels modulate the resting membrane potential in many cells and their dysfunction leads to cardiac, neuronal, renal, and metabolic disease.[12,26,27] In voltage-gated ion channels, the voltage sensor formed by four transmembrane helical segments (S1–S4) partially faces the lipid bilayer and thus can interact both with the membrane itself and with physiological and pharmacological molecules.[13] This structural characteristic of voltage-gated ion channels makes them susceptible to conformational changes upon zinc binding, and these changes can result in the activation or inhibition of the channel. As shown in Table 1, zinc can change the opening properties of K^+ channels in the oocytes of *Xenopus* species and in mammalian L929 cells.[28] Zinc reduces the ion current of the human ether-a-go-go channel (Kv11.1) through interaction with histidine residues of the channel. In addition, the activation of the ether-a-go-go family of K^+ channels, Kv10.2 and Kv12.1, is slowed by zinc binding on the channel's aqueous cleft in the extracellular region.[29] Extracellular binding of zinc to the Kv1.4 and Kv1.5 channels also leads to inhibition of their activities.[30,31] Kv1.2 channels, by contrast, are insensitive to zinc ions.[32]

In contrast to some voltage-gated K^+ channels, transient receptor potential channel A1 (TRPA1),[33] the pancreatic ATP-sensitive K^+ channel (K_{ATP}), and large-conductance voltage- and Ca^{2+}-activated Slo1 K^+ (BK) channel[19,34] can be directly or indirectly activated by a rise in intracellular zinc levels (Table 1). TRPA1 can be activated indirectly in response to zinc entry through ion channels, such as L-type Ca^{2+} channels, and is activated irrespective of the membrane potential and affects the sensing of pain and cold insult.[33,35] A rise in extracellular zinc levels is less effective, since extracellular zinc does not increase TRPA1 channel activity in somatosensory neurons.[36] The binding of zinc to glutamate, histidine, and cysteine residues of the intracellular domain of TRPA1 is required for its activation.[22] This aspect of zinc binding on the activation of TRPA1 may explain some of the pathological consequences of zinc toxicity.[36] Intracellular zinc activates K_{ATP} channels in both the pancreas (sulfonylurea receptor

Table 1 – Direct effect of zinc binding on ion channels

Channel type	Binding site	Effect
Potassium channel		
Transient receptor potential channel A1[29,33]	His or Cys residue in intracellular region	Activation
BK (MaxiK, Slo1, or KCa1.1) channel[34]	His, Glu, or Asp in intracellular region	Activation
ATP-sensitive K^+ channel (K_{ATP}, Kir6.2)[55,56]	Phosphorylation of Thr180/Ser372 residue	Activation/inhibition
Human ether-a-go-go channel (Kv11.1)[28]	Extracellular region	Inhibition
Ether-a-go-go channel (ERG, Kv12.1, Kv10.2)[29]	His328 of S4 in extracellular region	Inhibition
Voltage-dependent K^+ channel (Kv) 1.3[31]	Extracellular region	Inhibition
Voltage-dependent K^+ channels (Kv) 1, 4, 5[30,31]	Extracellular region	Inhibition
Calcium channel		
Voltage-dependent Ca^{2+} channel (CaV) 1.2[35,42]	Extracellular region of α1C subunit	Inhibition
CaV2.1[42]	Extracellular region of α1A subunit	Inhibition
CaV2.2[42]	Extracellular region of α1B subunit	Inhibition
CaV3.1[42]	Extracellular region of α1G subunit	Inhibition
CaV3.2[42]	Extracellular region of α1H subunit	Inhibition
CaV3.3[42]	Extracellular region of α1I subunit	Inhibition
Store-operated Ca^{2+} channel[43]	Cys residue in extracellular region	Inhibition
Ligand-gated channel		Inhibition
N-methyl-D-aspartate (NMDA) receptor channel[57]	Extracellular region of GluN2 subunit	Inhibition
γ-aminobutyric acid (GABA) receptor channel[45]	Extracellular region	Inhibition
Dopamine receptor channel[44]	Extracellular region	Inhibition
Sodium channel		
Tetrodotoxin-sensitive Na^+ channel[58]	Extracellular region	Inhibition
Tetrodotoxin-resistant Na^+ channel[58]	Extracellular region	Inhibition
Saxitoxin (STX) -blocked Na^+ channel[48]	Extracellular region near STX binding site	Activation/inhibition
Epithelial Na^+ channel (EnaC)[49]	His and Asp in extracellular region	Activation
Na^+/H^+ exchanger (NHE)[59]	Intracellular region	inhibition
Acid-sensing ion channel (ASIC)		
ASIC1[60]	Lys133 in extracellular region of ASIC1	Inhibition

Asp, aspartate; BK, large conductance Ca^{2+}-activated potassium channel; Cys, cysteine; Glu, glutamate; His, histidine; Lys, lysine; Ser, serine; Thr, threonine.

1/Kir6.2) and the heart (sulfonylurea receptor 2A/Kir6.2) in a dose-dependent manner by binding sites near or on the sulfonylurea receptor protein.[34] Similarly, BK channels, which are allosterically modulated by voltage and intracellular Ca^{2+} levels, can also be activated by a rise in intracellular zinc levels, which, similar to Ca^{2+} binding, leads to structural rearrangements of the BK channel.[29,33]

2.2. *Calcium channels and zinc*

Ca^{2+} channels are selective for Ca^{2+} ions and regulate cellular calcium concentrations, which are critically important in the regulation of excitability, exocytosis, motility, apoptosis, and transcription.[17] Ca^{2+} channels can roughly be divided into two classes: (1) voltage-dependent Ca^{2+} channels, and (2) ligand-gated Ca^{2+} channels such as the inositol trisphosphate receptor, ryanodine receptor, and store-operated Ca^{2+} channel (SOCC).[37] It has previously been found that zinc can replace Ca^{2+} in the binding sites of numerous transport proteins such as the mitochondrial Ca^{2+} transporter and the Ca^{2+} channels located in excitable membranes.[38] Although extracellular zinc cannot cross the cell membrane by diffusion, some Ca^{2+}-permeable channels such as voltage-dependent Ca^{2+} channels, N-methyl-D-aspartate receptors, and amino-3- hydroxy-5-methyl-4-isoxazolepropionate receptors are also permeable to zinc.[39] Zinc can only pass through the L-type Ca^{2+} channel when Ca^{2+} levels are low, because zinc has a lower affinity than Ca^{2+}.[38,40] However, zinc could strongly suppress the high-voltage dependent activated-Ca^{2+} channel including L-type and N-type Ca^{2+} channels, even in the presence of sufficient Ca^{2+} levels.[35,40,41] Based on experiments in human embryonic kidney tsA-201 cells,[42] the sensitivity of Ca^{2+} channels to zinc binding depends on whether zinc binds to the α1 pore region of the Ca^{2+} channel, as this region is crucial for selectivity and channel conductance (Table 1).

SOCCs refill intracellular Ca^{2+} stores and are a major Ca^{2+} entry route modulated by inositol 1,4,5-trisphosphate.[40,43] It has been suggested that the activity of SOCCs is strongly inhibited by heavy metals such as La^{3+}, Gd^{3+}, and Cd^{2+}, which is a characteristic of SOCCs. Similar to other heavy metals, zinc could act as a competitive inhibitor for Ca^{2+} permeation.[40] In physiological conditions, zinc competitively blocks the Ca^{2+} entry through binding a cysteine residue of SOCC.[43] In addition, zinc can modulate ligand-gated channels such as N-methyl-D-aspartate receptors, γ-aminobutyric acid receptors, and dopamine transporters through competition of zinc for their ligand binding sites.[44,45]

2.3. *Sodium channels and zinc*

Sodium ion (Na^+) channels can be subtyped as passive Na^+ channels, voltage-gated Na^+ channels, which are present in most excitable cells, and epithelial sodium channels (EnaCs), which are present in absorptive epithelia of the kidney, colon, lung, and sweat glands.[46,47] The most important role of voltage-gated Na^+ channels is in the initiation of action potentials in excitable cells. In comparison to other Na^+ channels, heart Na^+ channels show an approximately 100-fold higher

affinity for external zinc, as zinc is able to bind to a site within or near the saxitoxin binding site of heart Na^+ channels.[48]

ENaCs play a major role in the maintenance of the electrolyte balance between Na^+ and K^+, and their inhibition can be caused by high concentrations of extracellular Na^+, referred to as Na^+ self-inhibition, and by increases in intracellular Na^+ levels.[49] Apart from these modes of ENaC regulation, extracellular zinc can also prevent or reverse Na^+ self-inhibition, and, therefore, zinc may serve as a potential physiological regulator or ligand of ENaCs.[49]

2.4. *Acid-sensing channels and zinc*

Acid-sensing ion channels (ASICs) are permeable to cations and are activated by extracellular acidosis in response to pH changes and other stimuli such as pain.[50–52] In the brain, the activation of ASIC1a, a Ca^{2+} permeable subunit of ASIC, leads to acidosis-mediated ischemic brain injury. While exposure to excess zinc causes neuronal death, it has been suggested that micromolar levels of zinc could bind the extracellular domain of the ASIC1b subunit and thereby inhibit the activation of ASIC channels.[53]

3. Limitations

In this review, we outlined the direct modulatory action of zinc for several types of ion channels. The changes in activity of the ion channels discussed in this manuscript are induced by direct binding of zinc to the ion channel or through an increase in extracellular or intracellular zinc levels. However, what happens when zinc is released from ion channels or when cellular levels of zinc decrease is not well determined. It is also unclear whether the modulation of the ion channel activity by zinc is the result of a synergistic effect or not. Elucidation of this issue will require further research. In addition, changes in the cellular redox status also modulate channel activity, but it is unclear how zinc affects this aspect of ion channel regulation.

4. Concluding remarks

Zinc has a relatively high affinity for histidine, cysteine, aspartate, and glutamate residues present in many proteins, including ion channels. This chemical characteristic of zinc allows it to interact with both extracellular and intracellular binding sites in ion channels, leading to conformational changes and subsequent activation or inhibition of the ion channel. In physiological or pathophysiological conditions such as ischemia and metabolic syndrome, cellular zinc levels are altered, which may help in controlling cell homeostasis through the interplay with numerous ion channels, or may be detrimental to the cells. Recent molecular-genetic and electrophysiological studies have shown that a wide array of human diseases, including cancer, cardiovascular diseases, and nervous system disorders, are associated with channelopathies. These can be caused by either genetic or acquired factors such as toxins or drugs.[12,54] This review may contribute to a better interpretation of the effect of zinc dynamics in electrophysiological studies. In the future, a better understanding of zinc's role in ion channel regulation may shed light on the molecular basis of their biological specificity and the development of therapeutic strategies for channelopathy-related diseases.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF), and the funding was granted by the Ministry of Science, ICT & Future Planning of Korea (2012R1A2A1A03007595) and by the Ministry of Education of Korea (2010-0020224).

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