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Review Article

The direct modulatory activity of zinc toward ion channels

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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.

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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,

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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

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