Chapter 3

Ion Channels in Aging and Aging-Related Diseases

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Abstract

Aging in humans is the decline over function of time of biological processes that include the capacity to grow, to reproduce, to interact, and to adapt, resulting in progressive organ malfunctions, illnesses, and ultimately death. As the average life expectancy is estimated to be above 60 years for about 25% of the world's population by 2050, understanding the causes of and designing treatments for aging-related disease is a compelling priority. Although every organ and tissue undergoes the process of aging, it appears that only few pathogeneses are typically detected with high frequency in elderly individuals. These include cardiovascular disease, neurodegeneration, vision loss, and cancer. Therefore, aging could be measured by monitoring the occurrence and progression of these diseases. However, each of these medical conditions alone is not a good marker for aging as elder patients present comorbid chronic conditions. In addition, treatment of one disease does not significantly prolong life expectancy. Therefore, it appears that a possible antiaging therapeutic strategy should consider simultaneous treatment of several diseases or move toward identification of a common target among the biological processes involved in aging. In this chapter, we will discuss some of the basic concepts of the role of ion channels in aging and will present an overview of the function of ion channels in some of the most common aging-related diseases.

Keywords: ion channels, aging, aging-related diseases, sinoatrial node, neurodegeneration, glaucoma, cancer

1. Introduction

Ion channels are pore membrane-associated proteins that allow movement of ionic fluxes between intracellular and extracellular fluids and within intracellular compartments. About

1.5% of the human genome encodes more than 400 ion channels. In addition, heteromerization and alternative splicing further increase functional diversity of ion channels [1–3].

Most ion channels are selective as they can discriminate between electrical charge and size of ions and they can allow unidirectional movement of only a specific ion (mostly K^+, Na^+, Ca^{2+}, or Cl^-) through the pore. Changes of ionic fluxes and, consequently, variations of electrical charge across membranes control virtually every cellular event including contraction, neuronal conductance, secretion, proliferation, and cell death. Therefore, abnormal changes of ionic gradients can underlie age-dependent decline of physiological functions. In addition, malfunction of ion channels is often associated with organ failure [4] during the process of aging.

In a resting state, ATP-driven pumps generate and maintain ionic gradients resulting in high intracellular K^+ (the most abundant intracellular ion) and low Na^+ and Ca^{2+}. In addition, the cytosolic surface membrane of all living cells is characterized by the accumulation of a net negative electrical charge than the extracellular surface of the membrane (membrane potential) that can range from −20 mV in epithelial nonexcitable cells to −100 mV in neurons. Because of this separation of electric charge and ionic concentrations across the membrane, opening of a Na^+ ion channel produces a flow of a positive charge (current, *i*) caused by the movement of Na^+ ions from the extracellular environment to the cytosol (Na^+ current, iNa^+). The augmented concentration of positive charges in the cytosol decreases the net negative charge with a process called depolarization. In plants, depolarization is achieved by an outward Cl^- flux.

In neurons and muscle cells, such as cardiac myocytes, depolarization is a critical event that underlies neuronal signaling and contraction. Depolarization activates more Na^+ (via a positive feedback), K^+, and Ca^{2+} channels and the respective ions will cross the membrane according to their electrochemical gradients. Therefore, K^+ leaving the cells will counteract depolarization, an event called repolarization. Inactivation of Na^+ and Ca^{2+} channels in combination with the outward fluxes of K^+ will produce the falling phase of the action potential which will continue until the ionic balances across the membranes are reestablished (resting phase). Each cell type presents a collection of ion channels that shape amplitude and duration of the action potential differently. For example, in neurons, changes of ionic fluxes occur very rapidly producing action potentials with fast depolarization and repolarization (lasting less than 1 ms) that propagates as unidirectional waves along the axon. Frequencies, duration, and amplitudes of action potentials produce neuronal signaling that guarantees transfer and elaboration of information from different body compartments, external to internal environment, and vice versa [5].

In the heart, action potentials are much slower (400 ms) than in neurons and they mostly serve the purpose to control contraction. This event is regulated by a collaborative effort between surface membrane and intracellular Ca^{2+} channels (ICCs) (e.g., ryanodine receptors, RyRs) in which the initial small amount of Ca^{2+} ions entering the cell from the extracellular environment bind and activate RyRs channels located on intracellular Ca^{2+} stores. This event, called Ca^{2+}-induced Ca^{2+} release, produces large changes of cytosolic Ca^{2+} concentration that is used by contracting fibers to produce motion and guarantee a conversion of an electrical stimulus into a mechanical response [6].

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2. Ion channels in the aging mosaic of the sinoatrial node (SAN)

The sinoatrial node is a specialized bundle of neurons that innervate the heart and act as a "pacemaker" by generating electrical impulses at regular intervals that allow the heart to contract rhythmically. Typically, SAN dysfunction (SND) can be related to the use of specific medications (e.g., beta blockers) [7]; however, SAN function is known to decline during aging [8], resulting in pacemaker diseases in senior people. Unfortunately, SND can be corrected only by treating the extrinsic causes. Clinical manifestation of aging-dependent SND can be associated with a dramatic alteration of a series of parameters that can range from an increased action potential duration of the neurons composing the SAN to a reduction of the intrinsic heart rate [8] (IHR; defined as the rate at which the heart contracts without the contribution of the SAN and hormones). These phenomena are directly associated with changes in the activity of several ion channels that fail to control outward and inward ionic fluxes properly in the SAN and cardiac muscle. Interestingly, several study focusing on understanding age-dependent changes of gene expression revealed that expression of several channels are altered in the SAN and cardiac myocytes of aged animals. Perhaps counterintuitively, it was observed that in aged animals Na^+, Ca^{2+}, and K^+ channels increased their expression level in the SAN and atrial muscle [9–12].

It is predictable that an increased expression of Na^+ and Ca^{2+} channels would produce larger Na^+ and Ca^{2+} fluxes. The consequent increased cytosolic concentration of these two ions in neurons could explain the elongation of the aging-dependent action potential duration in the SAN because, for example, more time is required to remove Ca^{2+}. In contrast, increased K^+ currents would repolarize the cells faster and therefore increased K^+ efflux should accelerate the action potential duration.

Age-dependent changes of ion channel expression can also be specific to cardiac myocytes. For example, a significantly decreased RyR expression level has been found only in atrial cells that may be responsible for the age-dependent reduction of the IHR [9]. Furthermore, recent studies showed that an abnormal cytosolic Ca^{2+} concentration due to upregulation of the transient receptor potential vanilloid type 2 (TRPV2) calcium channel could cause alteration of posttranslational modification of progerin, which can contribute to the phenotype of premature aging linked to Hutchinson-Gilford progeria syndrome (HGPS) [13, 14].

3. Ion channels in the aging of the nervous system

The human nervous system is composed of two parts, the central nervous system (CNS) and the peripheral nervous system (PNS). Cells of the human nervous system mostly comprise neuronal cells, whose axons bundle in the PNS and nonneuronal cells such as glia cells, microglia, astrocytes, and oligodendrocytes. As any other cell, all cells of the nervous system are susceptible to aging and although aging dramatically increases the risk of developing cognitive disorders that are typical of the CNS such as Alzheimer's disease (AD) or PNS such as amyotrophic lateral sclerosis, only few elders contract these pathologies (www.alz.org;

www.pdf.org; www.alsa.org). This suggests that a purely genetic origin of these diseases linked to aging is unlikely as individuals can live for over 100 years without any overt behavioral sign of neurodegeneration. In addition, these diseases affect particular populations of cells in specific areas of the brain suggesting that perhaps aging is not the trigger of these diseases but only worsens preexisting conditions.

Changes in Ca^{2+} homeostasis have been linked to aging-dependent deterioration of neuronal activity [15–20]. However, it is not yet clear whether it is a decreased or increased cytosolic Ca^{2+} concentration that mediates its noxious effects on brain performance during aging. For example, Ca^{2+} channels have been found to be reduced in genetically modified mice with accelerated age-dependent decay in learning and memory [21, 22]. However, this conclusion is contradicted by another study in which it is demonstrated that a long-lasting intracellular Ca^{2+} might render neurons vulnerable to age [22]. Furthermore, elegant work by the Stutzmann laboratory reported an increase in type 2 RyR transcripts in brains with mild cognitive impairment compared to those with no cognitive impairment. In addition, they found a reduction in a specific type 2 RyR splice variant that is associated with antiapoptotic function in brains of patients with mild cognitive impairment and Alzheimer's disease [23].

3.1. Reactive oxygen species (ROS) and ion channels in aging

Although there is a considerably large amount of studies on aging-related neurodegenerative diseases, very little is known about the process of aging in normal neurons. Nevertheless, it is generally accepted that neurons of an aging brain are characterized by accumulation of reactive oxygen species over time that are probably generated by an altered target of rapamycin (TOR) pathway [24]. However, ROS has also a protective role in neurons but the mechanism that control the threshold to which ROS become toxic is still heavily debated.

The deleterious effects of free radicals on neuronal homeostasis can be attributed to the ability of these chemical species to interact with a large variety of targets such as DNA and lipids. However, recent research has brought to light that activity of several neuronal ion channels can significantly change upon chemical interaction with free radicals and that this event can be related to aberrant cognitive functions during aging. For example, oxidizing agents dramatically inhibit Na^+ channels activity without affecting the concentration of the channels at the surface membrane suggesting a direct effect of the agent on the Na^+ channel [25]. Inhibition of Na^+ channel activity dampens the ability to produce enough depolarization to generate an action potential and therefore affects the overall brain function.

Oxidation of K^+ channels that are expressed in brain neurons has been reported. For example, the activity of K^+ channels expressed in the hippocampus (which is the part of the brain that controls memory formation) can be increased by ROS [26] resulting in an inhibition of neuronal excitability and possibly incapacity to form or retain memory during aging. Interestingly, several studies have shown that ROS can increase or decrease cytosolic Ca^{2+} according to the type of Ca^{2+} channel analyzed. For example, oxidation of the "L-type" Ca^{2+} channel decreased Ca^{2+} currents [27]. However, the oxidative activity of β-amyloid protein (Aβ) produced in the brains of Alzheimer's patients increased the activity of L-type Ca^{2+} [28, 29], suggesting that distinct oxidative agents can exert different effects on Ca^{2+} homeostasis. In contrast, reducing

agents have been reported to increase activity of the "T-type" calcium channel [30]. This suggests that ROS agents can increase cytosolic Ca^{2+} concentration and that this event can contribute to loss of neuronal function in aging. Inositol 1, 4, 5-trisphosphate (IP_3) receptors (IP_3Rs) and RyRs are the two major intracellular Ca^{2+} channels that release Ca^{2+} from neuronal intracellular stores such as the endoplasmic reticulum (ER).

Intracellular Ca^{2+} channels mediate numerous Ca^{2+}-dependent processes, including cellular growth and development, gene expression, and neurotransmission [31–40]. Therefore, it is not surprising that aberrant ICC function has been implicated in aging and several age-related pathologies including Alzheimer's disease, Huntington's disease (HD), and glaucoma [41–48]. Phosphatidylinositol and IP_3 levels are reduced in brains of patients with AD and the ensuing smaller number of IP_3 binding sites correlates with the number of amyloid plaques and neurofibrillary tangles [19–24]. Importantly, similar IP_3R dysfunction was found in in vitro models for AD including primary neuronal cultures from mouse models of AD [44, 49, 50] and cortical neurons exposed to β-amyloid protein [49]. These findings are particularly interesting, given the selective response of IP_3R to elevated levels of oxidative stress. IP_3R-mediated Ca^{2+} release was increased following activation of M3 muscarinic receptors under conditions of elevated oxidative stress [51]. Similarly, nonlethal oxidative stress in neuronal cells resulted in a selective upregulation at both the transcriptional and translational levels of type 2 IP_3Rs [52]. These channels exhibit the strongest affinity for the endogenous ligand, IP_3, and are preferentially expressed in the membranes of the nuclear envelope, where they mediate nuclear Ca^{2+} release [52–55]. This nuclear Ca^{2+} release is thought to control gene expression responsible for cellular survival and death pathways, and therefore, represents a promising drug target for neurodegenerative diseases [56]. This is exemplified by the recent finding that homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1 (HERPUD1) is cytoprotective by preventing IP_3R-mediated Ca^{2+} transfer from the ER to mitochondria [57]. Analogously to IP_3Rs, several neurodegenerative and age-related disorders show RyR dysfunction contributing to disease pathology and progression. AD patients exhibit changes in neuronal RyR expression and in ryanodine binding that correlates with cognitive decline and Aβ deposition [42].

3.2. Aging of the nonneuronal cells in the nervous system

The vast amount of cells in the brain is nonneuronal cells such as glia, microglia, astrocytes, and oligodendrocytes. These cells maintain homeostasis, form myelin, and, importantly, they can provide protection to the CNS and PNS as they act as the first and main form of neuronal immune defense. Microglia acts as the resident innate immune system in the brain as they respond to and propagate inflammatory signals (e.g., impending from PNS) by producing proinflammatory cytokines that ultimately can generate cognitive consequences. Several clinical and experimental studies reported that both increased oxidative stress and increased inflammation are (among others) hallmarks of brain aging [30, 58]. Remarkably, it has been found that activation of microglia is dependent on the expression of the Kv1.5 potassium channel and β-amyloid peptide induces expression of the Kv1.5 potassium channels in microglia [59–61]. This suggests that increased oxidative stress in aging could produce

inflammation by upregulating K^+ channels in microglia and that alteration of ion channels could be one of the possible causes of aging-dependent decline of neuronal functions.

4. Ion channels and glaucoma

Glaucoma is an age-related, progressive optic neuropathy that manifests with pathological changes in the optic nerve, activation and remodeling of optic nerve head astrocytes (ONHAs), and slow progressive death of retinal ganglion cells, often leading to blindness. Although the exact pathophysiology is still not completely understood, there is evidence to support ischemic, mechanical, and inflammatory components. In an effort to protect the integrity of the optic nerve and prevent the loss of retinal ganglion cells, research efforts have recently concentrated on glioprotection approaches targeting ONHAs [62, 63]. Glia and neuronal cells alike utilize fine-tuned calcium signaling pathways to control physiological functions. Recent studies have revealed complex intracellular Ca^{2+} signaling pathways in primary ONHA culture [55] and for the first time described a differential distribution of type 2 IP_3Rs and type 2 RyRs in the ER and the membranes of the nuclear envelope. Hence, it is likely that these receptor subtypes activate specific Ca^{2+}-sensitive genes that determine cellular fate. Of particular interest for the role of aberrant Ca^{2+} signaling in glaucoma is the finding that exposure of ONHAs to elevated hydrostatic pressure, as a model for increased intraocular pressure in glaucoma, results in the differential upregulation of type 2 RyRs [64]. Given the nuclear membrane localization of type 2 RyRs in ONHAs [55], it is likely that RyR-mediated Ca^{2+} release differentially activates gene expression. Similar pathways of calcium signaling have been identified in astrocytes from other parts of the CNS and recently been reviewed in detail [65].

5. Ion channels and cancer

Cancer is a group of diseases that claim about 8.4 million lives every year (www.cancer.org). Although in the past decades, medical research has dramatically improved prevention, diagnosis, and treatment of cancer and despite being among the most preventable diseases, cancer remains a leading cause of death worldwide.

Virtually, cancer can develop in any tissue and although each cancer type can be characterized by its unique features, the basic mechanisms that generate cancers are similar in all forms of the diseases. In a normal and healthy tissue, cell proliferation and cell death are controlled by a very complex, timely, and integrated signaling network that includes a series of checkpoints to ensure proper division factors of the cell or death. Cancer originates from an uncontrolled proliferation of cells that evade cell death and can eventually invade and/or outspread into other body compartments (metastasis).

Cancer can be caused by a multitude of environmental factors that can be external such as smoking, sun exposure, and/or internal such as inherited faulty genes and/or infections.

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Although there can be a significant difference in the prevalence of cancers among different societies, overall cancer can affect every human being. Accordingly, aging is the highest single risk factor for developing cancer [66]. Recently, several ion channels have been found to play a major role in maintaining homeostasis of nonexcitable cells (**Figure 1**).

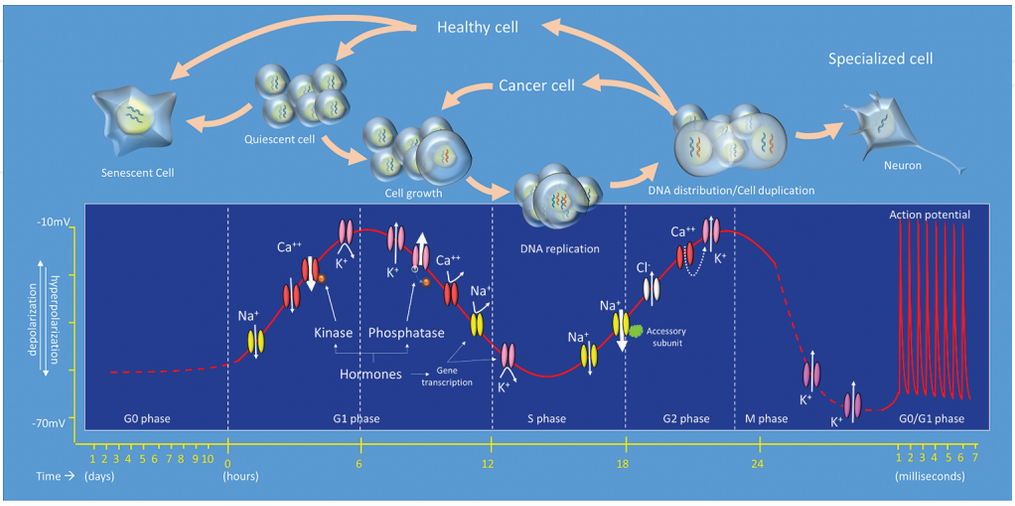

Figure 1. Schematic representation of the contribution of different ion channels to the membrane potential in function of time (e.g., nonexcitable cell vs. neuronal action potential). Overexpression and/or upregulation (e.g., via hormone-dependent regulation) of certain ion channels can contribute to suppress differentiation and increase duplication rate resulting in the generation of a cancerogenic phenotype.

In addition to the traditional role of allowing movements of ions across membranes, ion channels can also control mechanisms of transport, secretion, cell volume, and protein synthesis. For example, glucose transport is controlled by gradients of Na^+ [67, 68]. Furthermore, several transcription factors or proteins involved in secretory mechanism are activated by Ca^{2+} [69, 70]. Therefore, changes of intracellular ionic concentrations can regulate a variety of cellular event ranging from production of energy to protein synthesis, which are necessary for the ultimate process of cellular duplication. Several studies have reported that cancer cells of different histogenesis can express specific ion channels that can play an important role during proliferation [71].

One of the better characterized ion channels in cancer is the Kv11.1 (hERG1) potassium channel. This potassium channel is encoded by the human ether-a-go-go related gene 1 (hERG1), which has been found typically expressed in the mammalian heart in which it play a fundamental role in controlling repolarization and duration of action potential [72]. Remarkably, hERG1 channel has also been found expressed in different nonexcitable cancer cells but not in the organ from which the tumor has originated [73]. This suggests that the presence of this channel might provide a selective advantage to proliferation. Blockade or stimulation of hERG1 channel activity determined a strong inhibitory effect on cancer cell proliferation [74–78]. In addition, complete removal of the hERG1 protein from breast cancer cells determined death by activation of apoptosis [78]. These events indicate that the hERG1 is very important for cancer biology and its activity is kept under strict control.

Interestingly, the inhibitory effect on cell proliferation as a consequence of chronic stimulation of hERG1 channel was characterized by activation of a "cellular senescent program" [76, 79]. Senescent cells were initially described by Hayflick and Moorhead [80] as cells that have lost the ability to duplicate, though they may not die. Today, cellular senescence is defined as a permanent arrest of the cell cycle induced by a progressive increase of stresses [81–83]. At this time, it is not known what kind of stresses hERG1 agonists produce on cancer cells but their effect is mediated by permanent arrest of the cell cycle, increased expression of tumor suppressors (e.g., $p21^{waf/cif}$ and $p16^{INK4A}$) and decreased level of tumor markers (e.g., cyclins) resulting in a potent inhibition of cell proliferation [84–86]. This suggests that, by taking advantage of the ability to accelerate aging in cancer cells, hERG1 agonists could be used as an anticancer therapeutic strategy.

Other ion channels have been found playing fundamental roles in regulating biochemical signaling that underline important events in cancer biology which includes metastasis. Overtime, cancer cells acquire the ability to move and invade surrounding tissues by protruding membrane structures (invadopodia and pseudopodia) [87] through the intracellular space of the host organ. Remarkably, it has been discovered that ion channels are fundamental factors for regulation of invasion and migration of cancer cells. For example, the concerted activity of Ca^{2+}, K^+, and Cl channels that can exquisitely colocalize on the glioma surface membrane generates fluxes of ions and water that creates shrinkage of the membrane with consequent formation of invadopodia [88]. A direct consequence of this event is that cancer cells can move across tissue barriers (e.g., blood vessel) and colonize other body compartments. In addition, it has been shown that overexpression of Kv10 channels in which ion flux has been obstructed by a specific mutation did not lose the ability to promote cell proliferation [89, 90]. Although the mechanism through which this event occurs is not clearly understood, it appears that these channels can regulate activities of proteins that control proliferative cell signaling also when ion fluxes are not involved.

As hormones control most of the major organ functions by activating a variety of cellular signaling, it is not surprising that ion channels can be downstream effectors of hormone receptors. Growth of many cancers can depend on altered expression of hormone receptors. For example, high percentage of breast cancers are very sensitive to the action of insulin and/or sex hormones such as estrogen [91] or prostate cancer to testosterone [92]. Hormones can control ion channel activity by increasing their synthesis or by activating membrane signaling pathways (**Figure 1**). For example, hormones that bind G protein-coupled receptors (GPCR) produce release of the active $\beta\gamma$subunit of the heteromeric GTPase complex that ultimately binds and activates K^+ channels (e.g., GIRK). Alternatively, soluble hormone receptors can activate nongenomic signaling resulting in stimulation of kinases or phosphatases that modulate activity of ion channels by directly targeting these proteins [93–95]. Furthermore, as secretion is vastly controlled by intracellular changes in Ca^{2+} concentrations (e.g., Ca^{2+}-dependent insulin secretion), hormones must rely on ion channel function to be released in the body environment [96]. It is well established that with aging, organs become less sensitive to hormones. Although several examples of hormone-regulated ion channel activities have been proposed, knowledge on the role of these signalings in pathological conditions such as

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cancer, age-related disease, and/or aging is very limited. Therefore, it appears that there is a compelling need to study the role of hormonal regulation of ion channels to better understand both aging and cancer.

6. Modulation of ion channels

Another level of complexity of regulation of ion channels is added by a number of modulatory proteins that have been shown to bind channels and alter their biophysical properties.

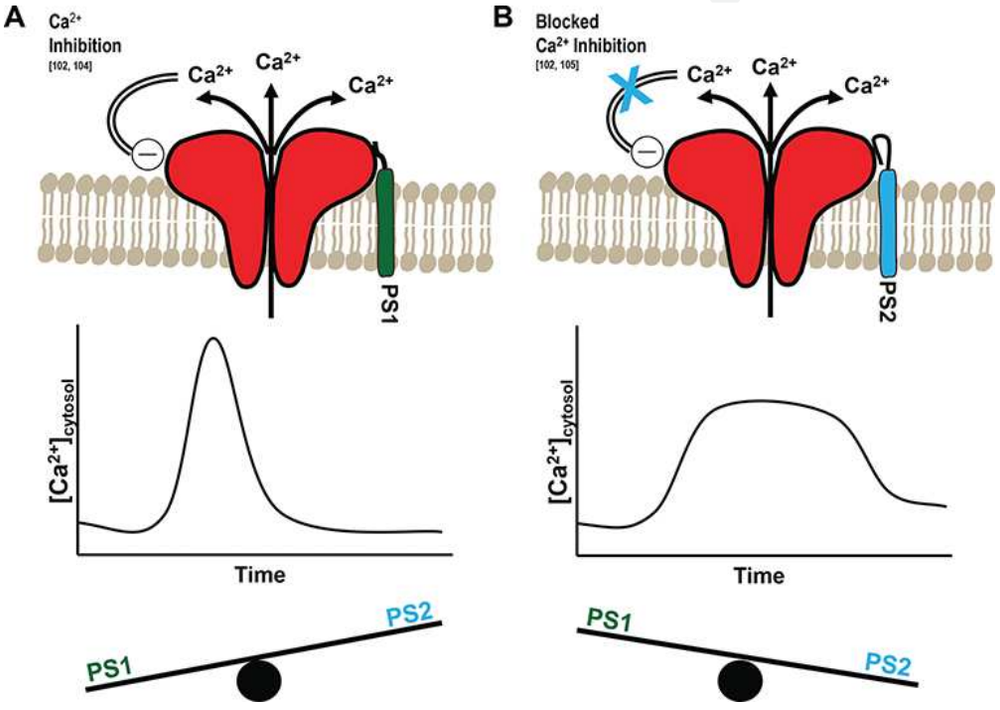

Figure 2. Presenilins differentially regulate RyR-mediated Ca^{2+} release.Representations of an individual RyR and its interaction with presenilin are shown in the top panels. Corresponding graphs below illustrate characteristics of Ca^{2+} transients mediated by RyR activity. Whole-cell cytosolic calcium concentrations (ordinate) are plotted over time (abscissa) to show the changes in the kinetics of Ca^{2+} transients dependent on presenilin binding to the RyR. Seesaws depict a predominant effect of presenilin 1 (PS1) over presenilin 2 PS2 or PS2 over PS1, as seen in young and aged animals, respectively [48]. (A) Binding of the PS1 N-terminal fragment to RyR increases open probability and results in heightened calcium release and fast channel inhibition by calcium at the RyR's inhibitory low affinity Ca^{2+} binding site. (B) Binding of PS2 to the RyR blocks inhibition at the low affinity Ca^{2+} binding site resulting in an increased duration of the Ca^{2+} transient.This figure was modified from reference [103], which was published under Open Access licence (®2015 by Andrew J. Payne *et al.*).

One of the best examples of involvement of ion channel modulation in aging includes Homer/Vesl proteins and the group of presenilins. The group of Homer proteins (reviewed in [97]) is a family of ubiquitously expressed scaffolding molecules. Through a conserved binding motif, Homer proteins interact with a number of synaptic proteins. Homer 1 proteins directly interact with IP_3Rs, RyRs, the group of transient receptor potential canonical (TRPC) channels, as well as mGluRs and some voltage-gated Ca^{2+} channels (reviewed in [97]). Intriguingly, in addition

to enhancing synaptic transmission and providing a means of regulating excitability through tethering plasma membrane proteins to receptors and channels in the ER by formation of Homer tetramers, Homer proteins can alter the biophysical properties of their binding partners [98–100]. These interactions, especially with intracellular Ca^{2+} channels, have recently attracted increased interest due to their alterations in age-related diseases in the nervous system. For instance, in the aging brain, loss of the short isoform, Homer 1a, correlated with the loss of cognitive and motor function in mice [46]. Similarly, upregulation of the long isoform, Homer 1c, in the retina of glaucomatous mice showed a statistically significant association with severity of the disease phenotype and disease progression [47]. Furthermore, loss of Homer 1c immunoreactivity at glutamatergic synapses after experimental stroke was identified as a potential biomarker for early neurodegenerative processes, prior to initiation of apoptotic pathways [101]. Similarly, binding of presenilin proteins to RyRs results in a functional change of intracellular Ca^{2+} release [102–105]. Recent studies have demonstrated that altered levels of presenilin proteins in the aging brain correlate with the presence and severity of impairments in cognitive and motor function [48]; **Figure 2**), identifying the group of presenilins as putative drug target for neurodegeneration. In summary, intracellular Ca^{2+} channels are critical mediators of intracellular Ca^{2+} homeostasis and respond differentially to aging and pathological stimuli including oxidative stress. Furthermore, intracellular Ca^{2+} signaling is differentially regulated in various cell types and tissues and by a large number of modulators, providing a multitude of targets for pharmaceutical intervention in conditions characterized by neurodegeneration and aging.

7. Perspective

Aging is a process common to all living organisms that is associated with a progressive failure to adapt to changes in the environment. As ion channels are evolutionary conserved proteins that all cells of all living creatures utilize to sense and adapt to variations of both extracellular and intracellular environments, it is not surprising that malfunction of ion channels increases disease susceptibility that often simulates ailments of getting older. This suggests that drugs targeting ion channels can hold promise for treating aging. However, in consideration of the fact that more than 400 genes encoding for ion channels subunits have been identified so far, the role of ion channels in aging and aging-related diseases remains significantly underexplored. In addition, aging-dependent alteration of a particular ion channel appears to be organ and/or tissue-specific indicating that pharmacologic therapies targeting a specific ion channel should be tailored to a particular organ.

The ultimate consequence of all diseases is pain which appears to get worse with age and can have serious negative impact on quality of life. In recent time, a substantial increased awareness on the critical role of ion channels in diseases and pain has been achieved so that ion channels are emerging as novel therapeutic targets in the treatment of pain.

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