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Review

Oxidation of ion channels in the aging nervous system

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ABSTRACT

Ion channels are integral membrane proteins that allow passive diffusion of ions across membranes. In neurons and in other excitable cells, the harmonious coordination between the numerous types of ion channels shape and propagate electrical signals. Increased accumulation of reactive oxidative species (ROS), and subsequent oxidation of proteins, including ion channels, is a hallmark feature of aging and may contribute to cell failure as a result. In this review we discuss the effects of ROS on three major types of ion channels of the central nervous system, namely the potassium (K^+), calcium (Ca^{2+}) and sodium (Na^+) channels. We examine two general mechanisms through which ROS affect ion channels: via direct oxidation of specific residues and via indirect interference of pathways that regulate the channels.

The overall status of the present studies indicates that the interaction of ion channels with ROS is multimodal and pervasive in the central nervous system and likely constitutes a general mechanism of aging susceptibility.

Contents

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1. Introduction

Aging is a fundamental feature of life which encompasses both physical and psychological change. The biological causes of aging are not known, but there is general consensus around the notion that its etiology is multifactorial. Theories of aging can be divided into two broad groups: those that explain aging as the result of accumulation of damage and those which see aging as the consequence of programmed-death processes. It is likely that the combined action of these two basic mechanisms shapes the aging process, with large variability between individuals.

The "free radical theory of aging", proposed by Harman in the 1950s (Harman, 1956), is one of the predominant theories of the damage group. Harman's original hypothesis posits that accumulation of reactive oxygen species (ROS) over time damages essential components of the cell, eventually leading to its failure. In fact, evidence shows that reducing oxidative damage extends lifespan, whereas enhancing oxidative damage shorten lifespan in both invertebrates and vertebrates (reviewed in (Beckman and Ames, 1998; Bokov et al., 2004; Kregel and Zhang, 2007; Sohal and Weindruch, 1996)). However, increasing antioxidant defenses generally does not prolong longevity beyond the species-specific maximum and in some cases it can shorten the life span (Gems and Doonan, 2009; Mockett et al., 2010; Ristow and Schmeisser, 2011). Therefore, whether reducing oxidative damage is sufficient to extend lifespan remains an open question. On the other hand, ROS act as signaling molecules in a number of physiological pathways (Droge, 2002; Forman et al., 2010; Maher, 2006; Veal and Day, 2011). This double-edged sword nature of ROS may explain why in certain cases antioxidants shorten lifespan. Nonetheless, the current opinion is that structural damage alone is not sufficient to account for the functional loss associated with aging and several corrective mechanisms have been proposed. One of the most popular is the "redox stress hypothesis of aging" which predicts that ROS can cause cell failure through interfering with signaling pathways and their associated components in addition to imposing direct damage thus incorporating both the beneficial and malign nature of ROS (reviewed in (Sohal and Orr, 2012)). Notwithstanding the details of the mechanisms through which ROS inflict damage, their targets offer another perspective to help us to better understand the aging process. In fact, while most of the experimental effort has focused on studying the effects of reducing oxidative damage, a comparatively small number of proteins targeted by ROS are known and studied. In this review we focus on one of them, the ion channels.

Ion channels are integral membrane proteins responsible for passive movement of ions across membranes (Hille, 2001). As such, they generate and shape electrical signals in cells while also having functions independent of their ability to conduct ions (for a review of non-conducting roles of ion channels see ref. (Kaczmarek, 2006)). The nervous system offers one of the most comprehensive examples of the importance of ion channels given the unique relationship that exist between neurons and the electrical signals they generate and exchange. It follows that oxidative modifications of ion channels by ROS has the potential to represent a major mechanism of aging vulnerability in the brain, a mechanism that may contribute to the cognitive decline characteristic of the late-phase of life. Here we examine the cases of two well-established substrates for ROS, the potassium (K^+) and calcium (Ca^{2+}) channels and one emerging substrate, the sodium (Na^+) channel. We discuss the modes through which aging-dependent oxidative processes affect these channels in the central nervous system. We review evidence showing that ROS impact ion channel function via both direct oxidation and indirect dysregulation of their signaling pathways. The general picture that emerges is one in which the interactions of ion channels with ROS is multimodal and pervasive in the brain.

2. Oxidation of K^+ channels

Direct evidence that oxidation of an ion channel can lead to functional deficits as a side effect of increased cellular oxidation during aging came from *Caenorhabditis elegans* (Cai and Sesti, 2009). This animal is attracted by salts, amino-acids, vitamins etc. that are primarily detected by the ASE neurons (Bargmann and Horvitz, 1991). The sensory capacity of these cells declines with age (Cai and Sesti, 2009; Maglioni et al., 2014; Minniti et al., 2009; Wu et al., 2006), an effect due, in part, by oxidation of a cysteine residue (cys113) on a voltage-gated K^+ channel named KVS-1 (Bianchi et al., 2003; Cai and Sesti, 2009). When KVS-1 channels are oxidized they conduct more current and consequently affect neuronal output; in fact, transgenic animals that express a KVS-1 mutant bearing a cysteine to serine replacement (C113S) retain their sensory capacity during aging or after being exposed to acute oxidative challenges. KVS-1 is homolog to KCNB1/Kv2.1 (Rojas et al., 2008) which carries a major somato-dendritic current in neurons of the hippocampus and cortex (Du et al., 1998; Murakoshi and Trimmer, 1999; Trimmer, 1991, 1993). KCNB1 is also susceptible to redox (Cotella et al., 2012; Wu et al., 2013). When exposed to oxidants, several cysteines, including cys73, the equivalent of cys113 in KVS-1, form disulfide bridges that cross-link KCNB1 subunits to each other. *In vitro* studies have shown that KCNB1 oligomers do not conduct current. In additon, they are poorly internalized and as a result build up in the plasma membrane. The cell responds by activating Src tyrosine kinases and c-Jun N-terminal (JNK), kinases which initiate an apoptotic program by targeting mitochondria in addition to generating more ROS (Fig. 1A). KCNB1 oligomers are present in the brains of aging mice indicating that KCNB1 is subject to a natural process of oxidation (Cotella et al., 2012). Large amounts of KCNB1 oligomers are detected in the brains of the 3xTG-AD mouse, a murine model of Alzheimer's disease characterized by premature and extensive oxidation (Chou et al., 2011; Cotella et al., 2012; McManus et al., 2011; Sensi et al., 2008; Smith et al., 2005; Yao et al., 2009). In a recent study, Frazzini and colleagues have shown that the non-conducting KCNB1 oligomers impair the excitability of 3xTg-AD neurons and that application of antioxidants restores normal excitability by rescuing KCNB1 current (Frazzini et al., 2016). Thus it appears that KCNB1 oligomerization may be a cause of functional impairment in the brain even though more studies

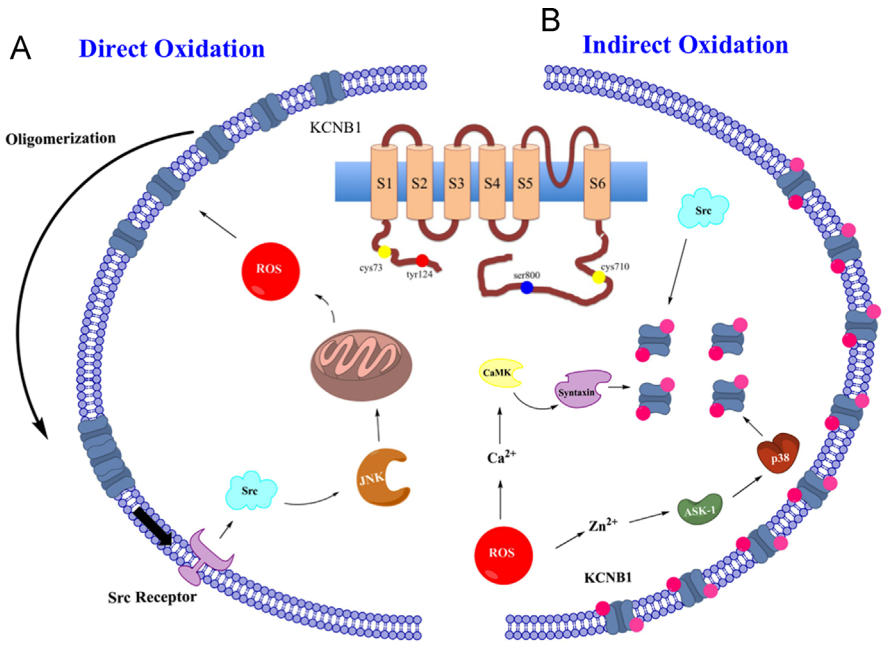

Fig. 1 – Different modes of modulation of KCNB1 by ROS. A) Oxidants promote cross-link of KCNB1 subunits to each other via the formation of disulfide bridges between several cysteines, including cys73 and cys710 (inset). As a consequence, KCNB1 oligomers transiently accumulate in the plasma membrane where their presence activates Src/JNK kinases signaling. This "death" pathway leads to mitochondria destabilization and oxidative stress. B) ROS also induce elevation of cytoplasmic Ca^{2+} and Zn^{2+} that contributes to apoptosis via a phosphorylation-mediated surge of KCNB1 channels to the plasma membrane. Zn^{2+} activates ASK-1/p38 signaling and independently, Src tyrosine kinases. Phosphorylation of KCNB1 at ser800 and tyr124 (inset) favours the interaction between the channel and the SNARE family protein syntaxin. Ca^{2+} activates CaMKII kinase which in turn acts to modulate the interaction of phopshorylated KCNB1 with syntaxin.

will be necessary to confirm this notion. In addition, KCNB1 can be indirectly affected by conditions of oxidative stress in the cell. Evidence shows that acute exposure of mammalian cells or primary neurons to oxidants, triggers the cytoplasmic release of zinc (Zn^{2+}) and calcium (Ca^{2+}) (McCord and Aizenman, 2013). These divalent ions initiate a series of molecular events that lead to sequential phosphorylation of KCNB1 channels by protein kinase A, apoptosis signal-regulating kinase 1, p38 MAPK-dependent kinase, c-Src tyrosine kinase, and Ca(2+)/calmodulin-dependent protein kinase II (Aras and Aizenman, 2005; McCord and Aizenman, 2013; Norris et al., 2012; Redman et al., 2007, 2009; Zhou et al., 2012). Phosphorylation of the channel enhances its forward trafficking to the plasma membrane giving rise to a K^+ current surge that is thought to induce apoptosis (McCord and Aizenman, 2013), (Fig. 1B). It remains to be determined whether the oxidative conditions typical of normal aging are sufficient to trigger this mechanism of apoptosis vulnerability. Nonetheless, KCNB1 surge is likely to be toxic when cellular oxidation is exacerbated as it is in certain neurodegenerative diseases. In summary KCNB1 is affected by ROS both directly and indirectly but whether these influences lead to brain dysfunction awaits validation in animal models. However, other K^+ channel types appear to be targets of ROS as well as being pervasively oxidized in the central nervous system. One of these channels is the KATP K^+ channel. In nature, KATP channels are heteromeric complexes formed by a pore forming subunit (Kir6.x) and a sulfonylurea receptor (SUR1 and SUR2A-B) (Clement et al., 1997; Inagaki et al., 1995) with different combinations resulting in channels with different attributes (Babenko et al., 1998; Cheng et al., 2008; Yamada et al., 1997). KATP sense variations in ATP/MgADP ratio and as such respond to metabolism changes and exert protection under certain metabolic stresses (reviewed in (McTaggart et al., 2010)). For example, during hypoxia, the closure of KATP channels acts to buffer the impact of the insult by slowing down calcium entry via depolarization of the plasma membrane (reviewed in (Rana et al., 2015)). KATP channels are generally downregulated in cellular environments subject to oxidation, including aging tissue and the Alzheimer's disease (AD) brain (Bao et al., 2013; Du et al., 2013; Liu et al., 2010; Raveaud et al., 2009; Toyoda et al., 1997; Tricarico and Camerino, 1994). Diazoxide, a specific KATP activator was shown to ameliorate hallmark lesions of AD in cultured neurons and rescued memory loss in 3x-Tg-AD mice (Liu et al., 2010). Diazoxide was also shown to be protective in NSC-34 motor neurons subjected to a variety of neurotoxic insults including oxidative damage via its modulation of KATP channels (Virgili et al., 2013). Notably, KATP channels can be directly modulated by thiol-redox reactions which act to decrease the opening probability. Thus, Tricarico and Camerino showed that KATP channels expressed in skeletal muscle fibers of old rats are roughly eight times less likely to open than those in young animals (Tricarico and Camerino, 1994). Sulfhydryl group-reducing agents rescue the open probability to "young" values whereas sulfhydryl group-oxidizing agents, abolish channel openings, thereby demonstrating that the robust decrease of the open

probability of the channel is due to modification of its thiol groups. Even though muscular KATP channels may be different from neuronal KATP channels, the fact that the former are susceptible to redox may suggest that side effect oxidation of these channels may constitute a mechanism of neuronal impairment in the aging brain.

Another important K^+ channel type, the calcium-activated K^+ channel (K_{Ca}) exhibits a consistent pattern of dysregulation during aging. K_{Ca} channels modulate a variety of physiological functions including cellular excitability, circadian rhythm, vasodilation, and cell proliferation (reviewed in (Vergara et al., 1998)). Studies show that K_{Ca} channel currents are upregulated in aging tissue (Hu et al., 2001; Misonou et al., 2006; Obermair et al., 2003; Turner et al., 2015) of the nervous system, (Farajnia et al., 2015; Power et al., 2002), skeletal muscle (Tricarico et al., 1997; Vergara and Ramirez, 1997) and endothelium (Behringer et al., 2013; Feher et al., 2014). K_{Ca} currents are also increased in the brains of murine models of neurodegeneration (for example the TgCRND8 mouse model of AD) and in mice subjected to cerebral ischemia (Gong et al., 2002; Ye et al., 2010). A theme common to all these conditions is increased oxidation. This implies that ROS may be the underlying cause of increased K_{Ca} activity and an example of this is found in the microvasculature. The opening of small and intermediate conductance K_{Ca} (SK, IK) channels initiate endothelial cell hyperpolarization which spreads to the smooth muscle cells to promote their relaxation. Vascular aging is associated with reduced blood flow and SK and IK channels are major culprits for this deficit. Using specific pharmacological blockers, Behringer and colleagues found that SK and IK channels conduct more current in the epigastric resistance arteries of aging mice compared to that of young mice (Behringer et al., 2013). Application of hydrogen peroxide (H_2O_2) activated K_{Ca} channels in young animals, whereas H_2O_2 scavengers decreased K_{Ca} current in the arteries of old animals. Similar results were obtained by Feher and colleagues who found that conducted dilation declines with age in coronary arterioles of human patients and SK and IK conductances are upregulated in those vessels (Feher et al., 2014). In summary, by conducting more current, K_{Ca} channels present in aging endothelial cells impair vasomotor control (Behringer et al., 2013). But is endothelial K_{Ca} upregulation due to oxidation of the channels? While this possibility cannot be ruled out, the most probable cause is likely to stem from an excess of intracellular calcium—due to a shift toward oxidation in the redox status of the cellular environment—which induces endothelial SK and IK opening. Examples of this mechanism can be found in both pathological conditions such as cerebral ischemia (Liao et al., 2010; Runden-Pran et al., 2002) and normal physiological conditions such as the aging hippocampus (reviewed in (Sesti et al., 2010)), a case that will be discussed in more detail in the section dealing with oxidation of Ca^{2+} channels. However, the third member of the K_{Ca} family, the maxi conductance (BK) channel is directly susceptible to redox. Santarelli and colleagues reported that in Slo1 channels expressed in mammalian cells, oxidation of three methionines (met536, met712 and met739) increases the open probability without other tangible effects on the properties of the channel (Santarelli et al., 2006). Tang and colleagues identified a single cysteine in Slo1, cys911, that when oxidized acts to decrease the open probability of the channel (Tang et al., 2004). Accordingly, BK channels can be oxidized *in vivo*, even though with controversial results. Thus, Gong and colleagues showed that oxidants enhance BK current in inside-out patches from pyramidal neurons of the hippocampus, by increasing the open probability (Gong et al., 2000). They also found that oxidized glutathione, (GSSG) activates the channels and glutathione (GSH) reverses those effects. In a subsequent study, Soh and colleagues came to opposite conclusions (Soh et al., 2001). They found that GSSG inhibits and GSH activates the channels present in excised patches from neonatal rat hippocampal neurons. These controversial results may have several explanations. One could be found in the complex dependence of BK channels to redox in which oxidation of methionine and cysteine residues has opposite effects on the open probability (Santarelli et al., 2006; Tang et al., 2004; Zhang et al., 2006). In addition, the presence of accessory subunits may contribute to BK dependence on redox. Recently, Hu and colleagues reported that oxidative stress acts to directly decrease BK current density in sheep uterine arteries during chronic hypoxia by downregulating its β1 accessory subunit (Hu et al., 2015). Another β-subunit of BK channel, β3, brings redox-dependent gates that block ion permeation (Zeng et al., 2003). Further, the Gong study was carried out using cells from adult animals whereas Soh used neurons dissociated from neonatal rats. The issue is significant and deserves further scrutiny though, considering that under physiological conditions GSH and GSSG are simultaneously present in the cell and therefore variations in their ratio may have a significant effect on the cell function via BK channel regulation.

In summary, K^+ channels are directly and indirectly affected by increased oxidation in the cell.

3. Oxidation of Ca^{2+} channels

Long Term Potentiation (LTP) is a major mechanism underlying learning and memory formation (Bliss and Collingridge, 1993; McNaughton et al., 1986; Morris et al., 1986). Different areas of the brain exhibit different forms of LTP. In the hippocampus, a large and transient increase in postsynaptic intracellular calcium leads to protein kinase-mediated potentiation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) component of synaptic strength (Fig. 2A). The N-methyl D-aspartate receptor (NMDAR) provides the major route for calcium entry (reviewed in (Malenka and Bear, 2004)). In addition, two NMDAR-independent mechanisms, that is, opening of voltage-dependent calcium channels (VDCCs) and release of calcium from intracellular calcium stores (ICS) further contribute to transient rise of free intracellular calcium during LTP (Berridge, 1998; Futatsugi et al., 1999; Johnston et al., 1992; Moosmang et al., 2005; Verkhratsky, 2002; Verkhratsky and Petersen, 2002; Wu et al., 2004). ICS release proceeds through calcium binding to ryanodine receptors (RyRs), a mechanism commonly known as calcium-induced calcium release (CICR) and activation of inositol triphosphate receptor (IP_3R) via metabotropic glutamate receptors (Berridge, 1998; Berridge

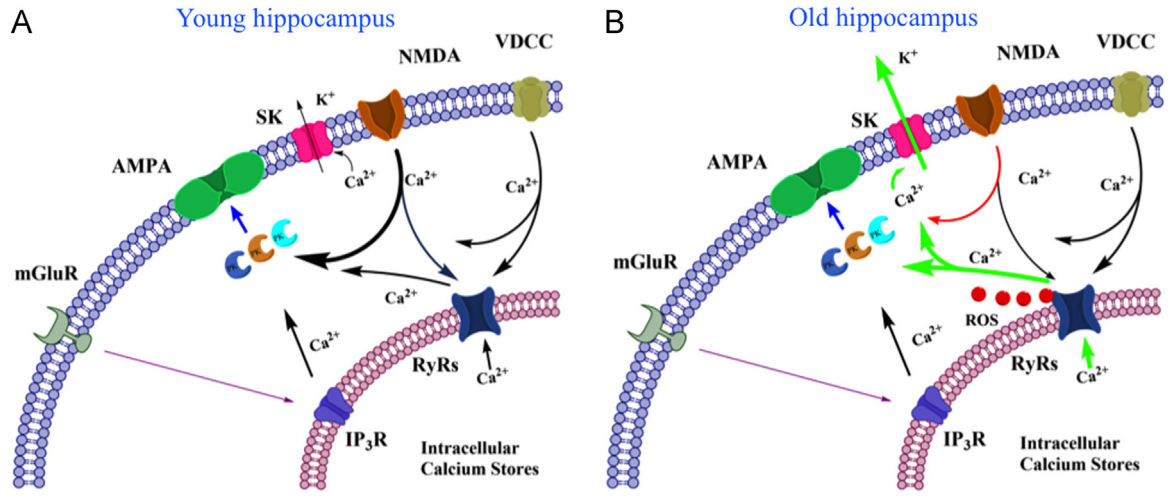

Fig. 2 – Major pathways leading to intracellular Ca^{2+} increase during LTP in the hippocampus. A) In young hippocampi, the NMDAR provides the major pathway underlying the transient increase in cytosolic calcium that potentiates the AMPA receptor component of synaptic strength. Along with this NMDAR-dependent mechanism, two NMDAR-independent mechanisms: 1) opening of VDCCs and 2) release of calcium from ICS through opening of RyRs (CICR) and IP_3R activation via metabotropic glutamate receptors, further contribute to elevate intracellular calcium. B) In aging hippocampi, the increased oxidation in the cells alters the equilibrium between the NMDAR-dependent and NMDAR-independent mechanisms by causing a progressive impairment of the NMDAR-dependent mechanism and a simultaneous potentiation of the CICR mechanism via direct oxidation of the RyRs. The surplus of calcium that follows, activates SK channels, which lower susceptibility to LTP induction by dampening the excitability of the membrane.

et al., 2000; Futatsugi et al., 1999). As the brain ages, there is a shift in the relative strength of the NMDAR-dependent and NMDAR-independent pathways which makes neurons progressively refractory to LTP induction (Barnes, 1979; Foster, 1999; Landfield et al., 1978). Studies have shown that higher frequency stimulation is necessary to induce LTP in old rodents and that LTP maintenance is generally impaired in those animals (Foster, 1999; Hsu et al., 2002). It turns out that the increased oxidation in the cell during aging causes both progressive impairment of the NMDAR-dependent mechanism (Bodhinathan et al., 2010b; Robillard et al., 2011; Yang et al., 2010) and at the same time an increase of free intracellular calcium via potentiation of the CICR mechanism (Bodhinathan et al., 2010a, 2010b; Kumar and Foster, 2004; Kumar et al., 2009; Norris et al., 1998; Oh et al., 2010; Thibault and Landfield, 1996) and according to a recent study, also of the IP_3R mechanism (Bansaghi et al., 2014). The surplus of calcium boosts opening of SK channels, which control the onset and duration of the slow after hyperpolarization (sAHP) —a key feature of memory impairment during aging (Faber, 2010). This decrease in synaptic excitability lowers susceptibility to LTP induction (Fig. 2B). Bodhinathan and colleagues showed that reducing agents are effective in decreasing the sAHP in old but not young rats, and that blockade of RyRs or depletion of intracellular calcium stores suppressed dithiothreitol (DTT) effects, whereas DTT-mediated decrease in sAHP was not affected by inhibition of other Ca^{2+} pathways such as VDCCs (Bodhinathan et al., 2010a). Additionally, pharmacological agents that block SK channels or VDCCs as well as inhibition of calcium release from ICS, all act to reestablish LTP induction at low frequencies (Bodhinathan et al., 2010b; Kumar and Foster, 2004; Norris et al., 1998). In conclusion, the dysregulation of SK channels and NMDARs that takes place in aging hippocampal neurons provides another example of how ROS can indirectly influence the function of channels by affecting their mechanisms of regulation. However, SK and NMDAR are not the only channels to be affected by ROS in this process of memory impairment: treatments that inhibit the CICR mechanism have the greater effect on aging animals, thus implicating the RyR as one of the major players (Bodhinathan et al., 2010a; Kumar and Foster, 2004; Paula-Lima et al., 2014). In fact, the RyR is a well-established redox-sensitive channel (reviewed in (Hidalgo et al., 2004, 2007; Lanner et al., 2010)). Ca^{2+} leakage through oxidation-modified RyRs has been extensively studied in muscle; for example Andersson and colleagues showed that in skeletal muscle fibers of old mice RyR1 is oxidized, cysteine-nitrosylated and lacks accessory subunit calstabin1 (Andersson et al., 2011). There is consensus that oxidative modifications of RyR1 give rise to channels that open more readily and thus leak calcium (Andersson et al., 2011; Anzai et al., 1998; Bull et al., 2007; Donoso et al., 2011; Favero et al., 1995; Hanna et al., 2014; Lanner et al., 2010; Marengo et al., 1998; Oda et al., 2015; Paula-Lima et al., 2014). However, RyR1 is not expressed in the hippocampus but RyR2 and RyR3 are, and all three RyR isoforms exhibit sequence and structural homology (Furuichi et al., 1994; Hakamata et al., 1992; Lai et al., 1992; Sharp et al., 1993; Takeshima et al., 1989). In particular, RyRs have large numbers of cysteines per subunit (roughly 100 in RyR1, (Lanner et al., 2010)), many of which are redox-sensitive (Aracena et al., 2006; Aracena-Parks et al., 2006; Voss et al., 2004). Thus, given the homology between the three RyR isoforms it appears likely that neuronal RyR2 and RyR3, like RyR1, are directly oxidable, a notion that receives support from the work of Bull and colleagues. This group showed that in single RyRs from rat brain cortex

incorporated into the lipid bilayers the redox state of the receptor determines its activation by Ca^{2+} (Bull et al., 2003, 2007). They further showed that the RyR2 and RyR3 from the cortex of rat brains subjected to cerebral ischemia, and thus to increased cellular oxidation, opened more readily and thus leaked more calcium than their respective RyRs in control brains, due to S-glutathionylation of not yet identified cysteine residues (Bull et al., 2008). Additionally the IP_3R is a putative player in ROS-mediated regulation of calcium release from ICS as recent evidence indicates that superoxide anion modifies thiol groups within the IP_3R leading to sensitization of calcium release (Bansaghi et al., 2014). Elucidation of the details of the mechanism awaits follow up studies.

In summary the RyR is directly affected by shifts in the redox status of the cell. This leads to leakage of intracellular calcium which promotes decreased LTP capacity via overactivation of SK channels. Hence, LTP provides a clear example of how oxidative conditions during aging can lead to physiological impairment via modification of ion channels.

4. Oxidation of Na^+ channels

Voltage-gated sodium (Nav) channels are responsible for action potential initiation in neurons (Hille, 2001). Modifications in the synthesis and/or trafficking of Nav channels that alter their surface expression can affect the electrical excitability of the neuron even when the conducting attributes of the channel, (i.e. gating, permeation, and selectivity) are not changed. An example in this sense is provided by the Nav1.1 isoform, a pore-forming subunit broadly expressed in the brain including the hippocampus (Trimmer and Rhodes, 2004) and one of its accessory subunits, Navβ2. Kim and colleagues showed that Navβ2 is a substrate for β-secretase 1 (BACE1) and γ-secretases and that Navβ2 processing is remarkably similar to that of amyloid precursor protein (APP) in the AD brain (Kim et al., 2007). Thus, Navβ2 undergoes sequential BACE1 and γ-secretase cleavage which releases a soluble intracellular domain (β2-ICD) which in turn, regulates Nav1.1 mRNA and protein levels (Fig. 3A). Experimental manipulations that act to decrease BACE1 activity diminish Nav1.1 synthesis and *vice versa,* increasing the activity of BACE1 augments Nav1.1 mRNA and protein levels. At the plasma membrane however, the situation is different. While neurons from BACE1-null mice express low amounts of Nav1.1 current density as expected, Nav1.2 current is increased, perhaps as a compensatory mechanism for reduced surface Nav1.1 (Hu et al., 2010)). Also the neurons from mice overexpressing BACE1 exhibit low amounts of Nav1.1 current because the channel is not properly translocated to the plasma membrane (Hu et al., 2010; Kim et al., 2007; Kim et al., 2011). This BACE1 activity-mediated mechanism may have profound implications for the aging of neurons in which Nav1.1-Navβ2 complexes operate. Evidence shows that the activity of BACE1 is upregulated in both aging human, monkey, mouse brains and primary cells (Cai et al., 2010; Che et al., 2014; Dobarro et al., 2013; Fukumoto et al., 2004; Kern et al., 2006; Miners et al., 2010; Solas et al., 2013; Wu et al., 2012). Evidence further shows that oxidative stress

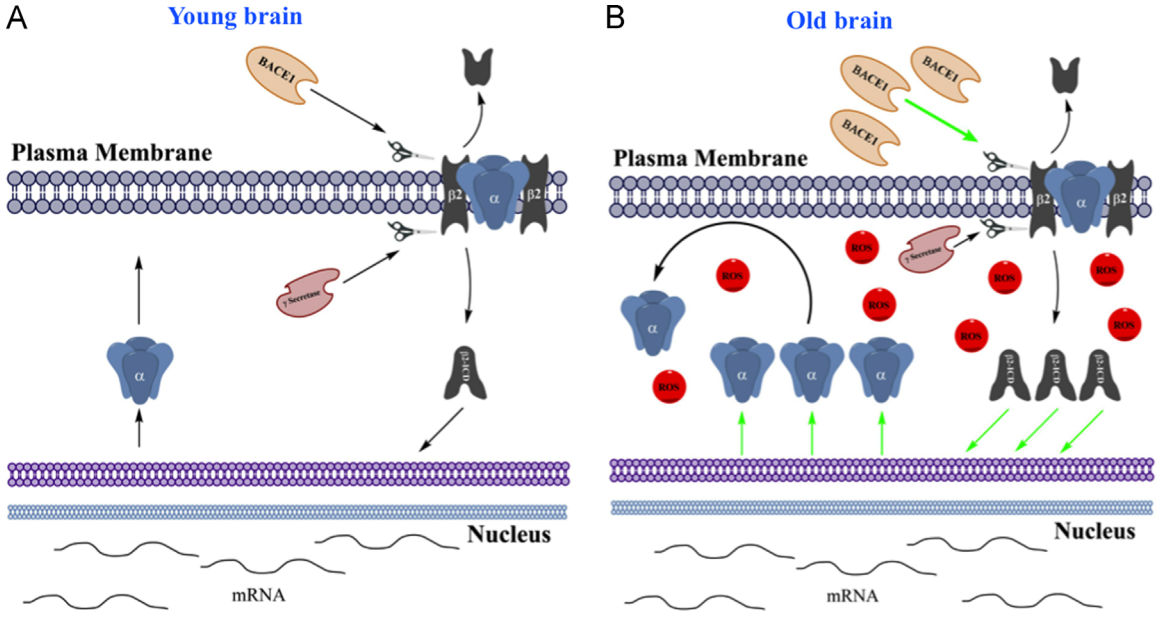

Fig. 3 – Nav1.1 current density depends on the activity of BACE1 and γ-secretases. A) Under normal conditions, sequential cleavage of Navβ2 by BACE1 and γ-secretases leads to the release of a soluble intracellular domain β2-ICD. This domain regulates the synthesis of Nav1.1 mRNA and protein levels acting at the transcriptional level. B) The oxidative conditions present in aging neurons act to upregulate both the activity and expression of BACE1, which results in augmented Nav1.1 transcription and translation. However, the newly synthesized channels fail to properly translocate to the plasma membrane, resulting in reduction of Nav1.1 current. This suggests that BACE1 may act as a indirect mechanism to decrease sodium current density and consequently reduce neuronal excitability during aging, but this hypothesis awaits further experimental support.

is a major underlying driving force of the upregulation of BACE1 expression and activity (Brown et al., 2014; Guglielmotto et al., 2009, 2010; Kizuka et al., 2016; Kwak et al., 2011; Mouton-Liger et al., 2012; Tamagno et al., 2002; Tan et al., 2013; Xiong et al., 2007). Together, this evidence argues that BACE1 may act to decrease sodium current density and consequent reduction in neuronal excitability during aging (Fig. 3B). Indeed, Randall and colleagues reported that mouse hippocampal CA1 pyramidal neurons showed the tendency to be less excitable as the animals aged (Randall et al., 2012). However this hypoexcitability did not stem from a decrease in the density of sodium current, as the BACE1 mechanism would predict, but rather from a shift in the voltage-dependence of activation of the current toward more depolarizing voltages. Fernandes and colleagues compared the functional properties of single sodium channels in excised inside-out patches from acutely isolated CA1 neurons of young and old rats. The unitary sodium conductance was moderately decreased in old cells compared to young cells and inactivation kinetics were also altered in old neurons leading to failure of fast inactivation (Fernandes et al., 2001). Moreover, fast inactivating sodium current density is higher in hippocampal neurons from BACE1-null mice, probably due to compensatory increase in Nav1.2 expression (Hu et al., 2010). As a result neurons are more excitable and the animals susceptible to seizures, although it is important to remember that the null-mouse is not physiologically representative. On the other hand, evidence shows that the levels of Nav1.1 protein are downregulated in certain areas of the aging cerebellum. Chung and colleagues examined the expression of Nav1.1 and Nav1.2 isoforms in the rat cerebellum and detected both increased and decreased Nav1.1 and Nav1.2 expression in Purkinjie fibers and granule cells, respectively (Chung et al., 2003). Further, Nav1.1 expression was decreased in the cerebellar nuclei of aging rats compared to control adults, whereas Nav1.2 expression did not change. Notably, Navβ2 is expressed throughout the cerebellum (Trimmer and Rhodes, 2004) and it is therefore tempting to speculate that the decrease in Nav1.1 expression reported by Chung *et al.* stems from increased BACE1 activity. Albeit, more evidence is needed to confirm this hypothesis, we do notice, that age-dependent downregulation of Nav isoforms and their accessory Navβ subunits has been reported to occur in aging muscle (Huang et al., 2015).

Like the other channel types examined thus far, Nav channels are susceptible to redox. Kassmann and colleagues showed that oxidation of several methionines in the Nv1.2, Nav1.4, Nav1.5 and Nav1.7 isoforms act in concert to suppress inactivation (Kassmann et al., 2008). However, studies from another group show that general oxidants (tert-butyl-hydroperoxide) as well as compounds that promote lipid peroxidation (E2-isoketal) potentiate inactivation of Nav1.5 channels (Fukuda et al., 2005; Nakajima et al., 2010). These studies prompt two considerations. First, there is evidence that inactivation kinetics of sodium currents are altered in aging neurons as shown by Fernandes and colleagues. Second, only pore-forming subunits were examined in *in vitro* studies whereas native channels are endowed by accessory subunits. Further, heterologous expression systems often do not recapitulate native cellular environments.

In conclusion, the evidence at hand points to ROS-modulation of Nav channels as an emerging mechanism of aging vulnerability in the brain. This hypothesis awaits confirmation as well as further elucidation of the details of the mechanisms.

5. Conclusions

The status of current studies indicate that the interactions of ion channels with ROS are pervasive in the central nervous system and thus likely to play a determining role in the aging process and in pathological conditions characterized by exacerbated oxidation, such as certain neurodegenerative diseases. Furthermore, oxidation of ion channels is widespread, although the discussion of non-neuronal cases was beyond the scope of this review.

The number of potential interactions between ROS and ion channels is virtually infinite but cells have multiple lines of defense against the toxic effects of ROS and their associated damage. Nonetheless, it is likely that many more cases await to be discovered. One factor limiting the pace of experimental inquiry is that ROS can simultaneously be construed as both “good” and “bad” molecules, and this can confound the interpretation of the results. In fact, this double-edged sword nature of ROS may be at the root of the problem of why pharmacological trials using antioxidants have generally failed. Oxidative modifications of ion channels have been successfully characterized *in vitro* where the controlled experimental conditions make possible to establish causative correlations between specific residues in the protein and changes in function. *In vivo* however, the situation is considerably more complex and ascertaining whether changes in the properties of a channel are caused by oxidation requires significant experimental effort. As the case of sodium channels shows, functional modifications in a channel during aging may be influenced by several factors that are not taken into consideration when the same channel is studied *in vitro*, including the presence of accessory subunits in the complex, different cellular environments etc. One way to circumvent these limitations is to employ transgenic animals harboring redox-resistant channel variants. This approach was successfully used in *C. Elegans*, in which worms expressing non-oxidable KVS-1 mutant channels enabled to establish causative relationships between oxidation of the channel, changes in neuronal excitability, and animal’s behavior during aging. Recent advances in mouse genetics techniques make now possible to use a similar strategy to answer crucial questions about the oxidation of channels in the central nervous system.

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