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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