Archives of Biochemistry and Biophysics 576 (2015) 8–16

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

Review

Mechanisms of oxidative stress resistance in the brain: Lessons learned from hypoxia tolerant extremophilic vertebrates

Valentina R. Garbarino [1], Miranda E. Orr [1], Karl A. Rodriguez, Rochelle Buffenstein *

Department of Physiology, Sam and Ann Barshop Institute for Aging and Longevity Studies, University of Texas Health Science Center at San Antonio, USA

ARTICLE INFO

Article history:
Received 16 December 2014
Available online 1 April 2015

Keywords:
Oxidative damage
Turtle
Hibernation
Hypoxia
Naked mole-rat
Brain
Antioxidant
Anoxia

ABSTRACT

The Oxidative Stress Theory of Aging has had tremendous impact in research involving aging and age-associated diseases including those that affect the nervous system. With over half a century of accrued data showing both strong support for and against this theory, there is a need to critically evaluate the data acquired from common biomedical research models, and to also diversify the species used in studies involving this proximate theory. One approach is to follow Orgel's second axiom that "*evolution is smarter than we are*" and judiciously choose species that may have evolved to live with chronic or seasonal oxidative stressors. Vertebrates that have naturally evolved to live under extreme conditions (e.g., anoxia or hypoxia), as well as those that undergo daily or seasonal torpor encounter both decreased oxygen availability and subsequent reoxygenation, with concomitant increased oxidative stress. Due to its high metabolic activity, the brain may be particularly vulnerable to oxidative stress. Here, we focus on oxidative stress responses in the brains of certain mouse models as well as extremophilic vertebrates. Exploring the naturally evolved biological tools utilized to cope with seasonal or environmentally variable oxygen availability may yield key information pertinent for how to deal with oxidative stress and thereby mitigate its propagation of age-associated diseases.

Introduction

The recent death of one of the most influential bio-gerontologists of all time, Dr. Denham Harman (1916–2014), the founding father of the Oxidative Stress Theory of Aging, forces one to reflect on the tremendous impact his paradigm shifting work has had in biomedical research as well as the outstanding issues involving his postulate. Dr. Harman's theory has enjoyed considerable impact and support as a basis of why and how we age. It also is considered a fundamental component of research concerning cancer, cardiovascular, and neurodegenerative diseases [1,2]. Moreover, this theory has also been ardently embraced in ecological and physiological studies as a mechanistic explanation for the observed life history trade off associated with allocating energy to reproduction or somatic tissue maintenance [3], suggesting ubiquitous importance throughout life's seasons.

Sixty years ago, Dr. Harman proposed that aging occurs when a cell is no longer able to balance the inevitable creation of reactive oxygen species [ROS] during aerobic metabolism with their neutralization by antioxidants. The irreversible destructive effects of these metabolic byproducts accumulate and cause oxidative damage, cellular degeneration, and functional decline. Additionally, they catalyze the further production of ROS that perpetuates damage and destruction of surrounding cells. Since damaged macromolecules in turn become ROS, oxidative damage becomes a self-propagating insult (Fig. 1). If left unchecked, this catalytic chain reaction often coincides with age-associated cumulative damage to cellular macromolecules and organelles. Further, when inadequate repair processes are available, organ functionality decreases and the incidence of age-associated morbidities such as neurodegenerative diseases increases [4–6].

The brain, in particular, is more susceptible to oxidative stress than other organs. Although the brain only accounts for ~2% of body mass it consumes 15–20% of the energy generated in the entire body. The high mass specific metabolic rate is attributed to the high proportion of omega-three polyunsaturated fatty acids (PUFAs)[2] in

* Corresponding author at: Sam and Ann Barshop Institute for Aging and Longevity Studies, University of Texas Health Science Center at San Antonio, 15355 Lambda Dr., STCBM 2.325, San Antonio, TX 78245, USA.

E-mail addresses: garbarino@livemail.uthscsa.edu (V.R. Garbarino), orrm3@uthscsa.edu (M.E. Orr), rodriguezk@uthscsa.edu (K.A. Rodriguez), buffenstein@uthscsa.edu (R. Buffenstein).

[1] Joint first authors.

[2] *Abbreviations used:* PUFAs, polyunsaturated fatty acids; NSC, neural stem cell; iPS, induced pluripotent stem cell; NO, nitrous oxide; CO, carbon monoxide; LTP, long-term potentiation; RNS, reactive nitrogen species; RON, reactive oxygen and nitrogen species; ROS, reactive oxygen species 8-oxodG, 8-oxo-7, 8-dihydro-29-deoxyguanosine; BER, base excision repair; mtDNA, mitochondrial DNA; MLS, maximum lifespan; SAM, senescence-accelerated mouse; CNS, central nervous system; HSP, heat shock protein.

http://dx.doi.org/10.1016/j.abb.2015.01.029
0003-9861/

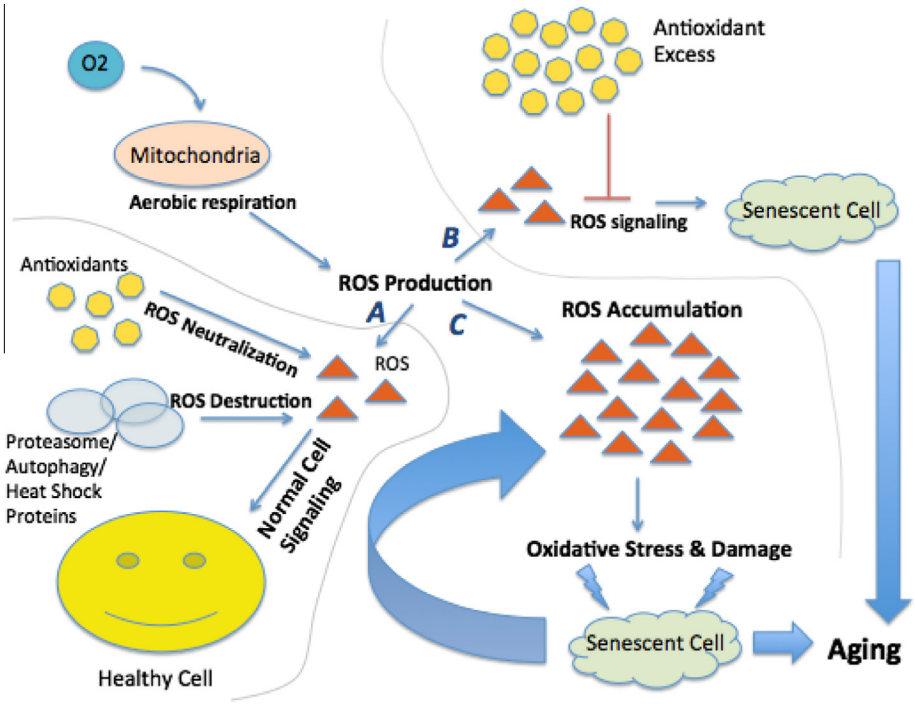

Fig. 1. The Oxidative Stress Theory of Aging. As an inevitable byproduct of aerobic respiration, the mitochondria in a normally functioning cell create reactive oxygen species (ROS). ROS in moderate amounts are beneficial and essential for normal cell signaling and cellular immunity. In a normally functioning cell, antioxidants may adequately neutralize excess ROS. If levels of ROS are unchecked they cause oxidative damage to the cellular constituents (protein, lipids, and DNA). These macromolecules may be protected to some extent by molecular chaperones mechanisms or, if damaged, removed from the cell by either autophagy or the proteasome. Damage that cannot be repaired or removed may accrue in the cell leading to impaired function and cell death. These cellular changes may accrue as the organism gets older, giving rise to the deleterious aging phenotype.

brain tissue [7]. These phospholipids are highly susceptible to peroxidation. Moreover, brain tissue contains high levels of redox-active iron and copper further enhancing its vulnerability to oxidative stress. Brain also has little potential to replenish damaged cells since it is composed mostly of terminally differentiated neurons and glia. As deaths associated with neurodegenerative diseases continue to increase in prevalence with few, if any, treatment options available, here we have focused the on what is known about oxidative stress in the brain, the impact thereof in cognitive function and the mechanisms of protecting this important organ in vertebrates, especially those living in extremely hostile habitats.

The physiological role of reactive oxygen species in the brain

Though oxygen provides the chemical energy essential for life, harnessing this element for metabolic activities carries a high cost due to the formation of highly volatile ROS. ROS are best known for indiscriminately attacking phospholipids, proteins and DNA. If left unchecked these insults can cause substantial damage at the cellular level and eventually affect the organism as a whole. As the central regulator of the entire organism and one of the most metabolically active tissues in the body, the brain must tightly regulate its oxygen handling and redox regulation to preserve somatic health.

In moderate amounts, ROS are essential for normal brain/cell function. Many endogenous cytoprotective molecules are upregulated by ROS, thereby triggering many adaptations to counteract and neutralize oxidative stressors [8]. Physiological ROS levels are extremely critical during brain development. In the developing brain, ROS contribute to healthy neural stem cell proliferation and differentiation and neurons produce high levels of physiologically active ROS to promote these critical functions. This is evidenced by decreased neural stem cell (NSC) proliferation rate and altered neuronal differentiation when neuronal cultures are supplemented with antioxidants [9–11]. Conversely, hypoxia conditioned media enhances NSC proliferation and favors neuronal survival over that of astrocytes [12]. Standard culture atmospheric conditions also influence cell survival, proliferation and fate determination in induced pluripotent stem cell (iPS) neurospheres [13–16]. While neurosphere number and size remain constant regardless of whether they are cultured at normal atmospheric conditions (21% O_2) or under hypoxia (1–5% O_2), culturing the iPS neurospheres in 1% oxygen increased gene expression of HIF-1A and VEGF and EPOR [10] angiogenic growth factors amenable to neurogenesis and brain development.

In the adult brain, ROS exerts physiological functions through the modulation of redox-sensitive proteins. ROS second messengers, such as nitrous oxide (NO) and carbon monoxide (CO) promote long-term potentiation (LTP) by inducing GMP-regulated glutamate release [17–21]. These reversible reactions alter synaptic plasticity and cellular metabolism through a delicate balance where high concentrations diminish LTP and synaptic signaling, and low concentrations enhance these processes.

Despite an age-associated decrease in CNS metabolic function with age, oxidative stress as measured by altered membrane lipids, oxidized proteins, and damaged DNA increase while natural antioxidant levels become dysregulated even in cognitively healthy individuals [22–24]. Gradually, physiological levels of ROS or reactive nitrogen species (RNS) start to exceed the brain's innate defenses. When compensatory defenses fail to counteract excess oxidative stress, impairments in neuronal function and cognition occur. The precise mechanisms involved in brain aging that lead to oxidative stress are complex; oxidative damage accrual is not uniform among individuals, or in the various brain regions, or even among cell types within the same specific brain region.