Available online at www.sciencedirect.com
SCIENCE DIRECT
Mechanisms of Ageing and Development 126 (2005) 1003–1010
mechanisms of ageing and development
www.elsevier.com/locate/mechagedev

Membrane alteration as a basis of aging and the protective effects of calorie restriction

Byung Pal Yu *

Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Received 2 November 2004; received in revised form 10 December 2004; accepted 15 March 2005
Available online 11 May 2005

Abstract

As has been experimentally determined, oxidative modification to biological systems can be extensive, although the identification and stochiometric relation of the reactive species that cause these alterations have not been fully elucidated. In this review, arguments are presented to support the notion that the combined effects of membrane lipid peroxidation and its by-products, reactive aldehydes are likely responsible for membrane-associated functional declines during aging. As evidence for a systemic response to overall oxidative stress, the molecular inflammation hypothesis of aging is discussed by considering that the activation of inflammatory genes act as a bridge linking normal aging to pathological processes.

Keywords: Biological membranes; Oxidative stress; Lipid peroxidation; Calorie restriction; Mitochondria; Reactive aldehydes

1. Introduction

No one would argue the importance of the cell membrane to the maintenance of cellular function and homeostasis. The cell membrane is a structural barrier that plays an essential role in protecting cellular integrity by restricting traffic between inside and outside the cell. Functionally, the membrane acts as a guard that regulates movement into the cytoplasm and as a transducer to amplify message signaling through the cytoplasm into the nucleus. The variety of intracellular metabolic requirements plus the extracelluar signals that are directed from outside the cell necessitate that the membrane be extremely responsive and dynamic in order to properly execute given functions (Vereb et al., 2003). Such complicated tasks are only possible when the membrane's chemical composition is stable and the complex infrastructure remains intact throughout the organism's lifespan (Yu, 1993).

Aging is often defined as time-dependent deleterious changes in function, accompanied by an increased inability to withstand stresses that make the organism vulnerable to disease. Biological metabolic systems are known to have evolved oxidation/reduction-coupling processes under aerobic conditions; thus, oxidative threats and innate protective mechanisms are deemed a part of life processes and traits. Because aging phenomena apparently occur in all biological systems examined so far, age-related changes in biological membrane systems should be no exception. Several investigators, including Spiteller (2002), postulate that the deterioration of membrane integrity is the underlying cause of the aging process. Earlier, Zs-Nagy (1994) proposed the essentiality of the cellular membrane in maintaining intracellular homeostasis during aging. Recent publications (Hulbert, 2003; Vereb et al., 2003) drew renewed attention to current views on membrane structure and its functional significance under normal conditions and during the aging process.

The cellular membrane's chemical composition, because of oxidation-responsive unsaturated fatty acids and redox-sensitive protein moieties, such as histidine and sulfhydryl groups as well its as membrane-associated, oxidant-producing activities, make it uniquely susceptible to various pro-oxidants including oxygen, free radicals and other

* Tel.: +1 760 451 2045; fax: +1 425 675 3578.
E-mail address: bpyu@earthlink.net.

0047-6374/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.mad.2005.03.020

reactive species (RS), particularly in the presence of transition metals such as Cu or Fe (Warner and Starke-Reed, 1997). The susceptibility of membrane lipids to oxidative alterations is related to two inherent properties, the chemical reactivity of the fatty acids composing the membrane bilayers and the cellular activities involved with membrane oxidation/reduction reactions. The first property is the peroxidizability of lipids caused by the unsaturation and conjugation of fatty acid double bondings. The second property relates to reactive species production, including the production of free radicals oxidants or reactive aldehydes, from the membrane sites, as a majority of sub and cellular membranes participates in such activities (Kikugawa, 1991). In a recent review, Spiteller (2001) gathered evidence on damaging oxidation by-products that indeed are generated from changes in membrane structure and not by superoxide as commonly assumed.

To appreciate the overall impact of oxidative stress on the membrane, it is essential to consider at least four related, but discrete aspects of oxidative stress: (1) the identity of the reactive species, (2) the specific targets of oxidative modification, (3) selective anti-oxidative defense systems aimed at reactive species and (4) the efficient repair and removal processes of oxidatively damaged cellular components (Yu, 1994). Because full discussions on these four aspects of oxidative stress are out of the scope of this paper, only relevant aspects pertaining to membrane modifications as potential targets of oxidative stress are considered.

2. Oxidative stress and membrane alterations

Before discussing specific topics related to oxidative membrane damage from free radicals and lipid peroxidation, a brief discussion on the major force influencing the cellular redox state of an organism would be helpful.

Oxidative stress is commonly referred to as a condition under which oxidative modification, i.e., damage is inflicted by reactive species (Sies, 1997). In biochemical and physiological terms, oxidative stress denotes a shift in the oxidation/reduction balance in favor of oxidation, which can impose an undue challenge to the biological system just like an acidic condition, challenges the body's pH buffering system.

It is worthy pointing out briefly some major differences between the original free radical theory of aging and the oxidative stress hypothesis of aging (Yu and Yang, 1996). In the original proposal of the free radical theory of aging, only superoxide and hydrogen peroxide were listed as reactive oxygen species that are linked to the metabolic rate of the organism. However, it is now clear that a host of other chemical entities, including non-radicals such as singlet oxygen (Klotz et al., 2000) and reactive aldehydes (Uchida, 2003) are shown to cause oxidative stress in entire biological systems, including the membrane structure. At present, there is no firm evidence to indicate that the free radical production is necessarily connected with metabolic rate and/or increases with age (Yu, 1996; Merry, 2002). One additional difference between the two hypotheses is that the original free radical hypothesis proposed that disease processes leads to aging, which is hard to accept based on what is known about aging today (Yu and Yang, 1996).

About the connection between metabolic rate and aging – an idea that has been in the aging literature since Rubner's proposal on the metabolic theory of aging in 1908 – Hulbert et al. (2004) recently examined this connection and found no straight correlation between the two. Thus, it seems clear that neither the rate of aging nor an organism's longevity are dependant on its metabolic rate or coupled with mitochondrial free radical production, as Rasmussen et al. (2003) also concluded. In fact, a recent paper by Speakman et al. (2004) showed that mice with higher metabolic rates lived longer. Thus, the experimental evidence supporting a common belief that mitochondrial aging is a biological aging clock (which is derived from the free radical theory of aging) is further weakened in wake of these new revelations.

Among most the likely targets of oxidative stress is the lipid–protein structured biological membrane complex for several reasons. For instance, most cellular activities-associated with the membrane involve reactive species production; lipids are exquisitely susceptible to oxidation and proteins contain various redox-sensitive moieties. As early as the 1970s, researchers interested in membrane biochemistry started to document evidence on age-related changes in various cellular organelles (Hegner, 1980). Schroeder (1984) proposed the membrane asymmetry hypothesis of aging based on the possibility of the re-arrangement and re-orientation of different phospholipid subclasses across the bilayer structure for the maintenance of membrane integrity during aging. Zs-Nagy (1994) proposed a membrane hypothesis of aging based on his long-held view that changes in the intracellular osmotic property and ionic permeability are keys to age-related cellular changes. More recently, Else and Hulbert (2003) developed the membrane pacemaker hypothesis of aging based on findings of the life-extending action of calorie restriction's ability to modify the fatty acid composition of the membrane.

Evidence shows that oxidatively modified proteins from reactive oxygen- or nitrogen-derived species also are found in aged tissues (Stadtman, 1988; Warner and Starke-Reed, 1997). However, evidence from the literature also shows that many oxidatively modified proteins may be the result of by-products such as reactive aldehydes caused by the lipid peroxidation process. Kikugawa (1991) delineates protein damage caused by oxidized lipids and cross-linked proteins derived from lipid hydroperoxides. Lucas and Szweda (1998) report adduct formation by the reactive aldehyde, 4-hydroxy-2-nonenal (HNE) in membrane proteins. Although no damage was found to membrane proteins specifically, the degree of membrane fatty acid unsaturation mediated oxidatively damaged proteins and mitochondrial DNA in liver and brain as reported recently (Pamplona et al., 2004).