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Review Article

Trends in oxidative aging theories

Florian L. Muller [a], Michael S. Lustgarten [b], Youngmok Jang [a], Arlan Richardson [a,b,c,d], Holly Van Remmen [a,b,c,d,*]

[a] *Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229-3900, USA*
[b] *Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229-3900, USA*
[c] *South Texas Veterans Health Care System, San Antonio, TX 78284-7762, USA*
[d] *Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229-3900, USA*

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Abstract

The early observations on the rate-of-living theory by Max Rubner and the report by Gershman that oxygen free radicals exist in vivo culminated in the seminal proposal in the 1950s by Denham Harman that reactive oxygen species are a cause of aging (free radical theory of aging). The goal of this review is to analyze recent findings relevant in evaluating Harman's theory using experimental results as grouped by model organisms (i.e., invertebrate models and mice). In this regard, we have focused primarily on recent work involving genetic manipulations. Because the free radical theory of aging is not the only theorem proposed to explain the mechanism(s) involved in aging at the molecular level, we also discuss how this theory is related to other areas of research in biogerontology, specifically, telomere/cell senescence, genomic instability, and the mitochondrial hypothesis of aging. We also discuss where we think the free radical theory is headed. It is now possible to give at least a partial answer to the question *whether oxidative stress determines life span* as Harman posed so long ago. Based on studies to date, we argue that a tentative case for oxidative stress as a life-span determinant can be made in *Drosophila melanogaster*. Studies in mice argue for a role of oxidative stress in age-related disease, especially cancer; however, with regard to aging per se, the data either do not support or remain inconclusive on whether oxidative stress determines life span.

Contents

Abbreviations: ApoD, apolipoprotein D; CAT, catalase; GCL, glutamate-cysteine ligase; Gpx1, glutathione peroxidase 1; MsrA, methionine-*S*-sulfoxide reductase; ROS, reactive oxygen species; SOD, superoxide dismutase.

* Corresponding author. Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, MSC 7762, San Antonio, TX 78229-3900, USA. Fax: +1 210 562 6110.
E-mail address: vanremmen@uthscsa.edu (H. Van Remmen).

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Introduction and historical background

Max Rubner, in his exploration of the relationship of metabolic rate (oxygen consumption) and body mass, first noted the now well-known inverse correlation between the rate of oxygen consumption and the longevity in eutherian mammals [1,2]. This observation was expanded further by Pearl, in the so-called rate-of-living hypothesis, which states that lifetime metabolic (energy) expenditure is finite and that life span is determined by how fast it is expended—in other words—that life span is strictly an inverse function of oxygen consumption or metabolic rate [3]. Although the rate-of-living hypothesis is no longer accepted [2,4,5], it directed the attention of aging research onto oxygen metabolism. The rate-of-living theory fits quite well with the observation that oxygen tension, in excess of that normally present in the atmosphere (21%), is toxic to almost all animals (fatal to mammals at 100% O_2 [6]). In the mid 1930s it was observed that metabolic rate and hyperoxic death are closely interrelated: high metabolic rate (brought about by hyperthyroidism) accelerated and a low metabolic rate (hypothyroidism) delayed death by hyperoxia in rats [7].

The origins of the free radical theory of aging go back to the mid 20th century, when it was discovered that oxygen free radicals, traditionally thought to be too reactive to exist in biological systems, are formed in situ in response to radiation and oxygen poisoning and are responsible for the associated toxicities [8,9] (Fig. 1). Noting that radiation "induces mutation, cancer and aging" (citing [10]) and, drawing on the rate-of-living hypothesis [3], Denham Harman proposed that oxygen free radicals (specifically hydroxyl, $OH^{\bullet}$, and hydroperoxyl, $HO_2^{\bullet}$, radicals) are formed endogenously from normal oxygen-utilizing metabolic processes and play an essential role in the aging process [11]. Interest in the free radical theory was at first very limited because of the persistent doubt about the existence of oxygen free radicals in biological systems, despite the reports by Gerschman et al. [8] and the detection of radicals by Commoner and co-workers [12,13]. The discovery of superoxide dismutase by McCord and Fridovich [14], and the demonstration of the existence of H_2O_2 in vivo by Chance [15] gave credibility and raised the profile of the hypothesis. In 1972, Harman proposed a modification of the free radical theory, giving a central role to mitochondria [16], because these organelles generate a disproportionately large amount of reactive oxygen species (ROS) in cells [15]. In subsequent years, much correlative evidence supporting the theory was published. The majority of studies verified the first aspect of Harman's hypothesis: that oxidative damage increases during aging (e.g., [17–19], reviewed in [19–21]). In agreement with Harman's modified proposal, that mitochondria are central to aging, it was discovered that mtDNA deletions (and, more recently, mtDNA point mutations) are induced by oxidative stress and dramatically accumulate with age in organisms ranging from worms to humans [22–24].

In the last 50 years, Harman's hypothesis has also been refined to encompass not only free radicals, but also other forms of activated oxygen. Many reactive oxygen species such as peroxides and aldehydes (which are not technically free radicals) also play a role in oxidative damage in cells. This realization led to a modification of the free radical theory, i.e., the oxidative stress theory of aging [25]. This modification of the free radical theory is based on the fact that a chronic state of oxidative stress exists in cells of aerobic organisms even under normal physiological conditions because of an imbalance between prooxidants and antioxidants. The imbalance leads to a steady-state accumulation of oxidative damage in a variety of macromolecules that increases during aging, resulting in a progressive loss in the functional efficiency of various cellular processes. In a recent review, Beckman and Ames made a useful addition to this debate by dividing the hypothesis into "strong" and "weak" versions [26]. The strong