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Review Article

Aging, Free Radicals, and Antioxidants

Envejecimiento, radicales libres y antioxidantes

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ABSTRACT

The article presents aging as a multifactorial, progressive biological process shaped by intersecting theories, with special focus on oxidative stress and free radical involvement. The Free Radical Theory of Aging posits that reactive oxygen species (ROS), produced both endogenously and via environmental exposures, induce cumulative molecular damage to lipids, proteins, and DNA impacting cellular and tissue integrity. This oxidative stress contributes to age-related degenerative diseases such as cancer and Alzheimer's. Although antioxidants (both endogenous enzymes and exogenous dietary compounds) offer protective mechanisms against ROS, empirical evidence on their efficacy in extending lifespan remains inconclusive, largely due to bioavailability challenges and systemic complexity. The article also addresses mitochondrial dysfunction and genomic instability especially mitochondrial DNA mutations as key contributors to aging, proposing a dynamic interaction between genetic regulation, oxidative insults, and physiological decline. Experimental findings from animal models suggest associations between oxidative damage and aging phenotypes, though not always consistent across species. The authors advocate for a comprehensive approach that integrates molecular, genetic, and environmental perspectives, urging evidence based public health strategies to manage the rising aging population. In sum, aging is characterized as a heterogeneous, irreversible process not reducible to a single cause but rather to a complex network of biological mechanisms.

Keywords: Cellular damage, oxidative stress, homeostasis, longevity, lipid peroxidation.

RESUMEN

En el artículo se examina el envejecimiento como un proceso biológico multifactorial, intrínseco y progresivo, vinculado a múltiples teorías complementarias. Se destaca el rol central de las especies reactivas de oxígeno (ROS), particularmente los radicales libres, como agentes prooxidantes que generan daño molecular acumulativo en lípidos,

proteínas y ADN, promoviendo disfunción celular y organular. La teoría del estrés oxidativo, propuesta por Denham Harman, sugiere que el desequilibrio entre prooxidantes y antioxidantes conduce a la peroxidación lipídica, mutaciones somáticas y senescencia celular. Aunque se han investigado estrategias terapéuticas basadas en antioxidantes endógenos y exógenos (enzimáticos y no enzimáticos), los resultados in vivo sobre longevidad y prevención de enfermedades asociadas han sido inconsistentes, posiblemente debido a la baja biodisponibilidad y efectos pleiotrópicos. Se revisan teorías genéticas como la del "reloj biológico", junto con la contribución mitocondrial al envejecimiento a través de la disfunción en la cadena de transporte de electrones y acumulación de daño en el ADNmt. El trabajo resalta la necesidad de un enfoque integrador que vincule modelos genéticos, moleculares y ambientales, así como la urgencia de establecer políticas de salud pública basadas en evidencia para abordar el aumento en la población adulta mayor.

Palabras clave: Daño celular, estrés oxidativo, homeostasis, longevidad, peroxidación lipídica.

INTRODUCTION

When referring to old age, one addresses a controversial subject today, not only because of what it entails, given that there is no single explanation of the process, but also because the number of older adults increases every year, posing a challenge due to the social and economic implications of their treatment. Faced with these realities and influenced by them, a debate has emerged regarding whether old age should be considered an illness or not. This debate has intensified due to the World Health Organization's (WHO) proposal to update the International Statistical Classification of Diseases and Related Health Problems (ICD-11), in which, without convening expert gerontologists, it is proposed that beginning in 2022, in the chapter corresponding to "Symptoms, signs, and clinical findings," the term senility and related terms that previously appeared and referred to pathologies be replaced with the term old age. This suggests a particular interest in emphasizing the pathological dimension of aging and the management of treatments and medications.

It is important and useful for many health professionals to remain up to date on the different schools of thought and theories that address the aging process from various perspectives, each with its own logic (Free Radical Theory, Mutation Accumulation Theory, Wear-and-Tear Theory, Disposable Soma Theory, Oxidation–Inflammation Theory, Telomere Theory, Immunological Theory, Mitochondrial Theory, among others). This is essential in order to understand this multifactorial process and to influence the quality of life of older adults, often starting from numerous questions related to physical and social well-being (Bloom & Zucker, 2023). As populations age at an accelerated pace, it becomes increasingly necessary to consider health policies focused on preventing chronic diseases such as diabetes, obesity, and depression, among others. Furthermore, any such proposals must fall within the norma-

tive framework of each nation, supporting sound public policies grounded in scientific evidence.

The free radical theory gains importance every day in understanding aging, as it refers to and proposes the cumulative damage generated by reactive oxygen species (ROS), which gradually deteriorate the body's cells and tissues over time, causing the so-called oxidative stress, a condition associated with diseases such as cancer and Alzheimer's. Alongside other theories, the sum of harmful reactions caused by free radicals that continuously occur in cells and tissues is considered responsible for, or contributes significantly to, the aging process (Wickens, 2001).

DEVELOPMENT

Old age will not be considered an illness by the authors, even though disabilities do appear in older adults associated with the loss of organic reserve and characteristic changes that emerge at different times and with varying intensities depending on individual variation. Such variation is related to one's prior lifestyle, predispositions to certain conditions, and the chronic diseases that often arise beginning in adulthood and accumulate with age (diabetes, rheumatism, arthritis, cardiac conditions, among others). In such cases, the older adult becomes a clinical patient according to the ailment they present, independent of the anatomical and physiological changes that manifest. Once susceptibility to illness increases, even under low-intensity stressors, it becomes important to recognize that anatomy and physiology must be understood as paired disciplines, each conditioning the other (Ribera-Casado & García, 2021; Miralles *et al*., 2022).

A series of gradual changes beginning around age 55 exist that, at younger ages, could be considered diseases, but at this stage are associated with the aging process itself. These include:

- Changes in skin elasticity and appearance
- Changes in posture and gait
- Weakening of pulmonary function
- Weakening of immunological mechanisms
- Decrease in height
- Decrease in heart rate
- Decrease in muscle strength
- Decrease in memory
- Decrease in sensory functions (hearing, touch, taste, smell, and sight)
- Hardening of arterial walls
- Osteoporos
- Loss of heat and cold adaptation
- Reduction in intestinal motility
- Reduction in total body water

Among others (Esmeraldas *et al*., 2019; Bonnet-Zamponi, 2016)

There are several perspectives from the biological standpoint of old age. Davies (1992) proposed that biological aging manifests as a progressive decline in the organism's capacity to maintain homeostasis under physiological stress. This functional decline is associated with decreased cellular viability and increased individual susceptibility. From a biomedical perspective, Johnson (1999) defined the aging process as a condition in which the probability of dying, which increases over time, and the age of the organism coincide with the oc-

currence of phenotypic changes in all individuals.

These ideas have proven useful in distinguishing between the aging process itself and diseases associated with aging (Hoyl, 2016). Both perspectives agree that aging is universal, continuous, irreversible, intrinsic, heterogeneous, and lethal, affecting all living beings without exception, occurring continuously without pauses, and manifesting differently in each individual, thus granting each person a certain "uniqueness." Aging occurs at the molecular, cellular, tissue, and organ levels.

The aging process has been and continues to be studied by many research groups and from different "angles," all attempting to explain a process that is multifactorial in nature, an approach that is more rational and accurate (Alvarado & Salazar, 2014; Piña *et al*., 2022; Rodríguez *et al*., 2012). There are theories, models, and proposals that contribute valuable knowledge to the study of aging; however, none alone can fully explain the process, suggesting the need to consider them collectively and relate them to one another as complementary.

One interesting approach is the genetic one, which includes several branches:

- Gene regulation, referring to the imbalance of factors involved in the organism's development and reproduction (Gladyshev, 2015).
- Modifications in gene expression, possibly caused by metabolism (Cutler, 1991).
- Genomic instability resulting from DNA alterations (Slagboom, 1989).

In summary, age is determined by genetic factors, and there is an "internal clock" that determines longevity (Goldstein & Cassidy, 2010). Another theory refers to the accumulation of cellular damage over long periods that cannot be repaired due to the weakening of the DNA repair system, resulting in mutations accumulating in the mitochondria and nucleus, which later lead to abnormal proteins (Avendaño-Monsalve *et al*., 2024).

Free Radicals

Aging itself is a multifactorial process which, due to its complexity, has given rise to various theories related to stochastic processes, the accumulation of waste products, somatic mutations, homeostatic catastrophe, immunology, the finite replicative capacity of cells, development, genetics, and even free radicals (Quintero *et al*., 2024). Some theories are more debated than others today, indicating that aging cannot be explained by a single theory, especially since each pertains to a different aspect or moment of the process. However, it is possible to discern that the genetic theory carries significant weight, as numerous genes and mutations are involved at every level. Matters related to free radicals in old age and degenerative diseases continue to be increasingly studied (Yang *et al*., 2024).

The relationship among theories that identify the accumulation of damage, arising from mutations and metabolic waste, explains how irreparable damage accumulates over time, becoming present in nuclear and mitochondrial DNA and potentially leading to the synthesis of abnormal proteins (Zorrilla, 2002). A valid explanation for these errors in repair mechanisms and accumulated mutations is related to free radicals generated when oxygen is excessively converted into energy, disrupting the balance between oxidant and antioxidant production, known as oxidative stress. These radicals can even lead to cell death by reacting with other compounds present

in cells (Quintanar & Calderón, 2009; González, 1995).

Studies on free radicals, like those in other theories, evaluate the presence of mutations and unrepaired molecular-level damage that originates in the process of obtaining energy from oxygen, which produces free radicals. These radicals, within normal ranges, help eliminate toxins; however, if overproduced or accumulated, they become harmful, even causing cell death (oxidative stress) (Korovesis *et al*., 2023; Hong *et al*., 2024). Free radicals have the capacity to combine with DNA molecules and even with proteins, which they deactivate, forming part of their involvement in the aging process (González, 1995).

At the cellular level, aging is also considered a result of genetic programming in the development and maturation of cells, controlled at the DNA and RNA levels, which at the same time are targets of free radicals. These radicals can intervene within the cell and therefore interfere with the proper functioning of some organ (Hayflick, 1983). In many organs, it is not possible to replace the cells that die, resulting in a decrease in their number and consequently altering proper organ function. The appearance of aldehydes as a result of oxidation, anchored to collagen, leads to a loss of tissue flexibility and alterations in the exchange of substances between cells, in which collagen plays a fundamental role.

What are free radicals?

Free radicals are atoms or groups of atoms that contain an unpaired electron, which makes them highly reactive as they attempt to capture an electron from other atoms in order to achieve stability. When this occurs, it is known as reduction, and the stable molecule that loses the electron (oxidation) becomes a new free radical that will repeat the electron-capturing process. In this way, a chain reaction begins and, due to the lack of specific receptors, it occurs randomly, damaging any cell or tissue (Čolak, 2008; Venereo & Justo, 2002). These electron transfers occur through metal ions without the participation of enzymes. Various studies suggest that free radicals can also be generated by smoking habits, environmental pollution, radiation exposure, and indiscriminate use of medications, among others (Finkel & Holbrook, 2000).

Since when do free radicals exist?

In 1900, free radicals were described by Gomberg, who observed the decomposition of hexaphenylethane into two triphenylmethyl radicals. Years later, Paneth and Hofeditz published the decomposition of lead tetramethyl into free radicals. In 1954, Gerschman proposed that superoxide anion radicals (O_2^-) and hydroxyl radicals (OH•) were responsible for the molecular mechanism of oxygen and radiation toxicity. In 1956, Denham Harman, after gathering evidence, proposed the theory involving free radicals in aging, together with genetic and environmental predispositions (Hernández & McCord, 2007; Maldonado *et al*., 2010).

The second era of free radicals began with the discovery of the enzyme superoxide dismutase (SOD) in 1969 by McCord and Fridovich, which opened the door to various hypotheses related to the antioxidant effects of free radicals on cells, their structures, and their products.

The third era of free radicals emerged ten years later, when evidence was presented on important biological effects involving the activation of guanylate cyclase (GC) by the OH derivative of the superoxide anion O_2^- (Bergendi *et al*., 1999).

In 1985, the concept of oxidative stress was proposed, and from that point on, a field of study emerged regarding its involvement in different pathologies as well as its participation in beneficial health processes (Maldonado, 2010; Mittal & Murad, 1977).

At the molecular level, free radicals are considered oxidizing agents because they contain one or more unpaired or free electrons, making them highly reactive as they try to achieve electrochemical stability by pairing with an electron from a stable molecule. When this occurs, the electron-donating molecule becomes a free radical with an unpaired electron, which will in turn seek to pair, thus initiating a damaging chain reaction of free radicals within fractions of seconds. They are considered related to aging and cellular damage, as they react with cellular structures and with the unsaturated fatty acids of phospholipid membranes, proteins, and DNA, modifying them and consequently altering their functions, which may explain the onset of certain pathologies such as cancer (Gutteridge & Halliwell, 1999; Okamoto *et al*, 1996). In some cases, free radicals are considered part of the defense mechanisms against bacterial and viral infections (Finkel & Holbrook, 2000). Their origin may lie in human metabolism, but also in environmental pollutants—whether atmospheric, aquatic, or soil—and in radiation, alcohol consumption, tobacco, drugs, among others (Llancari & Matos, 2011).

The sum of harmful reactions of free radicals that continuously occur in cells and tissues constitutes, in itself, the aging process or contributes significantly to it. This was Denham Harman's interpretation of how aging develops, accompanied by degenerative processes such as cancer and immunosuppression (Johnson *et al*., 1886), which complements his "aging clock theory," justified by mitochondrial disorganization that produces free radicals (Miquel, 2005).

The mitochondrial respiratory chain (or electron transport chain, ETC) is the main cellular source of reactive oxygen species (ROS), such as superoxide, which can be converted into H_2O_2 by superoxide dismutases (SOD). The latter forms highly damaging hydroxyl radicals (OH•) through the Fenton reaction in the presence of transition metals such as iron or copper (Collin, 2019). The harmful effects of these radicals are mainly due to their lack of charge and their small size, which allows them to move among cellular structures, damaging proteins and membrane lipids, causing lipid peroxidation and DNA breaks.

A key experimental element for accumulated mtDNA damage as a cause of aging emerged from homozygous knock-in mice expressing an error-prone version of PolgA, the catalytic subunit of mitochondrial DNA polymerase. These mice exhibited an increase in somatic mtDNA mutations, reduced lifespan, and the premature onset of aging-related phenotypes (Pinto & Moraes, 2015). Consistent with these findings, an inverse correlation was observed between the degree of oxidative mtDNA damage in various mammalian species and their maximum lifespan. Although this theory is logical and highly popular—likely due to the apparent ease of intervention with antioxidants—more recent studies have questioned simplistic perspectives on a direct relationship between ROS, oxidative damage, and aging (Cui *et al*., 2011).

There are also contradictory results that raise concerns about the topic across various species. First, the overexpression or knockout of antioxidant genes has not

always produced the expected results. For example: transgenic overexpression of Cu/Zn SOD in mice (76) and C. elegans did not increase lifespan (Pérez *et al*., 2009). Conversely, worms completely lacking SOD activity have a normal lifespan (Labunskyy & Gladyshev, 2013). Homozygous mice deficient in cytoplasmic Cu/Zn SOD accumulate massive oxidative damage and have reduced lifespan, which may be due to increased sarcopenia and cancer incidence in advanced life stages (Ligibel *et al*., 2020).

Antioxidants: Their Role

Homeostasis generally allows the body to maintain functional balance in the short-, medium-, and long-term through various mechanisms. In the case of oxidation, there are different mechanisms depending on the type of free radicals and the sites where they act (Avello & Suwalsky, 2006).

Antioxidants refer to substances present in low concentrations, considering the amount of potential oxidizable substrates, which constitute a protective, defensive system. They inhibit or significantly delay oxidative reactions by interacting with oxygen-derived free radicals, sacrificing their own structure to prevent harmful alterations to molecules (lipids, proteins, DNA, among others) that would otherwise alter previously established cellular processes and functions. They contribute to maintaining the necessary balance between oxidants and antioxidants, in favor of the latter.

Antioxidants are classified according to different parameters depending on the interests of researchers. Based on their origin, they are classified as endogenous antioxidants, those produced by the human body as a defense mechanism to control the excessive formation of free radicals, and exogenous antioxidants, those obtained from the diet, which may be natural (from fruits, vegetables, and meats) or synthetic (Mironczuk-Chodakowska *et al*., 2018). Exogenous antioxidants are "consumed" when they oxidize upon neutralizing free radicals, and therefore must be constantly replenished through the diet.

Currently, antioxidant activity and free-radical-scavenging capacity are being intensely studied in plants with recognized medicinal activity. These studies are based on the preference for natural over synthetic products (Warjeet, 2012). In plants, phenolic compounds, flavonoids, vitamins C and E, and carotenoids have been described and used, all of which have recognized medicinal and now antioxidant activity (Aluyor & Oboh, 2014). Plant-derived compounds possess well-known and established antioxidant activity. Microorganisms must also be mentioned as efficient producers of metabolites with specific antioxidant potential (Singh *et al*., 2019), recognized for their efficacy against fungal and bacterial infections (tetracyclines, amphotericin, penicillins, erythromycins, streptomycin, and vancomycin); against cancer (daunorubicin, bleomycin, mitomycin, and doxorubicin); in transplant rejection (rapamycin and cyclosporin); and in cholesterol control (mevastatin and lovastatin) (Demain, 2014).

To date, the consumption of antioxidants has not resulted in significant benefits related to in vivo longevity, possibly due to low bioavailability, considering that the most optimistic results came from in vitro experiments (Bjelakovic *et al*., 2007; Biesalski *et al*., 2010; Baguer & Menéndez-Álvarez, 2024) with doses considerably higher than those realistically consumable, meaning they do not reflect actual

effectiveness in living organisms. In studies applying high doses of antioxidants, some results have been discouraging, suggesting that not only bioavailability must be considered, but also other factors often overlooked. An example is Dr. Pauling's widely cited vitamin C supplementation (Pauling, 1971), which, even at low concentrations, can have a pro-oxidant effect in the presence of transition metals such as iron (Bast *et al*., 1991).

Lipid Peroxidation

It has been proposed that a major target of free radicals, due to their implications, is the cellular membrane, which contains lipids and proteins responsible for selective permeability into the cell and interactions with other cells. This structure is rich in polyunsaturated fatty acids, and when free radicals are present, a hydrogen (H) atom is extracted, producing a lipid radical that reacts with oxygen to form a lipid peroxyl radical. This radical propagates, initiating a chain reaction among the fatty acids present, causing lipid peroxidation through this oxidative chain reaction (Kim *et al*., 2012). An indicator of lipid peroxidation is the amount of malondialdehyde produced, which is stable and, at high levels, is associated with diseases such as cardiovascular disorders, cancer, and neurodegenerative conditions. It is also used as a marker in antioxidant therapies, where its reduction indicates effective treatment (Goodsell, 2004). Evidence also exists regarding the involvement of oxidative stress mechanisms in Parkinson's disease (Avello & Suwalsky, 2006). This membrane-level damage can be avoided by means of stable complexes formed by antioxidants (Halliwell, 1990).

Just as with fatty acids, free radicals can interact with proteins, oxidizing them. When this occurs, peptide chains fragment, resulting in loss of enzymatic activity and degradation of structural proteins, ultimately leading to dysfunction and cell death (Chrząszcz *et al*., 2021; Rani *et al*, 2021).

CONCLUSIONS

Aging results from several factors involved in multiple theories, which together reveal that there is no single explanation—thus adding greater complexity to the process.

The constant production of free radicals constitutes a physiological process with important implications in cellular senescence and oncogenesis. Nevertheless, other theories and molecular processes must be considered, particularly those associated with mitochondrial signaling.

Antioxidants are gaining increasing prominence in research related to various pathologies and aging.

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