

Heart Mitochondria: New Insights into Metabolism, Aging and Cardiovascular Disease

Mini Review

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Abstract

Oxidative stress and mitochondrial dysfunctions are among the major mechanisms of aging and in pathogenesis of cardiovascular diseases (CVD). Here we present some latest developments in this field. Normal heart must function in a very large range of physical activity, and this requires mitochondria change quickly the rates of oxidative phosphorylation. As a source of energy working heart oxidizes various substrates: fatty acids, aminoacids and pyruvate. At moderate workload, heart mitochondria produce minimal amount of superoxide radicals. At the rest, however, there is a risk that over-energized HM significantly increase production of superoxide and some of the radical become protonated forming highly lipophilic perhydroxyl radical. Mitochondrial phospholipids are rich in polyunsaturated fatty acids (PUFA). Perhydroxyl radical has very high affinity to PUFA and stimulates the so called isoprostane pathway of lipid peroxidation (IPLP). Among the products of IPLP are highly toxic isoketals and isolevuglandins that form adducts with phosphatidylethanolamine and the lysine-containing proteins of mitochondria. Evidently, IPLP is one of the major mechanisms of the slow but inevitable oxidative damages of mitochondrial phospholipids and proteins during aging. Heart and brain mitochondria possess a mechanism that prevents excessive formation of superoxide when the organ is at rest. The mechanism works at the level of the mitochondrial succinate dehydrogenase (SDH) and is known as the intrinsic inhibition of SDH by oxaloacetate. In resting heart, oxaloacetate prevents the energy-dependent reverse electron transport, which is the main mechanism of superoxide formation in the resting mitochondria. Upon increased workload, the flux of metabolites also increases, and incoming glutamate, pyruvate or acyl-carnitine instantly release inhibition of SDH. This regulatory mechanism at the SDH level is highly variable among organs and species. Taken together, the data presented suggest that overproduction of superoxide may cause oxidative damages by different mechanisms, depending on the tissue, for example, via perhydroxyl radical in cardiomyocytes or peroxynitrite radical in endothelium of blood vessels. The diversity in the mitochondrial metabolic phenotypes may explain the diversity in clinical pictures and outcomes of CVD among patients of different sexes and ethnicity.

Keywords: *Aging; Cardiovascular Diseases; Heart Energy Metabolism; Mitochondria; Oxidative Stress*

Abbreviations

ADP: Adenosine Diphosphate; CVD: Cardiovascular Diseases; HO₂•: Perhydroxyl Radical; IMM: Inner Mitochondrial Membrane; IPLP: Isoprostane Pathway of Lipid Peroxidation; MS: Mitochondrial Respiratory Metabolic States: MS-4 Resting Respiration, Mitochondria have Maximal Energization; MS-3: Active Oxidative Phosphorylation; MS-3U: Uncoupled Respiration; OAA: Oxaloacetate; PHR: Perhy-

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droxyl Radical ($\text{HO}_2\cdot$); PUFA: Polyunsaturated Fatty Acids; RET: Reverse Electron Transport; ROS: Reactive Oxygen Species; SDH: Succinate Dehydrogenase; SOD1: Cu-Zn-Superoxide Dismutase Outside Mitochondria; SOD2: Mitochondrial Mn-Superoxide Dismutase; SOR: Superoxide Radical ($\text{O}_2\cdot^-$).

Introduction

Recently, there have been several publications on cardiovascular diseases (CVD), which expressed doubts in the current understanding of the roles of low density lipoprotein cholesterol [1,2] and diets [3] in development of CVD. These two hypotheses are among the main “Pillars” of the current CVD paradigms [1]. As Reis have wrote [1]: “A new paradigm should be able to explain the aforementioned aspects, provide a rationale for the major cardiovascular risk factors, and substantially increase the success of clinical practice”.

Oxidative stress and mitochondrial dysfunctions are among the major mechanisms of aging and pathogenesis of CVD. In this Minireview we outline the latest developments in understanding of the roles of mitochondria in aging and oxidative stress, which are prerequisites of many systemic diseases, including neurodegenerative pathologies and CVD.

Participation of mitochondria in aging

Currently, there are numerous theories of aging, which together indicate on the complex nature of processes involved in the phenomenon, which include genetic and environmental interactions, global loss of heterochromatin, adult stem cell modification, hormonal regulation, telomere shortening, epigenetics, mitochondrial dysregulation, and the free radical theory [4,5]. Many of the listed mechanisms are interconnected and reflect different aspects of the aging process. For the last four decades the mitochondrial free radical theory of aging received considerable support and presently provides the best explanation for aging and longevity in mammals, birds, and multicellular animals in general [4]. Barja [4] summarized the results of experiments on various species of living organisms and selected those features, which affected the life span in all species tested. He concluded that only two known factors, without exclusion, correlate negatively with animal longevity in vertebrates including mammals and birds: the long life span is associated with (a) low rates of mitochondrial reactive oxygen species production and (b) low degree of fatty acid polyunsaturation of cellular membranes including the mitochondrial ones.

30 years ago it was established that polyunsaturated fatty acids (PUFA), when still being esterified with the membrane phospholipids, undergo autoxidation with formation of prostaglandin-like products with large isomerism [6]. This process is known as the Isoprostane Pathway of Lipid Peroxidation (IPLP), but the mechanism of IPLP initiation remained obscure. Recently it was proposed that perhydroxyl radical ($\text{HO}_2\cdot$), which is the protonated form of the superoxide radical ($\text{O}_2\cdot^-$) is responsible for initiation of IPLP [5,7].

Perhydroxyl radical (PHR) has very high affinity for PUFA and thus, even being produced at very low level, it stoichiometrically produces one of the highly reactive products of IPLP, such as isolevuglandins or isoketals, that form adducts with the lysine-containing proteins and phosphatidylethanolamine in the mitochondrial membranes [6,7]. Importantly, common antioxidants, like ascorbate, vitamin E and others, have no influence on longevity [4] and proven ineffective in preventing CVD and hypertension [8]. Barja [4] suggested that probably the mechanisms of oxidative damages to mitochondria are spatially separated from the protective effects of antioxidants. The PHR hypothesis of aging [5] supports the above Barja’s proposition. This could explain why diets and food additives with antioxidants have little or no effect on CVD.

It is known that, in addition to genetic mechanisms of aging, the greatest influence on the life expectancy of mammals is exerted by caloric restriction. It has been shown that caloric restriction significantly increases the life span of normal and diseased animals [9], most likely by lowering the steady-state levels of oxidative stress and damage [10]. The effects of caloric restriction on longevity of experimental animals was observed only if animals received 30 - 40% from “normal” calories of the *ad libitum* food consumption [9]. Evidently, in humans, if manipulations with diets are not associated with the sufficiently large restriction in calories, there is little or no effect of a diet on production of superoxide radicals by mitochondria. Prolonged restricted diet in humans has positive effects on prevention of atherosclerosis and CVD [11]. But this is only part of the overall problem of aging and oxidative stress. Because aging is directly associ-

ated with the rate of superoxide production, and hence PHR, different organs age at different pace due to differences in functions and mitochondrial metabolism.

Features of mitochondrial metabolism and superoxide radical production in the heart

According to the PHR model of aging, it is clear that regardless how small is production of PHR, it will cause some damages to the mitochondria either via impairing the cell's signalling, or directly via formation of adducts with phosphatidylethanolamine or lysine-containing proteins of the inner mitochondrial, and thus gradually cause mitochondrial dysfunctions. Importantly, the amount of PHR depends on the amount of superoxide produced by mitochondria. Some authors strictly associate the mitochondrial production of superoxide with the amount of oxygen consumption by the organ and assume that impaired mitochondrial function causes the accelerated aging phenotype [12]. Gonzalez-Freire, *et al.* [12] stated this common view: "Impaired mitochondrial function may cause an accelerated aging phenotype mainly in high energy demanding tissues such as brain, heart, and skeletal muscle, and in kidney and liver, two organs with essential metabolic roles". Here we see some hidden controversy between "progressive mitochondrial dysfunction" and "accelerated aging phenotype", which presumes the higher rate of reactive oxygen species production by dysfunctional mitochondria. For the sake of discussion, we present data from the classical review by Rolfe and Brown [13], which is very often referenced with a phrase: "although brain comprises only 2% of the body's mass (human), it consumes 20% of the body's total O₂ consumption at rest".

From table 1 we can see that in humans, heart is the most active organ in terms of oxygen consumption per unit of weight (OCI - Oxygen Consumption Index), as compared with other organs. In rats, however, the most actively respiring organ is kidney, which reflects the much higher general metabolic activities in smaller animals. However, the higher rates of oxygen consumption do not necessarily reflect higher rates of superoxide production and aging. At old age, liver and kidney are usually not the prime targets for medical attention, as compared with the heart, brain and skeletal muscle.

Organ	% Body mass	Human % O ₂ use	OCI	% Body mass	Rat % O ₂ use	OCI
Liver	2	17	8.5	5	20	4
Kidney	0.5	6	12	0.9	7	7.8
Heart	0.4	11	27.5	0.5	3	6
Brain	2	20	10	1.5	3	2
Skel. Muscles	42	20	0.48	42	30	0.7

Table 1: Contribution of the major oxygen-consuming organs of the body to body mass and standard metabolic rate.

OCI (Oxygen Consumption Index) = % O₂ consumption / % Body mass.

To the original table of [13] we added index OCI, which shows the relative amount of O₂ consumption by the unit of the organ's relative mass.

Conditions required for production of superoxide and perhydroxyl radicals

Let us look more closely at the mechanisms of O₂[•] production, which is the source of HO₂[•], that cause different organs age at different rates. Formation of PHR is proportional to the level of superoxide, which at any moment is determined by the rates of its production and elimination. Taking into consideration that PHR is extremely reactive and dangerous, it is understandable that removal of superoxide radicals by superoxide dismutases SOD2 (mitochondrial) and SOD1 (extramitochondrial) is of paramount importance for defending cells from the damaging effects of PHR. The activities of SOD2 and SOD1 are of the most importance for the heart and the central nerve system, where the alternative antioxidant systems are relatively weak, whereas the contents of PUFA are at the highest [14]. Because PHR interacts with PUFA inside the membranes, it is clear that most natural hydrophilic antioxidants will have no effect on the aging caused by HO₂[•]; but will have effects on aging caused by other radicals. The hydrophobic vitamin E simply does not react with PHR and thus not prevents IPLP.

Mitochondria produce superoxide radicals only when they are at rest, the metabolic State-4 (MS-4), and have high membrane potential ($\Delta\Psi$), which promotes the reverse electron transport that reduces the superoxide-producing sites on respiratory complex I [15]. Upon addition of ADP or uncoupler, or otherwise activation of dissipation of mitochondrial membrane potential, production of ROS becomes decreased to the basic low level. To stop the reverse electron transport-dependent production of superoxide, it is sufficient to decrease $\Delta\Psi$ by 20 - 30 mV [15]. That is why the actively functioning at all times mitochondria in the liver and kidney produce less reactive oxygen species, and thus age relatively slow. In the heart, skeletal muscles and brain mitochondria, the capacity for maximal oxidative phosphorylation manifold exceeds the rate of the resting respiration. Therefore, when these organs are at rest, the high respiratory capacity maintains sufficiently high $\Delta\Psi$ to stimulate the reverse electron transport-dependent production of superoxide and perhydroxyl radicals. Skeletal muscle mitochondria are much less studied in this respect, as compared with the brain and heart mitochondria, but having a 50-fold difference between the resting and maximal respiratory rates, they more likely behave similar to the heart mitochondria, which have a 9-fold difference [12]. In our studies, we have found that brain and heart mitochondria have a shutter mechanism, which reduces or even prevents the reverse electron transport, when mitochondria are at rest. The mechanism consists in the strong inhibition of succinate dehydrogenase (SDH) by oxaloacetate [16]. This mechanism varies significantly between various organs and animal species [16]. What is important, that upon activation of the specific function: the work load in the heart and neuronal activation in brain, the increased flux of alternative fuel substrates, such as activated fatty acids, glutamate or pyruvate, the SDH inhibition is instantly released and oxidative phosphorylation is activated, which stops production of superoxide [16].

Thus, the common view that oxidatively damaged mitochondria support the aging phenotype, that is produce more reactive oxygen species, is not correct. During aging, mitochondrial dysfunctions develop gradually, and of much more importance for the development of the aging phenotype is the fact that among humans many individuals significantly lower their physical and often also mental activities. This results in the average increase of the membrane potential in the heart, skeletal muscle and brain mitochondria, which promotes further superoxide-dependent aging and associated pathologies. This is the reason why moderate physical activities at any age help not only maintain fitness and health, but evidently also slow down aging at the organ's level. Maintenance of mental activities is also important for prevention of Alzheimer's disease.

There is, however, another highly important factor, which also affects the age-dependent increase in reactive oxygen species production during aging of humans. At certain age, many elderly people develop characteristic changes in the body structure and metabolism, which are designated as the Metabolic Syndrome [17]. The metabolic syndrome is characterized by increased utilization of fatty acids, which in the presence of other mitochondrial substrates: glutamate, pyruvate or succinate dramatically increases generation of superoxide by brain and heart mitochondria [16]. So far, only specific functional activity and caloric restriction can slow down the rate of aging due to diminishing production of superoxide radicals and thus the main aging agent perhydroxyl radicals [10,16].

Conclusions

In this article we emphasized the significance of mitochondria in aging and the diversity among different organs in development of the age-associated pathologies. Oxidative damages in cardiomyocytes and endothelial cells in blood vessels occur via different mechanisms [5,18,19]. Differences in the metabolic phenotype predetermined genetically, or changes during ontogenesis (aging), also greatly affect the rate of aging and predisposition to CVD. We also present the scientific reasons why moderate physical activity is important in slowing down aging and prevention of CVD.

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Conflict of Interest

None.

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