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Effects of exercise training and resveratrol on vascular health in aging

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ABSTRACT

Cardiovascular disease is a leading cause of death in the western world with aging being one of the strongest predictors of cardiovascular events. Aging is associated with impaired vascular function due to endothelial dysfunction and altered redox balance, partly caused by an increased formation of reactive oxygen species combined with a reduction in the endogenous antioxidant capacity. The consequence of these alterations is a reduced bioavailability of nitric oxide (NO) with implications for aspects such as control of vascular tone and low grade inflammation. However, it is not only aging *per se* but also the accumulative influence of physical inactivity and other life-style factors, which negatively affect the vascular system. Regular physical activity improves NO bioavailability, the redox balance and the plasma lipid profile and, at a functional level, reduces or even reverses a majority of the observed detrimental effects of aging on vascular function. The effects of aging and physical activity on vascular function are, in part, related to alterations in cellular signaling through sirtuin-1, AMPK and the estrogen receptor. The polyphenol resveratrol can activate these same pathways and has, in animals and in vitro models, been shown to act as a partial mimetic of physical activity. However, support for beneficial effects of resveratrol in human is weak and studies even show that resveratrol supplementation, similarly to supplementation with other antioxidants, can counteract the positive effects of physical activity. Regular physical activity remains the most effective way of maintaining and improving vascular health status and caution should be taken regarding potential interference of supplements on training adaptations.

1. Introduction

Aging is closely associated with microvascular and macrovascular impairments and is accordingly one of the strongest predictors of cardiovascular disease [1]. A major cause of the impaired vascular function is dysfunction of the endothelium with a consequent alteration in the formation of nitric oxide (NO) and other important vasoactive compounds as well as a reduction in skeletal muscle capillarization. An inherent part of vascular aging is also the process of atherosclerosis which is accompanied by low grade inflammation and oxidative stress [2]. Chronological age is however not the same as biological age, as biological age is strongly influenced by physical activity and other life style factors [3]. Physical activity induces chemical and mechanical signals that activate numerous biochemical pathways in the cardiovascular system promoting cardiovascular health [4,5]. Accordingly, exercise training, even for a brief period of weeks, has a prominent effect on vascular endothelial function by improving aspects such as the vasodilator-to-vasoconstrictor balance, reduced inflammation and oxidative stress and growth of capillaries in skeletal muscle [6–8].

There is a continuous search among researchers for natural compounds that can improve health and retard the effects of aging on the cardiovascular system and one compound that has received much attention is resveratrol. Resveratrol is a polyphenol present in plants that has been shown to increase longevity in specific experimental models and to improve health related aspects in mammals, but convincing evidence in humans on its beneficial effects remain scarce. The described beneficial effects of resveratrol range from increased NO production to increased antioxidant capacity and mitochondrial biosynthesis [9]. Given that exercise training has similar beneficial effects as described for resveratrol, it has been hypothesized that a combination of training and resveratrol could induce synergistic health promoting effects in aged individuals. However, studies in humans have shown that resveratrol in fact may reduce training induced adaptations [10,11]. The present review has a focus on the effect of aging and exercise training on vascular function but also covers how resveratrol may affect vascular function *per se* and in combination with exercise training. The review is centered on human data but also includes in vitro and animal data, especially in the sections on resveratrol, as most work in this area originates from non-human models.

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2. Structural and functional alterations of the vasculature in aging

Aging leads to the development of increased large artery thickening and stiffness as well as systemic and peripheral endothelial dysfunction in otherwise healthy older persons [12]. The stiffening of the large elastic arteries is mediated in part by functional changes in the endothelium and in part by structural changes in the arterial wall [12,13]. The latter is as a consequence of gradual fragmentation and loss of elastin fibers and accumulation of stiffer collagen fibers in the media of large arteries in addition to formation of advanced glycation end products (AGE), which crosslink the structural proteins, thus conferring additional stiffening [12,14]. The structural changes in the arterial wall may be caused and/or sustained by an age-related imbalance in the production and scavenging of free radicals as discussed below [15]. With regard to the alterations in endothelial function, one hallmark of aging is a shift of the vascular endothelium to a prothrombotic, profibrinolytic, proinflammatory, and vasoconstrictive phenotype [16]. One important mechanism underlying the age-related endothelial dysfunction is reduced bioavailability of NO [17,18] as this vasoactive compound is a potent vasodilator that suppresses platelet aggregation, leukocyte migration, cellular adhesion to the endothelium and attenuates vascular smooth muscle cell proliferation and migration [19].

2.1. Mechanisms underlying ROS-induced vascular senescence

Generation of reactive oxygen species (ROS) in the vessel wall has been proposed to be a major pathophysiological step favoring arterial senescence [20]. In support of this notion, a correlation between aging and indicators of oxidative damage to proteins, lipids, and nucleic acids has been demonstrated [21]. This detrimental effect of ROS can be explained by an age-related imbalance between pro- and anti-oxidants that leads to an unfavorable change in redox status. This imbalance activates specific redox-sensitive signaling pathways that promote vascular smooth muscle cell proliferation, migration, extracellular remodeling and consequently increased wall thickness and stiffness [15]. Aging is also associated with increased levels of superoxide that inactivate NO to form peroxynitrite. This intermediary reactive oxygen/nitrogen species is a powerful oxidant that easily crosses cell membranes leading to protein nitrosylation, which blunts the activity of antioxidant enzymes such as superoxide dismutase (SOD) [22,23]. Peroxynitrite also causes uncoupling of endothelial NO synthase (eNOS), thus leading to more superoxide production and reduced bioavailability of NO [24].

NAD-dependent deacetylase sirtuin-1 (SIRT1) is a member of the sirtuin family that has been suggested to be one of the most important pathways for the beneficial effects of resveratrol on the vasculature. Enhanced SIRT1 signaling is thought to be one of the most important pathways opposing vascular senescence due to its role in regulating redox status [25]. The expression and activity of SIRT1 has been shown to decrease in the vasculature with advancing age, and this contributes to endothelial dysfunction [26–28]. Accordingly, pharmacological activation of SIRT1 has been shown to upregulate SOD and catalase protein content and to normalize superoxide formation and endothelium dependent vasodilation [28]. In addition, SIRT1 signaling also protects against ROS-induced senescence by increasing eNOS protein content and activity [29] and SIRT1 also has the ability to repress the Forkhead transcription factor (FOXO) pathway, thus preventing DNA damage, cell cycle arrest and oxidative stress [30]. Finally, SIRT1 deacetylates liver kinase B1 (LKB1) leading to activation of AMP-activated protein kinase (AMPK). As with SIRT1, arterial expression of AMPK is reduced in older mice, however, pharmacological activation of AMPK for two weeks increased AMPK expression and reversed ROS driven endothelial dysfunction [31]. Although this effect of AMPK activation was independent of improved NO bioavailability, AMPK has been reported to phosphorylate and activate eNOS [32] and dysfunction of the AMPK-eNOS pathway may be one important mechanism underlying vascular dysfunction in aging.

2.2. Role of ROS in the age-related alterations in skeletal muscle blood flow regulation

Given the pronounced effects of advancing age on vascular structure and function, it is not surprising that also regulation of blood flow to various tissues has been reported to be altered in the aged state. Healthy young skeletal muscle is characterized by a precise matching of blood flow and metabolism and by an enormous vasodilator capacity that is essential for physical performance as it ensures that any increase in muscle work is precisely matched by increases in oxygen (O_2) delivery [33]. There is accumulating evidence for insufficient blood flow and O_2 delivery to contracting skeletal muscle in sedentary older subjects [34,35]. The mechanisms underlying the impaired matching of blood flow and metabolism have not been resolved but may include structural alterations in the vasculature, reductions in skeletal muscle mass and/or quality, increased skeletal muscle sympathetic neural outflow, and alterations in the balance of locally formed vasodilators and vasoconstrictors [36]. In addition, some evidence for a role of excess ROS levels for the impaired blood flow regulation in aging have been provided in the exercising human forearm and lower leg, as evidenced by increased blood flow in response to skeletal muscle contractions with oral intake of either ascorbic acid or an antioxidant cocktail comprised of vitamins C and E and α-lipoic acid [37,38]. In agreement with this suggestion, indications of increased levels of free radicals in response to an acute exercise bout in both muscle [39] and blood [40] have been provided. However, studies on animals and the human quadriceps have failed to demonstrate an effect of antioxidant supplementation on perfusion of the active skeletal muscle [41,42]. In accordance, acute exercise engaging the quadriceps muscle has been found to induce an intensity-dependent increase in venous plasma levels of oxidized glutathione (GSSG) in young but not older lifelong sedentary subjects [18]. Moreover, in the same subjects, antioxidant treatment improved NO availability only in the resting state [18]. These observations are in agreement with a higher basal level of ROS in aging [20] and suggest that the contraction-induced formation of ROS was reduced in these older subjects [18]. This suggestion is supported by observations in aged animals in which formation of ROS was increased at rest but not in response to muscle contractile activity [43,44].

The discrepancy in the abovementioned studies may in part be explained by differential effects of aging on redox status and regulation of exercise hyperemia in animals and humans. Given the physiological differences between various muscles, it may also be that the starting redox balance and regulation during contraction differs between the human quadriceps muscle and the forearm and lower leg muscles. Furthermore, differences in measurement techniques may also explain this discrepancy as the studies in which increased levels of ROS were detected used global markers of oxidative stress [39,40] whereas the studies in which no effects of aging were detected used secondary markers of ROS production and not global measurements [18,20,43,44].

To summarize, to what extent an imbalance between pro- and anti-oxidants leads to an impaired skeletal muscle blood flow regulation in aging may depend on the model and/or muscle of interest. Future studies should combine a variety of different measurements of redox status in both blood and muscle during