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Anti-inflammatory effects of resveratrol: possible role in prevention of age-related cardiovascular disease

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Abstract

Cardiovascular diseases are the most common cause of death among the elderly in the Western world. Resveratrol (3,5,4´-trihydroxystilbene) is a plant-derived polyphenol that was shown to exert diverse anti-aging activity mimicking some of the molecular and functional effects of caloric restriction. This mini-review focuses on the molecular and cellular mechanisms activated by resveratrol in the vascular system, and explores the links between its anti-oxidative and anti-inflammatory effects, which could be exploited for the prevention or amelioration of vascular aging in the elderly.

Keywords

resveratrol; aging; vascular dysfunction

Introduction

Age-specific mortality rates from heart disease and stroke increase exponentially with age, which imposes a huge financial burden on the health care systems in the Western world. Therefore, there is an urgent need for effective therapeutic strategies that have the potential to promote cardiovascular health in the elderly, preventing or delaying the development of atherosclerotic vascular diseases. During the past decade dietary supplementation with the plant-derived polyphenol resveratrol (3,5,4´-trihydroxystilbene) has emerged as a promising approach to counteract aging-induced pro-atherogenic phenotypic changes in the vasculature. The first population-based studies demonstrated that Mediterranean diets, which are rich in resveratrol, are associated with significantly reduced risk of cardiovascular disease in humans[1, 2]. Subsequently resveratrol was shown to exert significant anti-aging action in invertebrates[3, 4], mimicking many aspects of caloric restriction[5–8]. Importantly, resveratrol supplementation was also shown to exert anti-inflammatory and anti-oxidant effects in various mammalian models of aging and cardiovascular diseases[5, 7]. In this review, the potential mechanisms underlying the vasoprotective effects of resveratrol are considered and its use as a dietary supplement to promote cardiovascular health in the elderly is discussed.

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Role of oxidative stress and inflammation in cardiovascular aging

Our current understanding of the pathogenesis of age-associated cardiovascular diseases is that age-related oxidative stress may promote vascular inflammation even in the absence of traditional risk factors associated with atherogenesis (e.g., hypertension or metabolic diseases; reviewed recently elsewhere9). It is well-established that age-associated low-grade inflammation accelerates the incidence of coronary artery disease and stroke in the elderly9. There is abundant experimental data suggesting that increased activity of NAD(P)H oxidases and mitochondrial overproduction of reactive oxygen species underlie age-related oxidative stress in the vasculature promoting inflammation and endothelial damage 10–14. Nitric oxide (NO) is a crucial factor for the health and function of endothelial cells. Consequences of increased oxidative stress in aging include functional inactivation of NO by high concentrations of $O_2^{\cdot-}$ resulting in significant vasomotor dysfunction (recently reviewed elsewhere[15], increased apoptosis of endothelial cells16, 17, microvascular rarefaction and impaired mitochondrial biogenesis 18–20. The key role of endothelium-derived NO in protecting the cardiovascular system during aging is underscored by the findings that eNOS knockout mice exhibit a premature cardiac aging phenotype associated with early mortality[21]. The existing data also point to an important cross-talk between ROS production and inflammatory processes in the pathogenesis of cardiovascular aging[9]. On the one hand, ROS *per se* can act as signaling molecules activating pathways regulating inflammatory processes[22], including endothelial activation and secretion of inflammatory mediators. Specifically, mitochondria-derived H_2O_2 is thought to contribute to the activation of NF-κB in the vasculature, resulting in a pro-inflammatory shift in endothelial gene expression profile22. Increased NF-κB binding in aging is likely responsible for the increased expression of iNOS10, 22, [23], which is a major source of vascular peroxynitrite production. On the other hand, inflammation itself promotes cellular oxidative stress (e.g. by TNFα-mediated activation of NAD(P)H oxidases)[24]. In that regard it is important to note that both in laboratory rodents and humans there is an age-related up-regulation of TNFα and that disruption of TNFα signaling confers vasoprotection in aging 24.

Anti-oxidative and anti-inflammatory effects of resveratrol in aging

Previous studies have established that resveratrol can exert significant cardiovascular protective effects in various models of myocardial injury[25–27], hypertension[26, 28], and type 2 diabetes[7, 29–31]. Recent studies provide clear evidence that resveratrol treatment can also confer vasoprotection in aged mice and rats[7,22], attenuating ROS production, improving endothelial function, inhibiting inflammatory processes and decreasing the rate of endothelial apoptosis. The mechanisms underlying the cardiovascular protective action of resveratrol are likely multifaceted. Resveratrol was shown to up-regulate eNOS and increase NO bioavailability29, 32, [33], Resveratrol can also induce major cellular anti-oxidant enzymes (e.g. glutathione peroxidase, heme oxygenase, superoxide dismutase) in cardiac and vascular cells[34–37], which result in a marked attenuation of oxidative stress. Resveratrol both down-regulates vascular and cardiac expression of TNFα and inhibits NADPH oxidases in the vasculature29, 31, [38]. It is significant, that resveratrol was also shown to inhibit mitochondrial production of reactive oxygen species in the vasculature[30]. In addition, resveratrol both *in vivo* and at nutritionally relevant concentrations *in vitro* was shown to inhibit inflammatory processes, including NF-κB activation, inflammatory gene expression and attenuation of monocyte adhesiveness to endothelial cells[7, 25, 39–47], all of which may contribute to its cardioprotective effects in aging. Recent studies showed that resveratrol, via an eNOS-dependent pathway, induces mitochondrial biogenesis both in cultured endothelial cells and in endothelia of mice with accelerated vascular aging[20]. Further studies are evidently needed to determine whether the aforementioned vasoprotective effects of resveratrol are manifested in the cardiovascular system of elderly humans as well. In that

regard, studies on vessels isolated from non-human primates treated with resveratrol will also be highly informative.

The molecular targets of resveratrol, which mediate its diverse cellular effects, are the subject of ongoing investigations. On the basis of the structural similarity of resveratrol to diethylstilbestrol, resveratrol was characterized as a phytoestrogen[48]. Given the cardioprotective benefits attributed to estrogens at the time, this idea lead to a number of follow-up studies suggesting that some of the cardiovascular effects of high doses of resveratrol may indeed be modulated by activation of the estrogen receptor[49]. Yet, more recently the cardioprotective effects of estrogen replacement have become subjects of debate and there are also a number of studies extant, which suggest that the estrogen receptor is not the main cellular target of resveratrol in the vasculature. Since the original observation of Sinclair and co-workers[4] a large body of evidence has been published linking the cellular action of resveratrol to regulation of a pathway dependent on SIRT1, a mammalian homolog of the *Saccharomyces cerevisae* silent information regulator 2 (Sir2) protein[3, 5, 50–55]. There is an ongoing debate whether resveratrol is a direct activator of SIRT1, which catalyzes NAD+-dependent protein deacetylation and is a critical regulator of transcription, genome stability, apoptosis and metabolism. Although recent studies suggest that in cell-free assays resveratrol may not activate SIRT1 directly [56], there is strong evidence that resveratrol and its metabolites both *in vivo* and *ex vivo* can promote SIRT1-dependent cellular responses, as demonstrated by resveratrol-induced decreases in acetylation of various known SIRT1 targets8. Furthermore, resveratrol has been shown to up-regulate protein expression of SIRT1 in multiple cell types, including endothelial cells[20]. In addition, overexpression of SIRT1 in endothelial cells (similar to many other cell types) can mimic many of the effects of resveratrol [57], whereas depletion of SIRT1 tends to attenuate resveratrol-induced cellular effects[20, 30, 43, 57]. There is also solid evidence that inhibition of NF-κB by resveratrol is mediated via SIRT1[58]. SIRT1 is also needed for resveratrol-mediated induction of mitochondrial biogenesis and attenuation of mitochondrial oxidative stress in cardiovascular cells[20, 30]. In light of recent controversies regarding the interaction of resveratrol and SIRT1, further studies are needed to elucidate the role of SIRT1-regulated pathways in the vasoprotective action of resveratrol in aging and the cellular mechanisms responsible for resveratrol-induced up-regulation of SIRT1 in cardiovascular tissues. Future studies should also address the interaction of SIRT1-dependent pathways with alternative cellular targets of resveratrol (e.g. NQO2[59, 60], cyclooxygenase etc) in vascular endothelial and smooth muscle cells.

Nrf2 activation: a new target for resveratrol

There is increasing evidence that activation of NF-E2-related factor 2 (Nrf2) is a key mechanism by which resveratrol confers its cytoprotective effects in the cardiovascular system 27. Nrf2 is a basic leucine zipper transcription factor that regulates the coordinated expression of key antioxidant mechanisms in the cell by binding to the antioxidant response (ARE) elements in the promoter regions of target genes. The first evidence that resveratrol can activate Nrf2 came from studies on cultured PC12 cells61 and human lung epithelial cells62. Subsequent studies demonstrated that in cultured endothelial cells resveratrol also significantly increases transcriptional activity of Nrf2, which is associated with up-regulation of several Nrf2 target genes37. Many of these Nrf2 targets (e.g. NAD(P)H:quinone oxidoreductase 1, heme oxygenase-1) have been shown to promote endothelial health under conditions of increased oxidative stress34. Because Nrf2-driven pathways can be activated by concentrations of resveratrol readily achievable in vivo, future studies should elucidate whether Nrf2 activation contributes to the vasoprotective effects of resveratrol in aging. Recent evidence obtained using high fat diet-fed Nrf2−/− mice lend support to the hypothesis that Nrf2 activation plays an important role in the vasoprotective

action of resveratrol37. Further, induction of the Nrf2 target HO-1 has also been implicated in the cardioprotective effects of resveratrol under conditions of experimentally-induced ischemia36. At present it is not well understood how pathways governed by Nrf2 and SIRT1 cross-talk. Further studies are warranted to test the possibility that SIRT1 acts as a permissive factor, modulating Nrf2-driven responses in the vasculature. Future studies also should test the possibility that Nrf2-dependent pathways regulate SIRT1 expression at the level of transcription.

Perspectives

Although significant progress has been achieved in elucidating the cellular mechanisms activated by resveratrol, the specific roles for pathways regulating mitochondrial function, cellular antioxidant defenses and mechanisms involved in macromolecular repair need to be elucidated further. There is reasonable consensus that oxidative stress plays a central role in the development of atherosclerosis and that redox-sensitive molecular pathways (e.g. NF-κB) promote vascular inflammation in aging. Yet, recent large randomized clinical trials have shown no significant benefit when anti-oxidants targeted to the cell membranes (such as vitamin E) were given to patients with a high-risk coronary arterial disease profile. At present it is unknown whether administration of mitochondria-targeted antioxidants would affect progression of cardiovascular diseases in elderly patients. In various experimental settings, including studies in aged laboratory rodents, resveratrol was shown to attenuate free radical production in multiple cellular compartments (i.e. both in the mitochondria and the cytosol). Thus further studies on the effects of resveratrol on aging-induced oxidative stress and inflammation and their role in cardiovascular pathology are warranted. Importantly, these studies should determine whether anti-oxidative and anti-inflammatory effects of resveratrol are manifested in primates. Finally, research efforts should persist to fully elucidate the effects of resveratrol on microvascular alterations in aging. Future studies should extend the results of earlier investigations[63–65] assessing whether treatment with resveratrol can delay/prevent the age-associated decline in cerebral regional blood flow, the reduction in capillary and arteriolar density and angiogenesis, and the decline in spatial learning and memory in rodent and primate species and determine the roles of SIRT1 and Nrf2 in the microvascular protective effects of resveratrol treatment.

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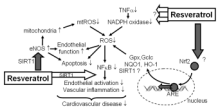

Figure 1.

Proposed scheme for the mechanisms by which resveratrol confers anti-oxidative and anti-inflammatory vasoprotective effects in aging. During aging increased NADPH oxidase- and mitochondria-derived ROS production enhances NF-κB activation, which promotes inflammatory cytokine and chemokine expression, endothelial activation and leukocyte adhesion. Increased oxidative stress also impairs endothelial vasomotor function and promotes endothelial apoptosis, which together with chronic low-grade vascular inflammation significantly increase the risk for the development of vascular diseases in the elderly. The model predicts that resveratrol, via up-regulating Nrf2-driven antioxidant enzymes and eNOS, down-regulating TNFα-activated NADPH oxidases, exerting mitochondrial protective effects and inhibiting NF-κB, significantly attenuates vascular oxidative stress and inflammation in aging. Empty block arrows: inhibition; filled block arrows: induction/activation.