Review
article

The importance of resveratrol in tissue aging: a review

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Abstract

Some theories point to the relationship between endocrinology and aging, while others support that aging is either linked to the immune system, or related to the thelomeres shortening and free radicals. However, what deserve the attention from the scientific community are the silent regulatory proteins 2 (Sir2). These proteins are dependent on Nicotinamide Adenin Dinucleodide (NAD^+) and can be activated by either caloric restriction or by a poliphenol, the resveratrol (3,5,4'-triidroxistilbene), also known as 3,5,4'stilbenetriol. Besides exerting benefits to health as a whole, resveratrol has been demonstrated to promote live extension. The resveratrol bring a diversity of benefits to health because they activate the same metabolic pathways as those activated by the caloric restriction, demonstrating to be efficient to increase the lifespan. Moreover, it seems that the regulation of the mitochondrial biogenesis by the resveratrol is a potential therapeutic target to deal with endothelial dysfunction and vascular diseases. In addition resveratrol could act as a prominent activator of Sirt1 by amplifying the relationship NAD^+/NADH, by increasing the expression of PGC-1 and by decreasing the expression of UCP2. A functional analysis of the resveratrol acting over the aging and the life extension brings up the need for the investigation of multiple tissues by the fact that resveratrol could be associated with the expression of genes in distinct metabolic functions that could be affected by aging.

Keywords: resveratrol, aging, tissues.

1 Introduction

Resveratrol, a polyphenol found in grapes, has been the subject of scientific research related to aging since the early 90's (LEKLI, RAY and DAS, 2010). Studies have shown that resveratrol is gaining importance in retardation of aging and also in prevention of several pathologies (XIA, DENG, GUO et al., 2010; BARGER, KAYO, VANN et al., 2008).

The endeavor to extend life with a healthy approach, led researchers to discover a family of enzymes / proteins called sirtuins (IMAI, 2009; LISZT, FORD, KURTEV et al., 2005). Mechanisms of how sirtuins act on aging are not yet clear, but their action on the extension of life is a fact (CIVITARESE, CARLING, HEILBRONN et al., 2007; ONYANGO, CELIC, McCAFFERY et al., 2009).

What caught the attention of researchers was the direct impact of resveratrol on sirtuins, especially on SIRT1 (MARKUS and MORRIS, 2008), showing a positive effect on life extension of some live beings of various species (DELLA-MORTE, DAVE, DEFAZIO et al., 2009). Resveratrol can activate some specific genes linked to aging, such as PGC-1a, UCP2, in histone deacetylation, and the ratio NAD^+ / NADH, evincing a positive effect on the biogenesis of mitochondria (FINLEY and HAIGIS, 2010). Researchers state that resveratrol enhances the synthesis of ATP improving muscle performance, synthesis of insulin by the islets of Langerhan and reduction of inflammatory processes, that is to say, all affecting the elderly (FINLEY and HAIGIS, 2010).

Perhaps resveratrol may be an ally, not only in prolonging life, but as a preventive of certain diseases associated with aging. This paper aims to present a review about the importance of resveratrol and its action mechanisms in the prevention of cell changes with aging.

2 Material and methods

The PubMed (www.pubmed.nl) and MEDLINE databases were used to conduct a literature search using keywords without restrictions. In this systematization, a search was conducted using the keywords: resveratrol, cell aging.

3 Results

3.1 Action mechanism of resveratrol

Grapes contain several types of vitamins, minerals and carbohydrates as well as phytochemicals called polyphenols (XIA, DENG, GUO et al., 2010). For the author, polyphenols, anthocyanins, flavonoids, phenolic acid and resveratrol, are the most important phytochemicals found in grapes because they activate various health supporting biological processes.

Resveratrol became popular when it was shown that a drink may provide more than 500 different types of antioxidants, including resveratrol itself, one of the most important antioxidant polyphenols found in red wine (LEKLI, RAY and DAS, 2010). According to Barger, Kayo, Vann et al. (2008), resveratrol is a natural compound that has been widely cited in scientific studies on the extension of life.

Resveratrol (3,5,4'-triidroxistilbene) is also found in several other plants such as eucalyptus, almond, mulberry, among others (LEKLI, RAY and DAS, 2010). Resveratrol can be found in the cis and trans isomeric form, both with similar biological activity. However, action of the trans form is most widely studied and best known (LEKLI, RAY and DAS, 2010). Positive effects of resveratrol have been

detected on the cognitive function, as anti-inflammatory, anticarcinogenic, and to enhance longevity (OOMEN, FARKAS, ROMAN et al., 2009).

Polyphenols work by activating the same metabolic pathways found in caloric restriction, thereby efficiently improving health as well as prolonging life (MARKUS and MORRIS, 2008). Lekli, Ray and Das (2010) state that moderate consumption of red wine has reduced cardiovascular and peripheral vascular risks, stroke and cancer, relating these benefits to resveratrol.

According to Csiszar, Labinskyy, Pinto et al. (2009) mitochondrial biogenesis regulation pathways are a potential therapeutic target to improve endothelial dysfunction and vascular disease. Resveratrol is produced to provide defenses for plants in various situations, such as response to trauma from, injuries, excessive ultraviolet light, infections from microorganisms, especially fungi. Morselli, Galluzzi, Kepp et al. (2009) argue that the action mechanism of resveratrol may be the trigger of cell autophagia in different organisms, promoting from life extension in microorganisms to the improvement of physical condition in humans submitted to stressful conditions.

3.2 The relation between resveratrol, sirtuins, NAD^+ / NADH and aging

One of the first targets of resveratrol are sirtuins, mainly SIRT1 (MARKUS and MORRIS, 2008). SIRT1 is involved in many metabolic processes, including lipid metabolism, cell cycle regulation, axonal degeneration, changes in myocytes and in the life span (DELLA-MORTE, DAVE, DEFAZIO et al., 2009). Nevertheless, SIRT1 is considered a mediator in the protection of mitochondria, showing that it is a repressor of the uncoupling protein 2 (UCP2) transcription because it is directly linked to its promoter (DELLA-MORTE, DAVE, DEFAZIO et al., 2009).

For Finley and Haigis (2010) the fractions of genes regulated by SIRT1 show that it controls mitochondria by regulating the activity of PGC-1a. Finley and Haigis (2010) argue that the overexpression of SIRT1 has reduced the levels of UCP2 stressing the greater ATP production, strengthening mainly insulin secretion in response to stimulation by glucose. Lekli, Ray and Das (2010) in their studies showed that resveratrol decreases insulin and IGF-1 levels. Shi, Wang, Stieren et al. (2005) claim that resveratrol is a major activator of sirtuins that may promote life extension in yeast. Finley and Haigis (2010) claim that resveratrol can significantly reduce the physical characteristics of aging since it is an activator of SIRT1.This demonstrates that the number of mitochondria decreases significantly in mice fed high calorie diets, and resveratrol treatment can reverse this decline precisely by activating SIRT1 and reducing the levels of PGC-1a acetylation, bringing about a potential increase in the number of mitochondria.

Morselli, Galluzzi, Kepp et al. (2009) state that resveratrol also acts as a prominent activator of SIRT1 in order to increase the NAD^+/ NADH ratio. These authors assert that UCP2 is a protein found inside the mitochondrial membrane able to guide the metabolic pathway of the enzyme ATP synthase via regulation of the electrochemical potential gradient of protons, leading to decreased levels of UCP2.

For Della-Morte, Dave, Defazio et al. (2010), studies show that the role of UCP2 is related to the production of ROS, essential for absorption of mitochondrial calcium for regulation of oxidative phosphorylation. Evidence on the relation of resveratrol with sirtuins and NAD^+ also becomes clear when Markus and Morris (2008) show that NAD^+ affects the metabolic pathway in the signaling of PGC-1a through SIRT1. In animal studies, Markus and Morris (2008) reported different doses of resveratrol, ranging from 0.1 to 1,500 $mg.kg^{-1}$. They state, that because resveratrol is absorbed and metabolized very quickly after oral ingestion in humans, it is very difficult to estimate a recommended dose or therapeutic treatment with this supplement.

Xia, Deng, Guo et al. (2010) also demonstrated that using grape seed extract rich in resveratrol, for rats, at a dose of 100 $mg.kg^{-1}$/day for 30 days the animals had a significant reduction of oxidative damage to the DNA related to aging and neural tissue. Xia, Deng, Guo et al. (2010), further state that resveratrol has significant antifungal effect, especially for infections such as Candida albicans. According to Civitarese, Carling, Heilbronn et al. (2007), rats submitted to caloric restriction mimicked the results obtained with resveratrol by an increase of mitochondria in liver tissue-regardless of activation of enzymes such as those of citrate synthase.

Lekli, Ray and Das (2010) corroborate the above authors by saying that resveratrol in yeast, by mimicking the mechanisms of calorie restriction would stimulate the sirtuins and increase stability of DNA extending the life span by about 70%. According to Markus and Morris (2008), resveratrol has also proven to act as a preventive in the oxidation of LDL due to its copper chelating action and as a ROS scanner. This vascular action has even more positive consequences when the vasodilating effects of resveratrol are evident showing that besides being an inhibitor of thromboxane A2, resveratrol is an inhibitor of NADH / NADPH oxidase showing nitric oxide signaling in the endothelium (MARKUS and MORRIS, 2008). It seems that resveratrol activates not only sirtuins, but also NAMPT, the enzyme that converts niacinamide into NAD^+, causing life extension by activation of SIRT1 (LEKLI, RAY and DAS, 2010). A functional analysis of resveratrol on aging and life extension leads to investigation in multiple tissues since resveratrol is linked to the expression of genes in different metabolic functions affected by age (BARGER, KAYO, VANN et al., 2008).

According to Barger, Kayo, Vann et al. (2008), results of studies with mice were surprising, showing that resveratrol changed nine hundred forty-seven genes (92%) related to aging by modifying gene expression. Five hundred and twenty two of these genes were significantly representative of the difference between control group and resveratrol group ($p < 0.01$).

Resveratrol has also proven extremely effective in the biogenesis of endothelial mitochondria (LEKLI, RAY and DAS, 2010; XIA, DENG, GUO et al., 2010). This author demonstrated in his studies that the ratio of the area of mitochondrial density in cytoplasmic volume in selective probes of mitochondria (MitoTracker) in endothelial cells was significantly higher with resveratrol treatment.

Results of Oomen, Farkas, Roman et al. (2009), on mortality among the control group and resveratrol group showed no significant differences, with nine deaths after 24 months (four in the control group and five in the resveratrol group). There was no significant difference in the numbers

Table 1. Major works carried out on resveratrol.

Article	Research	Group A	Group B	Group C	Reassessment
Barger, Kayo, Vann et al. (2008)	Preclinical hybrid male mice at 14 months	Control: Diet 84 kcal/week	Calorie Restriction Diet 63 kcal/week	Control + Resveratrol: 50 mg/week	After 30 months of age, tissues were collected from both groups to assess gene expression
Csiszar, Labinskyy, Pinto et al. (2009)	Clinical: endothelial cells of human coronary artery	Resveratrol 10 μmol.L^{-1} / 24 hours			Cell culture. SIRT1 activity assay and measurement of mitochondrial mass in the coronary arteries using MitoTracker in the administration of resveratrol 10 μmol.L^{-1}/24 hours
Oomen, Farkas, Roman et al. (2009)	Preclinical: 60 male mice C57BI / 6, aged 18 to 20 months submitted to cycles of 12 hours light / dark exposed to light at 8 hours	30 mice in the control group	30 mice supplemented with 150 μg resveratrol / gram in food		24 months old. Brain tissue was collected for histochemical analysis of cholinergic parameters, microvascular analysis in the hippocampus region made with electron microscope

of cholinergic cells and density of cholinergic fibers between the resveratrol and control groups. Electron microscope analysis of brain tissue revealed that the vascular density in the hippocampus was 15% higher in the resveratrol group when compared to the control group. The number of microvessels with vacuoles was significantly reduced by treatment with resveratrol in the hippocampus in both arterioles and cortex capillaries. Oomen, Farkas, Roman et al. (2009), report that worsening of the cerebrovascular condition is tied to activation of biochemical pathways involving SIRT1. The effects of resveratrol appear to be more prominent in the hippocampus as a result of increased microvascular density in that particular region.

The Table 1 summarizes the major works carried out on resveratrol.

4 Conclusion

Scientific evidence seems to indicate that resveratrol is a potent nutraceutical to prevent disease and delay aging. The vast majority of studies showed that resveratrol is an activator of sirtuins. Studies have established the action of resveratrol in processes such as activation of genes related to mitochondrial biogenesis, reduction of free radicals, ratio NAD^+ / NADH in mitochondrial protein deacetylation, in modulating the ATP and others. Almost all authors who work with sirtuins and aging state that the molecular mechanism of how sirtuins retard aging and enhance life extension is not yet clear. However, we believe that further studies establishing resveratrol as a modulator of the NAD^+ / NADH ratio and its anti-aging action is just a matter of time and necessity. We believe that further studies are needed to assert a plausible answer to this issue.

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Received March 12, 2011
Accepted May 31, 2011