REVIEW

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Resveratrol in Neurodegeneration, in Neurodegenerative Diseases, and in the Redox Biology of the Mitochondria

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ABSTRACT

Neurodegeneration is a process leading to the progressive loss of structure and functions of neurons. Many neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease have shown many common points at the subcellular level. Neurons are metabolically active cells and need a high amount of energy. Mitochondria are known as the energy synthesis center for cells, involved in the synthesis of adenosine triphosphate by oxidative phosphorylation. Rather than just being an energy synthesis center, it has critical importance for many cellular functions such as calcium homeostasis, cell proliferation, cell growth, and apoptosis. In the process of mitochondrial dysfunction, cellular functions are disrupted and cells enter the apoptotic or necrotic pathway. Resveratrol (tran s-3,5,4-trihydoxystilbene), a plant-derived polyphenol found in the seed of grapes, berries, peanuts, and wine, has many biological effects such as inhibition of lipid peroxidation, scavenging of free radicals, changes in eicosanoid synthesis, inhibition of platelet aggregation, anti-inflammatory and anticancer activity, and regulation of lipid metabolism. Through the reviewed literature, the current study investigated the protective role of resveratrol in neurodegenerative diseases. Studies show that resveratrol moderates mitochondrial function, redox status, and cellular dynamics in both *in vivo* and *in vitro* experimental models of neurodegeneration. Resveratrol suppresses reactive oxygen species production by reducing the activity of complex III due to its competition effect with coenzyme Q. In the present work, we discussed the protective effects of resveratrol on neurodegeneration, neurodegenerative diseases, and the redox biology of the mitochondria.

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INTRODUCTION

Neurodegenerative disease is a broad definition used to explain a group of diseases distinguished by progressive failure of neuronal performance and structural deterioration.[1] Mitochondria are key cytoplasmic organelles that play an important role in many cellular activities such as adenosine triphosphate (ATP) production, oxidative phosphorylation, maintenance of intracellular Ca^{+2} balance (calcium homeostasis), redox signaling, and apoptotic cell death.[2] Neurons are particularly sensitive to reactive oxygen species (ROS) than other organs due to their high oxygen need and poor antioxidant defense. Early stages of neurodegenerative illnesses are critically affected by any breakdown of this regulating system.[3] Mitochondrial dysfunction is thought to play a fundamental role in the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Damage to mitochondrial DNA (mtDNA) also plays an important role in the development of many diseases by causing ATP deprivation, leading to oxidative stress, high amount of ROS production, and apoptosis. Numerous antioxidant treatments have been found to shield neurons from oxidative stress by halting the generation of free radicals and preserving normal homeostasis.[4] Natural compounds that can modulate bioenergy have the potential to be used as neuroprotective agents. Resveratrol, a plant-derived polyphenol, has protective effects on neurodegenerative diseases with its antioxidant, anti-inflammatory, and metal-chelating properties by crossing the blood-brain barrier.[5] It has been shown to be effective in preventing redox degradation in brain cells.[6] Furthermore, resveratrol exerts antiapoptotic effects and modulates central nervous system function by modulating mitochondrial function, redox biology and dynamics.[6,7] Studies show that antioxidant compounds such as resveratrol can modulate mitochondrial function

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and dynamics and can have a cytoprotective effect.[8] Therefore, this review focuses on the relationship between neurodegenerative diseases, resveratrol, and the redox biology of the mitochondria.

Mitochondrial Biology

Mitochondria are the main energy provider for cellular functions by generating ATP. Mitochondria contain their own pool of mtDNA, which is critical for cell development, functionality, and survival. It has 4 parts: outer membrane, inner membrane, intermembrane space (IMS), and matrix.[2] The outer membrane consists of specific transport proteins and porins, and they allow free diffusion of small molecules into IMS. This membrane has many enzymes required for phospholipid and phosphoric acid synthesis, as well as monoamine oxidase, cytochrome c (Cyt c) reductase enzymes that play a catalyst role in the Krebs cycle. The inner membrane shows selective permeability, the electron transport chain (ETC) enzymes and enzymes of oxidative phosphorylation are situated here. They also have a means of transport for particular substances such as ATP, adenosine diphosphate, pyruvate, succinate, malate, citrate, and α-ketoglutarate.[9]

Generating Energy

Adenosine triphosphate can be produced through cellular respiration, the tricarboxylic acid cycle, ETC, and oxidative phosphorylation.[9] To understand mitochondria-related diseases, it would be appropriate to remember the ETC and oxidative phosphorylation pathway.[7] In many studies, it has been observed that electrons are transferred from reduced coenzymes to oxygen through a series of carriers in the respiratory system. Electrons flow from negative potential to more positive potential. These carriers, aligned according to their standard redox potentials, yield different complexes. The complexes that make up the protein components of the mitochondrial respiratory chain are multienzyme complexes with their own specific composition.[7,9]

Oxidative Stress

Under normal physiological conditions, there is a balance between ROS and antioxidants. The deterioration of this balance in favor of ROS, that is, the accumulation of free radicals in the cell or the insufficiency of endogenous defense systems is defined as oxidative stress. Molecular oxygen has 2 unpaired electrons in the parallel spin state.

MAIN POINTS

- Summary of resveratrol effects on neurodegeneration.
- Summary of resveratrol effects on neurodegenerative diseases.
- Summary of resveratrol effects on redox biology of the mitochondria.

Oxidation reactions occur with a single electron transfer to molecular oxygen by enzymes containing transition metals (such as Fe, Cu) in the organism.[10] The ROS includes both free radicals and bound radical molecules such as hydrogen peroxide (H_2O_2), superoxide radical ($O_{2^{\cdot -}}$), singlet oxygen ($1/2\ O_2$), and hydroxyl radical ($OH^{\cdot}$).[10] These free oxygen radicals combine with other radicals or non-radical agents. Thus, it causes many biological effects at the molecular level in the organism.[11] Superoxide anion is a highly reactive product generated in the ETC via mitochondrial complexes I and III. As depicted in Figure 1, the passage of O_{2^-} into the mitochondrial matrix leads to the generation of H_2O_2 by connecting with 2 protons (H^+), a reaction catalyzed by superoxide dismutase (SOD). Superoxide may also react with iron–sulfur proteins releasing ferrous iron (Fe^{+2}). Hydrogen peroxide can be catalyzed into water by antioxidant enzymes in the mitochondrial matrix which include peroxiredoxin, catalase, and glutathione peroxidase.[10]

Mitochondrial Redox Biology

The mitochondrial respiratory chain is important in the generation of reactive species production because of the electron leaks in complex I and complex III.[12] Oxygen is converted to water in mitochondria as a result of ETC reactions. In this metabolic process, 2%-3% of the oxygen in the mitochondria does not turn into water but forms a source for the formation of oxygen-derived radicals.[13] As shown in Figure 1, with a wide range of reactions, including proliferation, differentiation, and cellular death pathways, mitochondrial H_2O_2 plays a significant role in the regulation of cellular redox status.

Low to intermediate levels of H_2O_2 contribute to redox-sensitive signaling and transcriptional regulation, while high levels cause oxidative damage to cell components.[10] Free radicals can also originate from nitric oxide (NO). There is evidence to suggest that reactive nitrogen species, such as NO, can be formed in the mitochondria. Superoxide can react with NO produced by mitochondrial nitric oxide synthase, resulting in the formation of peroxynitrite. Peroxynitrite causes protein nitration and this modification leads to conformational changes in proteins, which triggers cell necrosis. High concentrations of NO can inhibit Cyt c oxidase and modulate mitochondrial energy metabolism by reducing oxygen consumption causing metabolic hypoxia. When cellular respiration is inhibited by NO, an outflow of Ca^{2+} occurs from the mitochondria and this causes activation of Ca^{2+}-dependent proteases.[14]

The Effect of Mitochondrial Dysfunction in Neurogenerative Disease

Alzheimer's Disease

Alzheimer's disease is the most prevalent age-related neurodegenerative illness. Mutations in genes encoding amyloid precursor protein (APP), presenilin-1 and

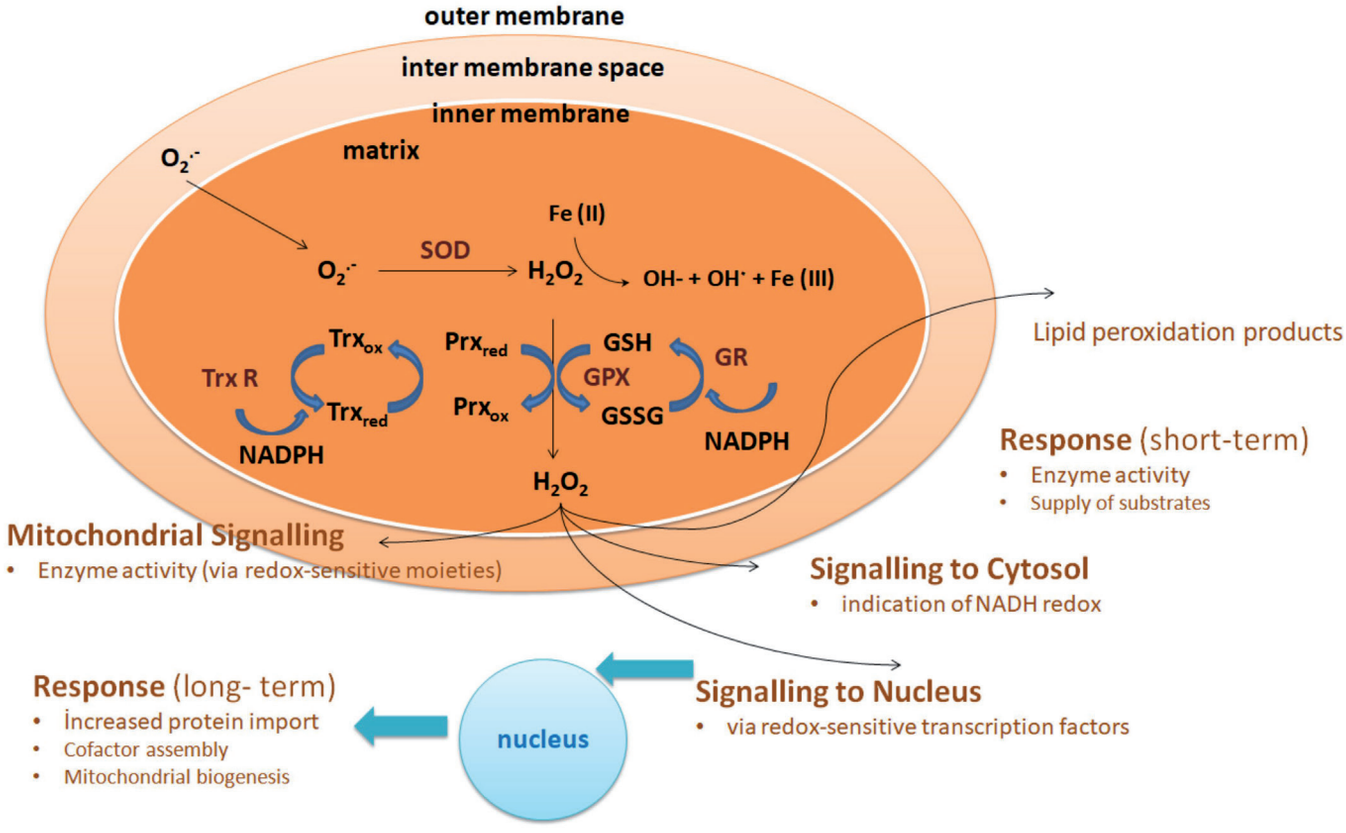

Figure 1. Possible mitochondrial hydrogen peroxide production. The production of H_2O_2 is a potential redox signal. The generation of H_2O_2 can modulate the activity of target proteins via the oxidation of critical protein thiols. Redox signaling can alter the enzyme, kinase, and phosphatase activities and also can affect the transcription factors in the mitochondria, cytosol, or nucleus. GPX, glutathione peroxidases; GR, glutathione reductase; GSH, reduced form glutathione; GSSG, oxidized form glutathione; HO_2•, hydroperoxyl radical; O_2−, superoxide; Prx, peroxiredoxin; SOD, superoxide dismutase; Trx, thioredoxin; TrxR, NADPH-thioredoxin reductase.

presenilin-2, or some alleles of apolipoprotein E pose a risk for AD.[15] A series of enzymes known as beta (β) and gamma (γ) secretase sequentially cleave APP to produce the proteolytic product known as amyloid-beta (Aβ) peptide.[16] Alzheimer's disease is characterized by extracellular senile amyloid plaques mainly composed of hydrophobic 40-42 amino acid long Aβ peptides and intracellular neurofibrillary tau tangles formed as a result of aggregation of hyperphosphorylated tau proteins.[16] There are several different theories explaining why there is neuronal cell death in this disease. The most important among these is the amyloid hypothesis. According to this theory, impaired Aβ metabolism triggers Aβ peptide aggregation and causes synaptic damage, neurofibrillary tangles, inflammatory response, increased oxidative stress, cell death, and ultimately AD. In particular, increasing numbers of studies are believed to be associated with well-defined neuropathological symptoms of AD, as well as intracellular lesions such as disruption of Ca^{2+} homeostasis, accumulation of Aβ, presence of Aβ in mitochondria causing mitochondrial dysfunction, and increased ROS production.[17]

The APP indeed accumulates in mitochondrial channels and Aβ has been found to interact with some mitochondrial proteins.[18] It has been argued that 2 molecular binding targets for Aβ in mitochondria, Aβ-binding alcohol dehydrogenase and cyclophilin D, are associated with this neurodegenerative disease. Decreased mitochondria numbers and reduced brain glucose metabolism are the earliest detected abnormalities in AD brains.[19] Decreased activity of key enzymes in oxidative metabolism, including the pyruvate dehydrogenase complex and alpha-ketoglutarate dehydrogenase in AD has been determined and significantly correlated with clinical state.[20] Since the functions of all enzymes are impaired in the presence of Aβ, a relationship between cascading amyloid theory and mitochondrial dysfunction has been proposed.[21] It has been determined that oxidative damage is both a biomarker of AD and plays a role in Aβ toxicity.

Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disease, involving the presence of Lewy bodies composed of fibrillary α-synuclein

in the substantia nigra pars compacta (SNPC) and deterioration of dopaminergic neurons.[22] This death of neurons is accompanied by the loss of astrocytes and a noteworthy increase and activation of microglia in the SNPC. Both chemical and genetic evidence suggest that mitochondrial dysfunction is associated with PD.[23] Several environmental toxins with inhibition of mitochondrial complex I have been shown to be involved in the epidemiology of sporadic PD.[23] The first link between mitochondrial dysfunction and PD emerged in 1983 and higher expression of Complex I and Complex IV was found in PD with α-synuclein pathology and parkin mutations in aged substantia nigra neurons.[24] This condition may cause impaired mitochondrial membrane potential, decreased ATP synthesis, and increased ROS release leading to oxidative stress in isolated mitochondria or intact cells.[25] It may cause impaired mitochondrial membrane potential, decreased ATP synthesis, and increased ROS release leading to oxidative stress in aged substantia nigra neurons.[25] Oxidative stress and mitochondrial dysfunction have primary roles in the pathogenesis of PD. In addition, mutations in PD-related genes such as the Parkinson's disease protein 7 (PARK7) gene, parkin, and phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) are also known to be associated with dopaminergic neuronal loss.[26] Studies have shown that mitochondrial respiration is ineffective, abnormal mitochondrial morphology occurs, and oxidative stress develops in mouse models with PINK1 deficiency.[26]

Huntington's Disease

Huntington's disease is an inherited disorder that causes the gradual degeneration of nerves. The protein called huntingtin (Htt) is thought to be essential for normal embryonic and neuronal development and is important in many cellular pathways, ion transport, vesicular trafficking, and production and transport of brain-derived neurotrophic factor.[27] One of the important mechanisms involved in the pathogenesis of HD is mitochondrial dysfunction.[28] Mitochondrial homeostasis and dynamics must be intact for continued ATP generation, calcium homeostasis, and antioxidant effects. Disturbances in this balance occur in the presence of mutant Htt protein. As a result, a decrease in ATP production, an increase in the level of reactive oxygen radicals, and a tendency to apoptosis are observed.[28] Transport, fusion, and fission mechanisms play a role in the control of mitochondrial homeostasis. During fusion, 1 mitochondrion combines with another mitochondria and exchanges content. In this way, damaged mitochondria can have contents that will help to repair itself by fusion with normal mitochondria.[28] On the contrary, in the event of fission, the mitochondrial content is released into the cytoplasm as a result of fragmentation, and in this case, factors that induce apoptosis such as Cyt c are revealed.[29] Huntingtin protein, which is localized in the outer mitochondrial membrane, interacts with proteins such as Htt-interacting protein 1, dynamin, and clathrin under normal conditions, keeping the fusion–fission cycles—in other words, mitochondrial dynamics under control.[30]

Another important factor associated with mitochondrial dysfunction in HD is decreased expression of peroxisome proliferator-activated receptor γ co-activator-1 alpha (PGC-1α) protein, which is thought to be related to transcriptional dysregulation caused by mutant Htt, and impaired function.[31]

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a progressive disease characterized by degeneration of the motor neurons.[32] About 90%-95% of the disease are sporadic, while 3%-10% are familial. In familial cases, the age of onset of the disease is earlier.[33] In 20% of the familial cases and 1%-5% of the sporadic cases, there is a mutation on the gene encoded by SOD1 enzyme.[32] The motor neuron damage as a result of oxidative stress is the key hypothesis in ALS. There are many studies showing that oxidatively damaged metabolites are increased in the neuronal tissues of postmortem sporadic and familial ALS.[34] Increased protein carbonyl levels were observed in the spinal cord and motor cortex. In the transgenic mutant SOD1 mouse model, mitochondrial dysfunction has been shown to occur at much earlier stages of ALS, before other manifestations of motor neuron damage. Mitochondrial abnormalities such as swelling and vacuolization have been observed in patients with ALS.[35]

Resveratrol

The natural phytocompound resveratrol (trans-3,5,4-tr ihydoxystilbene; $C_{14}H_{12}O_3$) has come to the attention of neuroscientists for its neuroprotective effects. Resveratrol has antioxidant activity and prevents or delays cellular damage and diseases caused by oxidative stress.[36] Resveratrol has many significant biological activities such as inhibition of lipid peroxidation, copper chelation, free radical scavenging, modulation of eicosanoid synthesis inhibition of platelet aggregation, vasodilator effect, modulation of lipid metabolism, anticancer effect, cardioprotective effect, and nervous system protective effect.[37] Draczynska-Lusiak et al[38] showed that antioxidants such as vitamin E or vitamin C and resveratrol defend neuronal cells from oxidative stress damage in vitro. Zini et al[39] examined the potential consequences of resveratrol treatment on mitochondrial respiratory chain in rat brain. They showed that resveratrol decreased the activity of complex III in competition with coenzyme Q in the rat brain. With the decrease of Complex III activity, resveratrol reduces the production of ROS products and clears them.[39] Resveratrol also decreases the production

of reactive species by upregulating antioxidant enzymes in mitochondria.[7]

Resveratrol is an activator of sirtuin1 (SIRT1), known as NAD-dependent deacetylase sirtuin-1, a DNA repair protein which prolongs cell life span. The SIRT1 deacetylates histone and nonhistone proteins, including transcription factors. It helps in the regulation of immune functions and contributes to prolonging the life span.[40] Resveratrol inhibits the nuclear factor κB signaling pathway thereby regulating the immune response to inflammation, infection, and cellular response to stimuli.[41] In addition, it has been determined to significantly inhibit the insulin-like growth factor-1 receptor (IGF-1R)/serine/threonine kinase (Akt)/Wnt pathways.[42]

Resveratrol and Mitochondrial Biogenesis

Numerous clinical diseases, including cellular energy imbalance, oxidative stress, and endothelial dysfunction, are caused by impairment in mitochondrial biogenesis.[43] Mitochondria are constantly being made and destroyed, and their density changes according to changes in energy requirements. Many endogenous and exogenous factors regulate mitochondrial biogenesis through PGC-1α. Resveratrol increases the activation of PGC-1α, and the expression level of PGC-1α is directly related to mitochondrial biogenesis. It has been shown that this pathway slows down the aging process, prevents many chronic diseases, and increases endurance in the muscles.[44] Possible mechanisms of the neuroprotective effects of resveratrol are summarized in Figure 2.

Resveratrol's Neuroprotective Effects Against Neurodegenerative Diseases

The neuroprotective effect of resveratrol supplementation was investigated at the neurobehavioral, neurochemical, and cerebrovascular levels. Studies have shown that resveratrol was effective in maintaining cognitive function.[45] It has been stated that resveratrol may have beneficial effects for neurological disorders due to its antioxidant effect. [45]

Recent studies have also demonstrated the immunomodulatory effects of resveratrol. Resveratrol effectively blocks gene expression of lipopolysaccharide-d erived proinflammatory molecules in microglial cells.[46] Resveratrol has been able to provide a neuroprotective effect by controlling neuroinflammation and enhancing adaptive immunity in people with AD.[47] Antitumor activity of resveratrol has also been reported.[48] Genetic and/or epigenetic changes cause cancer initiation and progression. Acetylation of histone and nonhistone proteins plays a crucial role in the epigenetic regulation of gene expression. The acetylation state of histones is controlled by the balance between the activity of histone acetyltransferases and histone deacetylases. An imbalance between the activity of these enzymes is associated with various types of cancer. Deacetylated histones promote genomic stability, while general hyperacetylation of histones can impair genomic stability and create a desirable environment for tumor cells. Resveratrol can activate SIRT1 which has deacetylase activity and thus exert antitumor activity.[49] SIRT1 also exerts antiaging effects

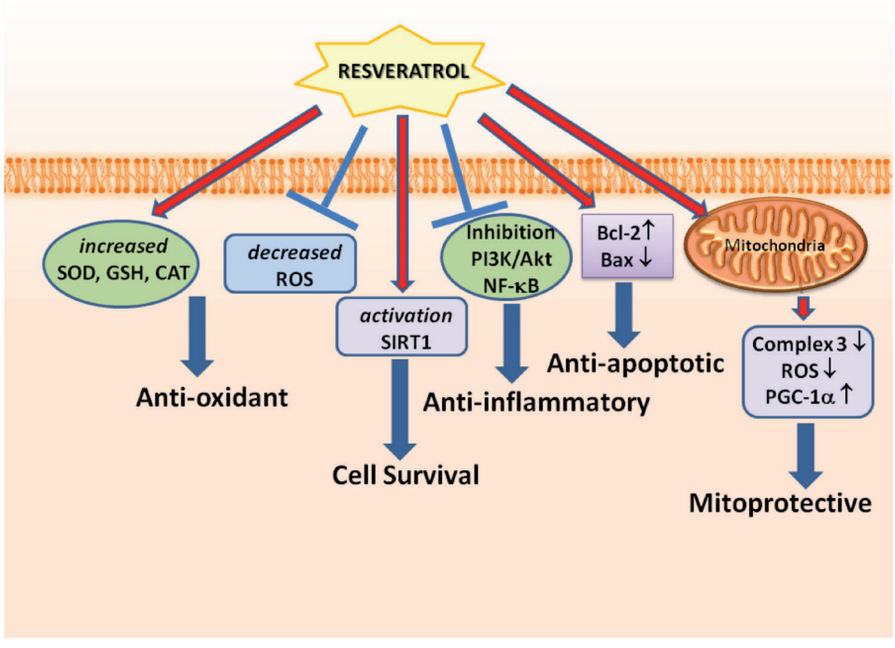

Figure 2. Possible mechanisms of the neuroprotective effects of resveratrol. Bax, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma/leukemia-2; CAT, catalase; NF κB, nuclear factor κB; PGC1α, peroxisome proliferator-activated receptor γ co-activator-1 alpha; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SIRT1, sirtuin1; SOD, superoxide dismutase.

through histone deacetylation and neuroprotection.[50] Some protective effects of resveratrol against ather osclerosis-associated endothelial dysfunction have also been demonstrated through the SIRT1, adiponectin, and calprotectin proteins.[51] In summary, resveratrol may have a protective effect against neurodegenerative diseases due to its SIRT-1-mediated anti-inflammatory and neuroprotective effects.

The beneficial effects of resveratrol for AD have emerged as a result of reducing β amyloid plaque as well as improving mitochondrial function, decreasing ROS activity and increasing neuronal cell survival by activating the SIRT1 pathway.[47] A study investigated the effects of resveratrol in mild-to-moderate cases of AD. This phase 2 randomized, placebo-controlled trial showed that resveratrol was detectable in the cerebrospinal fluid (CSF) and stabilized the progressive decline of Aß40 in CSF and plasma of AD patients compared to placebo-treated controls. It was demonstrated that resveratrol stabilized CSF Aß42 levels.[52]

Resveratrol was also demonstrated to significantly reduce CSF metalloproteinase 9 and modulate neuro-inflammation in AD subjects compared to placebo-treated controls. It was concluded that SIRT 1 activation by resveratrol could be key for the treatment or prevention of neurodegenerative diseases.[47] These results suggest that resveratrol can be used safely in Alzheimer's patients. Resveratrol was demonstrated to modulate astroglial functions. The neuroprotective impact of resveratrol on neuroglia cells is hypothesized to occur subsequent to the discharge of glutamate at the synaptic gap.[53] Resveratrol can enhance glutamate uptake by astrocytes, a course which promotes glutamine synthetase, an enzyme that converts glutamate into glutamine. Resveratrol can also promote the synthesis of glutathione.[53] Although the molecular mechanisms underlying the neuroprotective effect of resveratrol have not been definitively determined, experiments suggest that it may be important that it selectively upregulates mitochondrial antioxidant enzyme gene expression, particularly manganese superoxide dismutase.[43]

It was observed that resveratrol modulates mRNA levels and protein expression of apoptotic regulators Bax and Bcl-2 genes and promotes cell survival in rat PC12 cells. In addition, the use of resveratrol has a curative effect on the dopaminergic neurons.[54] Studies established that resveratrol could elicit neuroprotective effects on 1-met hyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-generated PD mice through free radical scavenging. Resveratrol treatment notably protected PD mice from MPTP-induced $OH^{\cdot}$ production, motor coordination destruction, and neuronal death.[55] Likewise, resveratrol decreased 6-hyd roxydopamine-stimulated oxidative injury and dopamine reduction in a rat model of PD.[56] In addition, resveratrol decreased dopamine-induced apoptosis in neuroblastoma cells.[57] Studies also implicate that resveratrol may possibly minimize mitochondrial dysfunction induced by impairment of parkin function. Parkin is a protein in humans and mice that is encoded by the PARK2 gene.[58] Parkin plays a critical role in ubiquitination, whereby it recognizes damaged proteins on the outer membrane of mitochondria and intervenes in the clearing out of injured mitochondria through proteasomal mechanisms.[59] Parkin increases cell survival by repressing both mitochondria-reliant and mitoc hondria-independent apoptosis. Mutations in the PARK2 gene are connected with mitochondrial dysfunction, directing neuronal death in PD.[60] A study which used fibroblast cultures commencing from 2 patients diagnosed with an early-onset form of PD with PARK2 heterozygous mutations showed that resveratrol caused a limited salvage of mitochondrial functions, possibly associated with the activation of the AMP-activated protein kinase/ SIRT1/PGC-1α pathway.[61]

Resveratrol significantly improved motor and cognitive impairments by inhibiting cyclooxygenase-1 activity in the HD model.[62] In addition, it protects against the cytotoxicity of mutant polyglutamine Htt through SIRT1 activation. It has been suggested that mutant polyglutamine Htt triggers striatal neurodegeneration by various mechanisms, such as mitochondrial dysfunction, oxidative stress, and apoptosis. Resveratrol protects cells against the toxic effects of mutant polyglutamine Htt by potentiating SIRT1 activity and induces indirect inhibition of p53.[63] Sirtuin1 interacts with p53 and deacetylates it. The activity of deacetylated p53 is reduced and p53-dependent apoptosis is inhibited. p53 activation, occurring in HD, is associated with enhanced mitochondrial oxidation.[64] Due to antioxidant properties, resveratrol can prevent impaired mitochondrial function through activation of the SIRT1–peroxisome proliferator-activated receptor γ co-activator-1 alpha (PGC1α) pathway. The PGC1α regulates the expression of antioxidant enzymes that inhibit ROS and consequently inhibits oxidative stress.[65]

Resveratrol has revealed a number of favorable effects that can slow down mitochondrial dysfunction associated with motor neuron damage observed in ALS. The antioxidant properties of resveratrol can reduce mitochondrial damage and ROS production; and in this context, Song et al[66] showed suppression of ROS levels following resveratrol treatment in ALS mice. As mentioned earlier, PGC-1α activation mediated by the resveratrol-SIRT1 interaction protects against mitochondrial fragmentation.[67] Zhao et al[68] reported that resveratrol increased the expression of PGC-1α, improving motor performance and survival in a mouse model of ALS. Resveratrol-induced SIRT1 activation also increased neuronal survival in ALS cell models.[69]

Negative and Side Effects of Resveratrol

There are studies showing that resveratrol can act as a prooxidant agent and therefore pathological effects may also develop.[70] Resveratrol can undergo auto-oxidation to semiquinones and to the more stable 4′-phenoxyl radical

causing ROS formation.[71] High doses of resveratrol induce apoptosis, while low doses induce cell proliferation.[72] Acting as a prooxidant, resveratrol can reversibly or irreversibly interrupt the cell cycle and also cause DNA damage.[73] Resveratrol is considered to be a phytoestrogen due to its structural resemblance to diethylstilbestrol and thus can act as an estrogen receptor agonist.[73] Studies underline the importance of dose dependence in resveratrol-induced cellular responses.[74]

No significant adverse effects of resveratrol have been reported in long-term clinical trials in healthy populations.[75] Up to 5 g daily has been reported to be well tolerated in healthy populations.[76] Orally administered resveratrol is metabolized by the gut microbiota[77], so observed effects may result not only from resveratrol but also from resveratrol metabolites. Studies to date have not found definite doses and administration intervals for resveratrol. An important drawback in the clinical use of resveratrol is its bioavailability. Although demonstrated safe, resveratrol does not have the best possible pharmacokinetic and pharmacodynamic properties.[78]

CONCLUSION

In studies on neurodegenerative diseases, the importance of mitochondrial dysfunction and oxidative stress has been frequently stated. Resveratrol, an antioxidant, is an important phytoalexin found in abundance in grapes and its products. It modulates mitochondrial function and dynamics with its cytoprotective, anti-inflammatory, and antioxidant effects. Identifying and targeting redox-regulated pathways in neurodegenerative diseases may provide a pathway for new treatment strategies. In this review, the literature on the effect of resveratrol on neurodegenerative diseases and mitochondrial dysfunction was reviewed. As a result, resveratrol has been shown to have a curative role on both cell and animal models of neurodegenerative diseases as a modulator of mitochondrial function, redox biology and dynamics. Despite the considerable advancement in the knowledge of resveratrol's effects on the brain, our understanding in this area is still in progress. The greater part of the research has been carried out in cell culture or in experimental animal models. Further studies are necessary to comprehend the effect of resveratrol on mitochondrial biogenesis and function. It is imperative that the acquired knowledge is transferred into actual treatments for neurodegenerative diseases.

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