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Review

Resveratrol—A boon for treating Alzheimer's disease?

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ABSTRACT

Resveratrol, a red wine polyphenol, is known to protect against cardiovascular diseases and cancers, as well as to promote antiaging effects in numerous organisms. It also modulates pathomechanisms of debilitating neurological disorders, such as strokes, ischemia, and Huntington's disease. The role of resveratrol in Alzheimer's disease is still unclear, although some recent studies on red wine bioactive compounds suggest that resveratrol modulates multiple mechanisms of Alzheimer's disease pathology. Emerging literature indicates that mechanisms of aging and Alzheimer's disease are intricately linked and that these mechanisms can be modulated by both calorie restriction regimens and calorie restriction mimetics, the prime mediator of which is the SIRT1 protein, a human homologue of yeast silent information regulator (Sir)-2, and a member of NAD^+-dependent histone deacetylases. Calorie restriction regimens and calorie restriction-mimetics trigger sirtuins in a wide variety of organisms, ranging from bacteria to mouse. In a mouse model of Huntington's disease, resveratrol-induced SIRT1 was found to protect neurons against ployQ toxicity and in Wallerian degeneration slow mice, resveratrol was found to protect the degeneration of neurons from axotomy, suggesting that resveratrol may possess therapeutic value to neuronal degeneration. This paper mainly focuses on the role of resveratrol in modulating AD pathomechanisms.

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1. Introduction

Alzheimer's disease (AD) is a progressive, age-dependent neurodegenerative disorder of the cortex and hippocampus, eventually leading to cognitive impairment of the brain. The presence of intracellular neurofibrillary tangles (NFTs) and extracellular amyloid beta (Aβ) plaques in these learning and memory regions are the hallmarks of AD (Selkoe, 2001; Tanzi and Bertram, 2005). AD occurs in two forms: familial and sporadic. In familial AD, mutations in the amyloid precursor protein (APP), presenilin 1, and presenilin 2 genes are the currently known causal factors (Selkoe, 2001; Tanzi and Bertram, 2005). Familial AD constitutes only a small portion of all AD patients (Reddy and Beal, 2005), and it has an early age of onset (younger than 65 years). In contrast, sporadic AD, constituting the vast majority of AD cases, is associated with a late age of onset (65 years and older). Although the specific causes of sporadic AD are still unknown (Selkoe, 2001), many causal factors seem to be involved in sporadic AD, including aging (Selkoe, 2001), mitochondrial defects (Reddy and Beal, 2005), apolipoprotein genotype (ApoE4) (Raber, 2004; Raber et al., 2004), insulin-dependent diabetes (de la Monte and Wands, 2005; Qiu and Folstein, 2006), environmental conditions (Lazarov et al., 2005), and diet (Kitazawa et al., 2005; Tchantchou et al., 2005). Irrespective of the cause, in both familial and sporadic AD, a 4-kDa Aβ peptide, a cleavage product of APP that is due to β and γ secretases, is a key factor in disease pathology (Selkoe, 2001, 2004).

Scientists around the globe have been trying for decades to treat and to abolish pathological symptoms of this disease that deprives humans of their intellect, but scientists have met limited success. In spite of Herculean efforts, only four Federal Drug Administration-approved drugs are currently available in the US market to treat AD pathology (Allain et al., 2003). These drugs mainly target cholinergic functions associated with AD, leaving a vast majority of other potential AD targets nearly unaffected by treatment. There is an urgent need for developing drugs based on multiple pathomechanisms of AD.

The enormous diversity of functions in natural compounds, such as resveratrol and other herbs, may provide a new generation of drugs for treating AD patients (Anekonda and Reddy, 2005; Bastianetto and Quirion, 2004; Howes and Houghton, 2003; Howes et al., 2003). There are an estimated 35,000 plant species of fruits, nuts, and vegetables that offer nearly 4000 flavonoids (Duncan et al., 2003; Nijveldt et al., 2001; Williams et al., 2004). Investigating and cataloguing the health benefits of all these natural compounds in general and resveratrol, in particular, will pose numerous research challenges to modern medicine for decades to come. Plant-derived drugs are popular because the public believes that herbs are naturally safer than synthetic drugs (Raskin et al., 2002). These beliefs may account for the sudden increase in herbal use in the last decade (Raskin et al., 2002). The U.S. market for herbal supplements has exceeded $7 billion per year (Glaser, 1999), and the projected worldwide sales of plant-derived pharmaceuticals and their precursors in 2002 exceeded $30 billion (Raskin et al., 2002). Today, one in three Americans uses herbal supplements, with the consumption level much greater among women (Morelli and Naquin, 2002; Tesch, 2003), patients undergoing surgery (Ang-Lee et al., 2001), and the elderly.

More than 50 different plant species – either in single, pure molecular form or in specific proportions of differing plant extracts – have been identified as potentially useful for treating AD symptoms, but their underlying molecular mechanisms and therapeutic value are largely unknown (Anekonda and Reddy, 2005; Howes and Houghton, 2003; Howes et al., 2003 and references therein). Recently, resveratrol, an herbal compound naturally found in purple wine, peanuts, and several other plants, appears to mimic the effects of calorie restriction or dietary restriction and to trigger sirtuin proteins (Howitz et al., 2003; Lamming et al., 2004; Sinclair, 2005; Wood et al., 2004). Sirtuins are evolutionarily conserved NAD-dependent histone deacetylases that participate in pathomechanisms of numerous age-related disorders and that have been found to extend the lifespan of yeasts, nematodes, fruit flies, mice, and rats (Cohen et al., 2004; Parker et al., 2005; Tissenbaum and Guarente, 2001; You and Mak, 2005). Although lifespan-promoting effects of sirtuins still need to be determined in humans, mounting evidence in the scientific literature suggests that it is just a matter of time before critical molecular mechanisms that linked to sirtuins and that are triggered by plant compounds are identified. This review focuses on the molecular mechanisms of resveratrol as relevant to treating AD pathology.

2. Why resveratrol deserves special attention

An epidemiological link between common red wine and a low incidence of cardiovascular disease led to the birth of what has been termed the "French Paradox", despite the fat-rich diets consumed by the French (Nanji and French, 1986). The realization that a moderate consumption of red wine is beneficial to health triggered a flurry of hypotheses across medical disciplines, including internal medicine, endocrinology, cardiology, oncology, and neurology. It soon became clear that red wine and its biological source – the purple grape (*Vitis vinifera*), especially its skin and seeds – contain numerous polyphenols, such as flavonoids (quercetin, catechins, gallocatechin, procyanidin, prodelphidins), and resveratrol, a phytoalexin that is naturally synthesized in response to fungal attack (de la Lastra and Villegas, 2005; Fremont et al., 1999; Pervaiz, 2003). In addition to purple grape, resveratrol is also found in peanuts, mulberries, and more than 70 other

plant species that are prone to fungal attack (de la Lastra and Villegas, 2005). There are two isomeric forms of resveratrol: biologically inactive *cis*-resveratrol and active *trans*-resveratrol (3,5,4′-trihydroxystilbene). There is a unique reason why *trans*-resveratrol (or simply resveratrol) is special: it mimics calorie restriction (CR)-type effects on a diverse group of organisms (earning the sobriquet *CR mimetic*) (Howitz et al., 2003; Lamming et al., 2004; Wood et al., 2004). Interestingly, biochemical pathways linked to the effects of CR (i.e., about 60% of ad libitum or normal calorie consumption) exhibit antiaging effects in organisms ranging from yeasts to mammals (Bordone and Guarente, 2005; Dirks and Leeuwenburgh, 2006; Sinclair, 2005).

Although CR has been found to be beneficial for its antiaging effects in lower organisms, there are at least three main concerns for using CR as a therapy in humans. First, CR therapy is unpopular when used to slow down the aging process or to treat age-related disorders like AD, possibly because not many people are inclined to give up their favorite foods and tastes. Second, several studies have examined the effects of short-term CR on humans, but CR therapy has not been tested extensively for long-term effects in treating AD or any other diseases (Dirks and Leeuwenburgh, 2006). Finally and perhaps most importantly, although CR in yeasts, nematodes, mice, and humans has been proven to have beneficial effects, many adverse effects have also been noted. These adverse effects include infertility, menstrual irregularities, hypertension, loss of libido, loss of strength and stamina, slower wound healing, and many psychological conditions, such as depression and irritability (Dirks and Leeuwenburgh, 2006). For these reasons, a CR mimetic, such as resveratrol and potentially many other herbal compounds, may serve as reliable therapeutic interventions for treating AD.

3. Calorie restriction and CR-mimetics induce sirtuins that modulate downstream pathways of aging

Calorie restriction without malnutrition exposes organisms to mild nutritional stress, which not only stimulates stress proteins, but also elevates the organism's defense mechanisms (Sinclair, 2005). Similar responses are also triggered by CR mimetics, such as resveratrol. CR and CR mimetics possibly package their disparate physiological, cellular, and molecular effects into one megacellular response cascade that, in turn, enhances longevity of the organism, besides protecting the organism from stress (Sinclair, 2005). Such effects of CR and CR mimetics have been postulated in hormesis and xenohormesis hypotheses, respectively (see Sinclair, 2005 for a detailed review on this topic). In yeasts, CR and CR mimetics trigger the over-expression of Sir2, an NAD-dependent class III histone deacetylase that participates in transcriptional silencing of telomeres and cell-mating type loci, recombination DNA, cell cycle regulation, and lifespan extension (Blander and Guarente, 2004; Guarente, 2000; Lamming et al., 2004). Sir2 also mediates the nutrient-sensing pathway of aging in nematodes and fruit flies (Parker et al., 2005; Tissenbaum and Guarente, 2001; Wood et al., 2004). Seven Sir2 homologs have been identified in mice and humans (sirtuins, SIRT1-7), offering promise for understanding the mechanisms of neuronal protection and aging (Denu, 2003; Frye, 1999, 2000; North and Verdin, 2005; Porcu and Chiarugi, 2005). All seven mammalian sirtuins express ubiquitously across different types of tissues and have been categorized under four classes of proteins: SIRT1–3 (class I), SIRT4 (class II), SIRT5 (class III), and SIRT6–7 (class IV) (Frye, 1999, 2000; Shi et al., 2005). SIRT1, SIRT6, and SIRT7 have been localized to the nucleus, with SIRT6 localized specifically to heterochromatic regions and SIRT7 to nucleoli (Michishita et al., 2005). SIRT2 has been localized to the cytoplasm, and SIRT3, SIRT4, and SIRT5, to mitochondria (Frye, 1999, 2000; Michishita et al., 2005; North et al., 2003; Shi et al., 2005).

Of the seven sirtuins, SIRT1 is the most extensively studied and the most implicated in lifespan extension of organisms, from yeasts to mammals, but the role of SIRT1 in mammalian longevity is still unclear. A few recent studies have provided good circumstantial evidence that SIRT1 can extend longevity in higher organisms. SIRT1 has been shown to trigger lipolysis and to mobilize fat in white adipose tissue by repressing the peroxisome proliferator-activated receptor-γ (PPAR-γ) (Picard et al., 2004). Mice genetically engineered to have a lower quantity of white adipose tissue were found to live longer (Bluher et al., 2003). One recent study using a German population, however, found no association between SIRT1 and aging (Flachsbart et al., 2006). Besides longevity, SIRT1 has also bee associated with a myriad of disease pathomechanisms, such as promyelocytic leukemia (Langley et al., 2002), B cell leukemia 11A (BCL11A) (Senawong et al., 2005), human non-small-cell lung cancer (You and Mak, 2005), prostate cancer (Kuzmichev et al., 2005), and human immunodeficiency virus (HIV) Tat protein transactivation (Pagans et al., 2005). It may be just a matter of time before new lifespan-extending mechanisms of sirtuins, particularly SIRT1 in mammals and the relationship between SIRT1 and CR mimetics, such as resveratrol, become known.

Further, in a recent study of the role of SIRT6 in aging, SIRT6 knockout mice were found to be smaller than normal mice, and they showed profound developmental abnormalities, including severe metabolic defects. They died about 4 weeks old, suggesting that SIRT6 is essential for the development and survival of these animals (Mostoslavsky et al., 2006).

Although the roles of SIRT1 and SIRT6 in human longevity still need to be elucidated, SIRT3 has been associated to a certain extent with human aging. The survivorship function of the G477T marker in elderly subjects showed that SIRT3 or a SIRT3-linked gene may be related to human longevity (Rose et al., 2005). In an investigation of 945 humans from 20 to 106 years old, variable number tandem repeat (VNTR) polymorphism in intron 5 of SIRT3 was associated with subjects in the oldest age category (Bellizzi et al., 2005). However, it is still unclear how this mitochondrially located SIRT3 can exert antiaging effects in humans.

4. Emerging roles of resveratrol in neuronal protection

Resveratrol has been found to exhibit the highest level of SIRT1 activation among small molecules tested (Howitz et al.,

2003) and to increase the lifespan in yeast nearly by 70% (Howitz et al., 2003), in the namatode *Caenorhabditis elegans* by 14%, and in the fruit fly *Drosophila melanogaster* by 29% (Wood et al., 2004). Because resveratrol and sirtuins have shown unprecedented promise for the development of new drugs that can potentially promote, for example, healthy aging, longevity, and neuronal protection, a focused effort has been made to screen thousands of small molecules, with an intention to identify resveratrol-analogues that can function as activators or inhibitors of sirtuins (Bedalov et al., 2001; Grozinger et al., 2001). Of the 1600 small organic molecules screened for their ability to inhibit ySir2-mediated silencing of the telomere, only three molecules (M15, A3, Sirtinol) were identified as inhibitors (Grozinger et al., 2001). In another screening for inhibitors, only 11 out of 6000 compounds tested rescued cell growth (Bedalov et al., 2001). This latter study identified splitomycin as one of the most potent inhibitors of Sir2. Activators and inhibitors of resveratrol activity may become implicated in therapies to AD patients.

Although the role of sirtuins in neuronal protection in AD is still in its infancy, two recent studies have provided some enlightenment. First, in studies of Huntington's disease, resveratrol-induced SIRT1 in the neurons from HdhQ111 knock-in mice and Sir2 in the neurons of polyQ mutant transgenic *C. elegans* (both models for Huntington's disease) rescued neuronal dysfunction caused by polyQ toxicity (Parker et al., 2005). Second, in studies of AD and Parkinson's disease, axonal degeneration was found to occur prior to the death of neuronal cells (Bedalov and Simon, 2004)—a sequence of events shown in wild-type mice, but not in Wallerian degeneration slow mice that possess a spontaneous dominant mutation at Wld^s locus. The delayed axonal degeneration in the Wld^s mice may be due to the expression of a mutant fusion protein that is made up of two fused amino acid fragments: amino-terminal ubiquitin fusion degradation protein 2a (Ufd2a) and the coding region of nicotinamide mononucleotide adenyltransferase 1 (Nmat1) enzyme (Araki et al., 2004; Bedalov and Simon, 2004). Delayed axonal degeneration may be due to the increased synthesis of nicotinamide adenine dinucleotide (NAD) and the subsequent increased expression of SIRT1, which in turn may activate genes responsible for neuronal protection (Araki et al., 2004; Bedalov and Simon, 2004). Further, in this study (Bedalov and Simon, 2004), resveratrol treatment prior to axotomy also decreased axonal degeneration. These two studies (Araki et al., 2004; Bedalov and Simon, 2004) have strongly implicated sirtuins in neuronal protection, and have shown that CR and CR mimetics can elevate sirtuin production in the human brain.

Besides the neuroprotective role of resveratrol through SIRT1 in Huntington's disease (Parker et al., 2005) and axotomy (Araki et al., 2004), resveratrol seems to modulate and to protect neurological functions in a few other neurological disorders, such as brain ischemia, stroke, seizure, and epilepsy. In rat hippocampal neurons, resveratrol inhibited voltage-activated K^+ currents, suggesting that it may be useful for treating ischemic brain injury (Gao and Hu, 2005). Resveratrol was also found to provide protection against toxicity that was induced by sodium nitroprusside (SNP) and 3-morpho-linosydnonimine (SIN-1)-induced NO in mixed hippocampal cells from Sprague–Dawley rats (Bastianetto et al., 2000) and against kainic acid-induced excitotoxicity in the cortex and hippocampus of Wistar rats (Virgili and Contestabile, 2000). In Fisher rats, resveratrol protected the auditory brain stem (via an antioxidant mechanism) from the noise-induced generation of ROS and from subsequent hearing loss (Seidman et al., 2003). In an anoxia-reoxygenation model for stroke using Wistar rat cerebral mitochondria, resveratrol inhibited cytochrome *c* release, decreased the production of superoxide anion (O_2) and O_2 consumption, and partly reversed the decline of the respiratory control ratio (Zini et al., 2002). After induced-stroke by the occlusion of common cortical arteries, resveratrol decreased delayed neuronal cell death and glial cell activation in Mongolian gerbils (Wang et al., 2002), prevented motor impairment, increased the levels of malodialdehyde, reduced glutathione, and decreased the volume of infarct in Wistar rats (Sinha et al., 2002). Resveratrol also protected neurons, via antiplatelet aggregation, against vasodilating and antioxidant effects in Long–Evans rats (Huang et al., 2001). In mixed glia from cerebral cortices of Sprague–Dawley rats, resveratrol suppressed induced interleukin-6 gene expression and protein secretion following hypoxia and glucose deprivation (Wang et al., 2001). Resveratrol attenuated increased levels of malodialdehyde following kainic acid-induced seizure and epilepsy in albino Wistar rats (Gupta et al., 2002). These findings provide evidence that resveratrol can be useful in protecting some animals suffering from different types of neurological disorders.

5. Molecular mechanisms of resveratrol-induced SIRT1 over-expression in AD

It is not clear which functions of resveratrol may be critical to neuronal protection in AD: whether traditionally known antioxidant properties are more effective than cytoplasmic signal transduction pathways or whether the direct modulation of neuronal functions is more effective than the modulation of glia/astrocyte functions. It is more likely that all of these functions may play important synergistic roles in treating AD and that narrowly targeted drugs may not be able to modulate disease symptoms effectively. Although mechanisms that link resveratrol to the over-expression of sirtuins and the subsequent protection of AD neurons are largely unknown, emerging findings suggest that resveratrol-induced SIRT1 expression may play an important role in protecting neurons from ROS, H_2O_2, NO, Aβ, and other intra- and extracellular insults in AD brains.

SIRT1 expression in the nucleus of AD neurons may play at least two important roles (Anekonda and Reddy, 2006). Resveratrol-induced SIRT1 has been found to deacetylate and repress p53 activity of the neurons and prevent the apoptotic death of these neurons; and also to suppress apoptotic activities of FOXO proteins and promote neuronal survival (Fig. 1, Section 1). FOXOs share functional similarities and participate considerably in cross-talk with p53 (You and Mak, 2005). In motoneurons, FOXO3a induces neuronal death through the Fas pathway, in cooperation with c-Jun N-terminal kinase (JNK) (Barthelemy et al., 2004). FOXO proteins directly induce *bim* gene expression and cause apoptosis in

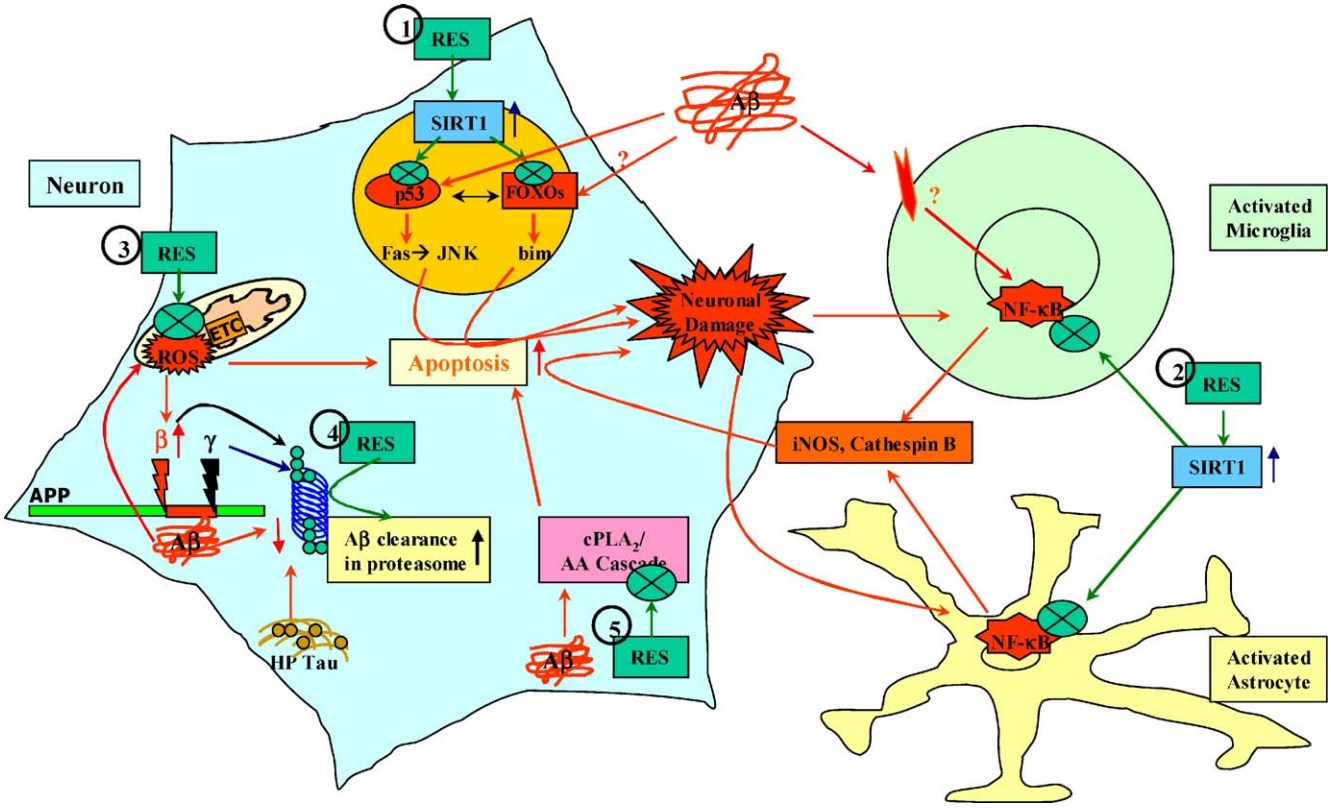

Fig. 1 – Molecular mechanisms of neuronal protection by resveratrol in Alzheimer's disease. (1) Resveratrol-induced SIRT1 deacetylates and represses p53 activity promoted by Aβ in neurons and prevent apoptotic death in these neurons. In addition, SIRT1 suppresses apoptotic activities of FOXO proteins and promotes neuronal survival. (2) Resveratrol-induced SIRT1 inhibits nuclear factor kappa B and subsequently suppresses nitric oxide synthase (iNOS) and cathespin B, the two toxic factors that mediate neurodegeneration in microglia and astrocytes, and protects AD neurons against Aβ-induced toxicity. (3) Resveratrol functions as an antioxidant and possibly prevents reactive oxygen species-induced Aβ production and apoptosis-mediated neurodegeneration. (4) Resveratrol modulates the ubiquitin proteasome system via an unknown mechanism and promotes hastened Aβ degradation without affecting Aβ-producing metabolism. (5) Resveratrol blocks nitric oxide-induced phospholipase A_2/arachidonic acid cascades in the cytoplasm and prevents apoptotic death of neurons.

sympathetic neurons (Gilley et al., 2003). These studies raise the possibility that FOXOs might be involved – either directly or in cooperation with p53 – in contributing to neuronal death in AD. Because resveratrol is known to trigger SIRT1 over-expression, it seems likely that resveratrol can effectively suppress both p53 and FOXOs, and can confer neuronal protection in AD brains.

Aβ-induced inflammatory reaction involves the activation of both microglia and astroglia in many neurological disorders, including AD (McGeer and McGeer, 1995; Monsonego and Weiner, 2003). In a recent study with mixed neuron/glia cultures of Sprague–Dawley rat, resveratrol-induced SIRT1 inhibited the nuclear factor kappa B (NF-κB) signaling in microglia and astrocytes, and protected AD neurons against Aβ-induced toxicity (Chen et al., 2005). According to this study, a non-fibrillar form of Aβ first binds to an unknown cell surface receptor that stimulates NF-κB signaling in microglia and astrocytes. This NF-κB signaling in turn controls the expression of both induced nitric oxide synthase (iNOS) and cathespin B, two toxic factors that mediate apoptosis and that lead to neurodegeneration (Fig. 1, Section 2). The toxic factors generated due to neurodegeneration, in turn, promote NF-κB signaling, providing evidence for a glia-loop hypothesis of AD pathology (Chen et al., 2005). Further, this study also showed that resveratrol-induced SIRT1 posttranslationally modifies Aβ-induced RelA/p65, a subunit of NF-κB, by deacetylating RelA/p65 at lysine 310. Acetylation and deacetylation at lysine 310 of RelA/p65 have been found to be an important mechanism in controlling the toxic effects of NF-κB signaling (Yeung et al., 2004). Although SIRT1 is known to deacetylate RelA/p65 at four other lysine residues (Lys122, 123, 218, 221), resveratrol did not seem to have a role in deacetylation in the latter four residues (Chen et al., 2005). IκBα kinase functions as an upstream signal inducer of NF-κB. Aβ can bind and activate IκBα in the cytoplasm, and the activated IκBα dissociates itself from NF-κB. The dissociated IκBα is ubiquitinated and eventually disintegrated by proteasome, leaving the free NF-κB to move inside the nucleus to trigger NF-κB-dependent protein transcription (Pervaiz, 2003). In PC12 cells, Aβ induces the degradation of cytoplasmic IκBα and increases the translocation of p65 to the nucleus. These processes were reversed when the cells were treated with resveratrol (25 μM), suggesting that

NF-κB, in addition to its upstream signal transduction, was affected by resveratrol treatments (Jang and Surh, 2003).

The soluble form of Aβ selectively accumulates in the endothelial cells of the blood vessels of AD brains, inhibits endothelial nitric oxide synthase (eNOS) activity, and causes deleterious effects on nitric oxide (NO) functions (Gentile et al., 2004; Guix et al., 2005). Such deleterious effects are linked to alterations in intracellular Ca^{2+} homeostasis (Gentile et al., 2004). CR, however, was found to increase the expression of eNOS in various tissues, including brain tissues, of 3- and 12-month-old male mice. This increased expression was associated with increased SIRT1, mitochondrial biogenesis, increased oxygen consumption, and increased ATP production (Nisoli et al., 2005). Interestingly, resveratrol was also found to enhance the expression of eNOS in a time- and dosage-dependent fashion in human endothelial cells (Wallerath et al., 2005). These studies strongly suggest that, in AD brains, resveratrol may increase eNOS, modulate the expression of SIRT1 and cellular metabolic functions, and provide protection to both nerves and blood vessels against Aβ-induced toxicity and that resveratrol may play a vital role at the junctions of neurovascular connections.

The molecular effects of resveratrol on sirtuins other than SIRT1 are still unknown. It has been recently noted that resveratrol activates SIRT1 in a substrate-specific fashion and, in vitro, promotes binding and deacetylation of peptide substrates containing Fluor de Lys, a non-physiological fluorescent moiety (Borra et al., 2005; Kaeberlein et al., 2005). This substrate-specific deacetylation was found to occur with Sir2 in three different yeast backgrounds and in human SIRT1 (Kaeberlein et al., 2005). Interestingly, resveratrol did not show significant enzyme activation of human SIRT2 (Borra et al., 2005). SIRT1 activity was also found to stimulate, in a dose-dependent fashion, the activity of the insulin-like growth factor-binding protein-1 (IGFBP-1) promoter, and SIRT1 was also found to deacetylate and enhance the function of forkhead box transcription factors O family (FoxO1) (Gan et al., 2005). Further, resveratrol (at μM concentrations) also mimicked these effects (Gan et al., 2005). According to this study (Gan et al., 2005), enhanced SIRT1 activity was associated with the increased mitogen-activated protein kinase, and was found to stimulate IGFBP-1 through both FoxO-dependent and independent mechanisms. The enhanced SIRT1 activity may also serve to suppress GTPase Rho and Rho-associated kinase, and may promote non-amyloidogenic or non-pathogenic pathways in APP processing (Tang, 2005). These studies demonstrate that resveratrol activates SIRT1 and perhaps modulates the conformational changes of SIRT1 (Borra et al., 2005) in SIRT1-dependent biological pathways that are yet to be discovered.

6. Resveratrol as a powerful antioxidant that clears mitochondrial ROS

In sporadic AD, ROS may activate β-secretase of the APP molecule and generate Aβ peptides in AD (Tamagno et al., 2002, 2003, 2005). In APP transgenic mice, chronic ROS production may result in oxidative damage to mitochondrial and cellular proteins, lipids, and nucleic acids, resulting in a shutdown of mitochondrial energy production (Reddy and Beal, 2005). Aβ enters mitochondria and interacts with an Aβ-induced alcohol dehydrogenase protein, disrupts the electron transport chain (ETC), generates ROS, and inhibits cellular ATP (Lustbader et al., 2004). These studies suggest that age-dependent interactions of Aβ with mitochondrial proteins cause mitochondrial dysfunction in AD (Anandatheerthavarada et al., 2003; Lustbader et al., 2004). There may be a vicious cycle of mitochondrial ROS inducing APP/Aβ production, with this Aβ in turn promoting the production of additional ROS in an unending cycle of AD pathophysiology (Fig. 1, Section 3).

In both in vitro and in vivo models of numerous pathologies, including AD, red wine/resveratrol has been traditionally recognized for its powerful antioxidant properties (Jang and Surh, 2003; Russo et al., 2003; Sharma and Gupta, 2002; Wang et al., 2002). In PC12 cells, resveratrol-protected cells from $Aβ_{25–35}$-induced toxicity, attenuated apoptotic cell death by influencing apoptotic-signaling pathways, reduced changes in the mitochondrial membrane potential, inhibited the accumulation of intracellular reactive oxygen intermediates, and attenuated NF-κB activation (Jang and Surh, 2003). In the study by Jang and Surh (2003), resveratrol reduced the expression of the pro-apoptotic Bax protein and blocked $Aβ_{25–35}$-induced pro-apoptotic c-Jun N-terminal kinase (JNK) via phosphorylation; thus, resveratrol seems to influence antioxidant mechanisms and intracellular signaling cascades. In a rat model of sporadic AD, resveratrol prevented cognitive impairment induced by intracerebroventricular streptozotocin, which may have resulted from the antioxidant effects of resveratrol (Sharma and Gupta, 2002). When human umbilical vein endothelial cells (HUVECs) were challenged with $Aβ_{25–35}$ toxicity, red wine micronutrients (presumably containing vitamin E, vitamin C, resveratrol, and quercetin), that were extracted from the skin of black grapes, protected these cells from oxidative damage, reduced ROS production, and prevented cellular DNA fragmentation. Resveratrol protected SH-SY5Y neuroblastoma cells from H_2O_2 and Aβ-induced toxicity (Savaskan et al., 2003), and protected hippocampal mixed neuronal/glial cultures of Sprague–Dawley rats against sodium nitroprusside (SNP)-induced nitric oxide (NO) toxicity (Bastianetto et al., 2000). In addition, resveratrol in mouse cortical neuronal cultures increased the production of heme oxygenase activity, which is responsible for degrading pro-oxidant heme (Zhuang et al., 2003). Resveratrol-induced protein kinase C (PKC) in hippocampal neuronal cell cultures of Sprague–Dawley rats was also found to protect cells from Aβ-induced toxicity (Han et al., 2004). In these studies, whether resveratrol was used as a pretreatment, a co-treatment, or a posttreatment, in all cases resveratrol exhibited its neuroprotective effects at 25 μM concentrations. These studies, taken together, suggest that besides its antioxidant property, resveratrol may also confer protection through its protective cell-signaling mechanisms.

7. Resveratrol-induced modulation of proteasome activity clears Aβ

Aβ toxicity in AD attenuates the activity of ubiquitin proteasome system (UPS), which is one of the main cellular, protein

quality-control mechanisms that enzymatically labels, transports, and finally degrades misprocessed and misfolded proteins (de Vrij et al., 2004; Hol et al., 2005; Song et al., 2005). Pathological accumulation of aberrant proteins is common in numerous neurological disorders, including AD. With increased accumulation of ubiquitinated proteins and a mutant form of ubiquitin (UBB^{+1}), the activity of proteasome decreases in the AD brain (de Vrij et al., 2004; Hol et al., 2005; Oh et al., 2005; Song et al., 2005). An ubiquitin-conjugating enzyme, E2-25K/Hip-2, appears to be required for UBB^{+1}-mediated neurotoxicity in AD (Song et al., 2003). The UPS degradation controls nearly all of the important components of APP metabolism: Aβ, APP, β-secretase, γ-secretase, presenelin-1, presenelin-2, tau, and ApoE ε4 (de Vrij et al., 2004; Flood et al., 2005; Qing et al., 2004).

In a recent study of HEK293 and N2a cells transfected with human APP_{695}, resveratrol [0–40 μM], but not quercetin and catechin – the other two powerful antioxidants present in red wine – attenuated the levels of intracellular- and extracellular-secreted Aβ (sAβ40 and sAβ42) clearance, in a dose- and time-dependent fashion (Marambaud et al., 2005). More importantly, resveratrol did not attenuate any other components of the APP metabolism tested (full-length APP, sAPPa, or APP C-terminal fragments C99, C89, C83, and AICD), suggesting that resveratrol had no effect on the production of α, β, or γ-secretases or Aβ (Fig. 1, Section 4). Also, resveratrol did not affect Aβ degradation by four important metalloendopeptidases-neprilysin (NEP), endothelin-converting enzyme-1 and -2 (ECE-1, ECE-2), and insulin-degrading enzyme (IDE) (Marambaud et al., 2005). In the Marambaud et al. (2005), the proteasome inhibitors lactacystin, Z-GPFL-CHO, and YU101 significantly prevented resveratrol-induced inhibition of Aβ activity, and the siRNA-directed silencing of the proteasome β5 subunit also prevented resveratrol-induced attenuation of Aβ activity. Interestingly, resveratrol did not appear to increase the activity of proteasome directly. Thus, Marambaud et al. (2005) concluded that resveratrol affected proteasome-mediated degradation of Aβ through a mechanism that does not increase the total activity of the proteasome. Resveratrol analogues, such as trimethoxy-resveratrol and TMS, were also found to decrease the total secreted Aβ, but not as effectively as did resveratrol, suggesting that resveratrol modulates the UPS system by an unknown mechanism to promote Aβ degradation and that resveratrol may have great therapeutic value.

8. Influence of resveratrol on the arachidonic acid cascade from cPLA2

Cytosolic Ca^{2+}-dependent phospholipase A_2 ($cPLA_2$) regulates the release of arachidonic acid (AA) from membranes; in turn, AA functions as a second messenger or precursor for a cascade of cellular functions (Funk, 2001; Leslie, 1997). Outside the central nervous system, AA is known to mediate apoptosis induced by oxidative stress and TNF-α (Arai et al., 2001). A recent study with rat cortical neurons has shown that low concentrations (1 μM) of soluble Aβ1–40 and Aβ1–42-induced $cPLA_2$ activation triggered AA-mediated neuronal apoptosis, suggesting that neuronal death in AD can also be mediated by the $cPLA_2$/AA-cascade (Kriem et al., 2005) (Fig. 1, Section 5). In this study (Kriem et al., 2005), inhibitors of cyclooxygenase-2 (COX-2) reduced Aβ-induced cell death by 55%. When released in small quantities, both AA and nitric oxide (NO) regulated long-term potentiation in hippocampal neurons and functioned as both intra- and intercellular messengers, especially carrying retrograde information from postsynaptic to presynaptic nerve endings. Both Aβ and NO, when released in large amounts, however, triggered the $cPLA_2$/AA-cascade. In a recent study with synaptosomes from the cortex of rats, resveratrol treatment (100 μM) prevented the NO-induced $cPLA_2$/AA-cascade, highlighting a new therapeutic target for resveratrol in AD neurons (Chalimoniuk et al., 2006).

9. Bioavailability of resveratrol

Bioavailability has been broadly defined as the "*absorption and utilization of a nutrient*" (Krebs, 2001). Recent literature on bioavailability of flavonoids and other phytochemicals suggest that these polyphenols undergo extensive phase I (oxidation, reduction, and hydrolyses) and phase II (glucuronic acid, sulfate, and methyl conjugations) biochemical changes immediately after ingestion (Williamson and Manach, 2005). The extent to which the human colon can absorb and metabolize resveratrol depends on the metabolic activity of microflora in the intestine and the functions of liver. There is considerable person-to-person variation in drug absorption and metabolic processes (Vitaglione et al., 2005; Walle et al., 2004; Wenzel and Somoza, 2005; Wenzel et al., 2005). After oral or intravenous injection of resveratrol in humans, resveratrol was rapidly (within 2 h, with a peak in < 30 min) metabolized into both glucuronic acid and sulfate conjugations of the phenolic groups in liver and intestinal epithelial cells (Vitaglione et al., 2005; Walsh et al., 2005; Wenzel and Somoza, 2005; Wenzel et al., 2005). Total recoveries of glucuronic and sulfate conjugations of resveratrol in human urine and feces were about 71–98% after oral doses and 54–91% after intravenous doses, with near zero recovery for the original resveratrol in the form of aglycone (Vitaglione et al., 2005). These studies clearly indicate that the circulating form of resveratrol – which is the form that is presumed to modulate numerous cellular and biochemical effects – is predominantly the modified metabolite, not the original aglycone.

Resveratrol bioavailability studies need to address at least three major issues in the years to come. First, there is a need to define the biological effects of the circulating glucuronic and sulfate metabolites of resveratrol and their functions in AD brains. This issue is particularly important because the antioxidant role of resveratrol seems to be considerably diluted during the extensive and rapid metabolization that the original aglycone form of resveratrol undergoes. Interestingly, many cell culture studies in AD, have highlighted the importance of antioxidant properties of resveratrol. Second, because of the low bioavailability of the aglycone form of resveratrol, some recent studies seem to suggest that other flavonoids found in red wine may also contribute to the longevity effects associated with resveratrol or that these other flavonoids might modulate resveratrol functions synergistically, such that resveratrol may become bioavailable in

the presence of other flavonoids. In the human liver, for example, epicatechin gallate and epigallocatechin gallates can effectively inhibit sulfotransferases (Pacifici, 2004), suggesting that consumption of such additional polyphenols, in addition to resveratrol, can facilitate resveratrol bioavailability. For the time being, it is not clear how these synergistic mechanisms work, the nature of toxic effects of resveratrol, and the dosages of resveratrol needed for direct consumption via red wine or indirect consumption through food supplements. Systematic clinical studies involving a large number of human subjects are required to address these critical issues.

10. Summary

Alzheimer's disease is a debilitating dementia, and only a limited number of therapeutic options are currently available to treat this disease. Interestingly, dozens of herbal compounds appear to be useful in treating AD, but only few of them have been tested using human subjects in systematic clinical trials. Of the herbal compounds found to be useful in modulating AD pathomechanisms, red wine seems to have unique properties particularly worthy of extended study. Besides its antioxidant effects, resveratrol, as found in red wine, is believed to bear the effects of the French Paradox that has been popularly noted in epidemiological studies. In addition, both resveratrol and CR regimens have been found to trigger sirtuin proteins. Cardioprotection, chemoprotection against cancers, and antiaging benefits all seem to be mediated through resveratrol and CR-induced activation of sirtuin and other proteins. Protection against Aβ toxicity in AD brains is also modulated by sirtuins. The efficacy of resveratrol in treating AD pathology depends on the extent to which resveratrol metabolites become bioavailable and influence both sirtuin-dependent and -independent signaling pathways in humans, and also depends on the next generation of clinical testing and research that will need to study the effects of resveratrol on a large number of human subjects.

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