PROSPECTS
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Cellular and Molecular Effects of Resveratrol in Health and Disease

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ABSTRACT

Resveratrol, a natural polyphenol abundantly found in grape skins and red wine, possesses diverse biochemical and physiological actions, including anti-inflammatory, anti-oxidation, anti-proliferation and promotion of differentiation, and chemopreventive effects. Recently, it is attracting increased attention due to its health benefits, especially in common age-related diseases such as cardiovascular disease, cancer, type 2 diabetes, and neurological conditions. In this review, we discuss the latest cellular and molecular findings that account for the beneficial actions of resveratrol. J. Cell. Biochem. 113: 752–759, 2012.

KEY WORDS: RESVERETROL; AGING; CELLULAR EFFECT; SIGNAL TRANSDUCTION PATHWAY; SIRT1; P53

Resveratrol ($C_{14}H_{12}O_3$; 3,4′,5-trihydroxystilebene) is a natural polyphenol mainly found in grapes, red wine, peanuts, and other plants [Marques et al., 2009; Shakibaei et al., 2009]. Although these plants and their extracts have been used for various therapeutic purqposes by ancient cultures, resveratrol itself was first described in 1940 as a phenolic component of the medicinal herb hellebore (*Veratrum grandiflorum*) [Baur and Sinclair, 2006]. Little attention had been paid to it until its ability to reduce the incidence of coronary artery diseases (so-called "French paradox") was discovered. In recent years, diverse benefits to age-related diseases such as cardiovascular disease, cancer, type 2 diabetes, and neurological conditions have been described [Markus and Morris, 2008]. The aim of the present review is to highlight latest cellular and molecular findings that account for the beneficial actions of it.

STRUCTURE AND BIOLOGICAL EFFECTS

Resveratrol is a phytoalexin that in nature protects the plant from injury, ultraviolet (UV) irradiation, and fungal attack [Shakibaei et al., 2009]. Resveratrol exists as cis- and transisomeric forms, with trans to cis isomerization facilitated by UV exposure. Its stilbene structure is related to the synthetic estrogen diethylstilbestrol. Two phenol rings are linked by a styrene double bond to generate 3, 4′,5- trihydroxystilbene (Fig. 1).

Abbreviations: AA, arachidonic acid; AD, Alzheimer's disease; ADP, adenosine 5′-diphosphate; ANG II, angiotensin II; AP-1, activator protein-1; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; ERK, extracellular-signal-regulated protein kinases; ET-1, endothelin-1; GLUT-4, glucose transporter-4; GM-CSF, granulocyte macrophage-colony stimulating factor; HO-1, heme oxygenase-1; IL, interleukin; JNK, c-Jun N-terminal protein kinase; LDLs, low-density lipoproteins; LPS, lipopolysaccharide; MAPKs, mitogen-activated protein kinases; MAPKK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; NAD, nicotinamide adenine dinucleotide; NADPH, nicotinamide-adenine dinucleotide phosphate; NF-κB, nuclear factor kB; NO, nitrogen monoxidum; Nrf2, nuclear factor-E(2)- related factor-2; PC, protein carbonyl; PD, Parkinson's disease; PG, prostaglandin; PI3K, phosphoinositide-3-kinase; PKC, protein kinase C; ROS, reactive oxygen species; SERCA2a, sarcoplasmic calcium ATPase; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; TNF-α, tumor necrosis factor α; UV, ultraviolet; 6-OHDA, 6-hydroxydopamine.

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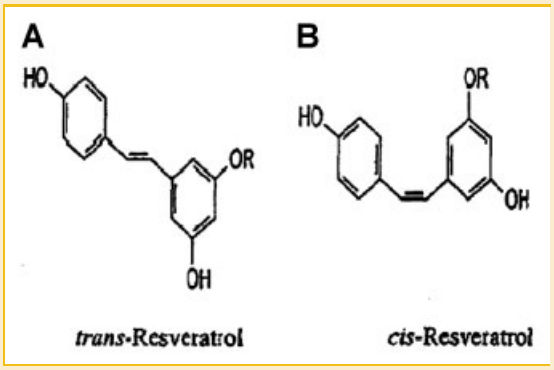

Fig. 1. Chemical structures of trans-resveratrol (A) and cis-resveratrol (B).

Many studies have demonstrated that resveratrol has a wide range of pharmacological properties, which has been suggested to be cardio-protective via various mechanisms such as its antioxidant activity [Fauconneau et al., 1997; Chen et al., 2009; Yu et al., 2009], anti-inflammation activity [Birrell et al., 2005; Chen et al., 2010], inhibition of platelet aggregation [Pace-Asciak et al., 1996], induction of nitrogen monoxidum (NO) production [Hsieh et al., 1999], and the ability to activate sirtuins, a class of nicotinamide adenine dinucleotide $(NAD)^+$-dependent deacetylases [Chen et al., 2009; Yu et al., 2009]. Resveratrol is also reported to have chemo-preventive activity; Jang et al. [1997] have suggested that it inhibits all three phases of tumor development: Initiation, promotion, and progression.

CARDIOVASCULAR PROTECTION

Epidemiological studies have revealed an inverse correlation between red wine consumption and the incidence of cardiovascular disease, a phenomenon commonly known as the "French Paradox", i.e., the fact that the incidence of myocardial infarction in France is about 40% lower than in the rest of Europe, despite a diet being traditionally rich in saturated fat [Renaud and de Lorgeril, 1992]. This led to the suggestion that resveratrol might be the active principle of red wine. Indeed, resveratrol protects the cardiovascular system by a large number of mechanisms including inhibition inflammatory response, promotion of vasorelaxation, anti-atherosclerotic properties, inhibition of low-density lipoprotein oxidation, and suppression of platelet aggregation (Fig. 2) [Hao and He, 2004; Saiko et al., 2008].

ANTIOXIDANT ACTIVITY

Oxidative stress has been shown to contribute to endothelial dysfunction and the development of atherosclerosis [Mietus-Snyder et al., 2000]. By attenuating hydrogen peroxide-induced cytotoxicity and intracellular accumulation of reactive oxygen species (ROS), resveratrol prevents oxidative stress [Jang and Surh, 2001; Liu et al., 2003; Chen et al., 2004; Leiro et al., 2004; Yu et al., 2009]. At a concentration of 1–100 μmol/l, resveratrol significantly inhibits

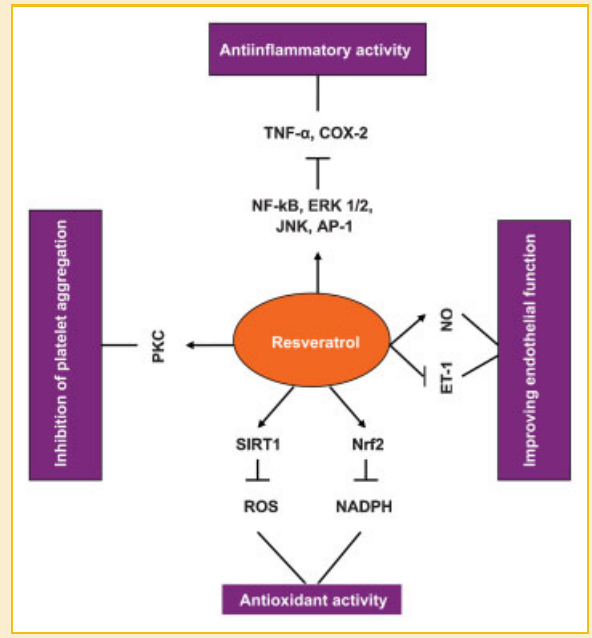

Fig. 2. Cellular and molecular effects of resveratrol in cardiovascular disease. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jcb]

intracellular and extracellular ROS production [Jang and Surh, 2001].

In addition, low-density lipoproteins (LDLs) play an important role in the formation of atherosclerotic plaques and in the endothelial inflammatory pathway [Fan et al., 2008]. Their oxidation is a main cause of endothelial injury and induction of the expression of pro-inflammatory molecules in endothelial cells. Notably, high plasma levels of very LDLs are associated with increased risk of atherosclerosis [Dichtl et al., 1999]; thus, removal of modified LDLs is important in the treatment of the inflammatory response. Resveratrol was found to protect lipids from peroxidative degradation [Bhavnani et al., 2001] and to stop the uptake of oxidized LDLs in the vascular wall in a concentration-dependent manner [Frémont, 2000]. Recent studies have demonstrated that dietary resveratrol can reduce aging- and exercise-induced oxidative damage and mitochondrial dysfunction [Ryan et al., 2010; Jackson et al., 2011; Sun et al., 2011].

Several mechanisms are postulated to explain the antioxidant activities of resveratrol. First, resveratrol has been reported to be a strong inhibitor of nicotinamide-adenine dinucleotide phosphate (NADPH)- and adenosine 5′-diphosphate (ADP)-Fe^+-lipid peroxidation and UV light-induced lipid peroxidation, and an efficient scavenger of radicals [Miura et al., 2000]. Stojanovic et al. [2001] found resveratrol to be an extremely efficient free radical scavenger in a model employing gammairradiation of liposomes. Resveratrol was 95% efficient at preventing lipid peroxidation, compared with ~65% for vitamin E and ~37% for vitamin C. Second, by targeting many intracellular molecules, resveratrol maintains cell viability and inhibits oxidation. The best known, however, is its ability to activate the sirtuin class of NAD^+-dependent histone deacetylases [Chen et al., 2009; Yu et al., 2009]. There are seven members of the

sirtuin class of enzymes in mammals—SIRT1 to SIRT7 [Baur and Sinclair, 2006]. Sirtuins regulate a number of intracellular pathways via the activation of transcription factors and enzymes responsive to nutrient availability. SIRT1 is the major sirtuin activated through both calorie restriction and resveratrol and mediates the beneficial effects of each on longevity and health [Brooks and Gu, 2009]. SIRT1 has been implicated in many vital processes, such as DNA repair, cell survival, gluconeogenesis, muscle cell differentiation, cell-cycle regulation, lipid metabolism, fat mobilization, and insulin sensitivity [Brooks and Gu, 2009]. Chen et al. [2009] reported that resveratrol inhibits hypoxia-induced apoptosis via the SIRT1–FoxO1 pathway in H9c2 cells. Resveratrol, via a pathway that involves the activation of SIRT1 and the upregulation of antioxidant defense mechanisms, attenuates mitochondrial reactive oxygen species (mtROS) production [Ungvari et al., 2009]. In addition to SIRT1, other sirtuins may have also involved in the antioxidant response. Recently, the studies by Yu et al. [2009] suggest that endogenous SIRT1,3,4,7 play an essential role in mediating cell survival in cardiac myocytes and resveratrol protects cardiomyocytes from oxidative stress-induced apoptosis by activating SIRT1,3,4,7. Third, various effects of resveratrol that may not involve in sirtuins. In cultured coronary arterial endothelial cells, resveratrol, in a dose-dependent manner, significantly increases transcriptional activity of nuclear factor-E(2)-related factor-2 (Nrf2) [Ungvari et al., 2010]. Accordingly, resveratrol significantly upregulates the expression of the Nrf2 target genes NAD(P)H: Quinone oxidoreductase 1, gamma- glutamylcysteine synthetase, and heme oxygenase-1 (HO-1) (29). Resveratrol treatment also significantly attenuated high glucose (30 mM)-induced mitochondrial and cellular oxidative stress [Ungvari et al., 2010].

ANTI-INFLAMMATORY ACTIVITY

Atherosclerosis is a chronic immuno-inflammatory disease, and pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-8, IL-13 and inflammatory mediators including histamine, leukotrienes, serotonin, prostaglandin (PG)E2 as well as PGD2 were involved in the development of atherosclerosis. TNF-α is a potent inducer of other inflammatory cytokines, including IL-1, IL-6, IL-8, and granulocyte macrophage-colony stimulating factor (GM-CSF) [Arend and Dayer, 1995; Butler et al., 1995]. There is considerable evidence demonstrating the anti-inflammatory properties of resveratrol, including inhibition of ROS in neutrophils, monocytes, and macrophages [Martinez and Moreno, 2000]. The release of various cytokines from macrophages and lymphocytes has been shown to be inhibited by resveratrol [Feng et al., 2002]. As early as 1999, Zhong et al. [1999] has demonstrated that resveratrol can significantly inhibition of the lipopolysaccharide (LPS)-induced synthesis of TNF-α and IL-1-β, and release of IL-6 from monocytes. Moreover, studies by Fulgenzi et al. [2001] reported that TNF-α–induced vascular permeability changes have been shown to be inhibited in vitro and in vivo by resveratrol. A recent study by Kang et al. [2010] demonstrate that resveratrol, at concentrations ranging from 0.1 to 10 μM, effectively inhibited LPS-induced TNF-α and IL-6 production with the downregulation of relative genes expression in macrophages.

In recent years, the important roles of cyclooxygenase (COX)-2 in various tumors and inflammatory diseases have been demonstrated [Kong et al., 2002]. COX-2 is strongly induced in activated monocytes and macrophages, one of the major mediators of inflammatory reactions. Subbaramaiah et al. [1998] indicated that resveratrol suppressed the synthesis of PGE2 by inhibiting COX-2 enzyme activity. Recently, Kang et al. [2009] demonstrated that resveratrol significantly attenuated COX-2 expression and inhibited inflammatory cytokines such as TNF-α, IL-6, and IL-8.

Inflammation involves a complex web of cytokine signals, as well as other components of signaling networks that include several kinases, such as mitogen-activated protein kinases (MAPKs), protein kinase C (PKC), phosphoinositide-3-kinase (PI3K), etc. [de la Lastra and Villegas, 2005]. MAPKs are activated by translocation to the nucleus, where they phosphorylate a variety of target transcription factors, including nuclear factor kB (NF-κB) and activator protein-1(AP-1) [Kundu and Surh, 2004]. NF-κB is a transcription factor for genes involved in cell survival, cell adhesion, inflammation, differentiation, and growth, which is activated by a variety of stimuli, such as carcinogenesis, inflammatory agents, such as TNF-α and H_2O_2, and tumor promoters [Dorai and Aggarwal, 2004]. Extensive research during the last few years has shown that most inflammatory agents mediate their effects through the activation of NF-κB and that most anti-inflammatory agents suppress NF-κB activation [de la Lastra and Villegas, 2005]. Resveratrol suppressed the expression of TNF-α, IL-6, IL-8, and COX-2 through a decrease in the intracellular levels of Ca^{2+} and extracellular-signal-regulated protein kinases (ERK 1/2), as well as activation of NF-κB [Csaki et al., 2009; Kang et al., 2009]. Treatment with resveratrol suppressed NF-κB-regulated gene products involved in inflammation (COX-2, matrix metalloproteinase (MMP)-3, MMP-9, vascular endothelial growth factor), inhibited apoptosis (Bcl-2, Bcl-xL, and TNF-α receptor-associated factor 1) and prevented activation of caspase-3 [Csaki et al., 2009].

AP-1 is another transcription factor that regulates the expression of several genes that are involved in cell differentiation and proliferation. AP-1 activation can upregulate genes, such as IL-8, among others. Most agents that activate NF-κB also activate AP-1 [Karin et al., 1997; Pervaiz, 2003]. Resveratrol has been shown to inhibit TNF-induced activation of AP-1 [Manna et al., 2000]. The activation of AP-1 is mediated by c-Jun N-terminal protein kinase (JNK) and the upstream kinase MEK (mitogen-activated protein kinase kinase or MAPKK) [Karin and Delhase, 1998]. TNF-induced activities of JNK and MEK were inhibited by resveratrol, thus providing a possible mechanism for AP-1 inhibition [Manna et al., 2000]. Resveratrol downregulate of AP-1 activity are miR-663 and dose dependent [Tili et al., 2010].

INHIBITION OF PLATELET AGGREGATION

Inappropriate platelet activation is another major contributor in the process of atherosclerosis. Platelets stick to the endothelial surface of blood vessels; they can activate the process of thrombus formation and their aggregation could set into motion the process of vascular occlusion. Platelets have also been linked to the synthesis of eicosanoids from arachidonic acid (AA) that contributes to platelet adhesion [Frémont, 2000]. Crescente et al. [2009] found that

resveratrol inhibited AA-induced platelet aggregation. Resveratrol at 25, 50, and 100 μM showed anti-platelet aggregation and inhibition of surface P-selectin-positive platelets in a concentration-dependent manner [Yang et al., 2008b]. Resveratrol (50 μM) inhibited the activity of PKC in the membrane fraction of platelets and decreased the percentage of membrane associated PKC activity in total PKC activity [Yang et al., 2008a]. In human platelet suspension resveratrol at relatively low concentrations (2 or 5 μM), which did not affect platelet function, significantly enhanced the inhibitory activity of PGs on platelet aggregation caused by collagen [Wu et al., 2007]. The mechanisms underlying this effect may be associated with the inhibition of PKC activation and protein tyrosine phosphorylation.

IMPROVING ENDOTHELIAL FUNCTION

One function of endothelial cells is to maintain a balance between vasodilators, like NO, and vasoconstrictors, such as endothelin-1 (ET-1) [Kinlay et al., 2001; Davignon and Ganz, 2004]. Their cooperation provides endothelial cell wall thromboresistance and prevents atherogenesis.

ET-1, a primary antecedent in coronary heart diseases, enhanced MAPK activity, phosphorylation and nuclear translocation. Resveratrol remarkably attenuated basal and ET-1-evoked protein tyrosine phosphorylation [El-Mowafy and White, 1999]. With administration of resveratrol, plasma ET-1 levels statistically decreased, in parallel with a significant elevation in NO levels [Zou et al., 2003]. Resveratrol inhibits strain-induced ET-1 gene expression, partially by interfering with the ERK1/2 pathway through attenuation of ROS formation [Liu et al., 2003]. Resveratrol also inhibits angiotensin II (ANG II)-induced cell proliferation and ET-1 gene expression, and does so in a manner which involves the disruption of the ERK pathway via attenuation of ROS generation [Chao et al., 2005].

Resveratrol also shows the ability to regulate the production of vasodilators. It has been shown that impaired production or activity of NO leads to vasoconstriction, platelet aggregation, and oxidative stress [Endres et al., 1998; Rubbo et al., 2002]. In isolated cells, resveratrol prevents the generation of NO [Cavallaro et al., 2003], which may be due to the fact that this compound could downregulate the protein expression or inhibit the activity of inducible NO synthase [Tsai et al., 1999; Lorenz et al., 2003; Donnelly et al., 2004]. The resveratrol modulation of the NO system and its ability to increase the levels of cyclic guanosine monophosphate (cGMP) in intact vascular tissue by influencing the endothelium-derived relaxing factor-NO-GMP system reinforces its positive effects on the cardiovascular system [Wang et al., 2007]. However, the property of resveratrol as a vasodilator is still poorly defined.

CANCER

Resveratrol has been reported to inhibit all three phases of tumor development: Initiation, promotion, and progression in various cancers (Table I). The induction of apoptosis is a key mechanism for most anti-tumor therapies. Resveratrol possess strong anti-proliferative properties in many cultured cancer cell lines, and acts both by arresting cell cycle and by inducing apoptosis [Bai et al., 2010; Gatouillat et al., 2010; Jiang et al., 2010; Kweon et al., 2010; Vanamala et al., 2010; Wang et al., 2010], but the apoptosis-inducing effects of resveratrol seemed diverse on different tumor cells [Bai et al., 2010; Gatouillat et al., 2010; Jiang et al., 2010; Kai et al., 2010; Kweon et al., 2010; Sun et al., 2010; Vanamala et al., 2010; Wang et al., 2010].

Resveratrol has been shown to interfere with signal transduction pathways, to modulate cell cycle regulating proteins and to induce apoptosis in multiple cancer cell lines with various mechanisms, including through a p53-dependent pathway and PKC/Akt pathway [Bai et al., 2010; Banerjee Mustafi et al., 2010; Gatouillat et al., 2010; Jiang et al., 2010; Kai et al., 2010; Sun et al., 2010; Vanamala et al., 2010]. The proapoptotic protein nuclear factor p53 plays a key role in protecting a cell from tumorigenesis, halting the cell cycle or initiating apoptosis if the cell is damaged. Mutations in p53 leading to its inactivation have been found in many human cancers, including brain tumors. Resveratrol initiates p53-dependent apoptosis in human cancer cells, including prostate cancer, colon cancer, and melanoma [Gatouillat et al., 2010; Kai et al., 2010; Vanamala et al., 2010]. In cultured K562 cells, resveratrol-activated PKC and ERK1/2 caused p53 phosphorylation and apoptosis [Banerjee Mustafi et al., 2010]. Resveratrol also inhibits cell proliferation and induction of G1/S growth arrest through the suppression of cyclin D1 expression, which may contribute to the

TABLE I. Effects of Resveratrol on Various Human Cancers in 2010

Modes	Cell lines used	Molecular targets	Cellular effect	Refs.
Prostate cancer	PCa cells	p53, MTAI/NuRD, p21, Bax	Apoptosis	Kai et al. [2010]
	LNCaP	G1/S, Cyclin-dependent kinase inhibitor 1A and B	Apoptosis, Cell cycle	Wang et al. [2010]
Medulloblastoma	UW228-3	Brain-associated SULTs	Intracellular bioavailability	Shu et al. [2010]
Leukemia	K562	Unfolded protein response (UPR), G1	Cell cycle arrest, Cell proliferation	Liu et al. [2010]
	AML-2	MRP1	Apoptosis, Cell cycle arrest	Kweon et al. [2010]
	K562	Akt, ERK1/2, Hsp70	Apoptosis	Banerjee Mustafi et al. [2010]
	CML cells	JNK/p62, AMPK	Autophagy	Puissant et al. [2010]
Breast cancer	MCF-7	BRCA-1	DNA strand breaks	Papoutsis et al. [2010]
Colon cancer	HT-29, SW480	IGF-1R/Alct/Wbt, p53	Apoptosis, Cell proliferation	Vanamala et al. [2010]
Bladder cancer	T24	p21, cyclin D1, MAPK/Akt	Apoptosis, Cell cycle arrest	Bai et al. [2010]
Glioma cells	U251	LDH, Akt, Caspase-3	Cell proliferation, Apoptosis	Jiang et al. [2010]
Melanoma	B16/DOX	G1/S, cyclin D1/cdk4, p53	Cell cycle arrest, Apoptosis	Gatouillat et al. [2010]
Endometrial cancer	HEC1B	β-arrestin 2, Akt/GSK3	Apoptosis	Sun et al. [2010]
Hepatocarcinoma	HepG2, Hep3B	MMP-2, MMP-9, TIMP-1, TIMP-2	Anti-invasive activity	Weng et al. [2010]

apoptotic cell death process [Bai et al., 2010; Gatouillat et al., 2010; Wang et al., 2010].

TYPE 2 DIABETES

Resveratrol also possess significant anti-diabetic activity. Palsamy and Subramanian, [2009] reported that resveratrol administration to diabetic rats improved hepatic glycogen content suggesting the anti-hyperglycemic potential of it. Resveratrol significantly improved not only glucose metabolism and oxidative injury but also impaired vascular responses in streptozotocin (STZ) induced diabetic rats [Zhang et al., 2009]. Treatment with resveratrol exhibits significant anti-diabetic potential by attenuating hyperglycemia, enhancing insulin secretion and antioxidant competence in pancreatic beta-cells of diabetic rats [Palsamy and Subramanian, 2010]. The effect of resveratrol is non-insulin dependent and triggers some of the similar intracellular insulin signaling components in myocardium such as eNOS, Akt through AMPK pathway and also by regulating the caveolin-1 and caveolin-3 status that might play an essential role in glucose transporter-4 (GLUT-4) translocation and glucose uptake in STZ-induced type-1 diabetic myocardium [Penumathsa et al., 2008]. Moreover, resveratrol alleviated diabetes mellitus-induced vasculopathy through attenuation of advanced glycation end product-receptor for advanced glycation end product-NF-κB signaling pathway [Jing et al., 2010]. Resveratrol also prevented diabetes-induced retinal ganglion cells death via Ca^{2+}/calmodulin-dependent protein kinase II down-regulation, implying that resveratrol may have potential therapeutic applications for prevention of diabetes-induced visual dysfunction [Kim et al., 2010]. Treatment of resveratrol prevents the decrease in the expression of SIR2 and increase in p38, p53 expression and dephosphorylation of histone H3 in diabetic kidney [Tikoo et al., 2008]. Resveratrol prevents memory deficits and the increase in acetylcholinesterase activity in STZ-induced diabetic rats [Schmatz et al., 2009]. A recent study gives insight into the possible role of resveratrol as a modulator of SIRT1, and enhances expression of reduced sarcoplasmic calcium ATPase (SERCA2a) and improves cardiac function in chronic type 1 diabetes [Sulaiman et al., 2010].

NEUROLOGICAL CONDITIONS

Accumulating experimental and epidemiological evidences have documented that resveratrol can exert protective activity against a number of neurodegenerative disorders (e.g., Alzheimer's and Parkinson's diseases, multiple sclerosis, amyotrophic lateral sclerosis). Many studies highlighted that this polyphenol could exert beneficial effects on cells not only through their antioxidant potential but also through the modulation of different pathways such as signaling cascades, anti-apoptotic processes, or the synthesis/ degradation of the amyloid β peptide (Fig. 3).

Epidemiologic studies have demonstrated moderate consumption of wine is associated with a lower incidence of Alzheimer's disease (AD) and improved neuropathology in a mouse model of the disease [Wang et al., 2006]. Marambaud et al. [2005] showed that resveratrol (20–40 μM) could markedly reduce the levels of secreted and intracellular amyloid-β peptides through promoting their clearing by proteosomal degradation. SIRT1 are implicated in the protection against AD as well as amyotrophic lateral sclerosis [Anekonda, 2006; Kim et al., 2007]. In addition, in wallerian degeneration slow mice, resveratrol has been shown to be protective against axotomy neuronal degeneration by enhancing SIRT2-mediated tubulin deacetylation [Suzuki and Koike, 2007]. However, conflicting results have been obtained by Karuppagounder et al. [2009]. Dietary supplementation with resveratrol protects against β-amyloid plaque formation and oxidative stress without detectable activation of SIRT1 [Karuppagounder et al., 2009]. Therefore, because resveratrol can activate SIRTs, it may have therapeutic potential in the management of AD and other neurologic diseases; however, further studies are needed.

Resveratrol may also be useful in dampening the excitatory neurotransmitter toxicity associated with glutamate and in dopaminergic neurodegenerative disorders such as Parkinson's disease (PD). This was illustrated by pretreating SH-SY5Y (human neuroblastoma) cells with resveratrol, which resulted in an inhibition

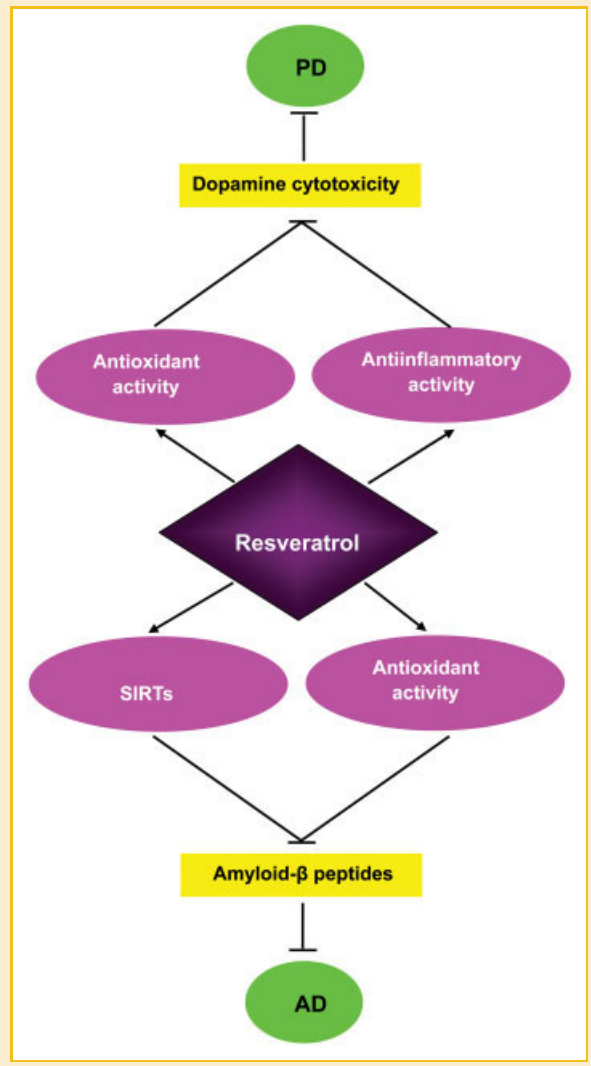

Fig. 3. Resveratrol exert protective activity against AD and PD via various mechanisms such as its antioxidant activity, anti-inflammation activity, and the ability to activate sirtuins. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jcb]

of dopamine cytotoxicity [Lee et al., 2007]. Jin et al. [2008] demonstrate that resveratrol exerts a neuroprotective effect on 6-hydroxydopamine (6-OHDA)-induced PD rat model, and this protection is related to the reduced inflammatory reaction. In addition, resveratrol was also found to be successful in upregulating the antioxidant status and lowering the dopamine loss [Khan et al., 2010]. Conversely, the elevated level of thiobarbituric acid reactive substances (TBARS), protein carbonyl (PC), and activity of phospholipase A2 in 6-OHDA group was attenuated significantly in resveratrol-pretreated group when compared with 6-OHDA-lesioned group.

SUMMARY AND PERSPECTIVES

All these studies demonstrate that resveratrol may have a potential against cardiovascular disease, cancer, diabetes, and neurodegenerative disorder. It may also interfere with normal physiological processes such as aging. However, further studies are required to clarify some discrepancies found in the literature. In addition, despite a large body of evidence demonstrating promising effects in rodents, human studies are still lacking and both preventive and therapeutic value of resveratrol in humans remains to be elucidated. Furthermore, resveratrol analogues with improved pharmacokinetic and pharmacodynamics will also make the field move forward. Safety during long-term administration, combined with its cost and future therapeutic potential, makes it an ideal agent for both prevention and therapy of chronic illnesses either alone or in combination with other drugs.

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