Resveratrol: A Therapeutic Approach to Neurodegenerative Diseases and Aging

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Abstract: Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenol present in black grapes and its derivatives. Several reports have shown that resveratrol can prevent or slow the progression of a wide variety of illnesses, including cancer, cardiovascular disease and ischemic injuries as well as enhances stress resistance and extends the lifespan of various organisms from yeast to mammals. The mechanism by which resveratrol exerts such a range of beneficial effects across species and disease models is not yet clear, although at the beginning it was proposed that the antioxidant properties of this drug may explain the majority of its beneficial effects. Another mechanism by which resveratrol could combat tumour formation is induction of cell cycle arrest and apoptosis. The last protective mechanism related with resveratrol is its role as activator of sirtuin 1. Resveratrol increases the affinity of sirtuin 1 for its acetylated substrates, possibly inducing a conformational change of the enzyme. The axis sirtuin 1/PGC-1 activated by the resveratrol is a signalling pathway involved in several cellular contexts and tissues, each of the actors involved may promote a separate slow down in the neurodegenerative process. This neuroprotective action is very likely due the fact that the central factor of this signal, PGC-1, promotes mitochondrial activity while neurodegenerative diseases are linked to mitochondrial failures. It is strongly suggested that the activation of the axis sirtuin 1 /PGC-1 by resveratrol could be a key feature of the mechanisms of neuroprotection by this polyphenol and give birth to new therapeutic prospects.

Keywords: Oxidative stress, cell cycle, sirtuin 1.

RESVERATROL

Resveratrol (3,5,4′-trihydroxystilbene) was first isolated from the roots of white hellebore (*Veratrum grandiflorum O. Loes*) in 1940 and later, in 1963, from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine. Initially characterized as a phytoalexin, resveratrol, a polyphenol present in black grapes and its derivatives, attracted little interest until 1992, when it was postulated to explain some of the cardioprotective effects of red wine. Since then, dozens of reports have shown that resveratrol can prevent or slow the progression of a wide variety of illnesses, including cancer, cardiovascular disease and ischaemic injuries as well as enhance stress resistance and extend the lifespan of various organisms from yeast to vertebrates [1, 2]. Recent reports indicate that resveratrol treatment alone has a range of beneficial effects in mice but does not increase the longevity of ad libitum-fed animals when started midlife in contrast to high-fat diet-fed mice [2-4].

ANTIOXIDANT PROPERTIES OF RESVERATROL

The mechanism by which resveratrol exerts such a range of beneficial effects across species and disease models is not yet clear [5], although at the beginning it was proposed that the antioxidant properties of this drug may explain the majority of its beneficial effects. Attempts to show favourable effects *in vitro* have met with almost universal success, and have led to the identification of multiple direct targets for this compound. However, results from pharmacokinetic studies indicate that circulating resveratrol is rapidly metabolized, and cast doubt on the physiological relevance of the high concentrations typically used for *in vitro* experiments [6, 7]. Further experiments are needed to show whether resveratrol or its metabolites accumulate sufficiently in tissues to recapitulate *in vitro* observations, or whether alternative higher-affinity targets, such as quinone reductase 2 (QR2), have the key roles in its protective effects [8, 9]. *In vivo* results have therefore become increasingly important in the attempts to understand how resveratrol is effective in the treatment of different diseases. It is also unclear what conclusion should be drawn from the studies described so far.

In reference to antioxidant action of resveratrol, it is widely accepted that resveratrol exert antioxidant effects, but it is not yet clear if this is primarily a direct scavenging effect or the result of the activation of pathways that up regulate cells' natural antioxidant defences. Reactive oxygen species (ROS) have been shown to have a role in the initiation and progression of cancer through directly damaging DNA and other macromolecules. In addition to its possible modulation of antioxidant enzymes involved in the Phase II response, resveratrol has an intrinsic antioxidant capacity that could be related to its chemopreventive effects. *In vivo*, resveratrol has been shown to increase plasma antioxidant capacity and decrease lipid peroxidation; however, it is difficult to assess whether these effects are direct, or the result of up regulating endogenous antioxidant enzymes. In addition, clinical trials of antioxidant molecules have yielded disappointing results, suggesting that phytochemicals could possess other properties that are more relevant to cancer prevention. Oxidation of low-density lipoprotein (LDL) particles is strongly associated with the risk of coronary heart disease and myocardial infarction. Resveratrol prevents LDL oxidation *in vitro* by chelating copper, as well as by directly scavenging free radicals (although other components of red wine are superior free radical scavengers) [10]. Treatment of normal rats with resveratrol does not affect lipid peroxidation, as reflected by the presence of thiobarbituric acid-reactive substances [11]. However, resveratrol can be detected in LDL particles from humans after consumption of red wine, rich in this compound, and the pure compound prevents increases in lipid peroxidation that are induced by tumours or UV irradiation [12, 13], in addition to blocking gentamicin-induced nephrotoxicity [14]. In stroke-prone, spontaneously hypertensive rats, resveratrol significantly reduces markers of oxidative stress

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such as glycated albumin in serum, and 8-hydroxyguanosine in urine [15]. Furthermore, in guinea pigs, resveratrol induces the activities of QR2 and catalase in cardiac tissue, and decreases the concentration of ROS generated by menadione [16]. These results indicate that resveratrol can suppress pathological increases in the peroxidation of lipids and other macromolecules *in vivo*, but whether the mechanism is direct, indirect, or both is not yet clear.

RESVERATROL AND CONTROL OF CELL CYCLE

Another mechanism by which resveratrol could combat tumour formation is induction of cell cycle arrest and apoptosis. The anti-proliferative and pro-apoptotic effects of resveratrol in tumour cell lines have been extensively documented *in vitro* and are supported by down regulation of cell cycle proteins and increases in apoptosis in tumour models *in vivo*. Although resveratrol has been found to target leukaemic cells preferentially *in vitro* in some studies, the specificity of these effects remains unclear as others have found that resveratrol inhibits growth and induces apoptosis in normal haematopoietic cells at similar doses. Some level of specificity could arise from the apparent increased susceptibility of cycling cells to the effects of resveratrol [17]. A more precise mechanism by which resveratrol could act is sensitization of tumour cells to other inducers of apoptosis. Resveratrol has been shown to sensitize several tumour lines, but not normal human fibroblasts, to TRAIL (tumour necrosis factor-related apoptosis-inducing ligand)-induced apoptosis. It remains to be seen whether the pro-apoptotic effects of resveratrol *in vivo* are related to these *in vitro* observations, or secondary to other effects, such as inhibition of angiogenesis.

RESVERATROL MEDIATES INCREASE IN LIFESPAN

The last protective mechanism related with resveratrol is its role as activator of sirtuin 1. The benefits of resveratrol, as we commented above, can be explained by its antioxidant properties or better if this substance acts through a specific genetic pathway that has evolved to increase disease- and stress-resistance. With regard to the latter proposal, there is already a wide evidence for the existence of health-promoting pathways that are activated by caloric restriction. It has been known since the 1930s that a severe lowering of caloric intake dramatically slows the rate of ageing in mammals and delays the onset of numerous diseases of ageing, including cancer, cardiovascular disease, diabetes and neurodegeneration. It is an attractive hypothesis that resveratrol might use the same pathways activated by caloric restriction in mammals, as it appears to do in lower organisms; however, proving this hypothesis will require a better understanding of these processes.

Resveratrol increases the affinity of sirtuin 1 for its acetylated substrates, possibly inducing a conformational change of sirtuin 1 [18]. The rat brain has receptors for polyphenols such as resveratrol. This indicates that this substance and its derivatives can pass the blood-brain barrier and several studies suggest it may have a protective effect in some neurodegenerative processes, as we will describe below in extends. Hence, the axis sirtuin 1/PPARγ coactivator-α (PGC-1) activated by the resveratrol (Fig. **1**) is a signalling pathway involved in several cellular contexts and, each of the actors involved may promote a separate slow down in the neurodegenerative process [19]. This neuroprotective action is very likely due the fact that the central factor of this signal, PGC-1, promotes mitochondrial activity while neurodegenerative diseases are linked to mitochondrial failures. It is strongly suggested that the activation of the axis sirtuin 1/PGC-1 by resveratrol could be a key feature of the mechanisms of neuroprotection by this polyphenol and give birth to new therapeutic prospects (Fig. **1**).

RESVERATROL AND NEURODEGENERATIVE DISEASES

Using the neurotoxin 3-nitropropionic acid, a mitochondrial complex II inhibitor and a well established experimental model of Huntington's disease, it have been reported that the beneficial effects of resveratrol against this neurotoxin might be attributed to its antioxidant activity [20]. However, several findings have converged on the notion that sirtuin 1's neuroprotective effect could be extended to degenerating neurons. Parker and co-workers [21] showed

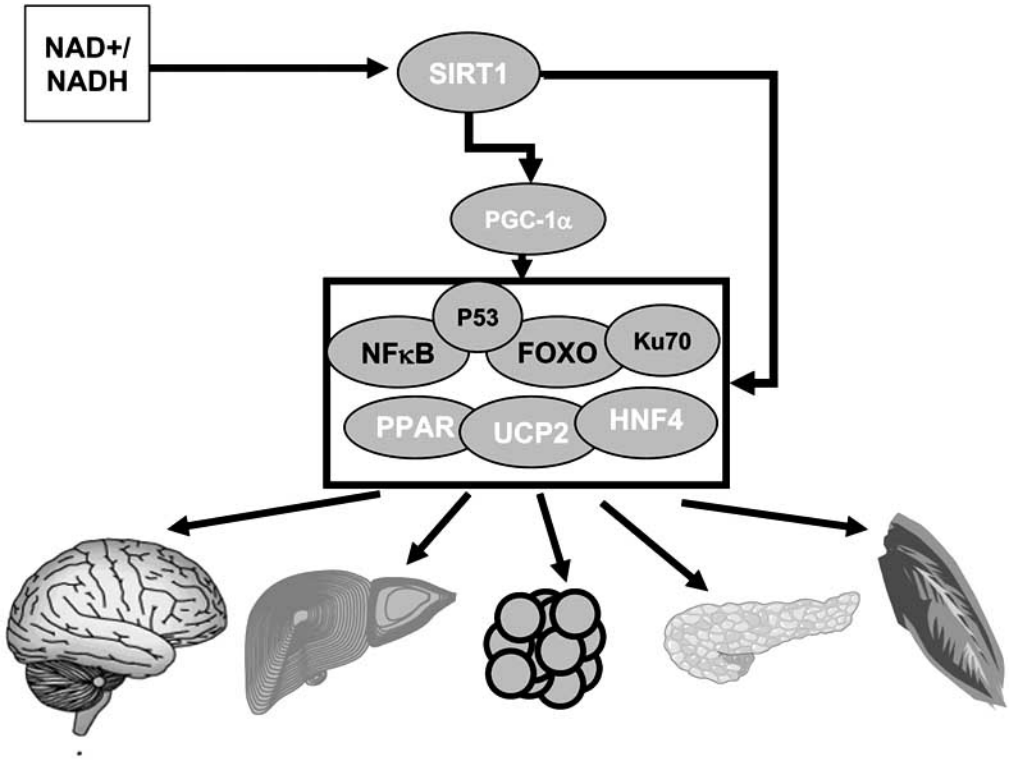

Fig. (1). Representative image of sirtuin1/PGC-1 crossroad and the tissues implicated in its regulation.

that resveratrol, acting through Sir2 and sirtuin 1 activation respectively, protected *C. elegans* and mouse neurons against the cytotoxicity of the mutant polyglutamine protein huntingtin. Huntingtin is the product of the gene mutated in the hereditary neurodegenerative disorder Huntington's disease, whose expansion of a polyglutamine stretch resulted in a mutant polypeptide that could form cytotoxic aggregates in neurons [22]. Although *C. elegans* has no huntingtin orthologue, over-expression of a huntingtin fragment in touch receptor neurons resulted in a gain-of-function mechanosensory defect that could model the disease. Both resveratrol and an increased sir-2.1 gene dosage alleviated the worm neuronal dysfunction in a DAF16-dependent manner. Furthermore, resveratrol decreased cell death associated with neurons cultured from a mutant huntingtin (109Q) knocking mice, in a manner that is reversible by two sirtuin 1 inhibitors, sirtinol and nicotinamide [23].

On the other hand a link between sirtuin 1 and Alzheimer's disease (AD) is also increasingly evident [24, 25]. The amyloid hypothesis [26] depicts that extracellular plaques consist of aggregated beta-amyloid (ßA) peptide generated from proteolytic cleavages of the amyloid precursor protein (APP) as the etiological agent of AD pathology [27]. Both intracellular and extracellular soluble oligomeric forms of ßA could in fact initiate synaptic malfunctions and the onset of AD symptoms [28, 29]. Nuclear factor κB (NF-κB) signalling in microglia is known to be critically involved in neuronal death induced by ßA peptides [30]. Chen and collaborators [31] showed that stimulation of microglia with ßA increased acetylation of RelA/p65 subunit of NF-κB at lysine 310. Over-expression of sirtuin 1 and resveratrol treatment markedly reduced NF-κB signalling stimulated by ßA and had strong neuroprotective effects. This result connects the known role of sirtuin 1 in modulating NF-κB activity [32] with AD. It should be kept in mind that for AD, as with other neurodegenerative diseases, the beneficial effect of resveratrol is multifaceted. Its immediate effect is more likely associated with its activity as an antioxidant [33, 34], but at a more extended time frame, its activation of sirtuin 1 and modulation of NF-κB signalling may result in other beneficial effects, such as anti-inflammation.

Another possible link between sirtuin 1 and AD came from the potential benefits of calorie restriction (CR) on AD symptoms and progression. It is well known in the epidemiology of neurodegenerative diseases that the incidence of sporadic Parkinson's disease (PD) and AD are both correlated with multiple genetic factors, diet and social behaviour [35]. High calorie diets are associated with the risk of AD, and CR has been proposed to protect against both PD and AD [36]. Firmer evidence for this idea was obtained when Patel [37] showed that short-term CR substantially decreased the accumulation of ßA plaques in two AD-prone APP/presenilin transgenic mice lines, and also decreased gliosis marked by astrocytic activation. In another study, Passinetti and colleagues [38] also showed that a CR dietary regimen prevents ßA peptide generation and neuritic plaque deposition in the brain of another mouse model of AD (Tg2576 mice). In this latter study, the authors suggested that CR resulted in the promotion of APP processing *via* the non-amyloidogenic α-secretase-mediated pathway. They observed a larger than two fold increase in the concentration of brain sAPPα (a product of α-secretase cleavage) and a statistically significant 30% increase in ADAM10 (a putative α-secretase) levels in CR animals compared to control. There also appeared to be a moderate increase in the levels of the insulin degrading enzyme, which has been associated to brain amyloid clearance [39]. In another recent report, the same group showed that CR resulted in reduced contents of ßA in the temporal cortex of squirrel monkeys, in a manner that was inversely correlated with sirtuin 1 protein concentrations in the same brain region [40]. It is not particularly clear in the above reports whether CR's effects in attenuating amyloid production were mediated through sirtuin 1 activation. Recent evidence suggests that this may indeed be the case, and may actually involve a novel signalling crosstalk [41].

More controversial is the relation ship among activation by resveratrol and PD. As it is well known PD is a neurodegenerative disease that is also characterized at the clinical level by bradykinesia, tremor and rigidity, and at the cellular level by a loss of dopamine neurons of the grey matter, and the frequent presence of intraneuronal inclusions named Lewy bodies, mainly composed of fibrillar α-synuclein [42]. Like AD, the familial form of PD concerns only a small proportion of patients (10%). The majority of them are suffering from a sporadic form and, if the genetic causes are fairly well identified, the reasons for the emergence of the sporadic contrary are still unclear. The involvement of mitochondrial dysfunction in the PD has been established for over two decades when it was discovered that the administration of 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP), causes the emergence of parkinsonism in laboratory animals but also in humans, through its active metabolite ion MPP^+, which inhibits the complex I of the chain of mitochondrial electron transport. It is well known that complex I is the major source of production of free radicals, the assumption is that the alteration of its functions could, beyond the declining production of ATP, give rise to increased oxidative stress, explaining the emergence of the disease. However, different authors working in different PD models conclude that sirtuin 1 activation does not play a major role in the protective effect of resveratrol against MPP^+ cytotoxicity, because sirtuin inhibitors such as nicotinamide and sirtinol did not counteract neuroprotection by resveratrol [43]. Instead, all works point to propose that antioxidative actions are responsible for neuroprotection by resveratrol against MPP^+ [43, 44]. However, it has been recently described that genetic inhibition of SIRT2 *via* small interfering RNA rescued α-synuclein toxicity [45]. Furthermore, the inhibitors of this enzyme protected against dopaminergic cell death both *in vitro* and in a Drosophila model of Parkinson's disease, and found that inhibition of SIRT2 rescued α-synuclein toxicity and modified inclusion morphology in a cellular model of PD [45]. However, increased sirtuin 1 expression or activity delays the toxic effects induced by α-synuclein, the protein that forms insoluble aggregates in several age-onset pathologies including PD. Resveratrol could be an interesting candidate for potential application in the treatment of PD only by its antioxidant properties [43].

Numerous studies have raised the possibility that resveratrol might be useful in protecting against brain damage following cerebral ischemia. Laboratory animals given intraperitoneal injections of resveratrol showed less motor impairment and significantly smaller infarct volume jointly with decreased delayed neuronal cell death and glial cell activation after ischemia. Similar effects were observed in wild-type, but not peroxisome proliferator-activated receptor-α–/– (PPARα–/–), mice [46]. Resveratrol administered intraperitoneally also prevented seizures induced by FeCl3, kainic acid [47] or pentylenetetrazole [48], and partially restored cognition in rats receiving streptozotocin intracerebroventricularly [49]. These results indicate that resveratrol is capable of penetrating the blood–brain barrier and exerts strong neuroprotective effects, even at low doses, after stroke or neurotoxin injured brain. Moreover, more studies are necessary to determine if these neuroprotective effects are mediated trough the stimulation of sirtuin 1 or by its antioxidant properties (1).

MODULATION BY RESVERATROL IN AGEING

As mentioned, in yeast, worms and flies, extra copies of the genes that encode sirtuins are associated with extended lifespan [50-52]. Inbred knockout mice that lack sirtuin 1 show developmental defects, have a low survival rate and have a significantly shorter lifespan compared with wild-type mice, although out

breeding seems to improve the phenotype significantly [53]. It has been postulated that the main function of sirtuin proteins might be to promote survival and stress resistance in times of adversity [54]. An evolutionary advantage arising from the ability to modify lifespan in response to environmental conditions could have allowed these enzymes to be conserved as species evolved, and to take on new functions in response to new stresses and demands on the organism. This could explain why the same family of enzymes has dramatic effects on lifespan in different organisms with seemingly dissimilar causes of ageing [55]. CR and intermittent fasting are implicated in most of the theories for successful brain aging [56]. The data from lower organisms have provoked intense research into the function of sirtuin proteins in mammalian systems. An *in vitro* screen for activators of sirtuin 1 identified resveratrol as the most potent of 18 inducers of deacetylase activity [57]. Subsequent work has shown that resveratrol extends the lifespans of *Saccharomyces. cerevisiae*, *Caenorhabditis elegans* and *Drosophila melanogaster*, but only if the gene that encodes Sir2 is present in these organisms. More recently, resveratrol was shown to extend the maximum lifespan of a species of short-lived fish by up to 59%, concomitant with the maintenance of learning and motor function with age and a dramatic decrease in aggregated proteins in elderly fish brains [58]; however, the extent to which this effect is Sir2-dependent, if at all, is not known. Moreover, resveratrol consistently recapitulates the protective effects of sirtuin 1 overexpression in cell culture, and Sir2/sirtuin 1 have been shown to be essential mediators of effects on adipogenesis, NF-κB acetylation, protection from mutant huntingtin protein, and lifespan extension in lower organisms [21, 50, 51, 59]. The question of whether enhanced sirtuin 1 activity and/or resveratrol treatment will increase mammalian lifespan looms large in the aging-research community.

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REFERENCES

[1] Baur, J. A., Sinclair, D.A. Therapeutic potential of resveratrol: the *in vivo* evidence. *Nat. Rev. Drug Discov.*, **2006**, *5*(6), 493-506.

[2] Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P.J., Poosala, S., Becker, K.G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.G., Lakatta, E.G., Le Couteur, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., Sinclair, D.A. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*, **2006**, *444*(7117), 337-342.

[3] Pearson, K.J., Baur, J.A., Lewis, K.N., Peshkin, L., Price, N.L., Labinskyy, N., Swindell, W.R., Kamara, D., Minor, R.K., Perez, E., Jamieson, H.A., Zhang, Y., Dunn, S.R., Sharma, K., Pleshko, N., Woollett, L.A., Csiszar, A., Ikeno, Y., Le Couteur, D., Elliott, P.J., Becker, K.G., Navas, P., Ingram, D.K., Wolf, N.S., Ungvari, Z., Sinclair, D.A., de Cabo, R. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab.*, **2008**, *8*(2), 157-168.

[4] Barger, J.L., Kayo, T., Vann, J.M., Arias, E.B., Wang, J., Hacker, T.A., Wang, Y., Raederstorff, D., Morrow, J.D., Leeuwenburgh, C., Allison, D.B., Saupe, K.W., Cartee, G.D., Weindruch, R., Prolla, T.A. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. *PLoS ONE*, **2008**, *3*(6), e2264.

[5] Fremont, L. Biological effects of resveratrol. *Life Sci.*, **2000**, *66*(8), 663-673.

[6] Walle, T., Hsieh, F., DeLegge, M.H., Oatis, J.E., Jr., Walle, U.K. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab. Dispos.*, **2004**, *32*(12), 1377-1382.

[7] Asensi, M., Medina, I., Ortega, A., Carretero, J., Baño, M.C., Obrador, E., Estrela, J.M. Inhibition of cancer growth by resveratrol is related to its low bioavailability. *Free Radic. Biol. Med.*, **2002**, *33*(3), 387-398.

[8] Hsieh, T.C., Wang, Z., Hamby, C.V., Wu, J.M. Inhibition of melanoma cell proliferation by resveratrol is correlated with upregulation of quinone reductase 2 and p53. *Biochem. Biophys. Res. Commun*., **2005**, *334*(1), 223-230.

[9] Buryanovskyy, L., Fu, Y., Boyd, M., Ma, Y., Hsieh, T.C., Wu, J.M., Zhang, Z. Crystal structure of quinone reductase 2 in complex with resveratrol. *Biochemistry*, **2004**, *43*(36), 11417-11426.

[10] Holvoet, P. Oxidized LDL and coronary heart disease. *Acta Cardiol.*, **2004**, *59*(5), 479-484.

[11] Turrens, J.F., Lariccia, J., Nair, M.G. Resveratrol has no effect on lipoprotein profile and does not prevent peroxidation of serum lipids in normal rats. *Free Radic. Res.*, **1997**, *27*(6), 557-562.

[12] Renaud,S., de L.M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet*, **1992**, *339*(8808), 1523-1526.

[13] Afaq, F., Adhami, V.M., Ahmad, N. Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice. *Toxicol. Appl. Pharmacol*., **2003**, *186*(1), 28-37.

[14] Morales, A.I., Buitrago, J.M., Santiago, J.M., Fernandez-Tagarro, M., Lopez-Novoa, J.M., Perez-Barriocanal, F. Protective effect of trans-resveratrol on gentamicin-induced nephrotoxicity. *Antioxid. Redox Signal.*, **2002**, *4*(6), 893-898.

[15] Mizutani, K., Ikeda, K., Kawai, Y., Yamori, Y. Protective effect of resveratrol on oxidative damage in male and female stroke-prone spontaneously hypertensive rats. *Clin. Exp. Pharmacol. Physiol.*, **2001**, *28*(1-2), 55-59.

[16] Floreani, M., Napoli, E., Quintieri, L., Palatini, P. Oral administration of trans-resveratrol to guinea pigs increases cardiac DT-diaphorase and catalase activities, and protects isolated atria from menadione toxicity. *Life Sci*., **2003**, *72*(24), 2741-2750.

[17] Ferry-Dumazet, H., Garnier, O., Mamani-Matsuda, M., Vercauteren, J., Belloc, F., Billiard, C., Dupouy, M., Thiolat, D., Kolb, J.P., Marit, G., Reiffers, J., Mossalayi, M.D. Resveratrol inhibits the growth and induces the apoptosis of both normal and leukemic hematopoietic cells. *Carcinogenesis*, **2002**, *23*(8), 1327-1333.

[18] Kaeberlein, M., McDonagh, T., Heltweg, B., Hixon, J., Westman, E.A., Caldwell, S.D., Napper, A., Curtis, R., DiStefano, P.S., Fields, S., Bedalov, A., Kennedy, B.K. Substrate-specific activation of sirtuins by resveratrol. *J. Biol. Chem.*, **2005**, *280*(17), 17038-17045.

[19] Nemoto, S., Fergusson, M.M., Finkel, T. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1{alpha}. *J. Biol. Chem.*, **2005**, *280*(16), 16456-16460.

[20] Kumar, P., Padi, S.S., Naidu, P.S., Kumar, A. Effect of resveratrol on 3-nitropropionic acid-induced biochemical and behavioural changes: possible neuroprotective mechanisms. *Behav. Pharmacol.*, **2006**, *17*(5-6), 485-492.

[21] Parker, J.A., Arango, M., Abderrahmane, S., Lambert, E., Tourette, C., Catoire, H., Néri, C. Resveratrol rescues mutant polyglutamine cytotoxicity in nematode and mammalian neurons. *Nat. Genet.*, **2005**, *37*(4), 349-350.

[22] Borrell-Pages, M., Zala, D., Humbert, S., Saudou, F. Huntington's disease: from huntingtin function and dysfunction to therapeutic strategies. *Cell Mol. Life Sci.*, **2006**, *63*(22), 2642-2660.

[23] Tang, B.L., Chua, C.E.L. SIRT1 and neuronal diseases. *Mol. Aspects. Med*., **2008**, *29*(3), 187-200.

[24] Anekonda, T.S. Resveratrol--a boon for treating Alzheimer's disease? *Brain Res. Rev*., **2006**, *52*(2), 316-326.

[25] Anekonda, T.S., Reddy, P.H. Can herbs provide a new generation of drugs for treating Alzheimer's disease? *Brain Res. Brain Res. Rev.*, **2005**, *50*(2), 361-376.

[26] Hardy, J., Selkoe, D.J. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*, **2002**, *297*(5580), 353-356.

[27] Pallas, M., Camins, A. Molecular and biochemical features in Alzheimer's disease. *Curr. Pharm. Des.*, **2006**, *12*(33), 4389-4408.

[28] Wirths, O., Multhaup, G., Bayer, T.A. A modified beta-amyloid hypothesis: intraneuronal accumulation of the beta-amyloid peptide--the first step of a fatal cascade. *J. Neurochem.*, **2004**, *91*(3), 513-520.

[29] Cuello, A.C. Intracellular and extracellular Abeta, a tale of two neuropathologies. *Brain Pathol.*, **2005**, *15*(1), 66-71.

[30] Valerio, A., Boroni, F., Benarese, M., Sarnico, I., Ghisi, V., Bresciani, L.G., Ferrario, M., Borsani, G., Spano, P., Pizzi, M. NF-kappaB pathway: a target for preventing beta-amyloid (Abeta)-induced neuronal damage and Abeta42 production. *Eur. J. Neurosci.*, **2006**, *23*(7), 1711-1720.

[31] Chen, J., Zhou, Y., Mueller-Steiner, S., Chen, L.F., Kwon, H., Yi, S., Mucke, L., Gan, L. SIRT1 protects against microglia-dependent amyloid-beta toxicity through inhibiting NF-kappaB signaling. *J. Biol. Chem.*, **2005**, *280*(48), 40364-40374.

[32] Yeung, F., Hoberg, J.E., Ramsey, C.S., Keller, M.D., Jones, D.R., Frye, R.A., Mayo, M.W. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. *EMBO J*., **2004**, *23*(12), 2369-2380.

[33] Frank, B., Gupta, S. A review of antioxidants and Alzheimer's disease. *Ann. Clin. Psychiatry*, **2005**, *17*(4), 269-286.

[34] Pervaiz, S. Resveratrol: from grapevines to mammalian biology. *FASEB J*., **2003**, *17*(14), 1975-1985.

[35] Mattson, M.P., Duan, W., Chan, S.L., Cheng, A., Haughey, N., Gary, D.S., Guo, Z., Lee, J., Furukawa, K. Neuroprotective and neurorestorative signal transduction mechanisms in brain aging: modification by genes, diet and behavior. *Neurobiol. Aging*, **2002**, *23*(5), 695-705.

[36] Mattson, M.P. Will caloric restriction and folate protect against AD and PD? *Neurology*, **2003**, *60*(4), 690-695.

[37] Patel, N.V., Gordon, M.N., Connor, K.E., Good, R.A., Engelman, R.W., Mason, J., Morgan, D.G., Morgan, T.E., Finch, C.E. Caloric restriction at-

tenuates Abeta-deposition in Alzheimer transgenic models. *Neurobiol. Aging*, **2005**, *26*(7), 995-1000.

[38] Wang, R., Wang, B., He, W., Zheng, H. Wild-type presenilin 1 protects against Alzheimer disease mutation-induced amyloid pathology. *J. Biol. Chem.*, **2006**, *281*(22), 15330-15336.

[39] Farris, W., Mansourian, S., Leissring, M.A., Eckman, E.A., Bertram, L., Eckman, C.B., Tanzi, R.E., Selkoe, D.J. Partial loss-of-function mutations in insulin-degrading enzyme that induce diabetes also impair degradation of amyloid beta-protein. *Am. J. Pathol.*, **2004**, *164*(4), 1425-1434.

[40] Qin, W., Chachich, M., Lane, M., Roth, G., Bryant, M., de Cabo, R., Ottinger, M.A., Mattison, J., Ingram, D., Gandy, S., Pasinetti, G.M. Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (Saimiri sciureus). *J. Alzheimers Dis.*, **2006**, *10*(4), 417-422.

[41] Qin, W., Yang, T., Ho, L., Zhao, Z., Wang, J., Chen, L., Zhao, W., Thiyagarajan, M., MacGrogan, D., Rodgers, J.T., Puigserver, P., Sadoshima, J., Deng, H., Pedrini, S., Gandy, S., Sauve, A.A., Pasinetti, G.M. Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. *J. Biol. Chem.*, **2006**, *281*(31), 21745-21754.

[42] Chen, L., Feany, M.B. [alpha]-Synuclein phosphorylation controls neurotoxicity and inclusion formation in a Drosophila model of Parkinson disease. *Nat. Neurosci.*, **2005**, *8*(5), 657-663.

[43] Okawara, M., Katsuki, H., Kurimoto, E., Shibata, H., Kume, T., Akaike, A. Resveratrol protects dopaminergic neurons in midbrain slice culture from multiple insults. *Biochem. Pharmacol.*, **2007**, *73*(4), 550-560.

[44] Alvira, D., Tajes, M., Verdaguer, E., Acuña-Castroviejo, D., Folch, J., Camins, A., Pallas, M. Inhibition of the cdk5/p25 fragment formation may explain the antiapoptotic effects of melatonin in an experimental model of Parkinson's disease. *J. Pineal. Res.*, **2006**, *40*(3), 251-258.

[45] Outeiro, T.F., Kontopoulos, E., Altmann, S.M., Kufareva, I., Strathearn, K.E., Amore, A.M., Volk, C.B., Maxwell, M.M., Rochet, J.C., McLean, P.J., Young, A.B., Abagyan, R., Feany, M.B., Hyman, B.T., Kazantsev, A.G. Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. *Science*, **2007**, *317*(5837), 516-519.

[46] Inoue, H., Jiang, X.F., Katayama, T., Osada, S., Umesono, K., Namura, S. Brain protection by resveratrol and fenofibrate against stroke requires peroxisome proliferator-activated receptor [alpha] in mice. *Neurosci. Lett.*, **2003**, *352*(3), 203-206.

[47] Gupta, Y.K., Briyal, S., Chaudhary, G. Protective effect of trans-resveratrol against kainic acid-induced seizures and oxidative stress in rats. *Pharmacol. Biochem. Behav.*, **2002**, *71*(1-2), 245-249.

[48] Gupta, Y.K., Chaudhary, G., Srivastava, A.K. Protective effect of resveratrol against pentylenetetrazole-induced seizures and its modulation by an adenosinergic system. *Pharmacology*, **2002**, *65*(3), 170-174.

[49] Gupta, Y.K., Chaudhary, G., Sinha, K., Srivastava, A.K. Protective effect of resveratrol against intracortical FeCl3-induced model of posttraumatic seizures in rats. *Methods Find Exp. Clin. Pharmacol.*, **2001**, *23*(5), 241-244.

[50] Kaeberlein, M., McVey, M., Guarente, L. The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. *Genes Dev.*, **1999**, *13*(19), 2570-2580.

[51] Tissenbaum, H.A., Guarente, L. Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*. *Nature*, **2001**, *410*(6825), 227-230.

[52] Rogina, B., Helfand, S.L. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*(45), 15998-16003.

[53] McBurney, M.W., Yang, X., Jardine, K., Hixon, M., Boekelheide, K., Webb, J.R., Lansdorp, P.M., Lemieux, M. The mammalian SIR2alpha protein has a role in embryogenesis and gametogenesis. *Mol. Cell Biol.*, **2003**, *23*(1), 38-54.

[54] Guarente, L., Picard, F. Calorie restriction--the SIR2 connection. *Cell*, **2005**, *120*(4), 473-482.

[55] Koubova, J., Guarente, L. How does calorie restriction work? *Genes Dev.*, **2003**, *17*(3), 313-321.

[56] Martin, B., Mattson, M.P., Maudsley, S. Caloric restriction and intermittent fasting: two potential diets for successful brain aging. *Ageing Res. Rev.*, **2006**, *5*(3), 332-353.

[57] Howitz, K.T., Bitterman, K.J., Cohen, H.Y., Lamming, D.W., Lavu, S., Wood, J.G., Zipkin, R.E., Chung, P., Kisielewski, A., Zhang, L.L., Scherer, B., Sinclair, D.A. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, **2003**, *425*(6954), 191-196.

[58] Valenzano, D.R., Terzibasi, E., Genade, T., Cattaneo, A., Domenici, L., Cellerino, A. Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate. *Curr. Biol.*, **2006**, *16*(3), 296-300.

[59] Picard, F., Guarente, L. Molecular links between aging and adipose tissue. *Int. J. Obes. (Lond)*, **2005**, *29*(Suppl 1), S36-S39.

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