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REVIEW

Metabolic effects of resveratrol: addressing the controversies

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Abstract Resveratrol, a polyphenol found in a number of plant-based foods such as red wine, has received a great deal of attention for its diverse array of healthful effects. Beneficial effects of resveratrol are diverse; they include improvement of mitochondrial function, protection against obesity and obesity-related diseases such as type-2 diabetes, suppression of inflammation and cancer cell growth and protection against cardiovascular dysfunction, just to name a few. Investigations into the metabolic effects of resveratrol are furthest along and now include a number of clinical trials, which have yielded mixed results. There are a number of controversies surrounding resveratrol that have not been resolved. Here, we will review these controversies with particular emphasis on its mechanism of metabolic action and how lessons from resveratrol may help develop therapies that harness the effects of resveratrol but without the undesirable properties of resveratrol.

Keywords Resveratrol · Sirt1 · PDE4 · AMPK

Abbreviations

AMPK	Adenosine monophosphate activated kinase
Sirt1	Sirtuin 1
SIR2	Silent information regulator 2
cAMP	Cyclic adenosine monophosphate
CAMKKβ	Calcium/calmodulin-dependent kinase kinase β
PDE	Phosphodiesterases
PKA	Protein kinase A
EPAC	Exchange protein activated by cAMP
COX	Cyclooxygenase
HOMA-IR	Homeostatic model assessment-insulin resistance
eNOS	Endothelial nitric oxide synthase
Nrf2	Nuclear factor erythroid 2- related factor 2

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Introduction

As the chronic diseases of aging such as cancer, diabetes, and neurodegenerative diseases have become an increasing burden on society, we have continued to search for drugs that can solve these problems. Finding a drug that could reduce the overall effects of aging could increase both the health span and lifespan of humans. One method that has consistently been shown to increase the lifespan of organisms from single-celled organisms to mammals is caloric restriction. This concept was originally discovered when McCay et al. [1] showed that caloric restriction could extend the lifespan of rats. More recently, caloric restriction has been shown to extend the lifespan of a range of species from yeast to mammals [2]. With the increasing epidemic of obesity, it has become clear that attempts at calorie restriction in humans are likely to fail. Therefore, many have searched for compounds that could act as calorie restriction mimetics. Focus on the pathways involved in the effect of calorie restriction on lifespan in yeast discovered the sirtuin enzyme *SIR2* to be a key mediator [3]. A high throughput screen for activators of SIRT1, the human homolog of the *Saccharomyces cerevisiae* enzyme

discovered the small molecule resveratrol (3,5,4′-trihydroxystilbene) [4]. Resveratrol is a natural product that can be found in several plant species including red grapes. In the 1990s resveratrol first received attention as a potential explanation of the "French Paradox," then later was characterized as a cyclooxygenase inhibitor and potential chemopreventive molecule [5]. Since its discovery as a potential calorie restriction mimetic, resveratrol has been shown to have beneficial effects in cardiovascular disease, metabolic disease, cancer and neurodegeneration. Much work has focused on how resveratrol is capable of having such wide-ranging effects, what the molecular targets are, and whether resveratrol treatment will be beneficial in humans. In this review, we will discuss the current research on the direct targets of resveratrol, the downstream effects of resveratrol in animals, and the current state of human clinical trials.

Molecular targets of resveratrol

Amidst much confusion, it has become clear that resveratrol potentially has several direct targets in the cell. Although the original discovery was as a cyclooxygenase inhibitor, it has subsequently been identified as an activator of Sirt1 [4]; an inhibitor of cAMP phosphodiesterases [6]; an inhibitor of the F1-ATPase [7]; an inhibitor of the estrogen receptor [8], and a modulator of numerous other targets. The poly-pharmacologic nature of resveratrol has sparked much debate about the most relevant targets for its downstream effects, much of this surrounding whether it truly is an activator of Sirt1, and whether Sirt1 is responsible for the downstream effects of resveratrol in vivo.

Sirtuins

The sirtuin family of proteins began receiving attention due to the ability of the *S. cerevisiae* SIR2 gene to modulate lifespan in yeast. It was shown that the extension of replicative lifespan due to caloric restriction depended on the presence of SIR2 [3], although a recent paper calls into question the magnitude of the lifespan expansion due to caloric restriction in this species [9]. It was further shown that deletion of Sir2 orthologs in other organisms ablated the effects of caloric restriction on lifespan [10, 11], although not in all systems tested [12, 13]. Increasing the expression of Sirt1 has extended lifespan in yeast [14], worms [15], and flies [10]. One group could not repeat these effects in *C. elegans* or Drosophila [16], thereafter the original group has repeated their result in *C. elegans* although with a smaller effect [17]. In drosophila, it has now been shown that Sir2 overexpression in the fat body can increase lifespan [18]. In mammals, sirtuins compose a family of seven proteins called Sirt1–Sirt7. Sirt1 is the closest homolog to the yeast SIR2, and has been most extensively studied for the effects of caloric restriction and lifespan extension. Overexpression of Sirt1 in mice partially phenocopies the effects of caloric restriction [19, 20], and overexpression of Sirt1 in the brain can extend lifespan [21]. However, some effects of Sirt1 overexpression in mice seem to contradict the effects of resveratrol, including an increase in atherosclerosis when the mice are placed on an atherogenic diet [22] and reduced mitochondrial and cardiac function [23].

Due to evidence showing the potential of increasing sirtuin activity to mimic the effects of caloric restriction, Howitz et al. [4] performed a high throughput screen for activators of human Sirt1 and identified resveratrol as the most potent activator. It was proposed that resveratrol activated Sirt1 by lowering the K_m for both the peptide and NAD^+ substrates of the enzyme. This screen involved the use of a fluorescently labeled peptide substrate, called Fluor-de-Lys, mimicking a short sequence from p53 that had been shown to be deacetylated by Sirt1 [24]. The direct activation of Sirt1 by resveratrol later became controversial, with evidence showing that the activation in the screen was due to interaction between resveratrol and the fluorescent moiety on the Fluor-de-Lys substrate [25–27]. Due to the proposed biological effects of resveratrol being mediated through Sirt1, further screens were performed to find novel sirtuin activating compounds (STACs). Several structurally distinct compounds, including SRT1720, were found by a screen using a TAMRA tagged substrate. However, the direct activation of Sirt1 by several of these compounds was also called into question [27, 28]. Recent experiments have shown possible explanations for the variety of results obtained for the activation of Sirt1 by resveratrol and STACs. One group showed that activation was possible with resveratrol if the fluorescent group on the peptide was replaced with large hydrophobic amino acids [29]. Further evidence for the dependence of activation on nearby hydrophobic amino acids came from Gertz and colleagues. First, through crystal structures of Sirt3 and Sirt5 co-complexed with resveratrol, they showed direct interaction between resveratrol and fluorescently labeled peptides in sirtuin active sites [30]. They then went on to show that resveratrol activated Sirt5 deacetylase activity towards longer unmodified peptides in a sequence-dependent manner [30]. In a later study, the same group screened a peptide library of 6,802 physiological acetylation sites for the resveratrol effect on Sirt1 deacetylation, showing both activation and inhibition for subsets of acetylation sites but the majority of acetylation sites unaffected [31]. There was a tendency for the activated peptides to have large hydrophobic residues C-terminal to the deacetylation site [31]. In another study, Hubbard et al. [32] showed that resveratrol activated deacetylase activity towards native substrate

peptides using in vitro coupling and mass spectrometry-based assays. The common theme among the peptides that showed resveratrol activation was a hydrophobic residue located one or six positions C-terminal to the acetylated lysine. The recent data on the resveratrol activity on Sirt1 clearly show that in vitro, resveratrol can activate Sirt1 activity towards peptide substrates with hydrophobic residues C-terminal to the acetylated lysine on the peptide. Unfortunately, very little data has been produced on Sirt1 activity towards native full-length proteins. It remains to be seen if the peptide substrates that are activated in vitro are relevant (or the most relevant) to the biological effects of resveratrol in vivo.

AMPK and PDEs

While the controversy over whether resveratrol was a direct activator of Sirt1 unfolded, other pathways for indirect activation of Sirt1 were explored. Several groups have shown that resveratrol activates AMP-activated kinase (AMPK), albeit indirectly [33–38]. Subsequently, it was shown that AMPK was also required for the metabolic effects of resveratrol in mice [39]. AMPK is a nutrient-sensing enzyme that is activated by depletion in energy as reflected by an increased AMP/ATP ratio [40]. Several mechanisms of this activation include caloric restriction [41, 42], exercise and glucose deprivation [40], and pharmacologic compounds such as metformin and AICAR. In AMPK knockout mice, the effects of resveratrol on weight gain, glucose tolerance, insulin sensitivity, and mitochondrial biogenesis are all ablated [39]. AMPK activation could indirectly activate Sirt1 activity, as AMPK activation is known to increase the intracellular NAD^+ pool [39, 43]. Questions still remain about how resveratrol could activate AMPK, and how the activation of AMPK and Sirt1 are related to each other.

Although AMPK is activated by an increase of the AMP/ATP ratio, there are other proteins that play a major role in the activation of AMPK. Under most circumstances, two well-known kinases phosphorylate AMPK on the T172 residue necessary for activation: LKB1 and calcium/calmodulin-dependent kinase kinase β (CamKKβ) [40]. LKB1 can modulate the activation of AMPK by energy depletion, and intracellular Ca^{2+} can activate CamKKβ, which in turn activates AMPK. It is possible that resveratrol could activate AMPK via depletion of ATP levels, or by activation of either LKB1 or CamKKβ. Although some evidence has shown that resveratrol can decrease ATP levels [44, 45], it seems to be dependent on doses of 50 μM or higher [46] and possibly the cell type used for the assay, and other studies have shown no effect of resveratrol on ATP levels [47]. Resveratrol has been shown to activate AMPK at doses 10 μM or lower, which are lower than those where ATP depletion has ever been measured [33, 38, 48]. One study showed that in an AMPK mutant that is insensitive to activation by AMP, resveratrol is no longer able to activate AMPK, arguing that activation is dependent on depletion of ATP [44]. However, this study only saw effects at doses >100 μM, calling into question the validity of this effect at lower concentrations [44]. In fact, several studies have shown that resveratrol leads to increased levels of ATP along with AMPK activation [32, 49].

An alternative pathway for activation of AMPK via inhibition of cyclic nucleotide phosphodiesterases (PDEs) was recently shown by Park et al. [6]. PDEs modulate the levels of intracellular cAMP by degrading it to AMP, counteracting the production of cAMP by adenylyl cyclases (ACs). The PDE family of proteins consists of 11 members and a large number of splice variants, capable of hydrolyzing either cAMP and/or cGMP (depending on the isoform) to AMP and GMP, respectively [50]. Park et al. [6] showed that resveratrol had no effect on the production of cAMP by ACs, but inhibited the breakdown of cAMP by PDE1, PDE3, and PDE4. They also tested PDE2 and PDE5 and showed no effect, while not studying the remaining PDE family members.

In cells, cAMP affects downstream processes through three major groups of effector proteins: protein kinase A (PKA), exchange proteins activated by cAMP (EPAC), and cyclic nucleotide regulated ion channels. It is possible for cAMP to activate AMPK through both a PKA-LKB1 pathway, and a pathway involving EPAC1 and CamKKβ [6, 51, 52]. In HeLa cells, which lack LKB1, resveratrol works through the EPAC1-dependent cascade [6]. In myotubes, which express both CamKKβ and LKB1, the activation of AMPK is also dependent on the EPAC1 cascade, but may also contain a contribution from PKA-LKB1 signaling. The actions of PKA on AMPK activation have been shown to be complicated. It has been shown that PKA can directly phosphorylate LKB1 on the S431 residue and increase its activity in neurons [53]. However, activation of AMPK by transiently overexpressed LKB1 is not dependent on phosphorylation at the S431 site [54]. Whether S431 in LKB1 is required for resveratrol to activate AMPK when LKB1 is expressed at physiological levels is not known. Activation of PKA by isoproterenol can inhibit AMPK [55], but activation of PKA by adiponectin can activate AMPK [56].Several other studies have found a relationship between cAMP-PDE signaling and AMPK activation in adipose tissue and muscle [57–59]. Some studies have also shown that PKA activation can lead to an increase in Sirt1 activity [60, 61].

Over the past two years, there has been an increasing amount of evidence that inhibition of PDE4 via rolipram or roflumilast can recapitulate some of the phenotypes of

resveratrol treatment such as extension of lifespan in a *C. elegans* model of a neurodegenerative disease [62], chemoprevention by elimination of tetraploid cells in cancer cell lines [63] and protection against diabetic nephropathy in streptozotocin-treated rats [64].

Other molecular targets of resveratrol

Part of the reason there has been so much controversy and debate over the direct target of resveratrol is the fact that it is poly-pharmacologic. A number of proposed direct targets have been shown, at least in vitro, since it first came to prominence. As mentioned above, before the studies showing resveratrol action on Sirt1 in the early 2000s, resveratrol first received attention as a cyclooxygenase (COX) inhibitor in 1997 [5]. It has been shown to be an inhibitor of COX-1 but not COX-2 [65], and to have cancer chemopreventive activity [5]. Also mentioned above was the discovery that resveratrol has an inhibitory effect on the F0F1 ATPase in mitochondria, potentially decreasing ATP production [7, 66]. A similar model has been looked at with resveratrol inhibition of complex I of the mitochondrial oxidative phosphorylation machinery [67, 68]. However, another group found that resveratrol worked by activating complex I resulting in increased NAD^+ levels in the cell and Sirt1 activation [69]. Also before the discovery of resveratrol as a sirtuin activator, resveratrol was studied as an estrogen receptor (ER) modulator [70, 71]. Originally, resveratrol was proposed as a strong ER agonist, but subsequent studies found it did not cause proliferation of mammary or uterine tissues [72]. A recent study by Nwachukwu et al. [8] shows a co-crystal structure of the ERα ligand binding domain with resveratrol, and proposes mechanisms by which resveratrol can mediate selective downstream effects through ERα. Resveratrol activates pathway specific effects on ERα by affecting recruitment of specific co-regulators. Another recent paper from Lee et al. [73] shows that resveratrol can be a direct activator of the Ataxia-Telangiectasia Mutated kinase (ATM). They show that resveratrol can stimulate ATM directly in the presence of oxidizers in an in vitro activity model. They also show that resveratrol activates ATM autophosphorylation and phosphorylation of substrates, such as p53, in vitro and in cell lines. However, because resveratrol can generate reactive oxygen species [74], and ATM is activated by oxidative stress [75], one cannot rule out the possibility that the effect of resveratrol on ATM activity in cell lines may, at least in part, be indirect. It is clear that resveratrol potentially interacts with a number of molecular targets both in vitro and in cell lines. Many of these targets converge on pathways related to metabolism and inflammation that are responsible for the phenotypes of resveratrol treatment in cells and animals.

Effects of resveratrol in animal models

Lifespan

Inspired by the research on the effects of caloric restriction and sirtuin genes on lifespan, the effects of resveratrol on organismal lifespan has been studied in species from yeast to non-human primates. Resveratrol has been shown to increase the lifespan of the yeast *S. cerevisiae* [4], the nematode *C. elegans* and the fruit fly *D. melanogaster* [76]. Lifespan extension has also been shown in the fish *N. furzeri* [77], another fish *N. guentheri* [78], and the bee *A. mellifera* [79]. In mammals, resveratrol did not extend the lifespan of healthy mice [80–82], but partially prevented premature death of mice fed a high fat diet [35, 80]. In rats, resveratrol also failed to extend the lifespan of animals on a normal diet [83]. In non-human primates, no lifespan studies have been performed with resveratrol. However, lifespan studies on caloric restriction have provided conflicting results [84, 85]. The lifespan studies across species appear to show that the effects of resveratrol are very dependent on the specific diet and conditions of the animals [86]. In mice, it appears that resveratrol is able to extend their lifespan when they are under metabolic stress. Below, we will discuss various ways in which resveratrol improves health span by reducing the effects of the diseases of aging.

Metabolism

The most robust effect that has been seen repeatedly with resveratrol treatment in vivo is its effect on metabolism. Resveratrol has been shown to relieve many of the negative effects of a high-fat diet in mice. As discussed above, resveratrol increased the lifespan of mice fed a high fat diet. In the same mice, resveratrol reduced body weight at a high dose, and reduced insulin resistance at a lower dose that did not cause reduction in body weight [35, 87]. Later, it was shown that the weight loss and improvements in the glucose tolerance test were dependent on the presence of AMPK [39]. Overexpression of Sirt1 is able to improve glucose tolerance in mice without changes in body weight or fat content [19, 88, 89]. With much of the focus of the resveratrol field on studying how resveratrol could work as a calorie restriction mimetic, the questions turned to how resveratrol could produce such profound metabolic benefits. One reproducible effect of resveratrol was an increase in mitochondrial content (Fig. 1) [6, 35, 39, 87]. Many of these studies pointed to the ability of resveratrol to upregulate the activity of peroxisome proliferator-activated receptor γ co-activator (PGC-1α), a so-called "master regulator" of mitochondrial biogenesis [90]. PGC-1α controls the expression of many downstream regulators of mitochondrial content in the cell, and can lead to switching

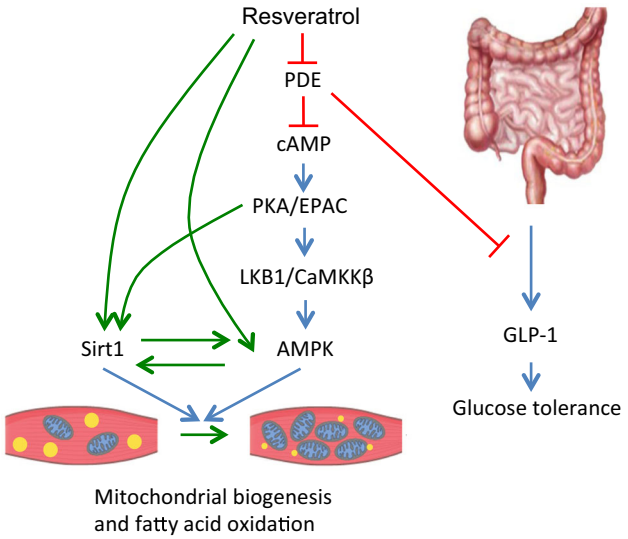

Fig. 1 Schematic of the molecular targets of resveratrol related to metabolism. Resveratrol potentially activates multiple targets, converging on pathways that lead to mitochondrial biogenesis and fatty acid oxidation. In the gut (*right*), where resveratrol concentrations are likely higher than plasma in animals, resveratrol leads to secretion of GLP-1 and an improvement in glucose tolerance. *Green* and *blue arrows* represent activation and *red bars* represent inhibition

of oxidative fiber types in muscle [91] an effect observed under resveratrol treatment [87]. In mice, overexpression of PGC-1α also leads to a decrease in the metabolic disorders that occur during aging [92]. It has been well-established that Sirt1 can deacetylate and activate PGC-1α [93]. AMPK activation can lead to increased Sirt1 deacetylation and activation of PGC-1α [94]. Treatment with resveratrol has been shown to increase both Sirt1 and PGC-1α activity in mice fed a high-fat diet [6, 39, 87]. Although several papers have shown that resveratrol treatment leads to increased mitochondrial biogenesis via Sirt1 deacetylation and activation of PGC-1α, other papers have produced conflicting results. The first paper to demonstrate an interaction between Sirt1 and PGC-1α actually demonstrated that overexpression of Sirt1 decreased PGC-1α activity in PC12 cells [95]. A recent paper from Higashida et al. [96] showed that this was also true in C2C12 myotubes [96]. They were unable to demonstrate an increase in mitochondrial biogenesis upon resveratrol treatment of rats, but could recapitulate the increase in mitochondrial biogenesis in C2C12 myotubes overexpressing PGC-1α. This effect was dependent on activation of AMPK, but not dependent on Sirt1 activity. Currently, the mechanism by which resveratrol leads to this increase in PGC-1α activity continues to be under debate in the literature.

As stated above, many of the downstream effects of resveratrol on metabolism do not occur in AMPK knockout mice [39]. The effects of resveratrol on Sirt1 and AMPK involve a complicated series of interactions. Pathways have been shown for both Sirt1 to activate AMPK, and for AMPK to activate Sirt1, complicating the debate over the true mechanism in vivo [94, 97–99]. Activation of AMPK leads to an increase in cellular NAD^+ levels through stimulation of nicotinamide phosphoribosyltransferase (NAMPT) activity [97]. Although increased NAD^+ levels in vivo have not been shown to directly stimulate Sirt1 activity, NAD^+ is a necessary cofactor for Sirt1 and increased NAD^+ has correlated with increased Sirt1 and PGC-1α activity [39, 94, 97]. One study demonstrated an increase in Sirt1 activity by decreasing the consumption of NAD^+ by another NAD^+ utilizing enzyme [100]. Sirt1 could possibly stimulate AMPK activity through the deacetylation of LKB1, an upstream regulator of AMPK activity [98, 99]. To further complicate this interplay, Sirt1 stimulation by resveratrol has been shown to be independent of AMPK activation [46], and AMPK stimulation by resveratrol has been shown to be independent of Sirt1 activation [6, 33, 39].

As mentioned above, resveratrol was shown to be a direct inhibitor of phosphodiesterase activity, increasing cAMP levels in cells. Amongst the PDE isoforms inhibited by resveratrol is PDE4, the most abundant PDE in skeletal muscle [6]. Inhibition of phosphodiesterases leads to an increase in cAMP levels and downstream activation of the cAMP effectors PKA and EPAC. In myotubes, it was shown that treatment with resveratrol stimulated a signaling cascade via cAMP and EPAC that led to the activation of AMPK and subsequently Sirt1 (Fig. 1). Importantly, many of the downstream effects of resveratrol were recapitulated by treatment with rolipram, a specific inhibitor of PDE4 [6]. In fact, several other studies have found metabolic effects due to PDE inhibition or knockout. Phosphodiesterases are important signaling regulators in pancreatic β-cells, regulating both Ca^{2+} levels and insulin secretion [101]. In PDE3B knockout mouse islets, both glucose and incretin-stimulated insulin secretion are greater than the secretion in wild-type islets [102]. The PDE4B knockout mouse also has metabolic phenotypes, including reduced fat content and serum leptin levels [103]. These previous data on PDE inhibition combined with the Park et al. study demonstrate that resveratrol may mediate some of its metabolic effects through the PDE-cAMP-AMPK pathway.

Price et al. published a study exploring the role that Sirt1 and AMPK play in the downstream effects of resveratrol using conditional knockout mice. Studies of full-body Sirt1 knockout mice have been challenging because the mice have limited viability and many developmental defects [104, 105]. To address these problems, Price et al. [46] knocked out Sirt1 specifically in adult animals using a

tamoxifen inducible knockout system, avoiding the developmental defects. The adult conditional knockout mice appeared largely normal. However, treatment with low doses of resveratrol led to an increase in mitochondrial content and function in wild type but not Sirt1 knockout mice. With the low-dose treatment, AMPK activation appeared to be dependent on Sirt1, whereas at a higher dose AMPK activation was Sirt1 independent. Interestingly, a previous study in Sirt1 knockout MEFs showed that AMPK activation by resveratrol was not Sirt1 dependent [39]. Despite the effects of resveratrol on mitochondrial biogenesis being Sirt1-dependent in the conditional knockout mice, there were several systematic effects in the mice that were Sirt1 independent. After being fed a high-fat diet, resveratrol improved glucose tolerance and reduced the amount of hepatic triglycerides in a Sirt1 independent manner [46]. A Sirt1 overexpressing mouse is also capable of reducing hepatic triglycerides and glucose intolerance [46], further displaying the complicated relationship between Sirt1, AMPK and metabolic effects in mice.

Despite the unclear picture of the direct molecular targets responsible for the metabolic effects of resveratrol, many of the effects have become clear in mammals from rodents to non-human primates. As discussed above, resveratrol treatment improves the glucose homeostasis and insulin sensitivity of mice fed a high-fat diet [35, 39, 46, 87, 106]. Resveratrol has also been shown consistently to reduce hepatic triglyceride content [46, 107]. Using a proposed Sirt1 activator, SRT1720, many of these same effects have been seen in mice fed a high fat diet including improved glucose tolerance, insulin sensitivity, mitochondrial content, and lifespan [108, 109]. In Zucker diabetic fatty rats, resveratrol lead to improved glucose and insulin tolerance. Subcutaneous adipose tissue from resveratrol-treated rats showed increased incorporation of pyruvate into triglycerides and increased adiponectin secretion. In subcutaneous and retroperitoneal adipose tissue from resveratrol-treated rats, there was an increase in mitochondrial respiration and cytochrome c oxidase IV protein, showing a potential increase in mitochondrial biogenesis in adipose tissue with resveratrol treatment [110]. In rhesus monkeys, resveratrol added to a high fat/high sugar diet did not prevent the development of insulin resistance, but was able to protect against β-cell loss in the pancreatic islets [111]. In visceral fat from rhesus monkeys fed a high fat/high sugar diet, resveratrol reduced adipocyte size and increased insulin sensitivity [112]. In *Microcebus murinus*, 33 months of treatment with resveratrol led to improvements on the homeostatic model assessment-insulin resistance (HOMA-IR) index and improved glucose tolerance [113]. The translation of these effects to human studies will be discussed below.

Inflammation

Chronic inflammation is increasingly accepted to play a major role in the diseases of aging [114] including metabolic disorders such as Type 2 diabetes [115]. One of the reasons that resveratrol has drawn so much attention as an anti-aging therapeutic is its ability to reduce inflammation. Even before studies showing resveratrol inhibition of COX2 or activation of sirtuins, resveratrol was shown to inhibit 5-lipoxygenase and cyclooxygenase products from rat peritoneal polymorphonuclear leukocytes [116]. Resveratrol treatment has also been shown to inhibit signaling through interleukin-10 and interferon-γ [117–119]. In human peripheral blood mononuclear cells, resveratrol has been shown to inhibit IL-17 production [120]. One important mediator of resveratrol's effect on inflammation is NF-κB. Activation of Sirt1 by resveratrol treatment can lead to downstream inhibition of NF-κB by the direct deacetylation of the p65 subunit [121]. Resveratrol has been shown to reduce NF-κB activation in leukocytes [122]. Sirt1 activation can also modulate several stress response transcription factors including hypoxia-inducible factors and FOXO1, FOXO3, and FOXO4 [123–127]. In rhesus monkeys, resveratrol reduced inflammation in the white adipose tissue of animals fed a high fat/high sugar diet [112]. In a mouse model of Crohn's disease, resveratrol reduced inflammatory cytokines [128]. It is clear that the anti-inflammatory properties of resveratrol can aid in its benefits to the health of aging animals.

Cardiovascular disease

The beneficial effects of resveratrol on the cardiovascular system have been reviewed extensively elsewhere [123, 129–131]. These effects are multifactorial, affecting various components of cardiovascular disease. In vascular function, resveratrol has been shown to promote vasodilation through effects on the expression and activity of endothelial nitric oxide synthase (eNOS) [132–136]. It has been proposed that resveratrol exerts these effects on eNOS via a direct Sirt1 deacetylation [137] or by transcriptional activation downstream of Sirt1 [138], and knockdown of Sirt1 expression blocked the induction of eNOS expression by resveratrol [139, 140]. AMPK is also capable of activating eNOS activity via a direct phosphorylation [141], and one group has shown that inhibition of AMPK blocks the effect of resveratrol on vasodilation in aortic rings [135]. There is also evidence that resveratrol can cause vasodilation by inhibiting vasoconstriction by angiotensin II [142] and its receptor [143].

Resveratrol has also been shown to have an effect on blood pressure in various model systems. In several rat models of hypertension, chronic treatment with resveratrol

decreased blood pressure [142, 144–148]. In some other rat model systems, resveratrol has not had an effect on blood pressure [149–152]. Recent data has reaffirmed that resveratrol can lower blood pressure in the spontaneously hypertensive rat model of hypertension, and that this effect coincides with the activation of AMPK both in vitro and in vivo [153]. The beneficial effects of resveratrol on cardiac hypertrophy also coincide with the activation of AMPK [153, 154]. Resveratrol has also been shown to lower blood pressure in a porcine model of hypertension [155]. Most recently, resveratrol has been shown to reduce the amount of arterial wall inflammation in high fat/high sugar fed rhesus monkeys [156].

Resveratrol likely mediates many of its cardioprotective effects through its ability to reduce oxidative damage and inflammation. Resveratrol is known to be a direct antioxidant [157], which was an early theory for how it mediated cardioprotection. Resveratrol is also capable of inducing the expression of many antioxidant enzymes including superoxide dismutase, glutathione peroxidase, heme oxygenase, and catalase [158–163]. The induction of these antioxidant genes may be mediated by nuclear factor erythroid 2- related factor 2 (Nrf2) [164]. In addition, resveratrol can down-regulate NADPH-oxidase leading to decreased production of reactive oxygen species [165–167]. Oxidative stress is known to be an important mechanism for cardiovascular disease during aging [168, 169]. Resveratrol is capable of reducing mitochondrial oxidative stress in the cardiovascular system [170] and has also been shown to reduce the oxidation of LDL [171]. In the cardiovascular system, resveratrol shows many of the anti-inflammatory effects discussed in the previous section. Treatment with resveratrol reduces the expression of NF-κB, IL-6 and IL-8, and TNF-α [134, 172, 173]. Resveratrol also has benefits in ischemia–reperfusion injuries [130, 174], possibly assisting in the protective effects during myocardial infarction.

Neuroprotection

Resveratrol has been shown to have some benefit in animal models of several neurodegenerative diseases. In Alzheimer's disease, resveratrol can reduce the accumulation of amyloid β (Aβ) peptides in various cell line models [175], and the accumulation of Aβ plaques [176]. An AMPK-mediated pathway was shown to be involved in the reduction of Aβ levels in cell-based models including in primary mouse neurons [177]. There is also evidence for a PDE-Sirt1-mediated pathway affecting the production of Aβ in cell lines [178]. Recently, studies have found that resveratrol can reduce microglial activation in Alzheimer's model via a NF-κB/STAT/TLR based anti-inflammatory effect [179]. The combination of resveratrol's antioxidant, anti-inflammatory, and amyloid lowering effects could combine to make it a potential treatment for Alzheimer's disease.

Resveratrol has also shown some promise in other neurodegenerative diseases including Parkinson's disease [180, 181], Huntington's disease [182], and multiple sclerosis [183]. One major mechanism of neuroprotection may be resveratrol's ability to prevent axonal degeneration through blocking the association between Sirt1 and its inhibitor DBC1 [184]. A recent paper showed that resveratrol could extend the lifespan of a *C. elegans* model of adult onset neuronal lipofuscinosis (ANCL). Mutation of the dnj-14 gene in *C. elegans* leads to a decrease in lifespan for the nematodes. Resveratrol was able to rescue the lifespan reduction in the dnj-14 mutants. This rescue was shown to be sirtuin independent, as deletion of the sir-2.1 gene did not remove the lifespan extending effect of resveratrol on the dnj-14. The lifespan extension effect of resveratrol was however, recapitulated by the PDE4 inhibitor rolipram, suggesting that neuroprotection in this model by resveratrol may be mediated by a PDE-cAMP pathway [62].

Resveratrol in humans

When resveratrol began to be studied in the late 1990s, its presence in red wine led some to hypothesize that resveratrol could explain the "French paradox," that those who consume a diet high in fatty foods and wine seem to have a lower incidence of coronary heart disease [185]. Although this idea was enticing in the early days of resveratrol research, it became clear that the amounts of resveratrol consumed in the diet would not lead to sufficient concentrations of resveratrol in the body to achieve the effects seen in cellular models of disease [186]. In fact, a recent epidemiological study has shown that urinary resveratrol concentrations solely from dietary consumption are not correlated with a reduction in any cardiovascular disease or cancer incidence [187]. When consumed, resveratrol becomes modified by glucuronidation and sulfation [188] thereby reducing its bioavailability. It is unlikely that resveratrol reaches serum concentrations above 1 μM from dietary consumption, or 10 μM from direct resveratrol supplement consumption [189]. It is possible that despite the low serum concentrations of resveratrol, the lipophilicity of the compound allows it to have higher concentrations within the relevant cells and tissues for its effects. Also, some tissues express glucuronidases capable of removing these groups from resveratrol and enhancing the intracellular concentration [190]. The glucose-lowering effect of resveratrol may in part be occurring in the gut, where its concentrations are likely much higher than in

serum. Glucose-lowering incretin glucagon-like peptide-1 (GLP-1), which is secreted by the gut, has numerous physiological effects that make it an attractive type 2 diabetes therapy: increased insulin secretion and insulin sensitivity and decreased glucagon secretion and appetite [191]. Indeed, GLP-1 receptor agonists or GLP-1 mimetics are one of the most widely utilized classes of drugs used to treat type-2 diabetes. One possible mechanism by which resveratrol lowers serum glucose levels may be via GLP-1. Secretion of GLP-1 is inhibited by PDE4D [192], and both resveratrol [6, 193] and the PDE4 inhibitor rolipram [6, 192] increase GLP-1 production (Fig. 1).

With the enticing health benefits in animal models, several clinical trials have focused on the use of resveratrol supplements to treat cardiovascular or metabolic diseases. In a series of Phase I dose escalation studies of resveratrol, it has been shown that resveratrol is generally safe in healthy subjects [194–197]. Higher doses were correlated with mild adverse effects such as diarrhea and nausea [195], but doses at 1 g/day or lower presented minimal side effects [195, 197]. Given the safety profile of resveratrol supplementation, clinical studies began to explore the effects of resveratrol on health. Brasnyo et al. [198] performed a trial with type 2 diabetic male patients receiving 10 mg resveratrol or a placebo for one month. The resveratrol treated group had improved HOMA-IR index, reduced glucose spike after a meal, and an increased pAKT:AKT ratio in platelets. Another trial treated 34 metabolic syndrome patients in a 6-month crossover trial receiving 100 mg of a resveratrol supplement [199]. The patients saw an improvement in flow-mediated dilation at the end of the 3-month treatment period with resveratrol that disappeared after removal of the treatment. Blood pressure and metabolic parameters tested were not affected. Type 2 diabetics receiving 250 mg resveratrol daily for 3 months had significantly improved fasting blood glucose, blood pressure, triglycerides and LDL cholesterol in another trial, compared to a control group receiving only standard of care for diabetes [200]. To examine the effects in cardiovascular disease, Tome-Carneiro et al. [201, 202] performed a trial with 75 subjects using placebo, grape extract lacking resveratrol, or grape extract supplemented with 8 mg of resveratrol over a full year. This trial explored the use of resveratrol treatment for pre-clinical benefits in subjects at high risk of cardiovascular disease. The trial found reduced ApoB and oxidized LDL levels in the resveratrol treated group compared to the no resveratrol grape extract or placebo groups. There also was a reduction in reactive oxygen species and the inflammatory markers CRP, TNF-α and IL-1β. To explore the effects of resveratrol on flow-mediated dilation, Wong et al. [203] performed a trial with 19 subjects including overweight men and post-menopausal women with high blood pressure. After treatment with varying doses of a resveratrol capsule or a placebo once per week, the investigators found that resveratrol caused an acute increase in flow-mediated dilation 45 min after treatment. Similarly, a trial of 40 patients after a myocardial infarction treated with 10 mg resveratrol for 3 months found some improvement in flow-mediated dilation and a decrease in LDL levels [204]. Two small trials exploring the effects of resveratrol on metabolic parameters found that resveratrol improved post-meal glucose levels in patients with impaired glucose tolerance, and reduced markers of oxidative stress in healthy subjects [205, 206]. The most recent small clinical trial reported that resveratrol had no positive effects on non-alcoholic fatty liver disease subjects given 3 g resveratrol daily for 8 weeks [207].

Three recent small controlled trials examined closely the effects of resveratrol on metabolic parameters in healthy and obese humans. Timmers et al. [208] treated 11 obese male patients with 150 mg/day resveratrol for 30 days in a crossover trial. During the treatment period, resveratrol improved insulin sensitivity on the HOMA-IR index, reduced systolic blood pressure, and reduced intrahepatic lipid content. A reduction in circulating levels of glucose and alanine aminotransferase was found in addition to markers of inflammation such as TNF-α. Microarray samples from muscle biopsies showed that resveratrol treatment up-regulated genes from pathways involved in mitochondrial oxidative phosphorylation, in line with the studies done in rodents. The muscle biopsies also showed that there was an increase in AMPK activity, Sirt1 level, and PGC-1α level in tissues from the resveratrol-treated group. A follow-up from this study examining adipose tissues from the subjects was recently reported [209]. This study found that the resveratrol treated subjects had lower mean adipocyte size and upregulation of expression of genes involved in adipogenesis [209]. Two subsequent studies found no effect of resveratrol on metabolic parameters. Yoshino et al. [210] performed a double-blind placebo-controlled trial with 12-week resveratrol supplementation of 75 mg/day. The patients in this study were 29 non-obese postmenopausal women. This trial found no effect of resveratrol on glucose homeostasis, insulin resistance, blood pressure, or markers of inflammation. A subset of the trial subjects had a skeletal muscle and adipose tissue biopsy taken. The biopsy results showed no increase in the expression of Sirt1, AMPK, NAMPT, or PGC-1α. Another randomized double-blinded placebo-controlled trial was done on 24 healthy obese male subjects. After treatment with 500 mg resveratrol daily for 4 weeks resveratrol-treated subjects showed no change in HOMA-IR, HbA_{1c}, cholesterol or triglyceride levels, blood pressure, or body fat composition. They also showed no changes in inflammatory markers or liver function. Similar to the Yoshino

et al. trial, a hyperinsulinemic euglycemic clamp study showed no significant changes with resveratrol treatment. This trial also found that resveratrol treatment did not affect levels of phosphorylated AMPK, or expression levels of PGC-1α, GLUT4, TNFα, or NF-κB [211].

Overall, the results of clinical trials in human present a very cloudy picture. Despite positive results for metabolic parameters and cardiovascular function in some trials, several other trials have shown no effects of resveratrol. These differences could potentially be due to the widely varying doses selected in the trials. The trials have also explored a diverse set of subjects with different clinical backgrounds, including differing degrees of impairment in glucose homeostasis. To better understand the role of resveratrol in humans, future trials will need to be well-designed and include larger patient populations.

Conclusions

As research into the diseases of aging became more prominent, the allure of caloric restriction and its ability to extend organismal lifespan increased. Resveratrol first came to the forefront as a potential chemopreventive molecule, then re-emerged as a potential calorie restriction mimetic, and continues to be studied for therapeutic potential in diseases ranging from cancer to metabolic disease to neurodegeneration. In laboratory models of these diseases of aging, resveratrol has shown an impressive ability to alleviate the symptoms. Unfortunately, like many other drugs that work well in animal models, resveratrol has not translated well to treatment in humans. Resveratrol has a low bioavailability in humans, as it is rapidly glucuronidated and sulfated as it is cleared through the body. So far, clinical trials have shown mixed results for metabolic and cardiovascular diseases. Unfortunately, since resveratrol is a natural substance it is not easily patent-protected, so it is unlikely any company will undertake the investment to perform any large-scale clinical trials that would clarify the therapeutic potential of resveratrol in human disease. Instead, work continues to focus on the molecular mechanisms underlying the beneficial effects of resveratrol in disease models. Two potential targets have come to the forefront as mediators of the metabolic effects of resveratrol: phosphodiesterases, whose inhibition leads to AMPK activation and Sirt1, which is thought to be activated directly. Although there is ongoing discussion in the scientific literature about what the direct target of resveratrol is, there is clear consensus that resveratrol's metabolic action converges on pathways involving AMPK, Sirt1, and PGC-1α. With the lack of results for resveratrol in humans, many have shifted focus to other compounds that more specifically target these pathways. There have been a series of structurally distinct sirtuin activating compounds developed by Sirtris that have been explored for therapeutic potential in diseases of aging [32, 212]. More recently, evidence is mounting that increasing NAD^+ levels in cells may work as an alternative pathway to increase sirtuin activity and improve health [213–216]. As that work is ongoing, we and other groups have begun to explore the potential of phosphodiesterase inhibitors, and more specifically PDE4 inhibitors to treat metabolic diseases. Indeed, the PDE4 inhibitor roflumilast, which is already an FDA-approved treatment for COPD, has been shown to lower blood glucose in individuals with Type 2 diabetes [217]. Other studies have also shown that PDE4 inhibition can recapitulate the effects of resveratrol in diabetic nephropathy and chemoprevention [63, 64]. In the future, work will continue to find molecules that can reproduce the therapeutic potential of resveratrol with a more favorable pharmaceutical profile.

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