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REVIEW

Resveratrol and Diabetes

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■ Abstract

Resveratrol is a stilbene compound, and a phytoalexin, synthesized by plants in response to stressful stimuli, usually caused by infection. It is abundantly present in red wine, ports and sherries, red grapes, blueberries, peanuts, itadori tea, as well as hops, pistachios, and in grape and cranberry juices. The anti-hyperglycemic effects of resveratrol seem to be the result of an increased action of the glucose transporter in the cytoplasmic membrane. Studies on rats with streptozotocin-induced diabetes have demonstrated that the expression of the insulin-dependent glucose transporter, GLUT4, is increased after resveratrol ingestion. Also, resveratrol enhances adiponectin levels, which could be one of the potential mechanisms by which it improves insulin sensitivity. Another important observation is that resveratrol induces the secretion of the gut incretin hormone, glucagon-like peptide-1. Resveratrol is also reported to activate Sir2 (silent information regulatory 2), a SIRT1 homolog, thus mimicking the benefits of calorie restriction. It produces a wide variety of effects in mammalian cells, including activation of AMP-activated protein kinase, which is involved in some of the same metabolic pathways as SIRT1, which may influence other mechanisms via the involvement of nuclear factor kappa B (NF-κB). In the near future, resveratrol-based therapies with either resveratrol or its analogs that have better bioavailability could be useful in the treatment of diabetes and its complications, either alone or in combination with other anti-diabetic drugs.

Keywords: diabetes · FOXO1 · glucose transport · GLUT4 · mitochondrial function · AMPK · SIRT1 · resveratrol

Introduction

Resveratrol (RSV), or 3,5,4-trihydroxystilbene, is a stilbene compound, and a phytoalexin, synthesized by plants in response to stressful stimuli, usually to infection. In addition to its presence in red wine, ports, and sherries, it is also found in red grapes, blueberries, peanuts, itadori tea, hops, pistachios, and in grape and cranberry juices [1-3]. RSV exerts beneficial effects in humans and may be helpful in preventing and treating metabolic diseases such as obesity and diabetes mellitus [4-5].

Anti-hyperglycemic action of RSV

RSV has anti-hyperglycemic effects in diabetic animals, which is associated with its stimulatory action on intracellular glucose transport. In the presence of RSV, glucose uptake is increased by different cells isolated from diabetic rats. Interestingly, in experiments on isolated cells, RSV has been able to stimulate glucose uptake in the absence of insulin [6-7]. The stimulation of glucose uptake induced by RSV seems to be the result of an increased action of the glucose transporter in the cytoplasmic membrane. Studies in rats with streptozotocin-induced diabetes have demonstrated that the expression of the insulin-dependent glucose transporter, GLUT4, after resveratrol ingestion is increased, compared with diabetic animals which were not given RSV [8-10]. It should be mentioned, however, that in some experiments in rats with streptozotocin-induced diabetes, RSV appeared to be ineffective and failed to decrease blood glucose [11-12].

Abbreviations:
AMP - adenosine monophosphate
AMPK - adenosine-monophosphate-activated protein kinase
cAMP - cyclic adenosine monophosphate
COX - cyclooxygenase
CR - calorie restriction
DN - diabetic nephropathy
DNA - deoxyribonucleic acid
DsbA-L - disulfide-bond A oxidoreductase-like protein
FOXO1 - forkhead box protein O1
GLUT4 - glucose transporter 4
GSTM - glutathione-S-transferases Mu
HbA1c - glycosylated hemoglobin
HDL - high-density lipoprotein
LDL - low-density lipoprotein
mRNA - messenger ribonucleic acid
NAD^+ - nicotinamide adenine dinucleotide
NADPH - nicotinamide adenine dinucleotide phosphate
NF-κB - nuclear factor kappa B
NO - nitric oxide
Nrf2 - nuclear factor erythroid 2-related factor 2
PPARγ - peroxisome peroxide proliferator activator receptor γ
ROS - reactive oxygen species
RSV - resveratrol
SIRT1 - sirtuin 1
SIR2 - silent information regulator 2
TNFα - tumor necrose factor α

It has been shown that RSV has anti-diabetic properties *in vitro* and *in vivo* by improving mitochondrial function and energy expenditure [13]. Several studies have demonstrated that RSV enhances adiponectin levels, which could be one of the potential mechanisms by which RSV improves insulin sensitivity. RSV also promotes adiponectin expression and improves insulin sensitivity in adipocytes, an effect which is mediated by inhibition of inflammation [14-15]. Recently, it has been demonstrated that RSV enhances adiponectin cellular levels and multimerization by upregulation of DsbA-L, which in turn is mediated by the FOXO1 and AMPK signaling pathways [16]. Consistent with this finding is that both FOXO1 expression and adiponectin mRNA expression are upregulated by RSV treatment in human visceral adipocytes [17]. However, while RSV treatment has been shown to significantly enhance the expression levels of DsbA-L, it has had little effects on the mRNA levels of adiponectin [15]. The exact reason for this discrepancy remains unknown, but FOXO1 has been found to suppress PPARγ gene expression [15]. It is widely known that PPARγ positively regulates adiponectin gene expression and secretion. In another study performed on isolated human adipocytes, RSV has effectively prevented insulin resistance induced by cell exposure to conjugated linoleic acid. In these experiments, insulin-stimulated glucose transport is elevated in adipocytes incubated with conjugated linoleic acid and RSV, compared with cells exposed to conjugated linoleic acid alone. This effect may be partially explained by an increase in PPARγ activity [18].

Apart from this effect, RSV has recently been suggested to induce the secretion of the gut incretin hormone glucagon-like peptide-1. A four week supplementation with 150 mg daily of RSV in obese patients, has not affected fasting or postprandial plasma levels of incretin hormone, but suppressed postprandial glucagon responses [19].

Resveratrol as a caloric restriction mimetic - the role of AMPK and SIRT1

RSV is the most studied caloric restriction mimetic. As one of the molecules through which calorie restriction improves lifespan extension or delays age-related diseases, initial studies of aging in yeast have identified silent information regulator 2 (Sir2), which is a NAD^+-dependent deacetylase. Homologues of Sir2 in higher eukaryotic organisms are referred to as sirtuins. SIRT1, the sirtuin that is most closely related to Sir2, is one of seven sirtuins in mammals. The beneficial effects of calorie restriction involve the function of SIRT1, which is induced by calorie restriction in various tissues. The significance of SIRT1 on the effects of calorie restriction has been demonstrated using genetically altered mice. Bordone *et al.* have reported that Sirt1 transgenic mice exhibited a calorie restriction-like phenotype, with reduced levels of blood cholesterol, adipokines, insulin, and fasting glucose and greater glucose tolerance than control mice [20].

RSV is reported to activate Sir2 (silent information regulatory 2), a SIRT1 homolog, thus mimicking the benefits of calorie restriction (without really restricting calorie intake) such as increasing lifespan in yeast, worms, flies, and fish [21-24]. Recently, the assumption that activation of Sir2, by direct binding with RSV, is responsible for extended lifespan has been challenged in experiments in multiple organisms [25-34]. For example, RSV is known to produce a wide variety of effects in mammalian cells, including activation of AMP-activated protein kinase (AMPK), which is involved in some of the same metabolic pathways as SIRT1, and which directly phosphorylates PGC-1α.

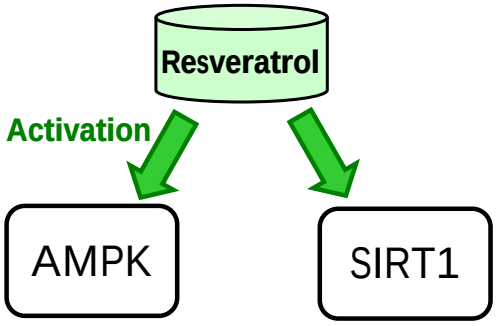

Figure 1. The main anti-hyperglycemic actions of resveratrol are attributed to the activation of SIRT1 with the involvement of AMPK.

[35-36]. SIRT1 may activate the kinase upstream of AMPK, but this pathway does not appear to be necessary for AMPK stimulation by RSV [36]. Recently, it has been reported that SIRT1 is essential for moderate doses of RSV to stimulate AMPK and improve mitochondrial function in vitro and in vivo [37].

In RSV-induced improvement of insulin's action, a key role is attributed to the activation of SIRT1 and AMPK (**Figure 1**). Activation of these enzymes by RSV has been demonstrated in numerous animal studies [38-42]. The importance of AMPK in RSV action has been additionally demonstrated in experiments on AMPK-deficient mice. In AMPK-deficient mice fed with a high-fat diet, RSV has been ineffective and has not reduced body fat nor has it improved insulin action [43]. However, more recent studies on the role of SIRT1 in the mechanism of RSV action suggest that its action should be reconsidered, since they have shown that RSV is not a direct activator of Sirt1 [44]. Although the exact mechanisms of RSV action are still unclear, there is no doubt that this compound is able to improve insulin action in different animal models of insulin resistance [45-46].

RSV is not a SIRT1-specific activator, and the mechanism by which it activates SIRT1 remains largely unclear. Although RSV may directly activate SIRT1 allosterically, AMPK is required upstream for the activation of SIRT1 by RSV [47-48]. In addition, Park *et al*. [49] have reported that RSV activates SIRT1 through the activation of AMPK, via the inhibition of phosphodiesterase 4 and the elevation of cAMP in cells, thereby providing a novel mechanism which explains the RSV-induced activation of SIRT1 [50]. A recent study reported by Price *et al*. have demonstrated a direct link between SIRT1 and the metabolic benefits of RSV. These authors reported that a moderate dose of RSV first has activated SIRT1 and then induced the de-acetylation of liver kinase B 1 and AMPK activation, leading to increased mitochondrial biogenesis and function [51]. Moreover, a high dose of RSV may directly activate AMPK, independently of SIRT1 [52].

RSV has also been documented to restore secretory function of β-cells disrupted by cytokine action; the decrease in glucose-stimulated insulin secretion resulting from exposure to cytokines has been found to be fully restored when pancreatic islets were pretreated with RSV. This protective action of resveratrol against cytokine-induced dysfunction of β-cells is suggested to result from the ability of RSV to activate NAD^+-dependent protein deacetylase Sirt1 [53].

Resveratrol and COX-1 inhibition

There have been several reports on RSV, including a study of RSV as an inhibitor of arachidonate metabolism via interactions with 5-lipoxygenase and cyclooxygenase (COX) pathways in leukocytes [54]. These reports have attributed the effects of RSV to the inhibition of prostaglandins synthesis via the inhibition of COX-1 [55]. They have shown that RSV can discriminate between COX-1 and COX-2, suggesting that it could result in the elimination of prostaglandin synthesis via COX-1 [56].

Resveratrol, NF-κB, and glutathione-S-transferase

RSV and other polyphenols have a low bioavailability in humans. However, *in vivo*, RSV and its metabolites accumulate in human cells in a tissue-specific and dose-dependent manner. A six-week supplementation regime with RSV has suppressed the binding of NF-κB, reduced reactive oxygen species (ROS) generation, and reduced the levels of TNFα and interleukin-6 (IL-6) in mononuclear cells. Furthermore, the plasma levels of TNFα and CRP have been significantly decreased. There have been no significant changes in fasting plasma concentrations of cholesterol (total, LDL, and HDL), triglycerides, or leptin in RSV-treated patients compared to healthy individuals receiving placebo [57]. A high-fat, high-carbohydrate diet induces inflammation and oxidative stress [58]. Healthy humans on a high-fat, high-carbohydrate diet, taking a single-dose supplement of RSV and

other grape polyphenols, had a significantly increased messenger RNA (mRNA) expression of the NADPH dehydrogenase (quinone) 1 and glutathione S-transferase-p1 genes, implying a strong anti-oxidant effect [59].

RSV exerts an inhibitory influence on cytokine action. Lee *et al*. have recently reported that exposure of isolated rat pancreatic islets to cytokines resulted in numerous unfavorable effects, such as increased DNA binding of NF-κB and increased production of nitric oxide (NO). All these deleterious effects appeared to be suppressed by RSV. The protective effect of RSV against cytokine-induced toxicity has been additionally confirmed in experiments demonstrating increased viability of islets exposed to cytokines and RSV, compared with islets incubated with cytokines but without resveratrol [60].

Resveratrol and clinical trials in humans

In a recent study among obese patients who have been administered a dietary supplementation of RSV (150 mg/d) for 30 days, there were no changes in fasting and postprandial incretin hormone plasma levels, but suppression on postprandial glucagon responses were documented [61]. Another study has been conducted among sixty-two patients with type 2 diabetes who received either oral hypoglycemic agents alone or oral hypoglycemic drugs plus RSV 250 mg/d for three months. Those receiving RSV showed an improvement in HbA1c after the completion of three months, suggesting an improvement of glycemic control among patients with type 2 diabetes after supplementation with RSV [62]. Another clinical trial enrolling nineteen patients with type 2 diabetes receiving RSV 2 x 5 mg for four weeks versus placebo, showed a decrease in insulin resistance via a RSV-induced amelioration of oxidative stress [63]. In another study with twenty-four obese patients who were administered high-dose RSV for four weeks, RSV has failed to show any significant improvement in insulin resistance [64].

Resveratrol, diabetic nephropathy, and diabetic neuropathy

Neurons are extremely susceptible to oxidant-induced damage which may be due to their high rate of oxygen consumption and low levels of antioxidant defense enzymes. Traditionally, the protective actions of RSV in diabetic neuropathy were attributed to its intrinsic radical scavenger properties. However, recently many other associated or separate mechanisms like upregulation of Nrf2, SIRT1 and inhibition of NF-κB have been proposed for its beneficial effect against nerve dysfunction [65].

Moreover, RSV has been demonstrated to reduce the expression of glutathione-S-transferases Mu (GSTM) in diabetic rats. *In vitro*, RSV has inhibited the proliferation of mesangial cells caused by high glucose and downregulated GSTM expression in a dose-dependent manner. These findings are suggestive of RSV's contribution to preventing the progression of diabetic nephropathy (DN). The reno-protection by RSV is in part mediated through the inhibition of high glucose-induced rat mesangial cell proliferation and downregulation of GSTM expression [66].

Conclusion

It has been demonstrated that RSV has anti-hyperglycemic effects by improving mitochondrial function and energy expenditure. Its action is mainly explained by the influence on AMPK and SIRT1 metabolic pathways, which may influence other mechanisms as the involvement of NF-κB. In the near future, RSV-based therapies, with either RSV or its analogs that have better bioavailability, could be useful in the treatment of diabetes mellitus and its complications, such as diabetic neuropathy and diabetic nephropathy, either alone or in combination with other anti-diabetic drugs. Further clinical studies are required to determine the usefulness of RSV in the management of diabetes mellitus and its complications.

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