Resveratrol plays important role in protective mechanisms in renal disease - mini-review

Resveratrol desempenha importante papel no mecanismo de proteção na doença renal - mini-revisão

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Abstract

Resveratrol (RESV) is a polyphenolic compound found in various plants, including grapes, berries and peanuts, and its processed foods as red wine. RESV possesses a variety of bioactivities, including antioxidant, anti-inflammatory, cardioprotective, antidiabetic, anticancer, chemopreventive, neuroprotective, renal lipotoxicity preventative, and renal protective effects. Numerous studies have demonstrated that polyphenols promote cardiovascular health. Furthermore, RESV can ameliorate several types of renal injury in animal models, including diabetic nephropathy, hyperuricemic, drug-induced injury, aldosterone-induced injury, ischemia-reperfusion injury, sepsis-related injury, and endothelial dysfunction. In addition, RESV can prevent the increase in vasoconstrictors, such as angiotensin II (AII) and endothelin-1 (ET-1), as well as intracellular calcium, in mesangial cells. Together, these findings suggest a potential role for RESV as a supplemental therapy for the prevention of renal injury.

Keywords: angiotensin II; endothelin-1; polyphenols; protective agents.

Resumo

Resveratrol (RESV) é um composto fenólico encontrado em várias plantas, como a uva e amendoim, e seus produtos derivados, como o vinho tinto. RESV possui uma variedade de bioatividades, incluindo antioxidantes, anti-inflamatória, cardioprotetoras, antidiabetes, anticancerígeno, quimiopreventivo, neuroprotetor, lipotoxicidade renal, e efeitos protetores renais. Numerosos estudos demonstraram que os polifenois promovem a saúde cardiovascular e podem reparar vários tipos de lesões renais em modelos animais, incluindo a nefropatia diabética, hiperuricemia, lesão induzida por droga, lesão induzida pela aldosterona, lesão de isquemia-reperfusão, lesões relacionadas com sepsis, e disfunção endotelial. Além disso, RESV pode prevenir o aumento de vasoconstritores, tais como angiotensina II (AII) e endotelina-1 (ET-1), bem como o cálcio intracelular, em células mesangiais. Em conjunto, estes resultados sugerem um importante papel para o RESV como uma terapia complementar na prevenção de lesões renais.

Palavras-chave: angiotensina II; endotelina-1; polifenóis; substâncias protetoras.

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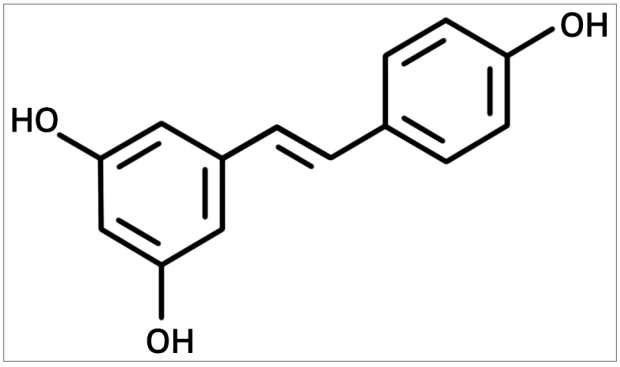
Introduction

Resveratrol, trans-3,5,4′-trihydroxydroxystilbene (RESV) (Figure 1), is a polyphenolic phytoalexin of natural occurrence in many plants and its processed products, such as grapes, berries, red wine, and peanut,[1] that presents numerous health benefits. RESV is one of the most important natural stilbenes and has been extensively studied. It has been shown to possess health-promoting properties, such as antioxidation, anti-inflammation, cardioprotection, antidiabetes, anticancer, chemoprevention, and neuroprotection.[2-6] Several studies performed in recent years have reported the potential health benefits of RESV in cardiovascular and renal disease.

RESV is a potent antioxidative agent that can act as a reactive oxygen species (ROS) scavenger and iron chelator.[7] In addition, RESV may have numerous protective effects against age-related disorders, including renal diseases, through the activation of

Figure 1. Structure of resveratrol.



the NAD^+-dependent deacetylase, silent mating type information regulation 2 homolog surtuin 1 (SIRT1). This protein has been implicated in calorie-restricted lifespan extension and delayed onset of age-related diseases. Furthermore, SIRT1 may regulate multiple cellular functions, including apoptosis, mitochondrial biogenesis, inflammation, glucose/lipid metabolism, autophagy, and adaptations to cellular stress, through the deacetylation of target proteins.[7]

An excess of ROS is involved in a variety of diseases and in the aging process, which implicate numerous cellular response pathways.[8,9] Oxidative stress is induced by an imbalance between ROS production and antioxidant defenses; therefore, exogenous antioxidants or the modulation of antioxidant enzymes can be expected to reduce oxidative stress. Previous studies have shown that RESV can directly scavenge ROS.[10] In addition to scavenging ROS, exogenously administered RESV modulates the expression and activity of antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, either through transcriptional regulation via nuclear factor E2-related factor 2 (Nrf2), activator protein (AP) 1, forkhead box protein O (FOXO), or through enzymatic modifications.[11]

Protective mechanism of RESV in renal diseases

Silent mating type information regulation 2 homolog (SIRT1)

Aging is an inevitable process that affects all organs; age-related disruption of cellular homeostasis results in reduced responsiveness to physiological stress and organ dysfunction. Seven mammalian sirtuins exist, and SIRT1 is the sirtuin most closely related to Sir2.[12] SIRT1 deacetylates several substrates and is an important regulator of a wide variety of cellular processes, including stress responses, cell survival, mitochondrial biogenesis, and metabolism in response to cellular energy and the redox status.[12,13] RESV has been shown to activate SIRT1 through multiple mechanisms.

Park *et al.*[14] demonstrated that RESV activates SIRT1 through the activation of AMP-activated protein kinase (AMPK). This was achieved via inhibition of phosphodiesterase 4 (PDE 4) and elevation of cyclic adenosine monophosphate (cAMP) in cells, thereby providing a new mechanism to explain SIRT1 activation by RESV.[14] A direct link between SIRT1 and the metabolic benefits of RESV were demonstrated in a more recent study by Price *et al.*[15]

SIRT1, p53, and Cisplatin

Cisplatin is a chemotherapeutic agent widely used for the treatment of malignant tumors in solid organs. However, a fundamental dose-limiting factor of cisplatin treatment is nephrotoxicity. Direct DNA damage, inflammatory injury, and oxidative stress have been recognized as the mechanisms by which cisplatin induces renal injury.[16]

In particular, cisplatin-induced apoptotic cell death after DNA damage is the major mechanism for cytotoxicity in renal tubule cells.[16] In response to DNA damage, p53 can induce cell cycle arrest and apoptosis; p53-induced apoptosis affects transcriptional activity and members of the Bcl-2 family in mitochondria.[17] In kidney disease, p53 is involved in the apoptotic process observed in ischemic injury and aristocolic acid-induced nephrotoxicity.[18]

Furthermore, it has been demonstrated that downregulation of p53 by small interference RNA is an effective way of preventing or treating cisplatin-induced nephrotoxicity.[19] Activation of p53 is regulated by posttranslational modifications of p53, such as ubiquitination, phosphorylation, and acetylation.[20] Notably, acetylation of p53 affects its affinity to bind DNA.[21]

Kim *et al.*[16] demonstrated that activation of SIRT1 by RESV reduces cisplatin-mediated p53 acetylation and ameliorates cisplatin-induced kidney injury through inhibition of the apoptotic pathway. SIRT1 protein expression was decreased by cisplatin in mouse proximal tubular cells and the SIRT1 activator, RESV, reduced cisplatin-induced p53 acetylation and apoptosis. Through *in vivo* experimentation, the authors revealed that SIRT1 activation by RESV decreased cisplatin-induced apoptosis in the kidney.[16]

Stiaccini *et al.*[22] were able to demonstrate that RESV is a strong SIRT1 activator with high activity on SIRT1 protein expression. In a recent study published by Schirmer *et al.*[23] SIRT1 mRNA levels were not changed in zebrafish exposed to 20-200 µM doses of RESV for 30 and 60 min. However, *in vitro* studies using rat cells[24] and human visceral adipocytes[25] showed that longer incubation times were required to observe changes in SIRT1 mRNA and protein expression. Indeed, in the *in vitro* study by Stiaccini *et al.*,[22] cells were incubated for 24 h with RESV 200 nM in order to measure increases in SIRT1 expression. However, RESV was a weak activator of the cell signaling system as it caused increases in SIRT1 expression.[22]

SIRT1, Smad3, and 5/6 nephrectomized

It is well documented that Smad3 phosphorylation is a key signaling mechanism underlying fibrogenesis in response to fibrogenic mediators, such as TGF-β, angiotensin II (AII), and advanced glycation end products.[26] The evidence to suggest that Smad3 acetylation is also an important signaling pathway leading to ECM production, includes data from experiments using a rodent model of CKD and cultured cells treated with TGF-β1. Significantly elevated levels of Smad acetylation were observed in rats with 5/6 nephrectomy and following TGF-β1 treatment in cultured cells. Furthermore, RESV significantly reduced Smad3 acetylation levels in the remnant kidney of 5/6 nephrectomized rodents and in cultured cells subjected to TGF-β1 treatment. Knocking down SIRT1 in cultured cells increased acetylation levels of Smad3 and attenuated the effect of RESV on Smad3 acetylation.[26]

RESV has been shown to protect the remnant kidney of 5/6 nephrectomized rats, a rodent model of chronic kidney disease (CKD).[27] In the same model, RESV treatment significantly attenuated the decline of glomerular filtration rates (GFR). In cultured mesangial cells, RESV reduced extracellular matrix (ECM) protein expression induced by tumor growth factor β1 (TGF-β1), and its effects were dependent on SIRT1. SIRT1 inhibits TGF-β1 signaling by deacetylating Smad3. The loss of the allele for SIRT1 aggravates kidney damage in 5/6 nephrectomized mice. Furthermore, knocking down SIRT1 enhances the effects of TGF-β1 on the ECM, and markedly suppresses the protective effects of RESV. This study provides strong evidence that SIRT1 protects the kidney in a rodent model of CKD through inhibition of TGF-β1 signaling by deacetylating Smad3, and reducing kidney fibrosis.[27] In summary, RESV treatment significantly attenuates renal damage in nephrectomized rats. The renal protective effects of RESV are associated with SIRT1 activation, and a reduction in Smad3 acetylation and TGF-β1 signaling.[27]

Resv as an antioxidant-forkhead box protein O1 (FoxO1) and superoxide dismutase (SOD)

RESV regulates the expression of target genes of FOXO, and may regulate cell survival and/or apoptosis through global modulation of gene expression via deacetylation of FOXO transcription factors.[28] SIRT1 plays an intermediary role in the action of RESV on FoxO1-mediated gene expression. The dephosphorylated form of FoxO1, which is distributed in the nucleus, is deacetylated by SIRT1, and upregulates the expression of gluconeogenic genes.[29]

FoxO1 belongs to a family of transcription factors that includes FoxO3a, FoxO4, and FoxO6 in mammals. These proteins play important roles in aging, cell metabolism, insulin resistance, and resistance to oxidative stress.[30] Recently, it was demonstrated in a rat model of diabetes that hyperglycemia induces FoxO1 phosphorylation and suppresses expression of FoxO1 in the kidney. Furthermore, H_2O_2 negatively regulated FoxO1 by PI3 kinase/AKT-dependent phosphorylation, and FoxO1 dowregulated the expression of catalase in mesangial cells.[31]

In a recent study by Kitada *et al.*[32] the authors demonstrated that RESV ameliorated renal injury and enhanced mitochondrial biogenesis with manganese superoxide dismutase (Mn-SOD) dysfunction in the kidney of *db/db* mice. This was achieved through improvements in the oxidative stress status in the kidney by ROS scavenger activity, normalization of Mn-SOD dysfunction, and partial rescue of glucose-lipid metabolism.[32]

Subauste & Burant[33] reported that excessive oxidative stress caused a decrease in total FoxO1 protein *in vitro*, an observation that was also made in db/db mice *in vivo*. The authors postulated that RESV protected adipocytes by increasing FoxO1/SIRT1-dependent antioxidant defenses.[33]

FoxO1, SOD and Diabetic Nephropathy

Oxidative stress has emerged as a critical pathogenic factor in the development DN. ROS are thought to play multiple roles in the pathogenesis and progression of DN since ROS production in the kidney is high in the presence of diabetes and DN.[34]

In a rat model of diabetes, RESV protects the kidney from oxidative stress induced by elevated expression of fibronectin and collagen IV. Under stress conditions, high levels of ROS have been shown to inhibit phosphorylation and acetylation of FoxO1 proteins, resulting in enhanced FoxO1-DNA binding activity.[35]

FoxO1 subsequently controls ROS levels by transcriptional regulation of a multilayered system.[35] Suppressed FoxO1 mRNA levels and elevated phosphor-FoxO1 levels correlated with the downregulation of catalase mRNA in the kidney of diabetic rats.[35] RESV has been shown to increase both FoxO and SIRT1 levels in multiple cell types,[29,36,37] and this was associated with increased longevity and defense against oxidative stress.[37]

Oxidative stress has been implicated in the pathogenesis of diabetic nephropathy (DN).[35] However, the mechanisms involved in ROS generation in diabetes have yet to be elucidated. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[38] and endothelial nitric oxide synthase (eNOS) uncoupling[38] in diabetic glomeruli have been shown to be major sources of ROS production in a rat model of DN.[38]

Wu *et al*.[35] observed that malondialdehyde (MDA), a product of lipid peroxidation, is a sensitive indicator of ROS levels. In that study, the authors observed that increased ROS levels and decreased SOD activity correlated with increased levels of fibronectin and collagen. These data suggest that enhanced oxidative stress increases expression of fibronectin and collagen IV. These findings also indicate that overproduction of ROS in diabetes is associated with the progression of DN, and that antioxidants may provide a useful treatment.[35]

Effects of resv on nitric oxide (NO)

Lipopolysaccharides (LPS) and RESV

The effect of LPS is accompanied by an elevation of NO in plasma and organs, which was not observed in the presence of RESV. There is much debate on this topic in the literature; some studies demonstrate the lack of NO involvement in the mechanism of action of RESV,[39] whereas others indicate the effects of RESV are mediated through NO.[40] Regardless, the data support the use of RESV as therapeutic treatment of endotoxemia-induced sepsis and endotoxemia-induced death.[41]

Subacute treatment (7 days) with RESV was effective at preventing lipopolysaccharide (LPS)-induced lethality in mice.[42] In prior studies, RESV attenuated LPS-induced renotoxicity,[43] neurotoxicity[44] as well as acute phase response in rats.[45]

Sebai *et al*.[43] reported a clear reduction in LPS-induced oxidative stress and lethality after subacute pretreatment with RESV, whereas acute RESV treatment administered 12 and 24 h before intoxication failed to reduce the lethality of LPS in mice.

Hypertension, Endothelial dysfunction, and RESV

Early treatment with RESV attenuates the development of hypertension and prevents endothelial dysfunction in spontaneously hypertensive rats (SHR). The mechanisms involved appear to be threefold: 1) attenuation of vascular oxidative stress resulting in increased NO bioavailability, 2) prevention of eNOS uncoupling possibly via inhibition of tetrahydrobiopterin (BH_4) oxidation by free radicals, and 3) increased expression of important proteins involved in the NO pathway, namely eNOS and soluble guanylyl cyclase (sGC).[46]

Endothelial dysfunction is a hallmark of hypertension.[47] Impairment of NO synthesis and/or bioavailability causes endothelial dysfunction. Oxidative stress, particularly induced by superoxide, scavenges NO by forming highly reactive peroxynitrite radicals.[48,49] Oxidative stress has also been shown to uncouple eNOS resulting in impaired endothelium-dependent relaxations.[50] Uncoupled eNOS generates ROS instead of NO, thereby reducing NO production and increasing oxidative stress.[51] In summary, oxidative stress can contribute to endothelial dysfunction by scavenging NO and uncoupling eNOS.

Numerous studies have shown that RESV significantly alters the NO response and increases endothelium dependent vasorelaxation.[52] RESV also increases expression of eNOS in cell culture studies.[53] The effects of RESV and other red wine polyphenols were assessed in spontaneously hypertensive rats (SHR). However, the findings of these studies are

not conclusive as most report no change in blood pressure,[54] and only one study in female rats reported a decrease in blood pressure.[55]

Bhatt *et al*.[46] demonstrated that RESV significantly attenuates the rise in blood pressure observed in SHR. Consequently, several studies have investigated the effects of RESV and other red wine polyphenols on endothelial function.[54-56] No change in blood pressure was observed following chronic RESV treatment in SHR in studies by Thandapilly *et al*.[54] It is interesting to note that in both studies, RESV was administered to adult SHR with established hypertension. In another study, RESV treatment normalized endothelial function and significantly lowered blood pressure in SHR.[46] Thus, it appears that the beneficial effects of RESV treatment on blood pressure may be related to events occurring prior to increases in blood pressure.

Protein nitrosylation is an indicator of peroxynitrite formation in vascular tissue. SHR had significantly elevated nitrotyrosine levels in the aortic homogenate as compared to Wistar Kyoto rats (WKY). Furthermore, elevated nitrotyrosine levels were normalized by RESV treatment. Thus, RESV prevents NO scavenging and increases its biological availability in SHR by lowering oxidative stress.[46]

In addition to scavenging NO, another important mechanism by which oxidative stress can contribute to endothelial dysfunction is by uncoupling the eNOS enzyme. The physiological consequences of eNOS uncoupling are particularly harmful, since it reduces the production of NO and results in formation of superoxides, thereby further increasing oxidative stress.[56] Superoxide production is sensitive to the eNOS inhibitor, L-NNA, suggesting that eNOS is most likely uncoupled in SHR. Interestingly, treatment with RESV normalizes superoxide production, which is suggestive of a novel role for RESV in preventing eNOS uncoupling.[51]

It is well recognized that oxidation of the cofactor tetrahydrobiopterin (BH_4) to BH_2 provides an important contribution to eNOS uncoupling. Interestingly, BH_4 supplementation abolished elevated superoxide production in SHR. This finding indicates that vascular oxidative stress contributes to endothelial dysfunction and hypertension by uncoupling eNOS, and possibly by oxidation of BH_4. It has been reported that BH_4 supplementation starting at an early age (5-16 weeks of age) suppressed the development of hypertension in SHR.[46] Furthermore, upregulated eNOS protein expression was observed in SHR as well as WKY rats receiving RESV, which is suggestive of transcriptional upregulation. Together, these data suggest that eNOS uncoupling plays an important role in endothelial dysfunction. RESV prevents eNOS uncoupling and rescues endothelial function in SHR.[46]

The effect of RESV in the presence of sodium nitroprusside (SNP) was investigated in SHR and WKY rats. SNP-induced vasorelaxation was similar in both groups. RESV significantly increased relaxation in response to higher doses of SNP in SHR.[46] The proximal mediator for NO-induced vasorelaxation is soluble guanylyl cyclase (sGC), and its β1 subunit is responsible for the responsiveness of sGC to NO.[57] Basal expression of sGC was higher in SHR as compared to WKY rats, which could be explained by a compensatory increase in response to reduced NO bioavailability. SHR and WKY rats treated with RESV demonstrated a greater expression of the sGC β1 subuni.[46]

Effects of RESV on renal organic ion transporters

Uric acid (UA) and RESV

Hyperuricemia, as a metabolic disorder, is usually associated with gout, kidney disease, hypertension, cardiovascular disease, inflammation, diabetes, and metabolic syndrome.[58] Reabsorption and secretion of uric acid (UA) are controlled by specific organic anion transport proteins in renal apical and basolateral membranes. Urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9) mediate urate reabsorption from the lumen of kidney tubules into the blood, and maintain blood urate homeostasis.[59] Human ATP-binding cassette, subfamily G, 2 (ABCG2) is located in the brush border membranes of renal proximal tubules to control urate secretion, and its gene mutation in *Xenopus* oocytes results in a reduction of the rate of urate transport.[60] ABCDG2 is associated with hyperuricemia and gout in Caucasian, Han Chinese, Japanese, and African-American subject.[61]

Uricosuric agents lower urate levels by regulating renal URAT1, GLUT9, and OAT1.[59] Therefore, these renal urate transport-related proteins present important targets for the prevention and treatment of hyperuricemia and gout.[62] Renal organic cation/carnitine transporters (OCTs and OCTNs) are involved in the excretion of organic cations, including organic drugs and their metabolites. Expression changes

of renal OCTs and OCTNs impair kidney organic cation balance and induce renal solute toxicity.[63,64] Downregulation of renal mOCT1, mOCT2, mOCTN1, and mOCTN2 has been demonstrated in hyperuricemic mice with renal injury.[65]

Uromodulin (UMOD), the most abundant protein in normal urine, is associated with hyperuricemia and kidney disease.[66] UMOD-deficient mice have reduced creatinine clearance and upregulated expression of major distal electrolyte transporters.[67] UMOD is a useful marker for renal dysfunction in hyperuricemia associated with abnormalities in renal organic ion transporters.[67]

In oxonate-induced hyperuricemic mice, RESV reduced serum urate levels and enhanced urate excretion. The antihyperuricemic effects of RESV were related to the regulation of renal mURAT1, mGLUT9, mABCG2, and mOAT1.[68] Moreover, improvements of renal function, as well as upregulation of renal mOCT1, mOCT2, mOCTN1, and mOCTN2 protein levels, contributed to the renoprotective effects of RESV.[68]

Serum urate level is most often linked to renal urate excretion. Renal urate transport becomes increasingly relevant in blood urate homeostasis. RESV reduces serum urate levels by downregulating mGLUT9 expression. As a consequence, this inhibits urate reabsorption, downregulates mABCG2, and upregulates mOAT1 expression to increase urate secretion in the kidney of hyperuricemic mice.[68] Therefore, it has been suggested that RESV exhibits antihyperuricemic effects through the regulation of different renal urate transport-related proteins to enhance renal urate excretion in hyperuricemic mice.[52]

Hyperuricemia is one of several well-described risk factors contributing to kidney function disorders. Creatinine, a substrate of OCT1 and OCT2 in renal proximal tubules, is also considered a biomarker of renal dysfunction.[64] Consistent with the amelioration of kidney dysfunction, renoprotective effects of RESV may be mediated by increased renal mOCT1 expression in hyperuricemic mice.[68,69]

Effects of resv on angiotensin II (AII) and endothelin-1 (ET-1) system

Angiotensin II (AII), Endothelin-1 (ET-1) and RESV

There is an increasing body of evidence that implicates the renin-angiotensin system (RAS) in the pathogenesis of chronic vascular disease. AII is an important component of RAS and a vasoactive peptide.[70] It appears from the literature that AII is able to *turn on* the synthesis of ET-1 in several vascular cell types, including cultured vascular smooth muscle cells.[71] ET-1 was shown to mediate the growth-promoting effect of AII, and thus plays an important role in cardiovascular disease and vascular remodeling.[72]

AII has also been shown to stimulate membrane-bound NADPH oxidase, which generates oxygen species in vascular smooth cells.[73] Previous reports indicate that ROS mediate ET-1 gene induction within cardiac fibroblasts, vascular endothelial cells, and smooth muscle cells.[73]

Zhang *et al.*[71] demonstrated that RESV exerts an antioxidant-like inhibitory effect on smooth muscle cellular proliferation and ET-1 gene expression induced by AII. In addition, RESV suppresses the extracellular signal-regulated kinase (ERK) pathway, reduces AII-induced cell proliferation, and reduces ET-1 gene expression. It is plausible that the AII-activated signaling pathway consists of a number of redox-sensitive steps, and that RESV treatment modulates the redox state of the cell through its antioxidants properties. In summary, RESV inhibits AII-induced ROS formation, ERK phosphorylation, ET-1 gene expression, and cell proliferation in vascular smooth muscle cells.[71]

Albertoni *et al.*[73] demonstrated that 24-h UA treatment in mesangial cells stimulated ET-1, AII, and the renin-angiotensin system. In further experiments by the same group (article in press) UA induced an increase in pre-proET-1 (ppET-1) mRNA expression and peptide synthesis, angiotensinogen (AGT) mRNA expression, and AII peptide production after 6 and 12 h. Furthermore, the study demonstrated that RESV reduced UA-induced ppET-1 gene expression and the production of AII and ET-1 in mesangial cells, suggesting that RESV is able to minimize the impact of these hormones on glomerular function (article in press).

In mesangial cells, UA induces an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$).[73] This increase in $[Ca^{2+}]_i$ is inhibited by RESV, providing the first direct evidence that UA induces an increase in $[Ca^{2+}]_i$ that is suppressed by RESV (article in press). The main novel finding of this study is that UA-induced increases in AII and $[Ca^{2+}]_i$ in smooth muscle cells are attenuated by RESV. This is achieved, at least in part, by RESV preventing the detrimental effects of hyperuricemia on glomerular function that lead to glomerulosclerosis (article in press).

Conclusions

RESV exerts protective effects against acute and chronic kidney injury through various mechanisms. RESV activates SIRT1 through multiple mechanisms, such as activation of AMPK via the inhibition of PDE 4 and the elevation of cAMP, downregulation of p53 by siRNA. SIRT1 subsequently inhibits TGF-β1 signaling by deacetylating Smad3.

RESV ameliorates renal injury and enhances mitochondrial biogenesis with Mn-SOD. Furthermore, RESV regulates the expression of FOXO target genes and may regulate cell survival and/or apoptosis through global modulation of gene expression via deacetylation of FOXO transcription factors. RESV has been shown to protect the kidney of diabetic rats from oxidative stress induced by increased expression of fibronectin and collagen IV. Additional benefits of RESV include attenuation of LPS-induced renotoxicity, neurotoxicity, and acute phase response in rat. RESV significantly alters NO response and increases endothelium-dependent vasorelaxation. It also reduces serum urate levels and enhances urate excretion in hyperuricemia. Finally, RESV prevents some of the effects of hyperuricemia on glomerular function that lead to glomerulosclerosis. Taking this into consideration, RESV may provide a useful supplemental treatment for preventing renal injury.

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