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Review

Resveratrol and diabetes: from animal to human studies ☆

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ABSTRACT

Diabetes mellitus is a serious disease affecting about 5% of people worldwide. Diabetes is characterized by hyperglycemia and impairment in insulin secretion and/or action. Moreover, diabetes is associated with metabolic abnormalities and serious complications. Resveratrol is a natural, biologically active polyphenol present in different plant species and known to have numerous health-promoting effects in both animals and humans. Anti-diabetic action of resveratrol has been extensively studied in animal models and in diabetic humans. In animals with experimental diabetes, resveratrol has been demonstrated to induce beneficial effects that ameliorate diabetes. Resveratrol, among others, improves glucose homeostasis, decreases insulin resistance, protects pancreatic β-cells, improves insulin secretion and ameliorates metabolic disorders. Effects induced by resveratrol are strongly related to the capability of this compound to increase expression/activity of AMPK and SIRT1 in various tissues of diabetic subjects. Moreover, anti-oxidant and anti-inflammatory effects of resveratrol were shown to be also involved in its action in diabetic animals.

Preliminary clinical trials show that resveratrol is also effective in type 2 diabetic patients. Resveratrol may, among others, improve glycemic control and decrease insulin resistance. These results show that resveratrol holds great potential to treat diabetes and would be useful to support conventional therapy. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clincial findigns to improved patient outcomes.

1. Introduction

Diabetes mellitus is a serious metabolic disease affecting 382 million people worldwide in 2013. The number of diabetics is estimated to be dramatically increasing to 592 million in 2035 [1]. According to the recent classification based on the etiology, clinical symptoms and way of treatment, diabetes is divided into different types. Among them, type 1 and type 2 diabetes are the most frequent and comprise more than 90% of all cases. Diabetes is associated with metabolic abnormalities and serious complications. Long-term complications include, among others, angiopathies, cardiovascular disorders, blindness, renal failure, neuropathies and increased risk of cancer [2]. Therefore, management of diabetes should be very effective to prevent diabetes complications and to improve quality of life of diabetic patients.

Since the discovery of insulin in the early 1920s, there has been tremendous progress in the treatment of diabetes. Pharmacological treatment is recently very effective and offers a wide spectrum of anti-diabetic drugs, such as human insulin, α-glucosidase inhibitors, dipeptyl peptidase-4 inhibitors, incretin analogues, biguanides, insulin secretagogues, insulin sensitizers and intestinal lipase inhibitor [3,4]. However, despite many efforts, currently used therapies are accompanied by side effects, namely hypoglycemia, gastrointestinal problems, body weight gain and other [3]. Therefore, new drugs and natural compounds are continually being tested to better prevent and treat diabetes [5].

Among various tested compounds, much attention has been paid to resveratrol because of its pleiotropic activity. Resveratrol (3,5,4'-trihydroxystilbene) is a natural, biologically active compound present in different plant species and having beneficial effects in both animals and humans. Resveratrol is known to induce, among others, anti-oxidative [6], cardio-protective [6,7], anti-cancer [8,9], anti-inflammatory [10], neuro-protective [11,12] and anti-obesity [13,14] effects.

In the last decade, anti-diabetic properties of resveratrol have been extensively studied in various animal models. The obtained results show that resveratrol is capable of inducing beneficial effects in diabetic animals and thereby ameliorates diabetes [13,15,16]. Moreover, human studies have been performed, providing interesting and promising data. This review summarizes the effects of resveratrol in animal models of diabetes and in diabetic humans.

2. Resveratrol and type 1 diabetes

Type 1 diabetes accounts for 5-10% of all diabetic cases and results from an autoimmune destruction of pancreatic β-cells. In type 1 diabetic

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patients, damage of these cells causes that insulin secretion becomes insufficient to prevent hyperglycemia. Therefore, insulin deficiency and the resulting frank hyperglycemia are the main hallmarks of type 1 diabetes. It is known that elevated blood glucose levels, together with other detrimental effects, lead over time to various diabetes complications [2]. Maintaining normoglycemia and preservation of pancreatic β-cells are therefore of major importance in type 1 diabetics. Animal studies clearly demonstrate that resveratrol decreases blood glucose levels and protects β-cells.

2.1. Effects of resveratrol on blood glucose levels

It is well established that resveratrol decreases blood glucose levels in animals with experimental type 1 diabetes. The blood glucose-lowering effect of resveratrol was found in rats with diabetes induced by streptozotocin (STZ) alone [17–23] and STZ with nicotinamide (NA) [24–27]. In animal models, STZ is used to destroy pancreatic β-cells and thereby induces insulin-deficient diabetes. In β-cells of animals exposed to STZ, DNA undergoes fragmentation and repairing mechanisms are activated. The crucial role in DNA repair is ascribed to poly(ADP-ribose) polymerase-1 (PARP-1). This enzyme catalyses the synthesis of poly(ADP-ribose) from NAD^+ and its action is usually beneficial to the cell. However, in the case of extensive DNA damage, an exaggerated action of PARP-1 leads to depletion of intracellular NAD^+ and ATP, and β-cells undergo necrosis. Therefore, animals with STZ-induced diabetes are characterized by substantial hyperglycemia. In STZ-NA-induced model, NA, acting via inhibition of PARP-1 and provision of NAD^+, partially protects β-cells against STZ and blood glucose levels are moderately elevated [28,29]. Numerous studies have demonstrated that resveratrol is capable of reducing blood glucose levels in animals with moderate and marked hyperglycemia. It is known that hyperglycemia in both animals and humans with type 1 diabetes results from the increase in hepatic glucose output and from the decrease in peripheral glucose utilization. Both these processes are regulated by insulin, and the rise in insulin secretion in type 1 diabetic subjects reduces blood glucose levels. It is well documented that the antihyperglycemic effect of resveratrol in type 1 diabetic animals results from the increase in blood insulin levels, the suppression of hepatic glucose output and the increase in peripheral glucose utilization (see below).

2.2. Effects of resveratrol on blood insulin levels and β-cells

The blood glucose-lowering effect of resveratrol in STZ-induced [20–22,30] and in STZ-NA-induced [24–27] diabetic rats is associated with the rise in blood insulin levels. Since pancreatic β-cells are the only source of insulin, this strongly suggests that resveratrol is capable of protecting these cells. Rodent studies have confirmed this assumption. The protective action of resveratrol on pancreatic tissue of type 1 diabetic animals has been demonstrated to be partially related to anti-oxidant activity of this compound. Resveratrol improves anti-oxidant defense in pancreatic tissue, *i.e.* increases activities of anti-oxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase) and protects cells from free radical damage [26]. Anti-oxidant activity of resveratrol in pancreatic islets is of particular importance given that anti-oxidant defense of β-cells is very weak, rendering them susceptible to oxidative stress [31]. Resveratrol was also found to reverse degenerative changes in β-cells of STZ-NA-induced diabetic rats [26] and to prevent STZ-induced β-cell apoptosis. The decrease in apoptosis is accompanied by blocking of the activity of caspase-3, is mainly due to the inhibition of PARP cleavage by resveratrol and is similar to the effect of nicotinamide [21].

It should be emphasized that resveratrol is effective not only in animals in which β-cells are damaged by STZ. Resveratrol attenuates also autoimmune destruction of these cells. This was demonstrated in NOD mice [32]. In this experimental model, diabetes develops with age in non-obese animals as a result of autoimmune destruction of β-cells. The diabetic mice are characterized by reduced number of pancreatic islets, insulitis and many other degenerative changes within islets. However, resveratrol delays the onset of diabetes in NOD mice and also ameliorates the severity of the disease. These effects are accompanied by increased total islet number, increased number of insulitis-free islets and improvement in general islet condition. The protective action of resveratrol on pancreatic islets is ascribed to the reduction of pathogenicity of lymphocytes in NOD mice. This is due to resveratrol-induced downregulation of chemokine receptor 6 (CCR6) expression on multiple inflammatory cell types and the resulting blocking of the migration of pathogenic cells to the pancreas [32]. Given that type 1 diabetes in humans has autoimmune background, data showing the effectiveness of resveratrol in mitigating autoimmune destruction of β-cells are particularly relevant.

2.3. Effects of resveratrol on peripheral glucose utilization and hepatic glucose output

Another important aspect of resveratrol action is its influence on skeletal muscle. It was demonstrated that skeletal muscle dysfunction in animals with type 1 diabetes is mitigated by resveratrol [17,30,33]. Resveratrol ameliorates skeletal muscle pathology via different mechanisms. It is known that this compound stimulates mitochondrial biogenesis and improves fatty acid metabolism in muscles of diabetic animals. Moreover, resveratrol decreases expression of NF-kappaB and pro-inflammatory cytokines (IL-1β and IL-6) in muscle cells [33] and thereby exerts anti-inflammatory effects. Recent research also indicates that resveratrol decreases oxidative stress in skeletal muscle of animals with insulin-deficient diabetes [30]. Both inflammation and oxidative stress are known to contribute to myopathy in type 1 diabetics [34].

Importantly, beneficial effects of resveratrol in skeletal muscle of diabetic animals are associated with increased GLUT4 expression [17] and with increased intracellular glucose transport [35]. It is thought that the action of resveratrol on muscle tissue involves both insulin-dependent and insulin-independent effects [35]. It is also known that effects of resveratrol in muscle cells of diabetic animals are mediated via PI3K-Akt pathway [17,30]. In muscle of diabetic rats resveratrol was demonstrated to increase Akt phosphorylation and this effect was dependent on PI3K [17,30].

Apart from changes in skeletal muscle, resveratrol was also found to beneficially affect the liver of diabetic animals. Under physiological conditions, one of the key functions of the liver is to maintain normoglycemia. However, in type 1 diabetics, due to insulin deficiency, this function is impaired and hepatic glucose output increases. Animal studies indicate that the regulatory role of the liver in glucose homeostasis may be restored by resveratrol. This is associated with resveratrol-induced changes in the activities of enzymes of carbohydrate metabolism in the liver of type 1 diabetic animals. Resveratrol decreases activities of key enzymes of gluconeogenesis [25], decreases the protein level of phosphoenolpyruvate carboxykinase, a rate-limiting enzyme for gluconeogenesis [17], increases activity of hexokinase and pyruvate kinase and decreases activity of lactate dehydrogenase and glucose-6-phosphatase [25]. Moreover, resveratrol increases glycogen synthase, decreases glycogen phosphorylase and increases liver glycogen content [25]. These changes lead to the shifting of the metabolic pathways toward reduced hepatic glucose output. It should be noted that effects of resveratrol in the liver are accompanied by increased blood insulin concentrations, suggesting that insulin, at least in part, is responsible for these changes [25].

Apart from metabolic changes in the liver, resveratrol is also known to exert hepatoprotective effects and ameliorates histological abnormalities in the liver of type 1 diabetic animals [22,25,36]. Resveratrol-induced hepatoprotection mainly results from improvement in anti-oxidant defense mechanisms and anti-inflammatory effects. Resveratrol increases the activity of antioxidant enzymes [22,36] and also decreases NF-kappaB and IL-1β contents in the liver of diabetic

rats [22]. Moreover, resveratrol also stimulates mitochondrial biogenesis in the liver of rats with experimental diabetes [33]. Some data also indicate that resveratrol activates AMPK and increases SIRT1 expression in the liver of STZ-induced diabetic rats [33,37].

In sum, the anti-diabetic action of resveratrol is recently well established in animal models of insulin-deficient diabetes. It is very likely that the direct influence of resveratrol on pancreatic β-cells plays a pivotal role in this action. Resveratrol-induced partial regeneration of β-cells in diabetic animals results in the increase in blood insulin levels [20–22,24–27,30]. Then, insulin decreases hepatic glucose output and increases glucose utilization by insulin-sensitive tissues. Some data indicate that beneficial effects of resveratrol result also from the direct, insulin-independent changes in skeletal muscle and the liver [22,35,36]. This action is associated with the anti-oxidative and anti-inflammatory effects of resveratrol and with beneficial effects of resveratrol on metabolic disorders. It must be also emphasized that the blood glucose-lowering effect of resveratrol in hyperglycemic animals contributes to the protection of β-cells from glucotoxicity and this, in turn, improves glycemic control.

3. Resveratrol and type 2 diabetes

Type 2 diabetes is a metabolic disorder characterized by impairment in insulin secretion and action. The resulting hyperglycemia usually develops gradually and the disease may be undiagnosed for years. The pathogenesis of type 2 diabetes is complex and involves both genetic predisposition and environmental factors. It is known that high-calorie diet and low physical activity increase the risk of type 2 diabetes [38,39]. Moreover, the incidence of type 2 diabetes increases with age and is higher in overweight or obese individuals compared with lean subjects. On the other hand, dietary intervention and increased physical activity may delay the onset of type 2 diabetes despite genetic predisposition [40,41]. It is recently well established that many factors contribute to the worsening of insulin action and to β-cell failure in type 2 diabetics, including inflammation and oxidative stress [42]. However, insulin resistance and a progressive β-cell failure are still essential problems in type 2 diabetic patients. In this context, resveratrol was demonstrated to beneficially affect both insulin action and pancreatic β-cells.

3.1. Effects of resveratrol on insulin resistance

Under physiological conditions, insulin action is preceded by a sequence of events involving insulin binding with transmembrane receptor followed by receptor autophosphorylation, phosphorylation of intracellular insulin receptor substrates and activation of effector proteins [43]. Insulin resistance, defined as impaired insulin action on target tissues, *i.e.* skeletal muscles, the liver and adipose tissue, disturbs glucose homeostasis and contributes to abnormalities in the whole organism. Numerous studies have demonstrated that resveratrol improves insulin action in animals with experimentally induced insulin resistance. This effect was shown in rats on a high cholesterol-fructose diet [35], in rats [44,45] and mice [46–50] on a high-fat diet, in rats fed a high-fat diet and treated with streptozotocin [51] and in fructose fed rats [52]. Partial reversal of diet-induced insulin resistance by resveratrol was also demonstrated in a swine model [53]. Resveratrol is also effective in animals with genetically determined insulin resistance and improves insulin action in obese Zucker rats [54,55], KKAy mice [56] and db/db mice [57,58]. Moreover, Marchal et al. [59], studying effects of resveratrol in grey mouse lemur, revealed that this compound decreases also age related insulin resistance.

Recent research shows that long-term administration of resveratrol (for 2 years, 80 and 480 mg/day for the first and second year, respectively) may improve insulin sensitivity in rhesus monkeys with diet-induced obesity. Significant improvement in insulin sensitivity was found in these animals at the level of visceral adipose tissue [60]. However, other study demonstrated that resveratrol fails to alter indices of insulin resistance in rhesus monkeys [61].

Animal studies are consistent and indicate that resveratrol improves insulin action in various models of insulin resistance. Resveratrol-induced decrease in insulin resistance is known to result from changes in skeletal muscle, the liver and adipose tissue.

3.1.1. Muscle insulin resistance

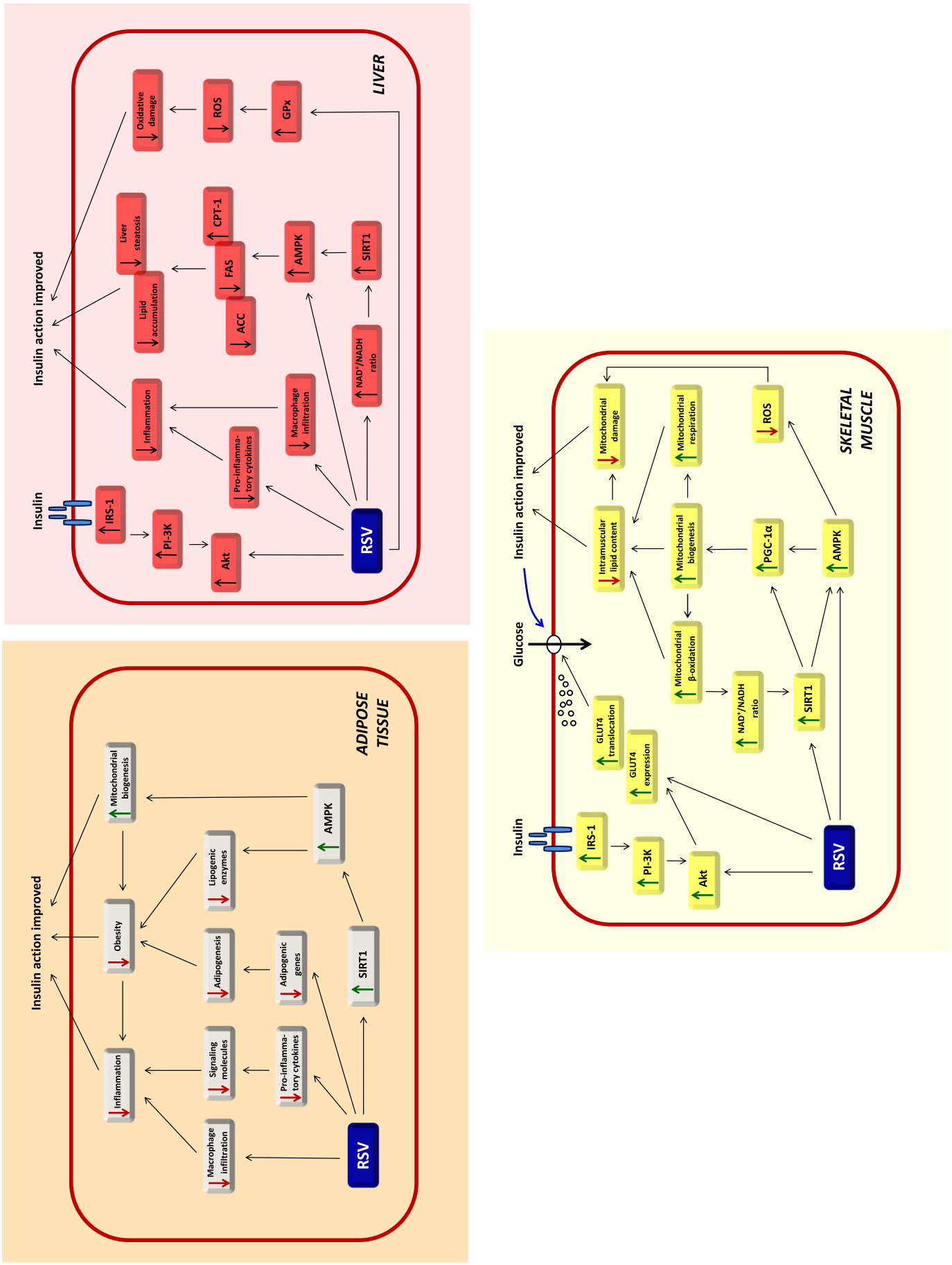
In skeletal muscle, stimulation of intracellular glucose transport is one of the main effects of insulin. Insulin-induced glucose transport requires translocation of glucose transporter GLUT4 to the plasma membrane and is preceded by a sequence of events involving various signaling molecules [43]. It is known that in type 2 diabetes insulin-induced glucose transport is impaired. Since skeletal muscle accounts for about 75% of the whole body insulin-induced glucose transport, this impairment markedly contributes to the rise in blood glucose levels [43].

Evidence from animal studies indicates that resveratrol promotes intracellular glucose transport in insulin-resistant rodents. The first animal experiments demonstrated higher glucose uptake by soleus muscle of rats fed a high cholesterol-fructose diet and receiving resveratrol than in animals that were not receiving this compound [35]. Subsequent studies confirmed these results, showing that in rats on a high-fat diet resveratrol improves insulin-stimulated glucose uptake by skeletal muscle [44,45]. Resveratrol-induced increase in intracellular glucose transport in insulin-resistant animals results from two events related to GLUT4. It is known that resveratrol enhances GLUT4 translocation to the plasma membrane of muscle cells [35,45] and also increases GLUT4 expression in skeletal muscle of animals with diet-induced insulin resistance [53] and in db/db mice [62].

Enhanced intracellular glucose transport in insulin-resistant animals ingesting resveratrol points to the improvement in insulin action. Resveratrol ameliorates insulin resistance in skeletal muscle via various mechanisms, including changes in metabolism and lipid accumulation. In skeletal muscle of rodents with diet-induced insulin resistance, resveratrol promotes mitochondrial biogenesis [63] and improves mitochondrial β-oxidation [44]. This leads to increased fatty acid oxidation and to reduced intramuscular lipid content in animals consuming resveratrol [44]. The latter effect is of great importance since increased intramyocellular lipid accumulation impairs insulin action and contributes to insulin resistance and type 2 diabetes [64]. Moreover, it is thought that muscle mitochondrial dysfunction accelerates intramuscular lipid deposition and impairs insulin action in humans [65]. Therefore, resveratrol-induced increase in mitochondrial biogenesis with a concomitant decrease in intramuscular lipid content seem to be essential for resveratrol action in muscle tissue.

Beneficial effects of resveratrol in muscle tissue of insulin-resistant rodents are strongly related to changes in the activities and/or expression of two intracellular regulators, *i.e.* SIRT1 and AMPK. SIRT1 (silent information regulator 1), is NAD^+ - dependent histone deacetylase involved in the regulation of many processes, such as mitochondrial biogenesis, inflammation, intracellular metabolism, stress resistance, apoptosis, glucose homeostasis and other. It is thought that SIRT1 activity/expression is reduced in type 2 diabetic patients, and this enzyme is being considered as a target for anti-diabetic drugs [66,67]. Resveratrol is known to activate SIRT1 in mammalian tissues [68]. In animals with diet-induced insulin resistance, resveratrol was also shown to activate muscle SIRT1 [44]. Activation of this enzyme is associated with increase in NAD^+/NADH ratio [63]. The importance of SIRT1 in the action of resveratrol was confirmed in mice with genetically induced insulin resistance, in which resveratrol increases protein level of SIRT1 in soleus muscle [56].

Apart from SIRT1, AMP-activated protein kinase (AMPK) is another enzyme involved in resveratrol action. AMPK regulates many physiological processes, including fuel metabolism, mitochondrial function and biogenesis, insulin secretion and action and other. A close link between


LIVER
Insulin action improved
Insulin
IRS-1
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RSV
Inflammation
Pro-inflamma-tory cytokines
Macrophage infiltration
Lipid accumulation
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CPT-1
ACC
AMPK
SIRT1
NAD+/NADH ratio
Oxidative damage
ROS
GPx
ADIPOSE TISSUE
Insulin action improved
Mitochondrial biogenesis
Obesity
Inflammation
Signaling molecules
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Insulin action improved
Glucose
Insulin
IRS-1
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RSV
GLUT4 translocation
GLUT4 expression
Intramuscular lipid content
Mitochondrial damage
Mitochondrial biogenesis
Mitochondrial β-oxidation
Mitochondrial respiration
NAD+/NADH ratio
PGC-1α
SIRT1
AMPK
ROS

dysregulation of AMPK and insulin resistance in rodents is recently well established [69]. Decreased AMPK activity occurs in animal models of diet-induced insulin resistance [70] and in insulin resistance determined genetically [54]. Although the direct link between AMPK activation and the improvement in insulin resistance in humans is not proven, it is known that commonly used insulin sensitizing drugs, metformin and the thiazolidinediones, activate AMPK in different tissues [69]. Similarly to these drugs, resveratrol also activates AMPK in insulin-resistant animals. In rodents with diet-induced insulin resistance, resveratrol restores the phosphorylation of AMPKα [47] and activates AMPKα in the skeletal muscle [63]. Similar effects were shown in KKAy mice, in which resveratrol increases protein level of AMPKα in soleus muscle [56]. Moreover, resveratrol was demonstrated to be ineffective in insulin-resistant animals with AMPK deficiency [63]. These results confirm the relevance of AMPK as a target for resveratrol.

It is also known that resveratrol reduces formation of reactive oxygen species in skeletal muscle of insulin resistant rodents. This effect is supposed to be also mediated by AMPK and contributes to the improvement in insulin action [63]. Resveratrol-induced up-regulation of AMPK in skeletal muscle is associated with deacetylation and activation of PGC-1α, probably via SIRT1-dependent manner [53,63], and leads to the increase in mitochondrial biogenesis. It is, however, suggested that pharmacological activation of AMPK and the resulting stimulation of mitochondrial biogenesis in skeletal muscle may be insufficient to improve whole-body energy expenditure and insulin action [71]. These results indicate that, apart from increase in mitochondrial biogenesis, other effects must be generated by resveratrol in skeletal muscle.

Resveratrol may also improve insulin signaling in skeletal muscle of insulin-resistant animals by increased phosphorylation of insulin receptor [35], increased protein levels of IRS-1 [56] and also enhanced expression of phosphorylated Akt [53,56] (Fig. 1).

3.1.2. Liver insulin resistance

Apart from skeletal muscle, resveratrol is also known to beneficially affect the liver of insulin-resistant rodents. This compound, among others, decreases hepatic lipid accumulation and ameliorates steatosis. These effects are associated with reduced expression of fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) and also with increased expression and activity of carnitine palmitoyl transferase-1 (CPT-1) [33,49,50,62,72–75].

In parallel with changes in skeletal muscle, resveratrol-induced effects in the liver are also associated with changes in AMPK/SIRT1 [47,50,56,58,62,76]. It is suggested that effects of resveratrol on FAS, ACC and CPT-1 are mediated via AMPK/SIRT1 axis [77,78]. In the liver of animals with diet-induced insulin resistance, resveratrol stimulates phosphorylation of AMPK [47] and increases protein expression of SIRT1 [50]. Additionally, resveratrol increases NAD^+/NADH ratio in the liver, which contributes to the activation of SIRT1 [83]. In animal models of insulin resistance determined genetically, resveratrol is also effective and increases expression and phosphorylation of AMPK and SIRT1 in the liver [54,56,58,62,76].

Importantly, resveratrol improves also insulin signaling in the liver of insulin-resistant animals and increases phosphorylation of several signaling proteins, including IRS-1, Akt and PI3K [79]. Moreover, resveratrol was found to increase the activity of glutathione peroxidase decreasing oxidative damage of the liver [76] and to reduce expression of pro-inflammatory cytokines in liver tissue [50, 74]. Resveratrol is also capable of reducing macrophage infiltration in the liver of animals on a high-fat diet [49] (Fig. 1).

3.1.3. Adipose insulin resistance

It is known that resveratrol affects also adipose tissue in type 2 diabetic subjects. Adipose tissue dysfunction plays an important role in the pathogenesis of type 2 diabetes. Under physiological conditions, adipocytes store excess of energy in the form of triglycerides or release glycerol and fatty acids, depending on the actual demand of the organism. However, increased accumulation of fat tissue leads to overweight or obesity. Adipose tissue-related impairment in insulin action results from various effects. It is known that increased release of free fatty acids plays an important role in the development of insulin resistance [80,81]. Moreover, adipose tissue secretes multiple adipokines which may also impair insulin action leading to insulin resistance [82]. In the last years, there is growing evidence that adipose tissue inflammation markedly contributes to insulin resistance and type 2 diabetes in humans [82–84]. In this context, anti-inflammatory effects of resveratrol in both animals and humans are of particular importance [10,85]. Numerous studies show that resveratrol is capable of reducing inflammatory processes in adipose tissue of insulin-resistant animals. This was found in genetically obese Zucker rats [81] as well as in rodents [46,49,54] and nonhuman primates [60] with diet-induced insulin resistance. Resveratrol attenuates high-fat diet-induced up-regulation of pro-inflammatory cytokines and their signaling molecules in adipose tissue and thereby reduces inflammation [46]. Beneficial effects of this compound are also associated with reduced macrophage infiltration in adipose tissue of obese rats [75] and mice on a high-fat diet [49]. Moreover, resveratrol induces white adipose tissue mitochondrial biogenesis and improves tissue metabolism in insulin-resistant rodents [55,63,86]. The latter effect is associated, among others, with reduced activity of lipogenic enzymes (glucose-6-P-dehydrogenase, acetyl-CoA carboxylase and lipoprotein lipase) [75]. Anti-diabetic action of resveratrol may be also related to anti-obesity effects of this compound [13,14]. It is well known that increased adiposity impairs insulin action and increases the risk of type 2 diabetes in humans [2,40]. Some studies show that resveratrol is capable of reducing adipose tissue weight in animals with insulin resistance [46,54,75,87]. Anti-obesity effect of resveratrol is associated not only with improvement in adipose tissue metabolism, but also with reduced adipogenesis in animals on a high-fat diet. The latter effect is due to down-regulation of key adipogenic genes [46]. However, it was also shown that resveratrol may improve insulin action without detectable changes in adiposity [55] or decrease in body weight [49,56]. This suggests that decrease in body weight is not a prerequisite to improve insulin action by resveratrol.

Similarly to other tissues, effects of resveratrol on adipose tissue are accompanied by changes in AMPK and SIRT1. It is known that resveratrol increases AMPKα phosphorylation/activity in white adipose tissue of insulin-resistant mice [63,87] and obese Zucker rats [54]. Moreover, in rhesus monkeys and mice with diet-induced insulin resistance, resveratrol was demonstrated to improve insulin sensitivity in adipose tissue and these effects are associated with increased SIRT1 expression [60,87] (Fig. 1).

It is well established that resveratrol is capable of attenuating insulin resistance in various animal models. This is of importance and points to the potential of resveratrol to treating different diseases associated with impaired insulin action, including type 2 diabetes. However, in the light of the possible use of resveratrol in type 2 diabetic patients, human studies are necessary to evaluate its therapeutic value.

Human studies addressing the anti-diabetic action of resveratrol are still limited, however, available data indicate that this compound is capable of decreasing insulin resistance. Brasnyó et al. [88] demonstrated for the first time that resveratrol administered for 4 weeks to

Fig. 1. Direct and indirect effects thereby resveratrol improves insulin action in skeletal muscle, liver and adipose tissue of animals with experimental type 2 diabetes. Some effects were also demonstrated in type 2 diabetic humans. RSV – resveratrol, ROS – reactive oxygen species, IRS1 – insulin receptor substrate 1, PI3K - phosphoinositide 3-kinase, Akt – protein kinase B, PGC1α – peroxisome proliferator-activated receptor γ coactivator-α, ACC – acetyl-CoA carboxylase, FAS – fatty acid synthase, CPT-1 – carnitine palmitoyltransferase 1, GPx – glutathione peroxidase.

overweight type 2 diabetic patients decreases insulin resistance. Subsequent studies confirmed the efficacy of resveratrol in insulin-resistant humans. Resveratrol administered for 4 weeks to obese type 2 diabetic patients was found to decrease insulin resistance [89]. Similar results were observed in overweight type 2 diabetic patients receiving resveratrol for 45 days [90]. In each of these studies, HOMA-IR index was calculated to determine insulin resistance and its values were significantly improved by resveratrol. It was also found that resveratrol administered to type 2 diabetic patients for 3 months slightly reduced fasting blood glucose levels and hemoglobin A_{1c} levels, showing long-term improvement in glycemia [91]. Moreover, resveratrol administered for 4 weeks to humans with age-related impairment in glucose tolerance was demonstrated to reduce postprandial blood glucose and insulin levels and slightly improved insulin sensitivity (determined by Matsuda index) [92]. A slight improvement in insulin sensitivity was also shown in patients with metabolic syndrome ingesting resveratrol for 3 months [93]. However, some studies demonstrated lack of effect. Resveratrol administered for two weeks to obese men did not significantly affect insulin resistance [94]. Moreover, in obese humans with type 2 diabetes, resveratrol was given for 4 weeks and failed to change blood glucose and blood insulin levels and did not affect insulin resistance [72]. Similarly, in overweight type 2 diabetic patients, resveratrol administered for 60 days failed to ameliorate insulin resistance [95]. Lack of effects of resveratrol administered for 8 weeks on insulin resistance and inflammation was also found in overweight or obese man with nonalcoholic fatty liver disease [96]. It was also demonstrated that resveratrol is ineffective in healthy people and does not induce any significant changes in insulin sensitivity and inflammatory status [97,98] (Table 1).

The discrepancies among studies in the efficacy of resveratrol in insulin resistant humans may be explained by differences in experimental conditions, such as dose of resveratrol and time of treatment, age and body weight of patients, duration and severity of diabetes, diabetes complications, nutrition and other.

Compared with animal studies, human data are less conclusive, however, preliminary clinical trials indicate that resveratrol may decrease insulin resistance in type 2 diabetic patients. Beneficial effects of resveratrol in humans with type 2 diabetes appear to be linked to changes in SIRT1 and AMPK [89,99]. Resveratrol administered to obese insulin-resistant humans was found to activate AMPK and increase PGC-1α and SIRT1 protein levels in skeletal muscle [89]. Similar changes were observed in skeletal muscle of patients with type 2 diabetes, in which resveratrol increased SIRT1 expression as well as p-AMPK to AMPK expression ratio [99]. In type 2 diabetic humans, resveratrol was also found to induce Akt phosphorylation [88].

3.2. Effects of resveratrol on blood insulin levels and β-cells

Under physiological conditions, insulin secretion from pancreatic β-cells is tightly regulated and is influenced by many factors, including nutrients, nervous system, some hormones and other [100,101]. In type 2 diabetic humans, insulin resistance leads to the increased demand of insulin, β-cells secrete more hormone and blood insulin levels are initially elevated. However, prolonged overstimulation of these cells and exaggerated insulin secretion, together with other detrimental factors, contribute to the progressive β-cell failure and, over time, insulin supply becomes insufficient. It is known that the β-cell failure in type 2 diabetic patients is generated by glucotoxicity, lipotoxicity, oxidative stress, inflammation, amyloid formation, endoplasmic reticulum stress and other factors [42].

Table 1
Effects of resveratrol in humans.

Effect	Resveratrol dose/ time of treatment	Subjects	References
Insulin resistance ↓	5 mg twice a day 4 weeks	Type 2 diabetic patients	[88]
Insulin resistance ↓ Blood glucose levels ↓ HOMA-β ↓ Systolic blood pressure ↓	500 mg twice a day 45 days	Type 2 diabetic patients	[90]
Insulin resistance — Blood glucose levels ↓ Diabetic ulcer size ↓	50 mg twice a day 60 days	Type 2 diabetic patients	[95]
Blood glucose levels ↓ Systolic blood pressure ↓	250 mg per day 3 months	Type 2 diabetic patients	[91]
Insulin resistance ↓ Blood glucose levels ↓ Plasma inflammation markers ↓ Systolic blood pressure ↓	150 mg per day 30 days	Obese men	[89]
Insulin resistance — Blood glucose levels — Intestinal and hepatic lipoprotein production ↓	First week 1 g per day second week 2 g per day two weeks	Obese men	[94]
Postprandial glucagon responses ↓	150 mg per day 30 days	Obese men	[110]
Insulin resistance ↓	1, 1.5, 2 g per day 4 weeks	Older adults	[92]
Insulin resistance — Plasma inflammation markers — Systolic blood pressure —	500 mg 3 times a day 4 weeks	Obese men	[72]
Insulin resistance ↓ Systolic blood pressure —	500 mg 3 times a day 90 days	Patients with metabolic syndrome	[93]
Insulin sensitivity – Plasma inflammation markers — Systolic blood pressure —	75 mg per day 12 weeks	Nonobese women with normal glucose tolerance	[98]
Insulin resistance —	3 g per day 8 weeks	Overweight or obese men with nonalcoholic fatty liver disease and IR	[96]
Metabolic and inflammatory status in skeletal muscle —	250 mg per day 8 weeks	Healthy aged men	[97]

↓, Decrease; —,unchanged.

The compensatory hypersecretion of insulin is accompanied by changes in islet β-cell mass. In type 2 diabetic patients, β-cell mass is usually reduced [42]. Abnormalities in β-cell structure and function which develop in type 2 diabetes are extensively studied using various animal models. In animal models of type 2 diabetes, blood insulin levels and β-cell mass may be increased or decreased, depending on the kind of the model [102,103]. Over the past few years, effects of resveratrol were studied using rodents in which β-cell mass and blood insulin levels were increased or decreased. Interestingly, the obtained data clearly show that resveratrol is effective in both cases.

In animals with insulin resistance and hyperinsulinemia, resveratrol was found to reduce blood insulin concentrations. This effect was demonstrated in rodents with diet-induced hyperinsulinemia [47–50,52] and in the genetically obese Zucker rats [54]. On the other hand, in rodent models of type 2 diabetes with decreased β-cell mass and hypoinsulinemia, resveratrol appears to increase blood insulin levels, as shown in db/db mice [57,62].

Long-term studies with resveratrol reveal the effectiveness of this compound in nonhuman primates with abnormalities in islet structure and function. In rhesus monkeys, diet-induced increase in the α-cell/β-cell ratio in pancreatic islets was significantly improved by resveratrol administered to these animals for 2 years [61].

The mechanism underlying resveratrol action is complex and involves different effects. It is very likely that one of the most important is attenuation of insulin resistance in diabetic animals and humans. The improvement in insulin action leads to decrease in blood glucose levels and thereby prevents deleterious effects of hyperglycemia on β-cells, known as glucotoxicity [104]. Moreover, resveratrol was also demonstrated to reduce blood lipid levels in diabetic subjects and thereby decreases so-called lipotoxicity. The attenuation of both glucotoxicity and lipotoxicity is well known to restrain β-cell failure in diabetes [104,105]. Another advantage of resveratrol-induced decrease in insulin resistance is reduced demand of insulin. As a result, less insulin is secreted from β-cells and thereby β-cell failure is also reduced.

Protective action of resveratrol on pancreatic β-cells is also related to its well-documented anti-oxidative capacity. Resveratrol was demonstrated to reduce oxidative damage in β-cells of type 2 diabetic animals [48,57,62,106]. This is very important since insulin-secreting cells are particularly susceptible to the oxidative damage [31]. Moreover, oxidative stress is increased in diabetes and contributes to the progressive β-cell failure.

It is known that that resveratrol exerts also anti-inflammatory action, decreases levels of inflammatory markers [26] and thereby protects pancreatic β-cells of type 2 diabetic animals. Recently, there is growing evidence for the important role of inflammation in the progressive β-cell dysfunction in type 2 diabetic humans. It is thought that in type 2 diabetes inflammatory response is initiated to promote β-cell repair and regeneration. However, over time, chronic inflammation develops leading to the functional impairment of the insulin-secreting cells [83].

Resveratrol was also demonstrated to reduce pancreatic triglyceride content in animals on a high-fat diet [48]. It was also found that in mice on a high-fat diet with increased β-cell mass, resveratrol returns β-cell mass to the values observed in control animals. This is related to beneficial effects on expression of apoptosis-related factors in pancreatic islets (bcl-2 and bax) [48]. Moreover, resveratrol increases SIRT1 expression and decreases uncoupling protein-2 (UCP2) expression in islet cells [48]. UCP-2 is a mitochondrial membrane protein which uncouples oxygen consumption from the production of ATP and thereby negatively modulates insulin secretion [107]. Increased UCP-2 expression in β-cells is proposed to protect these cells against reactive oxygen species. On the other hand, up-regulation of UCP-2 in the insulin-secreting cells, observed, among others, in some animal models of diet-induced β-cell dysfunction [48], is a marker of stress conditions [108,109]. In this context, decrease of UCP-2 expression caused by resveratrol is beneficial and points to the functional improvement of β-cells.

In db/db mice, an animal model of type 2 diabetes with decreased β-cell mass, resveratrol was shown to improve islet structure and function, reduces oxidative stress, restores islet architecture, decreases islet destruction, markedly reduces islet fibrosis and attenuates other degenerative changes. Moreover, resveratrol partially prevents β-cell failure and increases β-cell mass [57,62] (Fig. 2).

Importantly, beneficial effects of resveratrol on β-cells were also shown in type 2 diabetic patients. Recent studies demonstrated that

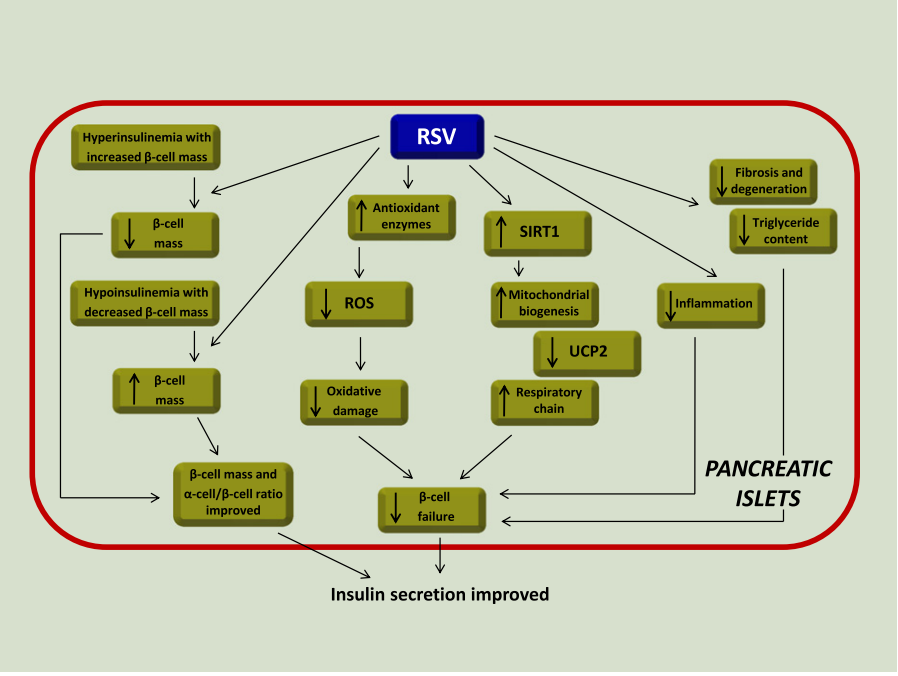

Fig. 2. Direct and indirect effects thereby resveratrol improves insulin secretion from pancreatic islets of animals with experimental type 2 diabetes. RSV – resveratrol, ROS – reactive oxygen species, UCP2 – uncoupling protein 2.

resveratrol significantly reduced blood insulin levels in patients with hyperinsulinemia. This effect was accompanied by a concomitant decrease in homeostasis model of assessment for β-cell function (HOMA-β) [90]. However, other studies demonstrated that, although resveratrol induced some beneficial effects in type 2 diabetic patients, blood insulin levels and HOMA-β were unchanged by this compound [88]. These results indicate that resveratrol is capable of improving β-cell function not only in rodents and nonhuman primates, but also in humans with type 2 diabetes.

4. Conclusions and additional remarks

Resveratrol is known to have numerous health-promoting effects in both animals and humans. It is recently well established that this compound induces also beneficial effects in animals with experimental insulin-deficient diabetes, including antihyperglycemic action and protection of pancreatic β-cells and has a potential to support the conventional treatment of type 1 diabetes. However, human studies remain to be performed to verify the effectiveness of resveratrol in type 1 diabetics.

A large body of evidence indicates that resveratrol exerts also anti-diabetic action in animal models of type 2 diabetes. It is known that resveratrol improves pancreatic islet structure and function and decreases insulin resistance in diabetic animals. Effects of resveratrol are strongly linked to changes in expression and activity of AMPK and SIRT1 in different tissues of diabetic animals. Resveratrol is also known to have anti-oxidant and anti-inflammatory properties and thereby ameliorates diabetes. It must be emphasized that resveratrol is capable of inducing a wide variety of effects in different tissues and this pleiotropic action leads to the therapeutic effect in the whole organism.

Preliminary human studies addressing the effects of resveratrol in type 2 diabetes confirm the effectiveness of this compound. It is of particular importance that resveratrol improves glycemic control and decreases insulin resistance. Apart from these changes, ingestion of resveratrol may also have other health benefits in type 2 diabetic humans [89,90,94,110], including reduced diabetes complications [95] (Table 1).

The available data indicate that effective doses of resveratrol in insulin-resistant humans are very diverse (Table 1). In this context, it is important to note that the mechanisms of resveratrol action may differ depending on its dose. Treatment with lower doses of resveratrol may activate SIRT1, whereas higher doses activate AMPK in a SIRT1-independent manner [111]. Moreover, in some cases resveratrol may be less effective at higher doses compared with effects induced by this compound at lover doses [75,112]. It was demonstrated that doses of resveratrol lower than 0.5 g per person may be sufficient to improve insulin action, decrease blood glucose levels and to induce other effects. Studies on the toxicity of resveratrol in humans show that this compound is well tolerated and doses up to 0.5 g per day for long periods may induce only moderate and reversible side effects [113].

Human studies, although provide promising results, are not fully consistent. The discrepancies may result from differences in experimental conditions. Moreover, two major limitations in the human clinical trials are sample size and the short duration of the trials. However, the current state of knowledge encourages the further research which would result in common use of resveratrol in diabetic humans.

Disclosures

None declared.

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