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Review

Resveratrol, obesity and diabetes

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ABSTRACT

Resveratrol belongs to the large group of biologically active substances found in plants. This compound is classified as phytoestrogen because of its ability to interact with estrogen receptor. Numerous beneficial effects of resveratrol described in the literature involve cardioprotective, anti-cancer, anti-inflammatory and antioxidant action. Recently, this broad spectrum of effects is enlarged by new data demonstrating a great potency of this compound in relation to obesity and diabetes. It is well established that resveratrol exerts beneficial effects in rodents fed a high-calorie diet. In some studies, resveratrol was reported to reduce body weight and adiposity in obese animals. The action of this compound involves favourable changes in gene expressions and in enzyme activities. The accumulating evidence also indicates the benefits of resveratrol in diabetes and diabetic complications. It is known that resveratrol affects insulin secretion and blood insulin concentration. In animals with hyperinsulinemia, resveratrol was found to reduce blood insulin. Moreover, numerous data indicate that in diabetic rats, resveratrol is able to reduce hyperglycemia. The mechanism of resveratrol's action is complex and is demonstrated to involve both insulin-dependent and insulin-independent effects. These data point to the potential possibility of use of resveratrol in preventing and/or treating both obesity and diabetes.

Contents

1. Introduction

Resveratrol (3, 5, 4′-trihydroxystilbene; Fig. 1) belongs to the large group of polyphenols found in different plant species. The richest natural source of resveratrol is *Polygonum cuspidatum* — a plant root extract of which have been used in oriental folk medicine. Considerable amounts of resveratrol were also found, among others, in peanuts, groundnuts, Itadori tee, grapevines and red vine (Burns et al., 2002; Pervaiz, 2003). Apart from natural sources, this compound is recently available in tablets and is recommended as a dietary supplement. In the last years, the interest in resveratrol substantially increased and its broad biological activity at the cellular level has been demonstrated. The cardioprotective (Hung et al., 2000; Das et al., 2005), anti-cancer (Atten et al., 2001; El-Mowafy and Alkhalaf, 2003), anti-inflammatory and antioxidant (de la Lastra and Villegas, 2007) properties of resveratrol are quite well characterised. Moreover, resveratrol, as a component of red wine, is thought to be responsible for the "French paradox" i.e. low mortality due to coronary heart disease as a result of moderate consumption of red wine (Kopp, 1998). The most recent data reinforced this theory and indicated that resveratrol play a crucial role in cardiovascular protection provided by grapes and wines (Bertelli and Das, 2009). Although it is known that in humans resveratrol is rapidly absorbed after its oral administration and is detected in both plasma and urine, data concerning the potential beneficial effects of the pure compound in humans are still very limited (Bishayee, 2009).

However, the most recent data derived from animal studies open a new, promising perspective of the potential use of resveratrol in

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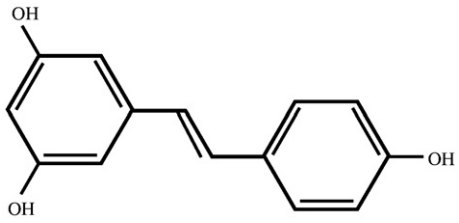

Fig. 1. The chemical structure of *trans*-resveratrol.

preventing and/or treating serious metabolic disorders such as obesity and diabetes. The prevalence of both these diseases is very high, especially in Western countries, and tends to be increased (Ashcroft and Rorsman, 2004). Numerous natural compounds, including resveratrol, are intensively studied in the context of their potential benefits in obesity and diabetes. Data concerning resveratrol published in the last few years are summarized in this article.

2. Resveratrol and obesity

Long-term rodent studies provided convincing evidence that resveratrol exerts favourable effects in animals consuming a high-fat diet. Experiments on mice fed a high-calorie diet demonstrated that resveratrol (incorporated into a diet, 0.04%; for 15 weeks or 15 months) increased their survival and motor function and changed the expression of numerous genes towards the expression found in animals on a standard diet (Baur et al., 2006; Lagouge et al., 2006). Moreover, in mice on a high-fat diet, resveratrol diminished total body fat content and decreased depots of epididymal, inguinal and retroperitoneal white adipose tissue (Lagouge et al., 2006). More recently, numerous beneficial effects of resveratrol were also revealed in rats fed a high-fat diet (Aubin et al., 2008; Shang et al., 2008a,b; Rocha et al., 2009). In these animals, resveratrol substantially reduced visceral fat index and liver mass index (Shang et al., 2008a,b). Interestingly, in some studies, this compound was reported to reduce body weight gain in rats (Aubin et al., 2008) and mice (Lagouge et al., 2006) fed a high-fat diet. Unfortunately, in the other experiments this effect was not observed (Baur et al., 2006; Rocha et al., 2009). Resveratrol (10 mg/kg body weight; administered for 8 weeks) appeared to be also ineffective in reducing body weight gain in obese Zucker rats, although a slight decrease in body fat content was found (Rivera et al., 2009). Moreover, in obese Zucker rats, resveratrol induced beneficial changes in lipid parameters. In these animals, administration of resveratrol resulted in a significant reduction in plasma triglycerides, free fatty acids, cholesterol and liver triglycerides comparing with obese Zucker rats non-treated with resveratrol (Rivera et al., 2009). Interesting results were obtained by Ramadori et al. (2009). They observed beneficial effects of long-term intracerebroventricular infusion of resveratrol in mice on a high-energy diet. In these animals, resveratrol normalised hyperglycemia and substantially reduced hyperinsulinemia.

Data from the literature indicate that resveratrol is not only able to partially compensate for the deleterious effects of a high-calorie diet, but it is also able to induce changes that are similar to calorie restriction. The latter effect was demonstrated by Barger et al. (2008). They found that resveratrol (4.9 mg/kg body weight) given to normal mice for 15 months prevented cardiac and skeletal muscle dysfunctions induced by ageing and attenuated age-related changes in gene expressions. Some effects evoked by the compound were indeed comparable to changes observed in mice on a calorie-restricted diet. In the other study, Pearson et al. (2008) have reported resveratrol-induced beneficial changes in gene expression and reduction in signs of ageing in mice on a standard diet. Effects caused by resveratrol paralleled those found in mice on a calorie-restricted diet or evoked by every-other-day feeding. Calorie restriction mimetic effects of resveratrol seem to be particularly noteworthy since dietary restriction is thought to prevent some diseases of ageing such as insulin resistance, type 2 diabetes, dyslipidemia or cancer (Smith et al., 2004; Holloszy and Fontana, 2007).

The mechanism thereby resveratrol exerts favourable effects is proposed to be related to induction of genes for oxidative phosphorylation and mitochondrial biogenesis. Numerous data indicate that activation of an NAD^+-dependent protein deacetylase, Sirt1, is pivotal for resveratrol's action (Lagouge et al., 2006; Lee et al., 2009). Sirt1 catalyzes, among others, deacetylation and activation of peroxisome proliferator gamma coactivator-1α (PGC-1α), a cofactor in mitochondrial biogenesis (Rodgers et al., 2005). It was demonstrated that the beneficial effects induced by resveratrol in mice fed a high-fat diet were accompanied by activation of Sirt1, whereas in experiments with embryonic fibroblasts obtained from $Sirt^{-/-}$ mice, resveratrol appeared to be ineffective and failed to decrease PGC-1α acetylation and to modulate the expression of PGC-1α target genes (Lagouge et al., 2006). Increased expression of PGC-1α and UCP-1 in brown adipose tissue was also observed in *ob*/*ob* mice receiving resveratrol (Mayers et al., 2009). The important role of Sirt1 activation in the action of resveratrol was additionally supported by results demonstrating that synthetic activators of Sirt1 induced effects comparable to those caused by resveratrol (Feige et al., 2008). Moreover, other studies have reported that modest overexpression of Sirt1 alleviated, similarly to resveratrol, unfavourable changes induced by a high-fat diet (Pfluger et al., 2008). It is also known that calorie restriction per se increases expression of Sirt1 (Cohen et al., 2004). Lee et al. (2009) provided further evidence supporting the importance of Sirt1 activation in the mechanism of resveratrol's action. They revealed that in both RIN cells and isolated pancreatic islets, overexpression of Sirt1 or activation of Sirt1 by resveratrol effectively prevented cytokine-induced cytotoxicity.

Activation of Sirt1 is not the sole effect thereby resveratrol mimics calorie restriction and reduces the pathological consequences of a high-calorie diet. It has been proposed that some benefits of resveratrol result from phosphorylation/activation of 5′-AMP-activated protein kinase (AMPK). Once activated, AMPK inhibits acetyl-CoA carboxylase enhancing oxidation of fatty acids and decreasing their synthesis (Hardie and Pan, 2002). A substantial increase in AMPK activity induced by resveratrol was reported in rats fed a high-fat diet (Baur et al., 2006; Shang et al., 2008a,b) as well as in obese Zucker rats (Rivera et al., 2009). The relevance of both AMPK and Sirt1 in the energy metabolism and mitochondrial biogenesis is well known and has been described in detail in review articles (López-Lluch et al., 2008; Cantó and Auwerx, 2009; Steinberg and Kemp, 2009).

Some data also point to the involvement of the central nervous system in the action of resveratrol since intracerebroventricular infusion of this compound was reported to induce numerous beneficial effects in mice on a high-energy diet (Ramadori et al., 2009).

Apart from the above-described effects, studies on isolated cells demonstrated the ability of resveratrol to induce short-term effects which appear already within minutes upon exposure. In isolated rat hepatocytes, resveratrol (10–100 μM) was found to inhibit fatty acid synthesis (especially palmitate) from acetate. This effect appeared already after 20 min of incubation with the tested compound and was accompanied by reduced activity of acetyl-CoA carboxylase, but fatty acid synthase was unchanged. Some studies also demonstrated reduced accumulation of triglycerides in cells exposed to resveratrol. In freshly isolated rat hepatocytes incubated for 30 min with 25 μM resveratrol, acetate incorporation into triglycerides decreased (Gnoni and Paglialonga, 2009). Similarly, in HepG2 cells incubated with resveratrol, triglyceride accumulation was reduced comparing with control cells (Shang et al., 2008b).

The direct influence of resveratrol on metabolism of cells of white adipose tissue was also demonstrated. Exposure of freshly isolated rat adipocytes for 90 min to resveratrol resulted in reduced basal and insulin-induced glucose conversion to total lipids. This effect was

accompanied by diminished glucose oxidation and increased release of lactate. Moreover, resveratrol potentiated the lipolytic response to epinephrine and attenuated the ability of insulin to counteract lipolysis in adipose cells. The increase in cAMP found in adipocytes incubated with resveratrol is proposed to be responsible for enhanced lipolytic rate (Szkudelska et al., 2009a). Our recent studies also revealed the potent ability of resveratrol (6.25–50 μM) to reduce glucose- and alanine-derived ATP content in isolated rat adipose cells already within minutes after treatment (unpublished data). These data imply that short-term exposure to resveratrol results in diminished lipid accumulation in both hepatocytes and adipocytes. It is therefore possible that reduction of adiposity and/or body weight induced by resveratrol in rodents on a high-energy diet is due to both long-term (e.g. changes in gene expression) and short-term (e.g. changes in enzyme activities) effects evoked by this compound.

The activity of resveratrol in relation to obesity may also involve other effects. Experiments on isolated cells revealed inhibition of adipogenesis in the presence of resveratrol (Rayalam et al., 2007, 2008; Park et al., 2008; Yang et al., 2008). Its anti-adipogenic activity was substantially enhanced by the other natural compound genistein. The combination of both resveratrol and genistein allowed to obtain much stronger effects at lower concentrations of each compound (Rayalam et al., 2007; Park et al., 2008). The above-described effects are summarized in Table 1 and Fig. 2.

3. Resveratrol and diabetes

Diabetes is associated with relative or absolute insulin deficiency. Numerous natural, plant-derived compounds have been reported to affect secretion and action of this hormone (Pinent et al., 2008). The impact of resveratrol on insulin secretion was studied for the first time by Zhang et al. (2004). Experiments on INS-1 cells demonstrated lack of effect, however, other studies have provided compelling evidence that the insulin-secreting cells are significantly influenced by resveratrol. Electrophysiological measurements allowed to demonstrate that resveratrol binds to sulfonylurea receptor (SUR) and is a blocker of pancreatic ATP-sensitive K^+ channels. It was also observed that resveratrol displaced binding of glibenclamide, a sulfonylurea drug that blocks ATP-sensitive K^+ channels in β-cells and is applied in type 2 diabetes to enhance insulin secretion (Hambrock et al., 2007). Under physiological conditions, ATP-sensitive K^+ channels are normally blocked as a result of the increase in the ATP/ADP ratio resulting from metabolism of glucose or other fuel secretagogues. The rise in the ATP/ADP ratio induces depolarization of the plasma membrane and triggers secretion of insulin (Henquin, 2000). Further studies regarding the action of resveratrol performed on MIN6 cells additionally revealed that the tested compound directly blocked ATP-sensitive K^+ channels and voltage-gated K^+ channels thereby depolarizing the plasma membrane. The inhibition of ATP-sensitive

Table 1
Effects of resveratrol on different parameters related to obesity.

Parameter	Effect	Animals/cells	Dose/concentration of resveratrol Treatment/time of incubation	References
Survival, motor function	Increased	Mice on a high-calorie diet	In a diet, 0.04%, for 114 weeks (survival) or for 24 months (motor function)	Baur et al. (2006)
	Increased	Mice on a high-fat diet	In a diet 400 mg/kg/day, for 15 weeks	Lagouge et al. (2006)
Body fat	Reduced	Mice on a high-fat diet	In a diet, 400 mg/kg/day, for 15 weeks	Lagouge et al. (2006)
	Slightly decreased	Obese Zucker rats	10 mg/kg body weight, intragastrically, for 8 weeks	Rivera et al. (2009)
Inguinal, epididymal and retroperitoneal adipose tissue depots	Reduced	Mice on a high-fat diet	In a diet, 400 mg/kg/day, for 15 weeks	Lagouge et al. (2006)
Visceral fat index and liver mass index	Reduced	Rats on a high-fat diet	In a diet, 100 mg/kg/day, for 10 weeks	Shang et al. (2008a,b)
			6 mg/l of drinking water (approximately 1 mg/kg body weight/day), for 45 days	Rocha et al. (2009)
Body weight gain	Reduced	Female rats on a high-fat diet	In a diet, 20 mg/kg/day, for 8 weeks	Aubin et al. (2008)
	Reduced	Mice on a high-fat diet	In a diet, 400 mg/kg/day, for 15 weeks	Lagouge et al. (2006)
	Unchanged	Mice on a high-calorie diet	In a diet, 0.04%, for 18 to 24 month of experiment	Baur et al. (2006)
	Unchanged	Rats on high-fat diet	6 mg/l in drinking water (approximately 1 mg/kg body weight/day) for 45 days	Rocha et al. (2009)
	Unchanged	Obese Zucker rats	10 mg/kg body weight, intragastrically, for 8 weeks	Rivera et al. (2009)
Plasma triglycerides	Decreased	Obese Zucker rats	10 mg/kg body weight, intragastrically, for 8 weeks	Rivera et al. (2009)
	Unchanged	Mice on a high-calorie diet	In a diet, 0.04% for 18 months	Baur et al. (2006)
Dysfunction of cardiac and skeletal muscle induced by ageing and other signs of ageing	Reduced	Male C57BL/6NIA mice on a high-calorie diet	In a diet, 0.01% or 0.04%, from12 to 27 month of age	Pearson et al. (2008)
	Reduced	Normal mice	In a diet, 4.9 mg/kg/day, for 15 months	Barger et al. (2008)
Fatty acid synthesis	Reduced	Isolated rat hepatocytes	1–100 μM, 60 min	Gnoni and Paglialonga (2009)
Fatty acid synthase activity	Unchanged		25 μM, 30 min	
Acethyl-CoA carboxylase activity	Reduced			
Acetate conversion into triglycerides	Decreased			
Basal and insulin-induced glucose conversion to lipids	Reduced	Isolated rat adipocytes	125 and 250 μM, 90 min	Szkudelska et al. (2009a,b)
Glucose oxidation	Reduced			
Lactate production	Increased			
Epinephrine-stimulated lipolysis	Enhanced	Isolated rat adipocytes	10 and 100 μM, 90 min	Szkudelska et al. (2009a,b)
Antilipolytic action of insulin	Reduced		1, 10 and 100 μM, 90 min	
ATP content	Reduced		6.25–50 μM, 15–90 min	unpublished data
Adipogenesis	Inhibited	3T3-L1 adipocytes	100 μM, 48 h	Rayalam et al. (2007, 2008)
	Inhibited		25 and 100 μM (individually or combined incubation with quercetin), 48 h	Yang et al. (2008)
	Inhibited	Human adipocytes, 3T3-L1 adipocytes	12.5 or 100 μM (combined incubation with genistein and quercetin), 3 or 14 days	Park et al. (2008)

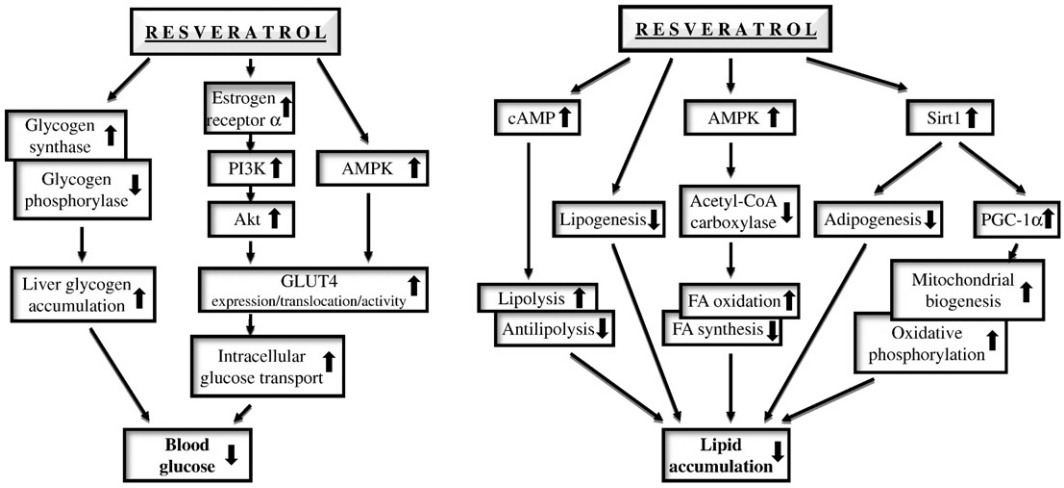

Fig. 2. Schematic representation of effects induced by resveratrol and leading to reduced blood glucose levels and diminished lipid accumulation.

K^+ channels appeared to be quite considerable as demonstrated in experiments with glibenclamide, a potent blocker of these channels; the effect induced by 30 μM resveratrol was comparable to that of 20 μM glibenclamide. According to these results, resveratrol stimulated insulin secretion in mouse, hamster and rat β-cell insulinoma lines (MIN6, Hit-T15 and RIN-m5F). However, this insulinotropic action was noticed when cells were incubated in the medium without glucose which is the main physiological stimulator of insulin secretion. It should be also emphasized that cells used in these studies differed from normal pancreatic β-cells (e.g. their insulin-secretory response to glucose was substantially weaker compared with freshly isolated β-cells) (Chen et al., 2007).

Studies on pancreatic islets provided new data on the action of resveratrol in the insulin-secreting cells. Unlike in the insulinoma cells, in freshly isolated rat pancreatic islets, resveratrol (1–100 μM) appeared to exert an insulin-suppressive effects — the compound clearly attenuated glucose-induced insulin secretion. This effect was observed at a broad spectrum of stimulatory concentrations of glucose, however, resveratrol was ineffective at non-stimulatory glucose (Szkudelski, 2006, 2008). The study of the dynamics of glucose-induced insulin secretion with the use of perifused pancreatic islets demonstrated the inhibitory effect already within minutes upon exposure to resveratrol (Szkudelski, 2006). The amplifying pathway of insulin secretion, which is independent of the closure of ATP-sensitive K^+ channels in β-cells, was also reported to be abated in the presence of the tested compound (Szkudelski, 2007). Furthermore, experiments on isolated rat pancreatic islets revealed the inhibitory effect of resveratrol on insulin secretion induced not only by glucose, but also by mitochondrial fuels — leucine and glutamine — suggesting an impairment in mitochondrial metabolism in β-cells (Szkudelski, 2006). The mechanistic experiments confirmed this assumption and evidenced that the attenuation of the insulin-secretory response in the presence of resveratrol was due to metabolic disturbances in islet cells. Under physiological conditions, glucose-induced secretion of insulin is preceded, among others, by oxidative glycolysis and hyperpolarisation of the inner mitochondrial membrane in β-cells (Henquin, 2000). However, in cells incubated with resveratrol, glucose-induced hyperpolarisation of the mitochondrial membrane was demonstrated to be substantially blunted. Analysis of metabolic activity of islet cells exposed to resveratrol revealed reduced oxidation of glucose and enhanced release of lactate indicating an impairment in oxidative metabolism of glucose. These effects resulted in diminished ATP content in pancreatic islets exposed to the tested stilbene (Szkudelski, 2007). The importance of metabolic disturbances in the mechanism of resveratrol's action was additionally confirmed by data showing that the tested compound failed to affect insulin release when this process was induced without metabolic events in β-cells (Szkudelski, 2007). Although metabolic disturbances are of major importance, an inhibition of protein kinase C (PKC) in β-cells was suggested to be also involved in the insulin-suppressive action of resveratrol (Szkudelski, 2006, 2008). The inhibition of PKC activity in the presence of resveratrol has been previously demonstrated in experiments in vitro (Slater et al., 2003; Atten et al., 2005). The proposed mechanism thereby resveratrol reduces insulin secretion from normal β-cells is presented in Fig. 3.

Data from the literature indicate that resveratrol exerts estrogenic/anti-estrogenic activity because of its ability to bind estrogen receptor (Bowers et al., 2000). Therefore, some effects induced by this compound are mediated via estrogen receptor. However, experiments with pancreatic islets incubated in the presence of estrogen receptor antagonist, ICI 182,780, demonstrated that reduced secretion of insulin evoked by resveratrol was independent of estrogenic/anti-estrogenic activity of this compound (Szkudelski, 2007). In the studies concerning the effects induced by resveratrol in islet cells, the

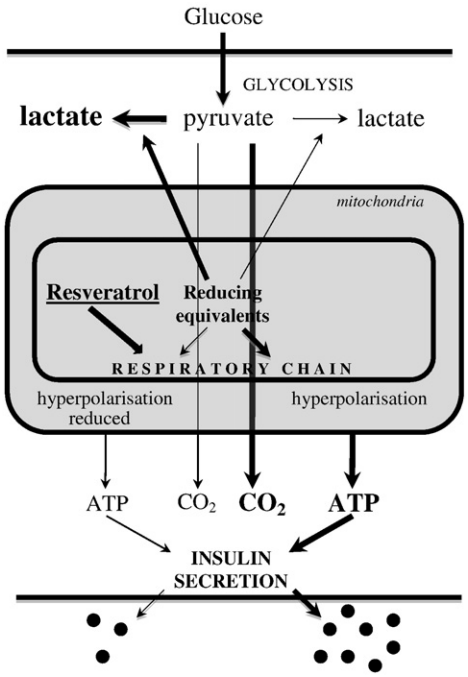

Fig. 3. Schematic representation of effects induced by resveratrol and leading to reduced insulin secretion from normal β-cells.

important finding was that the attenuation of the insulin-secretory response elicited by this compound was transient and disappeared after its withdrawal from the incubation medium (Szkudelski, 2006). This indicates that resveratrol reduces secretion of insulin without permanent damage of β-cells.

The above-presented data from the in vitro studies point to the high activity of resveratrol on the insulin-secreting cells, whereas results obtained in vivo imply that this compound may also influence blood insulin concentrations (Table 2). The effect of resveratrol on blood insulin was investigated in normal, hyperinsulinemic and diabetic animals, however, different results were obtained depending on experimental conditions. In one study, in normal non-fasted rats, a bolus of resveratrol, i.e. 50 mg/kg body weight given intragastrically, reduced blood insulin at 30 min. This effect may be explained by high dose of the tested compound since 10 mg resveratrol appeared to be ineffective (Szkudelski, 2008). On the other hand, Chi et al. (2007) demonstrated that resveratrol (3 or 10 mg/kg body weight) significantly increased blood insulin in overnight fasted rats 90 min after intraperitoneal administration. Results of the long-term studies performed on normal rats are considerably more consistent since the influence of prolonged administration of resveratrol on blood insulin was found to be negligible. The lack of effect was shown in rats receiving resveratrol per oral for 30 days (5 mg/kg body weight) (Palsamy and Subramanian, 2008, 2009) as well as for 4 or 8 weeks (10 mg/kg body weight) (Rivera et al., 2009).

Interesting data were obtained in experiments on mice and rats in hyperinsulinemic conditions. In mice with a marked hyperinsulinemia induced by a high-fat diet, resveratrol incorporated into a diet substantially diminished blood insulin comparing with animals consuming a high-fat diet without this compound (Baur et al., 2006; Lagouge et al., 2006). In the other study, in rats with hyperinsulinemia induced by a high cholesterol–fructose diet, resveratrol (1 mg/kg body weight; administered per oral for 15 days or 15 weeks) also significantly reduced blood insulin (Deng et al., 2008). A clear-cut blood insulin-lowering action of resveratrol (given for 4 or 8 weeks at the dose 10 mg/kg body weight) was also noticed in obese Zucker rats with hyperinsulinemia (Rivera et al., 2009).

The effects of resveratrol on blood insulin concentrations in diabetes were investigated using two experimental animal models: a model of diabetes which is similar to type 1 diabetes in humans (streptozotocin-induced diabetic rats) and a model which is similar to type 2 diabetes in humans (streptozotocin–nicotinamide diabetic rats). In the short-term experiment on streptozotocin–nicotinamide diabetic rats, a considerable hyperinsulinemic effect of resveratrol was shown. In this experiment, blood insulin in diabetic and non-diabetic rats was similar, whereas resveratrol (3 or 10 mg/kg body weight) substantially increased insulinemia 90 min after its oral administration. A similar rise in blood insulin was evoked by glybenclamide (Chi et al., 2007). In the other study on streptozotocin–nicotinamide diabetic rats in which resveratrol (5 mg/kg body weight) was administered orally for 30 days, blood insulin was also increased. In this case, the effect of resveratrol was similar to those induced by the other sulfonylurea glyclazide (Palsamy and Subramanian, 2009). On the other hand, Su et al. (2006), using the same model of diabetes, obtained different results. They demonstrated that in streptozotocin–nicotinamide diabetic rats receiving resveratrol at very low doses (0.5 mg/kg body weight) for 14 days,

Table 2
Effects of resveratrol on the insulin-secretory cells, blood insulin concentrations and insulin sensitivity.

Parameter	Effect	Animals/cells	Dose/concentration of resveratrol Treatment/time of incubation	References
Pancreatic ATP-sensitive K^+ channels	Blocked	Isolated mouse β-cells	100 μM	Hambrock et al. (2007)
	Blocked	Mouse insulinoma β-cell line (MIN6)	3 μM	Chen et al. (2007)
Voltage-gated K^+ channels	Blocked	Mouse insulinoma β-cell line (MIN6)	30 μM	
Basal insulin secretion	Stimulated	Mouse insulinoma β-cell line (MIN6)	3–100 μM, 60 min	Chen et al. (2007)
	Unchanged	Isolated rat pancreatic islets	1–100 μM, at non-stimulatory glucose, 90 min	Szkudelski (2006)
Glucose-induced insulin secretion	Reduced	Rat pancreatic islets	1–100 μM, 90 min	Szkudelski (2006)
Glucose oxidation	Reduced			Szkudelski (2008)
Lactate release	Increased			Szkudelski (2007)
ATP content	Reduced			
Blood insulin concentration	Reduced	Normal rats	50 mg/kg body weight, intragastrically, 30 min	Szkudelski (2008)
	Unchanged	Normal rats	10 mg/kg body weight, intragastrically, 30 min	Szkudelski (2008)
	Increased	Overnight fasted rats	3 or 10 mg/kg body weight, intraperitoneally, 90 min	Chi et al. (2007)
	Unchanged	Normal rats	5 mg/kg body weight, for 30 days	Palsamy and Subramanian (2008, 2009)
	Unchanged	Normal rats	In a diet, 10 mg/kg body weight, for 4 or 8 weeks	Rivera et al. (2009)
	Reduced	Mice on a high-fat diet with hyperinsulinemia	In a diet, 0.04%, for 6 months	Baur et al. (2006)
	Reduced	Mice on a high-fat diet with hyperinsulinemia	In a diet, 400 mg/kg/day, for 16 weeks	Lagouge et al. (2006)
	Reduced	Rats on a high-fructose diet with hyperinsulinemia	1 mg/kg body weight, administered orally for 15 days or 15 weeks	Deng et al. (2008)
	Reduced	Mice on a high-fat diet with hyperinsulinemia	79.2 ng/day, intracerebral infusion for 5 weeks	Ramadori et al. (2009)
	Reduced	Obese Zucker rats with hyperinsulinemia	In a diet, 10 mg/kg body weight, for 4 or 8 weeks	Rivera et al. (2009)
	Increased	Streptozotocin–nicotinamide diabetic rats	3 or 10 mg/kg body weight, administered orally, 90 min	Chi et al. (2007)
	Increased	Streptozotocin–nicotinamide diabetic rats	5 mg/kg body weight, administered orally for 30 days	Palsamy and Subramanian (2009)
	Reduced	Streptozotocin–nicotinamide diabetic rats	0.5 mg/kg body weight, intragastrically, 3 times a day for 14 days	Su et al. (2006)
	Unchanged	Streptozotocin-induced diabetic rats	3 or 10 mg/kg body weight, intragastrically, 90 min	Chi et al. (2007)
Insulin sensitivity	Increased	Mice on a high-fat diet	In diet, 0.04%, for 6 months	Baur et al. (2006)
		Mice on a high-fat diet	In diet 400 mg/kg/day, for 16 weeks	Lagouge et al. (2006)
	Increased	Obese Zucker rats	10 mg/kg body weight administered for 4 or 8 weeks	Rivera et al. (2009)
	Decreased	Primary hepatocytes	10 to 200 μM, 16 h	Zhang (2006)
	Decreased	Human primary myotubes	100 μM applied 30 min prior to insulin stimulation and 20 min after	Fröjdö et al. (2007)

insulinemia was deeply reduced compared with non-treated diabetic animals. This effect was seen already on the second day of resveratrol administration.

Data concerning the influence of resveratrol on blood insulin concentrations in animals with streptozotocin-induced diabetes are very scanty. In one study, in streptozotocin-induced diabetic rats with considerable hypoinsulinemia, resveratrol (3 or 10 mg/kg body weight) failed to change blood insulin 90 min after oral administration. A similar lack of effect was demonstrated for glybenclamide (Chi et al., 2007). In this case, the lack of effect may be explained by a substantial damage of β-cells.

Numerous data indicate that chronic overstimulation of insulin secretion contributes to β-cell failure, whereas temporary rest of these cells ameliorates their endocrine activity and may delay the onset of the overt diabetes (reviewed by Hansen et al., 2004). Therefore, the insulin-suppressive effects of resveratrol found in some experiments may be considered as beneficial to health in the context of preventing diabetes.

Apart from proper insulin secretion and blood insulin concentration, cellular action of this hormone is of great importance. Long-term studies on mice consuming a high-fat diet revealed that in these animals resveratrol incorporated into a diet (0.04%) was able to increase insulin sensitivity (Baur et al., 2006; Lagouge et al., 2006). A substantial improvement in insulin sensitivity was also found in obese Zucker rats treated with resveratrol (10 mg/kg body weight/day) for 4 or 8 weeks (Rivera et al., 2009). On the other hand, in vitro studies of Zhang (2006) demonstrated the inhibitory action of resveratrol on insulin signalling pathway in different kinds of cells, including hepatocytes. The tested compound abated insulin-induced activation of Akt and MAPK and disrupted the interactions between insulin receptor substrates and some downstream binding proteins. Besides, the presence of resveratrol in the incubation medium reversed the effects of insulin on transcription of some enzymes. In the other study, resveratrol appeared to inhibit class IA phosphoinositide 3-kinase (PI3K) and to attenuate PI3K-protein kinase B (PKB) pathway (Fröjdö et al., 2007) (Table 2).

Another important aspect of resveratrol's action is its influence on blood glucose concentrations. This effect was intensively studied in both normoglycemic and hyperglycemic animals (Table 3). The majority of available data indicate that resveratrol does not affect blood glucose concentrations in normoglycemic animals. In short-term studies, resveratrol (10 or 50 mg/kg body weight) given intragastrically to normal rats did not change blood glucose at 30 min (Szkudelski, 2008). The lack of effects was also noticed in animals treated with resveratrol for a longer period. In rats receiving 5 mg resveratrol per kg body weight orally for 30 days (Palsamy and Subramanian, 2008, 2009) or intraperitoneally for 42 days (Silan, 2008) blood glucose concentrations remained unchanged. Similarly, resveratrol given at higher dose (20 mg/kg body weight) for 28 days to rats was also ineffective and blood glucose was unchanged (Juan et al., 2002). The lack of effects was also confirmed in rats receiving resveratrol intraperitoneally (10 or 20 mg/kg body weight) for 30 days (Schmatz et al., 2009).

Surprisingly, Su et al. (2006) and Chi et al. (2007) have noticed blood glucose-lowering properties of resveratrol in normal rats. Administration of this compound at very low doses (0.25–0.75 mg/kg body weight) to overnight starved rats resulted in a clear-cut decline in glycemia 90 min after treatment. Moreover, the glycemic response to an intravenous glucose challenge (2 g glucose/kg body weight) appeared to be diminished in rats that received resveratrol (0.5 mg/kg body weight) compared with non-treated animals (Su et al., 2006). According to these results, the other study also demonstrated that an oral gavage of resveratrol (0.5–10 mg/kg body weight) significantly diminished blood glucose in overnight starved rats 90 min after administration. In these animals, resveratrol (10 mg/kg body weight) was also found to reduce rise in glycemia after oral glucose treatment (1 g/kg body weight) (Chi et al., 2007).

In diabetic animals, the majority of data points to the blood glucose-lowering effect of resveratrol. In streptozotocin–nicotinamide diabetic rats, this effect was demonstrated in both acute and long-term experiments. In the former case, 90 and 120 min after oral administration of resveratrol (0.5 mg/kg body weight) to diabetic rats, hyperglycemia significantly decreased compared with non-treated diabetic animals. Moreover, in streptozotocin–nicotinamide diabetic rats, resveratrol (0.5 mg/kg body weight) administered for 14 days was also able to substantially reduce blood glucose (Su et al., 2006). Other studies on streptozotocin–nicotinamide diabetic rats have confirmed previous data since resveratrol (5 mg/kg body weight) given orally for 30 days also diminished hyperglycemia. Interestingly, the anti-hyperglycemic activity of this compound was comparable to those induced by sulfonylurea glyclazide (Palsamy and Subramanian, 2008, 2009).

In streptozotocin-induced diabetic rats, resveratrol was applied for 14 days (0.5 mg/kg body weight) and was also shown to substantially reduce hyperglycemia (Su et al., 2006). The blood glucose-lowering properties of this compound in streptozotocin-induced diabetic rats were confirmed in many other studies in which resveratrol was given orally (2.5 mg/kg body weight for 15 days) (Thirunavukkarasu et al., 2007; Penumathsa et al., 2008) or injected intraperitoneally (5 mg/kg body weight for 42 days) (Silan, 2008). However, Schmatz et al. (2009) demonstrated no effects of resveratrol (10 or 20 mg/kg body

Table 3
Effects of resveratrol on blood glucose concentrations in normal and diabetic rats.

Parameter	Effect	Animals	Dose/treatment/time	References
Normoglycemia	Unchanged	Normal rats	10 or 50 mg/kg body weight, intragastrically, 30 min	Szkudelski (2008)
	Unchanged	Normal rats	5 mg/kg body weight, orally or intragastrically, for 30 days	Palsamy and Subramanian (2008, 2009)
	Unchanged	Normal rats	5 mg/kg body weight/day, intraperitoneally, for 42 days	Silan (2008)
	Unchanged	Normal rats	20 mg/kg body weight, orally, for 28 days	Juan et al. (2002)
	Unchanged	Normal rats	10 or 20 mg/kg body weight/day, intraperitoneally, 30 days	Schmatz et al. (2009)
	Decreased	Normal rats	0.25–0.75 mg/kg body weight, intragastrically, 90 min	Su et al. (2006)
	Decreased	Overnight starved rats	0.5–10 mg/kg body weight, intragastrically, 90 min	Chi et al. (2007)
	Decreased	Rats with intravenous glucose challenge	0.5 mg/kg body weight, intragastrically, 90 min	Su et al. (2006)
	Decreased	Rats after oral glucose treatment	10 mg/kg body weight, intragastrically, 90–120 min	Chi et al. (2007)
Hyperglycemia	Decreased	Streptozotocin–nicotinamide diabetic rats	0.5 mg/kg body weight, intragastrically, for 8–14 days	Su et al. (2006)
	Decreased	Streptozotocin–nicotinamide diabetic rats	0.5 mg/kg body weight, intragastrically, 90–120 min	Su et al. (2006)
	Decreased	Streptozotocin–nicotinamide diabetic rats	5 mg/kg body weight, orally or intragastrically, for 30 days	Palsamy and Subramanian (2008, 2009)
	Decreased	Streptozotocin-induced diabetic rats	0.5 mg/kg body weight, intragastrically, 10–14 days	Su et al. (2006)
	Decreased	Streptozotocin-induced diabetic rats	2.5 mg/kg body weight, orally, for 15 days	Thirunavukkarasu et al. (2007), Penumathsa et al. (2008)
	Decreased	Streptozotocin-induced diabetic rats	5 mg/kg body weight/day, intraperitoneally, for 42 days	Silan (2008)
	Unchanged	Streptozotocin-induced diabetic rats	10 or 20 mg/kg body weight/day, intraperitoneally, for 30 days	Schmatz et al. (2009)

weight) administered intraperitoneally for 30 days to streptozotocin-induced diabetic rats on hyperglycemia.

These data, although sometimes not fully coherent, allow to conclude that prolonged administration of resveratrol effectively reduces blood glucose in hyperglycemic conditions, but this compound does not affect glucose levels in animals with normoglycemia. This important feature of resveratrol implies the possibility of its potential use as an anti-hyperglycemic agent.

The blood glucose-lowering activity of resveratrol seems to involve both insulin-independent and insulin-dependent effects. The former ones are well documented in studies in vitro showing the direct stimulatory effects of resveratrol on glucose uptake. In soleus muscle, adipocytes and hepatocytes isolated from streptozotocin-induced diabetic rats and incubated in the presence of resveratrol (0.01–1 μM), but without insulin, glucose uptake was found to be substantially increased (Su et al., 2006). In the other study, in L6 rat skeletal muscle cells exposed to 100 μM resveratrol, glucose uptake was also significantly potentiated compared with control cells (Breen et al., 2008). Similarly, in $HepG_2$ cells, resveratrol at very low concentrations (0.17–1.70 μM) was able to increase intracellular glucose uptake (Su et al., 2006). A prolonged (8 h) incubation of H9c2 cardiac myoblast cells with resveratrol also enhanced glucose uptake in an insulin-independent manner (Penumathsa et al., 2008). Furthermore, it was demonstrated that in rats fed a high cholesterol–fructose diet and receiving resveratrol (1 mg/kg body weight) per oral gavage for 15 days or 15 weeks, glucose uptake by soleus muscle and liver was substantially increased compared with uptake observed in tissues of animals non-treated with resveratrol (Deng et al., 2008).

Different mechanisms are proposed to be responsible for resveratrol-induced intracellular glucose transport. The effect on glucose transporters GLUT1 and GLUT4 are often taken into consideration. In the in vitro studies of Breen et al. (2008), stimulation of glucose uptake by L6 myotubes exposed to resveratrol was mediated via activation of sirtuins and required phosphorylation of AMPK. However, in this study, resveratrol-induced glucose uptake was without translocation of GLUT1 and GLUT4 to the plasma membrane and was thought to be due to increased intrinsic activity of GLUT4. Moreover, conversely to insulin-stimulated glucose transport, resveratrol-induced glucose uptake by L6 myotubes was not accompanied by phosphorylation of Akt/PKB (Breen et al., 2008). In the myocardium isolated from streptozotocin-induced diabetic rats receiving resveratrol (2.5 mg/kg body weight) for 2 weeks, increased phosphorylation of AMPK, expression of GLUT4 and association of GLUT4/caveolin-3 were found compared with diabetic animals non-treated with resveratrol (Penumathsa et al., 2008). The enhanced expression of GLUT4 was also confirmed by the other study. This effect was detected in soleus muscle of streptozotocin-induced diabetic rats treated with resveratrol (3 mg/kg) for 7 days (Chi et al., 2007). The influence of resveratrol on GLUT4 was also demonstrated in rats on a high cholesterol–fructose diet. In these animals, administration of resveratrol enhanced translocation of GLUT4 to the plasma membrane comparing with rats on a high cholesterol–fructose diet, but non-treated with this stilbene (Deng et al., 2008).

Deng et al. (2008) have provided interesting results demonstrating a pivotal role for estrogen receptor in the mechanism of resveratrol action. These authors revealed that both insulin-dependent and insulin-independent stimulatory effects of this compound on cellular glucose uptake require activation of estrogen receptor-α. The action of resveratrol was found to involve early and late phase via the p38/Erk- and p38/Akt-dependent pathways, respectively. Moreover, PI3K was demonstrated to be engaged in the late phase. The relevance of PI3K for the blood glucose-lowering action of resveratrol has been previously demonstrated in vivo in diabetic rats (Chi et al., 2007).

Apart from the above-described results, other effects of resveratrol related to diabetes should be mentioned. In streptozotocin–nicotinamide diabetic rats, resveratrol (5 mg/kg body weight) administered orally for 30 days substantially attenuated changes in the activities of numerous enzymes of the glycolytic pathway in the kidney and liver. Simultaneously, resveratrol was able to increase glycogen synthase and to reduce glycogen phosphorylase activities in the liver of diabetic rats with a concomitant increase in liver glycogen stores (Palsamy and Subramanian, 2009). The direct impact of resveratrol on glycogen accumulation was also observed in vitro. In hepatocytes derived from streptozotocin-induced diabetic rats, resveratrol (0.1–10 μM) significantly enhanced glycogen synthesis (Su et al., 2006). Su et al. (2006) reported that administration of 5 mg resveratrol per kg body weight (orally, for 14 days) substantially reduced blood triglycerides in both streptozotocin-diabetic and streptozotocin–nicotinamide diabetic rats.

It should be also mentioned that resveratrol was demonstrated to alleviate diabetic nephropathy. Low doses of the compound (5 or 10 mg/kg body weight) given orally for two weeks to diabetic rats reduced renal dysfunction and oxidative stress in these animals (Sharma et al., 2006). Experimental data also indicate the effectiveness of resveratrol in reducing the severity of chemically-induced pancreatitis (Li et al., 2006, 2009; Wang et al., 2008). This is thought to result from the lowering of pancreatic oxidative free radicals and diminishing of pancreatic tissue infiltration of neutrophils (Li et al., 2006). In the other study, resveratrol-induced attenuation of the pathological changes in the pancreatic tissue has been ascribed to reduced intracellular calcium overload (Wang et al., 2008). Recently, the inhibitory effect of resveratrol on islet amyloid polypeptide fibril formation in INS-1 cells was demonstrated (Mishra et al., 2009; Radovan et al., 2009). It is also known that resveratrol may influence secretion and blood concentrations of some adipokines (Baur et al., 2006; Rivera et al., 2009; Szkudelska et al., 2009b). Disturbances in blood adiponectin levels are thought to contribute to obesity-related insulin resistance and diabetes. However, data regarding the effects of resveratrol on adipokines are recently insufficient to be conclusive.

4. Conclusions

Data published in the last few years imply that resveratrol exerts numerous beneficial effects in obesity and diabetes and thereby may be helpful in preventing and treating both these diseases. The obtained results indicate a broad spectrum of activities of resveratrol not only in relation to diabetes but also to diabetic complications. However, further studies are required to clarify some discrepancies found in the literature. Moreover, despite a large body of evidence demonstrating promising effects in rodents, human studies are still lacking and both preventive and therapeutic value of resveratrol in humans remains to be elucidated.

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