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Review

Resveratrol and obesity: Can resveratrol relieve metabolic disturbances?☆

Marlies de Ligt, Silvie Timmers, Patrick Schrauwen *

Department of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, 6200MD Maastricht, The Netherlands

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ABSTRACT

There is an increasing need for novel preventive and therapeutic strategies to combat obesity and related metabolic disorders. In this respect, the natural polyphenol resveratrol has attracted significant interest. Animal studies indicate that resveratrol mimics the effects of calorie restriction via activation of sirtuin 1 (SIRT1). SIRT1 is an important player in the regulation of cellular energy homeostasis and mitochondrial biogenesis. Rodent studies have shown beneficial effects of resveratrol supplementation on mitochondrial function, glucose metabolism, body composition and liver fat accumulation. However, confirmation of these beneficial effects in humans by placebo-controlled clinical trials remains relatively limited. This review will give an overview of pre-clinical and clinical studies examining the effects of resveratrol on obesity-induced negative health outcomes. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. Introduction

The prevalence of obesity is increasing tremendously worldwide. A recent systematic analysis for the Global Burden of Disease Study reported a worldwide increase in overweight and obesity between 1980 and 2013 from 28.8% to 36.9% in men and 29.8% to 38.0% in women [1]. Obesity presents a health risk, partly due to ectopic fat accumulation; fat accumulation in non-adipose tissue such as liver and skeletal muscle. Accumulation of fat in the liver, when unrelated to alcohol intake, is a strong independent marker of dyslipidaemia and insulin resistance. Insulin resistance in turn predisposes to the development of type 2 diabetes (T2D) [2–4]. Impaired mitochondrial function is also often seen in obese and/or T2D patients [5]. Mitochondria play a central role in energy homeostasis and substrate metabolism. Therefore, reduced mitochondrial function has substantial effects on glucose and lipid metabolism, deteriorating metabolic health.

The rise in obesity prevalence is predominantly caused by changes in lifestyle, such as decreased physical activity and increased intake of energy-dense food. The primary solution for this obesity epidemic, and its related negative effects on public health, should therefore also be sought in changing lifestyle. Increasing the amount of physical activity or decreasing energy intake are proven effective therapeutic strategies to positively influence health outcomes related to obesity. Correspondingly, restricting calorie intake for six months leads to an improvement in insulin sensitivity [6], which in turn is accompanied by an increase in muscle mitochondrial biogenesis [7]. However, people in general have difficulties following strict exercise training or dieting regimes. Alternative treatments are therefore highly sought after. This has led to the search for compounds that can initiate beneficial health effects similar to those from exercise training or calorie restriction.

2. Resveratrol

Resveratrol (3, 5, 4′ trihydroxystilbene) is a polyphenol naturally present in and produced by several plants. The richest source of natural resveratrol is *Polygonum cuspidatum*, a plant known from traditional Chinese and Japanese medicine [8]. Smaller amounts of resveratrol can also be found in peanuts, grapes, red wine and mulberries [9]. In 2003, Howitz et al. [9] identified resveratrol as a small-molecule activator of sirtuin 1 (SIRT1). SIRT1, like all members of the sirtuin family, requires nicotinamide adenine dinucleotide (NAD^+) for its deacetylating activity [10]. The dependence of SIRT1 on NAD^+ strongly links its activity to cellular energy levels. SIRT1 is induced both by calorie restriction and exercise [11] and plays an important role in the regulation of lipid and glucose homeostasis [12]. The fact that SIRT1 is closely connected to cellular energy levels and energy homeostasis makes it an interesting molecular target for treatment of metabolic disorders such as obesity. Considering resveratrol has been identified as a small-molecule activator of SIRT1, it is not surprising that resveratrol has been said to have calorie restriction-like effects [13–16]. However, there is debate

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* Corresponding author at: Department of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, PO Box 616, 6200MD Maastricht, The Netherlands. Tel.: +31 43 388 1502; fax: +31 43 367 0976.
E-mail address: p.schrauwen@maastrichtuniversity.nl (P. Schrauwen).

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whether resveratrol activates SIRT1 directly [9,17,18] or rather via activation of AMP-activated protein kinase (AMPK) [19,20]. AMPK and SIRT1 both play a crucial role in energy homeostasis and their activity is closely interrelated. It is therefore difficult to identify whether resveratrol activates SIRT1 or AMPK or both, either direct or indirect. Recently, Park et al. [21] proposed that the metabolic effects of resveratrol might result from competitive inhibition of cAMP-degrading phosphodiesterases, leading to elevated cAMP levels. Consequently, through a cascade of effects, this could lead to activation of AMPK, followed by an increase in NAD^+ and finally an increase in SIRT1 activity [21]. Unfortunately, the exact mechanism is still unknown. Despite the mechanism of action, resveratrol is a promising candidate for treatment and prevention of metabolic diseases by mimicking calorie restriction-like effects.

The aim of this review is to evaluate the potential effects of resveratrol on obesity-related health outcomes mainly in humans, both in experimental and clinical settings (see Table 1 for an overview of published peer-reviewed clinical trials on resveratrol and obesity-related health outcomes). Studies that used grape extract containing resveratrol or other formulas with multiple components are not taken into account. The effects of resveratrol on mitochondrial function, body composition, energy expenditure, insulin resistance and liver fat accumulation will be evaluated.

3. Effects of resveratrol on muscle mitochondrial function

Excessive energy intake and a low level of physical activity will lead to accumulation of fat in adipose tissue. In turn, this excessive fat accumulation can lead to lipid overflow and accumulation of fat in non-adipose tissue, such as the liver and skeletal muscle [22,23]. In general, muscle fat accumulation correlates negatively with insulin sensitivity [24] especially when mitochondrial fat oxidative capacity is low. Indeed, T2D patients and people at high risk of developing T2D are characterised by high intramyocellular lipid levels and a decreased mitochondrial fatty acid oxidative capacity [25,26]. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a crucial regulator of mitochondrial metabolism and biogenesis, and a downstream effector of the AMPK-SIRT1 signalling pathway [27]. Several studies have reported a reduction in PGC-1α gene expression in T2D patients [28,29]. This disrupted gene expression pattern can also be seen in non-diabetic offspring of T2D patients [29]. It has been suggested that a low PGC-1α gene expression can lead to reduced generation of mitochondrial proteins, resulting in loss of mitochondrial capacity and decreased insulin sensitivity [29]. Exercise training and calorie restriction are proven effective strategies to improve muscle mitochondrial oxidative capacity, paralleled by improvements in whole body insulin sensitivity [7,30,31]. Thus, six months of calorie restriction has been shown to increase expression of AMPK, PGC-1α and SIRT1, increase mitochondrial DNA content and reduce fasting insulin levels [7]. Therefore, improving muscle oxidative capacity appears to be an effective strategy for counteracting obesity-induced insulin resistance and T2D.

A couple of animal studies have actually investigated the effects of resveratrol on muscle mitochondrial capacity. A rodent study by Lagouge et al. [32] included four different intervention groups: male C57BL/6J mice on a high-fat diet (HFD) with or without a dose of 400 mg/kg/day (mpk) of resveratrol or on a chow diet with or without resveratrol (400 mpk). The intervention period was 15 weeks. They found that mitochondria in non-oxidative muscle fibres of resveratrol-treated HFD mice were larger and denser, and mitochondrial DNA content increased compared with HFD animals that did not receive resveratrol. Um et al. [20], who also treated male C57BL/6J mice whilst on a HFD with 400 mpk resveratrol, reported increased mitochondrial content (measured by cytochrome C protein levels and mitochondrial DNA) compared with no resveratrol-treatment after an intervention period of 13 weeks. In addition, they measured a decrease in the content of the fatty acid intermediates diacylglyceride and ceramide in skeletal muscle. To further investigate mitochondrial activity, both studies measured PGC-1α expression in skeletal muscle. PGC-1α mRNA [20,32] and protein [32] significantly increased in resveratrol-treated animals. Additionally, resveratrol treatment increased physical endurance of mice, as evidenced by increased running time [20,32]. A recent study by Price et al. [17], using two different doses of resveratrol (25–30 mpk and 215–300 mpk), also found beneficial effects of resveratrol on mitochondrial biogenesis and function. The mice were fed a HFD of a standard diet for eight months. The HFD led to significantly impaired function of mitochondria isolated from skeletal muscle. Supplementation with either of the two resveratrol doses for eight months prevented the HFD-induced mitochondrial dysfunction. Thus, increases were measured compared with HFD animals without resveratrol supplementation in: ADP-stimulated respiration (state 3), FCCP-induced maximal oxidative respiration (state u), mitochondrial membrane potential, and cellular ATP levels. These levels were comparable to mice fed a standard diet. In addition, treatment with resveratrol resulted in a fibre type switch towards more oxidative muscle fibre types, and prevented the HFD-induced decline in mitochondrial content (measured by citrate synthase activity and by mitochondrial DNA content). Interestingly, when SIRT1 knockout mice were used none of the above-mentioned effects of resveratrol were observed. Moreover, SIRT1 overexpression resulted in similar effects as resveratrol treatment in wild type mice. The authors therefore concluded that SIRT1 plays a crucial role in improving mitochondrial function by resveratrol supplementation (25–30 mpk). Chen et al. [33] performed a study with male Sprague–Dawley rats fed a normal diet, HFD or HFD with resveratrol (100 mpk by intragastric administration) and found results comparable to Price et al. [17]. Hence, resveratrol-treatment increased SIRT1 activity and mitochondrial biogenesis, compared to a HFD without resveratrol. Furthermore, resveratrol reverted the decline in subsarcolemmal mitochondrial citrate synthase and electron transport chain activities and decreased IMCL content. Pearson et al. [34] investigated the effects of resveratrol on muscle mitochondrial function in a non-obese animal model. One-year old male C57BL/6NIA mice received a chow diet, both diets with and without resveratrol added (~30.9 mpk). An additional group of mice were fed every-other-day, which is a form of calorie restriction. They concluded that resveratrol shifts muscle mitochondrial gene expression patterns in mice on a standard diet towards those on a calorie restriction diet.

Together, these findings from animal studies indicate that resveratrol can influence mitochondrial biogenesis via activation of the AMPK–SIRT1–PGC-1α axis. This has led to the generally accepted idea that improving mitochondrial function by resveratrol supplementation is a promising strategy for improving metabolic health in humans. In accordance with findings from rodent studies, we have demonstrated in a previous clinical trial that resveratrol-treatment leads to activation of AMPK, increases SIRT1 and PGC-1α protein levels and increases citrate synthase activity [13]. Thus, Timmers et al. [13] studied 11 obese but otherwise healthy males receiving a dose of 150 mg resveratrol or placebo per day for 30 days, in a double-blind cross over design. No difference was found in mitochondrial content, in contrast to animal studies [20,32]. However, muscle mitochondrial fatty acid oxidative capacity was improved on a fatty acid-derived substrate (state 3 respiration), as determined by increased mitochondrial respiration. In contrast to data from animal studies, IMCL content in the vastus lateralis muscle was increased upon resveratrol-treatment. Combining the improvement in muscle fat oxidative capacity, increased IMCL content and other beneficial metabolic adaptations found in this study, the hypothesis emerged that resveratrol-treatment could have an endurance training-like effect [14,30]. One other human intervention investigated the effect of resveratrol on mitochondrial function, although indirectly by examining gene expression pathways related to mitochondrial function [15]. Thus, Yoshino et al. [15] studied non-obese postmenopausal women with normal glucose tolerance. Fifteen women received resveratrol (75 mg per day) and fourteen women received placebo, for a period of 12 weeks. Contradicting Timmers et al. [13], they concluded that