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Minireview

Cellular effects of resveratrol in skeletal muscle

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ABSTRACT

Resveratrol is a stilbene found naturally in various plants with the highest concentration in the skin of grapes and peanuts. The function of this compound in plants is to confer resistance against bacterial and fungal infection. The effects of resveratrol in animals and humans are currently an area of intense investigation. Resveratrol has been shown to have a plethora of health benefits including protection against cardiovascular disease, various cancers, type II diabetes, and also has life extending properties. The beneficial effects of resveratrol in skeletal muscle have been given less attention in the literature compared to other tissues. Therefore, the focus of this review is to highlight the cellular effects of resveratrol in skeletal muscle. Resveratrol has been shown to alter protein catabolism and muscle function, and confer resistance against oxidative stress, injury, and cell death of skeletal muscle cells. The mechanisms underlying these resveratrol-induced adaptations in skeletal muscle are discussed.

Contents

Introduction

Resveratrol is a stilbene found naturally in various plants with the highest concentration found in the skin of grapes and peanuts. The function of this compound in plants is to confer resistance against bacterial and fungal infection. The physiologic benefits in animals and humans are currently an area of intense investigation. Interest in resveratrol has been stimulated by the quest for the explanation of the "French Paradox", the observation that despite a high fat diet the French have a much lower than expected incidence of cardiovascular disease. It has been hypothesized that the consumption of resveratrol in red wine protects the French against the health consequences of a high fat diet (Cordova et al. 2005; Poussier et al. 2005; Rosenkranz et al. 2002). Interest in resveratrol has also stemmed from the fact that it mimics many of the cellular effects and life-extending properties of caloric restriction; the first non-genetic intervention to slow the intrinsic rate of aging in mammals (Wood et al. 2004). It is hopeful that resveratrol will be the magic pill that is our "fountain of youth".

Resveratrol has a plethora of health benefits including life extending properties. Resveratrol supplementation starting in adulthood extended the medium and maximum lifespan of a short lived fish in a dose dependent manner with the highest dose increasing each by 56% and 59%, respectively (Valenzano et al. 2006). Resveratrol also has been shown to increase the maximum lifespan of *Saccharomyces cerevisiae* (Howitz et al. 2003), *Drosophila melanogaster* (Wood et al. 2004), and *Caenorhabditis elegans* (Gruber et al. 2007). The effect of resveratrol on maximum lifespan of mammals has not been tested yet.

Resveratrol supplementation has been shown to attenuate many age-related diseases such cardiovascular disease, various types of cancers, neurodegeneration, and type II diabetes. To elucidate the underlying mechanism of action of resveratrol, much research has been focused on particular tissues and cell types such as smooth muscle cells, myocardial cells, hepatocytes, and a multitude of various cancer cell lines. Less attention has been given to the effects of

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resveratrol on skeletal muscle. It has been shown that the action of resveratrol on skeletal muscle is an important aspect of its ability to protect against the negative effects of a high fat diet and also plays an essential role in its ability to improve insulin sensitivity and glucose tolerance. The focus of this review is the cellular effects of resveratrol on skeletal muscle. Resveratrol has been shown to alter metabolism, protein catabolism and function, and confer resistance against oxidative stress, injury, and cell death of skeletal muscle cells. The mechanisms underlying these resveratrol-induced adaptations in skeletal muscle will be discussed.

The effects of resveratrol on skeletal muscle metabolism

Resveratrol supplementation alters fatty acid and glucose metabolism of skeletal muscle as shown in vitro and in vivo. Resveratrol has been shown to protect animals from metabolic disease and improve health and survival while on a high fat diet (Baur et al. 2006; Lagouge et al. 2006). Lagouge et al. reported that high doses of resveratrol (200–400 mg/kg/day for 15 weeks) protected mice from diet induced obesity (Lagouge et al. 2006). The mice on a high fat diet with resveratrol (HFR) gained significantly less weight and were comparable in weight to control mice on a standard chow fed diet than those mice on a high fat diet without resveratrol (HF). The body fat content of the mice on the HFR was comparable to the control fed mice with a body fat percentage of 18%, while the HF mice had a significantly elevated body fat percentage of approximately 27% (Lagouge et al. 2006). In contrast, Baur et al. reported that although resveratrol supplementation was beneficial in protecting high fat fed mice against some of the negative health consequences of obesity, such as insulin resistance, the supplementation did not protect them from weight gain (Baur et al. 2006). The body weight of the high fat fed mice with resveratrol was slightly lower than high fat fed mice without resveratrol for months 3–5 after starting resveratrol supplementation, but beyond that point the body weights were not significantly different (Baur et al. 2006). The reason for the discrepancy is not clear, however, it may be due to the dose of the resveratrol used and/or to the length of the study. The study by Lagouge et al. was 15 weeks at a dose of 400 mg/kg/day (Lagouge et al. 2006) while the study by Baur et al. was approximately 15 months using a dose of 22.4 mg/kg/day (Baur et al. 2006).

The difference in weight and fat gain in the study reported by Lagouge et al. was not due to differences in food consumption or spontaneous activity (Lagouge et al. 2006). Instead, it was shown that resveratrol increased basal energy expenditure and thermogenesis. In humans, skeletal muscle is mainly responsible for energy expenditure and thermogenesis, rather than brown adipose tissue. The authors demonstrated that resveratrol increased the size and content of mitochondria as well as the mitochondrial enzyme activity in non-oxidative muscle fibers, which contributed to an increase in maximal oxygen consumption of those fibers (Lagouge et al. 2006). It was shown that resveratrol induced the expression of genes for oxidative phosphorylation and mitochondrial biogenesis. The change in gene expression was mediated through the activation of peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) via the deacetylation by the silent information regulator 2 mammalian ortholog (SIRT1) (Lagouge et al. 2006). Another target gene of PGC-1α is uncoupling protein-3 (UCP3) which was found to be elevated in mice fed the HFR diet (Lagouge et al. 2006). UCP3 is preferentially expressed in skeletal muscle and adipose tissue and has been implicated in regulating the flux of lipid substrates into the mitochondria and in the protection against obesity (Dulloo and Samec 2001; Fisler and Warden 2006). Therefore, these adaptations induced by resveratrol appear to enhance fatty acid oxidation in skeletal muscle in these mice.

In contrast Barger et al. did not find that resveratrol supplementation increased expression of PGC-1α nor UCP3 in skeletal muscle of healthy mice (Barger et al. 2008). Although the expression of PGC-1α was not altered by resveratrol supplementation, it may be possible that the activity may have been altered. PGC-1α activity is regulated by post-transcriptional modifications; deacetylation increases its activity. However, it was also shown by others that resveratrol treatment decreased UCP3 expression in C2C12 myotubes (Amat et al. 2007), an indication that PGC-1α activity may not be altered by resveratrol. The disparity in the results may very well be dependent on the experimental conditions, where in combination with high fat feeding resveratrol increases activity of PGC-1α and increases expression of UCP3 to metabolize elevated levels of fat intake, but with a standard diet or in cell culture it may not. Alternatively, the disparity may be due to the difference in dosing where a low dose does not activate PGC-1α and UCP3 (4.9 mg/kg/day) (Barger et al. 2008) while a high dose does (200–400 mg/kg/day) (Lagouge et al. 2006).

Resveratrol was also shown to protect mice from insulin resistance while on a high fat diet (Baur et al. 2006; Lagouge et al. 2006). Animals on a HFR diet had lower circulating levels of insulin and improved glucose tolerance compared to those mice on HF diet (Baur et al. 2006; Lagouge et al. 2006). Resveratrol also improves glucose tolerance in diabetic rats (Chi et al. 2007; Su et al. 2006). Skeletal muscle is responsible for 80% of the glucose clearance from the blood and therefore plays an essential role in glucose homeostasis. Resveratrol has been shown to stimulate glucose uptake by skeletal muscle. Some have shown that resveratrol can stimulate glucose uptake independent of the action of insulin as well as enhance insulin-dependent glucose transport (Chi et al. 2007; Deng et al. 2008; Park et al. 2007).

The mechanism of resveratrol-induced glucose transport, with and without the presence of insulin, is debatable. In skeletal muscle cells, insulin alone stimulates glucose transport via the activation of the PI-3 kinase/Akt signaling pathway which leads to the translocation of Glut4 transporters to the plasma membrane. Park et al. demonstrated in C2C12 myotubes that resveratrol-induced glucose transport, independent of insulin, is mediated via activation of AMP-activated protein kinase (AMPK) and does not involve PI-3 kinase/Akt signaling (Park et al. 2007). However, resveratrol enhanced insulin-stimulated glucose transport does involve PI-3 kinase/Akt signaling. Activation of AMPK by resveratrol, in conjunction with insulin, led to enhanced phosphorlyation of Akt compared to insulin stimulated phosphorylation of Akt by PI-3 kinase alone (Park et al. 2007). Barger et al. showed that resveratrol enhanced insulin-stimulated glucose transport in soleus muscle, but not in the extensor digitalis longus (EDL) muscle of mice (Barger et al. 2008). The authors demonstrated that the enhanced glucose uptake in the soleus in resveratrol fed mice was not attributed to increased Akt phosphorlyation (Barger et al. 2008). The level of insulin-stimulated Akt phosphorylation was similar with or without resveratrol (Barger et al. 2008). Others have demonstrated that resveratrol-induced glucose transport, independent of insulin, is dependent on PI-3 kinase/Akt signaling (Chi et al. 2007). Deng et al. showed that glucose transport is dependent upon Erk/p38 in an early phase (1 h) upon resveratrol treatment and p38/PI-3 kinase signaling in a late phase (14 h) (Deng et al. 2008). Furthermore, activation of the estrogen receptor was required for resveratrol-induced glucose transport with or without insulin (Deng et al. 2008). Although disagreement exists concerning the mechanism, it is consistent in these studies that resveratrol increases glucose transport in skeletal muscle with and without the presence of insulin. However, in stark contrast, one group found that resveratrol inhibited insulin stimulated activation of PI-3 kinase/Akt signaling in human primary myotubes, rat L6, and human rhabdomyocarcoma CCL muscle-derived cell lines (Frojdo et al. 2007). Although not demonstrated in skeletal muscle cells, the same group showed that resveratrol inhibited insulin-stimulated glucose uptake into adipocytes (Frojdo et al. 2007).

Resveratrol supplementation was also shown to increase the protein levels of Glut4 transporters in soleus muscle of streptozotocin-induced diabetic rats which may contribute to the anti-hyerglycemic effects of resveratrol (Chi et al. 2007). However, resveratrol supplementation in healthy mice did not increase the protein content of

Glut4 in the soleus, despite its ability to increase glucose transport, or in the EDL (Barger et al. 2008).

The discrepancies in the resveratrol-dependent effects in similar cell lines or tissues are difficult to explain, but has been recently discussed (Cucciolla et al. 2007). Aside from differing experimental conditions and concentration of resveratrol used, other explanations may include wrong methods of preparation and storage of resveratrol and/or strong genotype/phenotype variations of the cell lines employed due to cell passages (Cucciolla et al. 2007).

In summary, resveratrol may enhance fatty acid oxidation, at least in high fat fed animals, and improve glucose homeostasis by enhancing glucose transport and possibly by increasing the expression of Glut4 transporters in skeletal muscle.

The effects of resveratrol on protein catabolism and muscle function

Skeletal muscle wasting is a symptom associated with many diseases and conditions including cancer, heart failure, and AIDS which translates into significant losses in muscle strength and endurance. Resveratrol has been investigated as a possible treatment to prevent muscle wasting. Resveratrol has been consistently shown to inhibit protein degradation and to attenuate atrophy of skeletal muscle fibers in vitro (Busquets et al. 2007; Russell et al. 2006; Wyke et al. 2004; Wyke and Tisdale 2006). In C2C12 myotubes resveratrol treatment inhibited protein degradation induced by proteolysis inducing factor (PIF) (Wyke et al. 2004), Angiotensin I and II (Russell et al. 2006), and the phorbal ester 12-0-tetradecanoylphorbol-13-acetetate (TPA) (Wyke and Tisdale 2006). Furthermore, incubation of the isolated rat EDL muscle in resveratrol significantly reduced protein degradation compared to control muscle (Busquets et al. 2007).

It appears that resveratrol may inhibit protein degradation by inhibiting the activation and translocation of nuclear factor kappa beta (NF-kB) to the nucleus (Russell et al. 2006; Wyke et al. 2004; Wyke and Tisdale 2006). Resveratrol may inhibit activation of NF-kB via the inhibition of I-kB kinase (IKK) (Holmes-McNary and Baldwin 2000). It was shown that resveratrol inhibited PIF-induced I-kBα and nuclear binding of NF-kB in C2C12 myotubes (Wyke et al. 2004) also prevented Angiotensin II-induced (Russell et al. 2006) and TPA-induced (Wyke and Tisdale 2006) nuclear accumulation of NF-kB.

Although resveratrol consistently attenuates protein degradation in vitro, it is still debatable whether these effects occur in vivo. It has been shown that resveratrol supplementation (1 mg/kg/day) in MAC 16 tumor bearing rats did significantly attenuate weight loss and protein degradation in skeletal muscle as well as reduce the NF-kB activity (Wyke et al. 2004). However, resveratrol supplementation (1–25 mg/kg/day) in rats bearing the Yoshida AH-130 ascites hepatoma or the Lewis lung carcinoma had no effect on loss of body weight or skeletal muscle mass (Busquets et al. 2007). Again, the disparities between studies are difficult to explain. It is important to point out that resveratrol treatment attenuated MAC 16 tumor growth (Wyke et al. 2004) and therefore attenuation of skeletal muscle wasting may have been, in part, an indirect effect secondary to inhibition of tumor growth. The effects of resveratrol on Yoshida AH-130 ascites hepatoma or the Lewis lung carcinoma tumor growth was not reported (Busquets et al. 2007). However, if resveratrol did not effect tumor growth in this study it may be a possible explanation why resveratrol did not attenuate muscle wasting in this experimental model.

Resveratrol supplementation to mice on a high fat diet has been shown to improve muscular strength and endurance compared to control mice on a high fat diet without supplementation (Lagouge et al. 2006). Resveratrol supplementation in high fat fed mice increased grip strength, motor coordination, and increased average distances run at exhaustion. Resveratrol induced myofiber remodeling similar to that seen by exercise training, but in the absence of increased physical activity. Resveratrol supplementation induced a fiber type transition from glycolytic type II fibers towards more oxidative type I fibers which would contribute to increased muscular endurance. It was not determined what adaptations contributed to increased muscle strength, but it was shown that resveratrol treatment increased the expression of genes involved in striated muscle contraction (Lagouge et al. 2006).

The effects of resveratrol on oxidative stress, injury and death

Resveratrol has antioxidant and anti-inflammatory properties and can protect against cellular stress, injury and death. Ischemia and reperfusion injury (I/R injury) to skeletal muscle can be a serious condition with the likelihood of it occurring during trauma and reconstructive surgery. Resveratrol supplementation has been shown to protect against I/R injury (Elmali et al. 2007; Ikizler et al. 2006). Typically, I/R injury is associated with the production of reactive oxygen species, oxidative stress and damage, inflammation, and cell death via necrosis and apoptosis. After 4 h of ischemia and 4 h of reperfusion induced by use of a tourniquet, intraperitoneal administration of resveratrol protected skeletal muscle from I/R injury (Elmali et al. 2007). Resveratrol administration (10 mg/kg) reduced the amount of edema, changes in myofiber diameter, polymorphonuclear leukocyte (PMN) infiltration, malondialdehyde (MDA) levels, and segmental necrosis in the gastrocnemius or tibialis anterior compared to controls not receiving resveratrol after the I/R protocol (Elmali et al. 2007). Ikezler et al. also reported that resveratrol supplementation protects against I/R injury (Ikizler et al. 2006). Resveratrol (20 mg/kg/day) was administered to rats for fourteen days before the animals were subjected to the I/R protocol. Resveratrol protected skeletal muscles from oxidative stress and injury as determined by MDA, carbonyl and protein sulphydryl levels as well as venous levels of myoglobin, lactate dehydrogenase, creatinine phosphokinase (Ikizler et al. 2006). Resveratrol protects skeletal muscle from cellular stress and I/R injury.

The detailed mechanisms of how resveratrol protects skeletal muscle against I/R injury has not been investigated. However, details are beginning to be elucidated regarding the protective effects of resveratrol against I/R injury in the heart (Das et al. 2008). The thioredoxin system, consisting of thioredoxin, thioredoxin reductase and NADPH, is essential in regulating the cellular redox status in the heart and skeletal muscle and protects myocytes from cellular stress and death (Rohrbach et al. 2006). It was shown that the protective effects of resveratrol against I/R injury in cardiomyocytes are, at least in part, dependent upon upregulation of thioredoxin reductase-2 (TrxR2), the mitochondrial isoform (Das et al. 2008). Resveratrol reduced the myocardial infarct size, level of apoptosis, and oxidative stress induced by I/R injury. However, inhibition of TrxR2 abolished most of the protected effects of resveratrol (Das et al. 2008). It was determined that the survival signal induced by resveratrol that protected cardiomyocytes from I/R injury and death involved upregulation of TrxR2 which may lead to increased Akt signaling and increased expression of the anti-apoptotic protein Bcl-2 and decreased production of reactive oxygen species by the mitochondria (Das et al. 2008). In skeletal myoblasts under cellular stress, reducing the level of TrxR2 by small interfering RNA causes a dramatic enhancement of apoptosis and mitochondrial reactive oxygen species release (Rohrbach et al. 2006). Hence, resveratrol-induced upregulation of TrxR2 may be a potential mechanism in its protection against I/R injury in skeletal muscle as well. Future research will elucidate this possibility.

Conclusion

Resveratrol has been shown to have a plethora of health benefits such as the protection against heart disease and certain cancers as well as potential life-extending properties. Cellular mechanisms of resveratrol-induced health benefits have been of intense investigation in recent years. In skeletal muscle, resveratrol has thus far been shown to alter metabolism, inhibit protein catabolism, improve function, and protect against cellular stress. First, resveratrol appears to alter fatty acid and glucose metabolism. Resveratrol may induce metabolic adaptations to

favor fatty acid oxidation, at least in animals eating a high fat diet; a condition where it may be most beneficial. Resveratrol has anti-hyperglycemic effects by enhancing glucose transport in skeletal muscle. Secondly, resveratrol also has anti-catabolic effects in skeletal muscle via the inhibition of protein degradation. This has been consistently shown in vitro, but still debatable in vivo. Thirdly, resveratrol also has been shown to improve strength and endurance of skeletal muscle. Lastly, resveratrol has antioxidant properties and can protect skeletal muscle from oxidative injury and death due to I/R injury.

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