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Dietary Activators of Sirt1

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Abstract

Calorie restriction (CR) is a non-genetic manipulation that reliably results in extended lifespan of several species ranging from yeast to dogs. The lifespan extension effect of CR has been strongly associated with an increased level and activation of the Sir2 histone deacetylase and its mammalian ortholog Sirt1. This association led to the search for potential Sirt1-activating, life-extending molecules. This review briefly outlines the experimental findings on resveratrol and other dietary activators of Sirt1.

Keywords

Calorie restriction; lifespan; resveratrol; sirtuins

1. Introduction

The search for mechanisms behind the lifespan extension effect of reduced caloric intake has been ongoing since McCay's first demonstration that calorie restriction (CR) by limiting caloric intake to 60–70% of an *ad libitum* diet extends the life of rodents (McCay, et al. 1989). Since then, CR has been shown to have a lengthening effect on the lifespan of a number of species ranging from yeast (Lin, et al. 2000) to dogs (Lawler, et al. 2007) and possibly even primates (Ingram, et al. 2006). Theories on the possible mechanisms involved in these lifespan extending effects have been intensively investigated, many of which have been shown to play at least some role in the CR effect. Some of these theories include decreased oxidative damage, altered glucose utilization, increased insulin sensitivity, neuroendocrine changes, enhanced stress responsiveness, hormesis, and changes in gene expression. One of the compelling findings has been the association between increased levels of sirtuins and the lifespan extension effect of CR. Sirtuins are members of the silent information regulator 2 (Sir2) family, a family of Class III histone/protein deacetylases (HDACs). The enzymatic activity of most sirtuins has been shown to be dependent on nicotinamide dinucleotide (NAD), suggesting that the activity of these enzymes is dependent on the nutritive state of the organism. Members of this family of deacetylases include five homologues in yeast (Sir2 and Hst1-4), Sir2.1 in *Caenorhabditis elegans*, dSir2 in *Drosophila melanogaster* and seven mammalian sirtuins (Sirt1-7) (Dali-Youcef, et al. 2007; Frye 1999).

2. CR and sirtuins in *Saccharomyces cerevisiae*

The activity of Sir2 was first shown to regulate lifespan in *S. cerevisiae*. In 2000, Guarente's lab discovered that Sir2 was a requirement for the increase in replicative lifespan by CR which was achieved by limiting the concentration of glucose (2% to 0.5%) in yeast cultures (Lin et

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al. 2000; Lin, et al. 2002). CR in yeast by amino acid depletion also affects replicative lifespan, although the effect differed among three different histone deacetylase mutants (Jiang, et al. 2002). Other Sir2 homologs were found to explain CR's positive effects on lifespan extension (Perrod, et al. 2001). In yeast, Hst2 extends lifespan by stabilizing repetitive ribosomal DNA (Lamming, et al. 2005). Cellular senescence in yeast can be induced by the exponential accumulation of extra-chromosomal ribosomal DNA circles (ERCs) which cause the nucleoli to swell, eventually leading to death. One mechanism by which Sir2 extends yeast lifespan is thought to be by inhibiting the formation of ERCs (Kaeberlein, et al. 1999). Replicative lifespan in yeast is measured by the number of cell divisions that a mother cell goes through and is reflected by the number of budding scars. Chronological lifespan in yeast is a temporal assessment of the time yeast remains viable in a non-replicative phase. CR in yeast has been shown to increase both replicative and chronological lifespan; however, unlike replicative lifespan, chronological lifespan may be decreased by Sir2 in certain long-lived yeast strains (Fabrizio, et al. 2005).

3. CR and sirtuins in *C. elegans* and *D. melanogaster*

In *C. elegans*, CR can be achieved by either diluting its food source, bacteria, or by a mutation in the EAT2 gene which affects pharyngeal function and leads to reduction of food intake (Lakowski and Hekimi 1998). Each of these methods of CR extends lifespan in worms (Klass 1977; Vanfleteren and Braeckman 1999). The lifespan extension in *C. elegans* induced by CR has been shown to be dependent on Sir2.1 (Wang and Tissenbaum 2006). In addition, a duplication of the Sir-2.1 gene in *C. elegans* extends lifespan by up to 50% (Tissenbaum and Guarente 2001). A more demanding form of dietary restriction (DR), dietary deprivation, has also been shown to increase lifespan in non-reproductive worms, however, this effect was not dependent on Sir2.1 (Kaeberlein, et al. 2006; Lee, et al. 2006).

In *D. melanogaster*, one way to achieve CR is to dilute the amount of macronutrients, including yeast extract and sugar in the diet (Mair, et al. 2005; Tatar 2007). CR in normal flies extends lifespan by slowing down the normal aging process (Pletcher, et al. 2002). Lifespan extension by CR requires dSir2 in *D. melanogaster* (Guarente 2005; Rogina and Helfand 2004). An increase in dSir2 extends lifespan, whereas a decrease in dSir2 blocks the lifespan extending effect of CR in *D. melanogaster* (Rogina and Helfand 2004). However, in a study by Newman *et al*., unlike in yeast, mutations in dSir2 did not shorten lifespan (Newman, et al. 2002).

4. CR and sirtuins in vertebrates

For more than 70 years CR has been shown to increase lifespan in mammals, yet its effect on human lifespan is still not known. One complicating factor is the unlikely probability of maintaining such a lifestyle on a long-term basis. The belief that many of the benefits of CR are due to the induction and activation of sirtuins has led to the search for sirtuin activators that may be used as dietary supplements to promote health and longevity. Sirt1 is the most extensively studied of the seven mammalian sirtuins (Sirt1-7) and shares a catalytic domain of ~275 amino acids with other sirtuins. It is also the mammalian sirtuin that shares the most sequence similarity with Sir2 in yeast (Frye 2000). Sirt1 deacetylates a large number of transcriptional factors and cofactors involved in cell growth, differentiation, stress resistance, reducing oxidative damage, and metabolism (Brunet, et al. 2004; Cohen, et al. 2004; Higami, et al. 2004; Lee, et al. 1999; Luo, et al. 2001; Motta, et al. 2004; Vaziri, et al. 2001; Weindruch, et al. 2002; Yeung, et al. 2004). Sirt1 is also a regulator of PGC-1α (Rodgers, et al. 2005), a transcription co-activator that plays a key role in regulating mitochondrial biogenesis, adipogenesis, muscle cell differentiation, and energy metabolism in multiple tissues. Most recently, it has been shown that Sirt1 is involved in regulating the circadian transcription of

several core clock genes (Asher, et al. 2008; Nakahata, et al. 2008), making a possible connection between lifespan and circadian rhythm.

Evidence has accumulated implicating Sirt1 in the lifespan-extending effects of CR (Cohen et al. 2004; Leibiger and Berggren 2006). Other mammalian sirtuins have been suggested as mediators of other beneficial aspects of CR including the decreased incidence of age-related disorders, such as cardiovascular disease, diabetes and cancer (Bordone and Guarente 2005). Levels of Sirt6 are increased upon nutrient deprivation in cultured cells. Sirt6, like Sirt1 levels, are also increased in the brain, kidney and heart of mice after a 24hr fasting period, and in white adipose tissue (WAT), heart and brain of rats fed a calorie-restricted diet for a minimum of one year (Kanfi, et al. 2008). In addition, mice lacking Sirt6 develop a degenerative disorder that in some respects mimics models of accelerated ageing (Mostoslavsky, et al. 2006). Sirt7-deficient mice undergo a reduction in mean and maximum lifespan and develop heart hypertrophy and inflammatory cardiomyopathy (Vakhrusheva, et al. 2008). Sirt7 has also been shown to be an essential regulator of tissue homeostasis in the heart. However, varied lines of investigation have implicated Sirt1 in longevity and led to the assumption that it is the predominant sirtuin involved in lifespan extension.

In rodents, CR increases the expression of Sirt1 in many tissues including brain, fat, kidney and liver (Cohen et al. 2004; Nisoli, et al. 2005). Many of the phenotypes of CR are induced by the increased activation of Sirt1. Sirt 1 decreases adipogenesis, stimulates free fatty acid mobilization in adipocytes (Picard, et al. 2004), induces gluconeogenesis in hepatocytes (Rodgers et al. 2005), and induces fatty acid oxidation in skeletal muscle (Gerhart-Hines, et al. 2007). Sirt1 also seems to mediate some neuro-protective effects (Araki, et al. 2004; Qin, et al. 2006). In Sirt1-over-expression mice there is a decrease in fat mass, total cholesterol level, fasting blood insulin and glucose levels, as well as a delay in reproductive maturity and enhanced oxygen consumption (Bordone, et al. 2007). These are phenotypes typical of CR mice. However, all the phenotypes in these Sirt1 over-expressing mice do not appear to be consistent with changes seen in CR; and whether these mice have an extended lifespan remains to be seen.

There have been a limited number of studies on alternate nutrition manipulations that result in increased activation of Sirt1. One study found that the decreased levels of Sirt1, found in the diabetic rat kidney, is overcome by alternate-day fasting (Tikoo, et al. 2007). In addition, alternate-day fasting, CR and CR in conjunction with exercise increased Sirt1 mRNA levels in human muscle tissue (Civitarese, et al. 2007; Heilbronn, et al. 2005). Previous studies in rodents using a maternal low protein diet have shown that limiting protein during lactation increases longevity and Sirt1 expression in offspring (Martin-Gronert, et al. 2008).

5. Dietary supplements and Sirt1

There have been studies assessing the ability of different nutritive supplements to induce Sirt1 activity. Sirt1 mRNA levels were shown to increase in adipose tissue with a sixteen-week treatment of a combination of ephedrine, caffeine and the anti-diabetic drug Pioglitazone in nondiabetic human subjects (Bogacka, et al. 2007).

It has been assumed for many years that consumption of fish on a regular basis protects from cardiovascular disease (Bang 1990). Several studies have shown that omega-3 fatty acids can improve cardiovascular and autoimmune disorders. Docosahexaenoic acid (DHA) promotes neurite growth and strengthens the periventricular vascular system against hemorrhage. When autoimmune prone (NZBxNZW)F1 mice were fed either a 5% corn oil or 5% fish oil (FO) AL diet, a significantly increased lifespan was noted in the FO-fed mice. The same held true for the 5% corn oil vs. the 5% fish oil on 40% CR diets (Jolly, et al. 2001). A recent publication reports that dietary supplementation of omega-3 fatty acids is effective in reversing the

reduction of sirt1 levels in rats with mild traumatic brain injury (Wu, et al. 2007). It will be interesting to determine the effects of omega fatty acids on longevity in the same model.

6. Plant polyphenols

Polyphenols are the most abundant antioxidants found in food. They are known to have a protective effect against cardiovascular diseases (Basu and Lucas 2007) and cancers (Bracke, et al. 2008; Kampa, et al. 2007) and there is some evidence of neuroprotective effects (Singh, et al. 2008; West, et al. 2007). Sinclair and colleagues examined a set of plant polyphenols for their effect on Sirt1 catalytic rate. These sirtuin-activating compounds (STACs) included butein, piceatannol, fisetin, quercetin and resveratrol. Butein is a major biologically active component of the stems of Rhus verniciflua Stokes. It has been shown to have anti-inflammatory (Lee, et al. 2007), blood-pressure-lowering ((Kang, et al. 2003), and anti-cancer effects (Wang, et al. 2005). Piceatannol is a naturally occurring, hydroxylated analog of resveratrol and has long been used as a food additive and as a herbal medicine throughout Asia (Gerhart-Hines et al. 2007; Wolter, et al. 2002; Yokozawa and Kim 2007). It has been shown to have anti-cancer properties (Potter, et al. 2002). Fisetin is commonly found in strawberries and other fruits and vegetables and has been shown to stimulate signaling pathways that enhance long-term memory (Maher, et al. 2006). Quercetin is the active component of many medicinal plants. Foods rich in quercetin include capers, lovage, apples, tea, onions, citrus fruits, green vegetables and most berries. Quercetin has been demonstrated to be a significant anti-inflammatory and anti-cancer agent (Shaik, et al. 2006) and has been shown to have protective properties against a number of diseases (Knekt, et al. 2002). Resveratrol was first known for its antioxidant and antifungal properties. It is found in raspberries, blueberries, grapeskins, peanuts and some pine trees. Resveratrol has been shown to have a wide range of biological effects, including anti-platelet, anti-inflammatory, anti-cancer, anti-mutagenic and protection from atherosclerotic disease. Each of these polyphenols was shown to have a stimulatory effect on Sir2 activity in yeast.

6.1 Resveratrol in yeast

When tested on *S. cerevisiae*, the polyphonols butein, fisetin and resveratrol increased lifespan by 31%, 55% and 70%, respectively. Resveratrol however, produced the highest level of Sir2 activation among all the small molecules tested (Howitz, *et al.* 2003).

The ability of Sir2 to extend lifespan in yeast is thought to be due to a role in the stabilization of repetititve DNA sequences. Assays quantifying extrachromosomal DNA indicated resveratrol was able to reduce levels of these potentially toxic molecules. Another study done in three different yeast strains found that resveratrol had no detectable effect on Sir2 activity *in vivo*, as measured by rDNA recombination, transcriptional silencing near telomeres, and life span. *In vitro* analyses found that resveratrol enhances binding and deacetylation of peptide substrates that contain Fluor de Lys, a non-physiological fluorescent moiety, but has no effect on binding and deacetylation of acetylated peptides lacking the fluorophore. These authors deduced that the mechanism accounting for longevity effects of resveratrol may not be due to Sir2 activation (Kaeberlein, *et al.* 2005).

6.2 Resveratrol in *C. elegans* and *D. melanogaster*

After the discovery that resveratrol could extend the lifespan of yeast, possibly in a Sir2 dependent manner (Howitz et al. 2003), several studies began to ask whether resveratrol or its derivatives may someday be a “magic bullet” for aging interventions in humans. A first step taken to address this intriguing question was to evaluate resveratrol in invertebrate model systems including the worm *C. elegans* and the fruitfly *D. melanogaster* (Wood, et al. 2004). *C. elegans* and *D. melanogaster* are two genetically tractable systems that have relatively short

lifespans (mean lifespans of 2–3 weeks and 2–3 months, respectively), making them ideal for studying basic biological questions in aging and screening for prolongevity compounds (Kenyon 2005; Partridge, et al. 2005). By taking advantage of these two model organisms, Wood *et al.* have demonstrated that supplementation of resveratrol can extend lifespan of a standard *C. elegans* strain N2 and several *D. melanogaster* strains (Canton S, *w*1118 and *yw*) in a dosage- and diet-dependent manner (Wood et al. 2004). Two concentrations of resveratrol were tested, 50 and 200 μM, with the higher concentration resulting in a greater lifespan extension. The pro-longevity effect of resveratrol in these two models has subsequently been confirmed in several studies. Bauer *et al*. have shown that resveratrol increases lifespan of a short-lived fly genetic strain (Bauer, et al. 2004). Cruber *et al*. have demonstrated that lifespan extension by resveratrol is associated with a small decrease in fecundity early in life in *C. elegans* (Gruber, et al. 2007). Viswanathan et al. have demonstrated the pro-longevity effect of resveratrol in *C. elegans* in their study on transcriptomic changes induced by this compound (Viswanathan, et al. 2005). These experiments seemed to provide strong evidence that resveratrol is an effective pro-longevity compound for metazoans. However, this conclusion has recently been challenged by a study conducted by Bass *et al*. (Bass, et al. 2007). These researchers have reported no or undetectable lifespan extension by resveratrol in *C. elegans* and *D. melagnogaster*. The causes of this disparity are not clear. One possibility is the difference in potency of resveratrol, which is thought to be very sensitive to light and oxygen (Yang, et al. 2007). This may not be the main factor since Bass *et al*. have confirmed the intactness of their resveratrol using HPLC (Bass et al. 2007). More studies should be conducted to resolve this issue, such as using more potent and stable versions of resveratrol, multiple strains and various diets. In the experiments showing a prolongevity effect, resveratrol appears to increase lifespan through pathways related to DR or CR in *C. elegans* and *D. melanogaster*. Wood *et al*. have found that resveratrol does not further extend lifespan of flies under a restricted diet with reduced amount of macronutrients compared to the full diet, and does not extend lifespan of *D. melanogaster* with mutations in the dSir2 gene (Wood et al. 2004). In addition, in transgenic *C. elegans*, Sir2 activation through increased Sir2.1 dosage or treatment with resveratrol specifically rescued early neuronal dysfunction phenotypes induced by mutant polyglutamines (Parker, et al. 2005). Genomic and genetic analyses has demonstrated that resveratrol mediates lifespan extension through a Sir2.1-dependent ER stress pathway in *C. elegans* (Viswanathan et al. 2005). Considering the negative results in the studies of resveratrol, it would be important to conduct more studies to address the relationship between DR and resveratrol. Nevertheless, the functional studies on resveratrol in invertebrates so far indicate that resveratrol may be a potent pro-longevity compound effective as a potential CR mimetic.

6.3 Resveratrol in vertebrates

One of the first compelling studies on resveratrol revealed its ability to prevent the progression of carcinogenesis in several experimental models including carcinogen-treated mouse mammary glands in culture, and a mouse skin cancer model (Jang, et al. 1997). Since then, animal studies on resveratrol have reported therapeutic effects on the growth of tumors in several tissues including breast, lung, liver and colon (Banerjee, et al. 2002; Carbo, et al. 1999; Hecht, et al. 1999; Schneider, et al. 2001).

One of the first studies to show an effect of resveratrol on lifespan was a study on a very short-lived seasonal fish, *Nothobranchius furzeri*. Resveratrol supplementation starting at the beginning of sexual maturity caused an increase in both median and maximum lifespan that was dose-dependent and not linked to fertility. Resveratrol treatment also delayed the onset of the age-related decay in locomotor activity and cognitive performance, and reduced the expression of neurofibrillary degeneration in the brain of these fish (Valenzano and Cellerino 2006).

Two recent reports indicate that resveratrol treatment produces beneficial effects similar to the effects of CR in mice. The first study showed that resveratrol treatment protected mice against insulin resistance and premature death induced by a high-calorie and high-fat diet (Baur, et al. 2006). The second study showed that resveratrol significantly increases aerobic capacity which is associated with an induction of genes for oxidative phosphorylation (Lagouge, et al. 2006). Both studies showed an increase in mitochondrial biogenesis, PGC-1α activity, AMP-activated protein kinase and motor function.

One notable benefit of CR has been its positive effects on brain and cognition in rodent models. In a mouse model of Huntington's disease, resveratrol-induced Sirt1 protected neurons against polyglutamine toxicity (Parker et al. 2005). The neuro-protective effects of resveratrol were also evaluated in an *in vitro* model of Parkinson's disease in rat cerebellar granule neurons (CGNs). The loss of cell viability and apoptosis in CGNs were prevented by the addition of resveratrol (1 μM to 100 μM). However, these neuroprotective effects were not mediated by the activation of Sirt1 (Alvira, et al. 2007). Other studies have raised the possibility that resveratrol may modulate lifespan through alternate pathways, independent of its activation of Sirt1. RNA interference experiments showed that the inhibitory effects of resveratrol on insulin signaling pathways are not weakened in cells with reduced expression of Sirt1 (Zhang 2006).

7. Other Sirt1 activators

A recent study has described the identification and characterization of small molecule activators of Sirt1 that are structurally unrelated to, and 1,000-fold more potent than resveratrol. These compounds bind to the Sirt1 enzyme-peptide substrate complex and enhance the catalytic activity. In diet-induced obese and genetically obese mice, these compounds improve insulin sensitivity, lower plasma glucose and increase mitochondrial capacity (Milne, et al. 2007).

8.0 Summary

Like CR, resveratrol has been reported to extend lifespan in organisms ranging from yeast to mice fed high-fat diets. Sir2 and its mammalian homolog Sirt1 have been shown to mediate many of the health benefits including the life-extending effects of CR. Whether the beneficial effects of resveratrol and other polyphenols in mammals are mainly mediated through Sirt1 remains unclear. Resveratrol does have other cellular targets including cyclooxygenases, lipooxygenases, kinases, ribonucleotide reductase, adenylyl cyclase, aromatase and DNA polymerases (Pirola and Frojdo 2008) and may work in parallel to Sirt1. In addition, Sirt1 over-expression has not yet been shown to result in lifespan extension in mammals. In our attempts to discover the keys to a healthy long life we are likely to come across several biological molecules that play roles equally important as Sirt1. Either way, it is hard to deny the potential of Sirt1-activating compounds for the treatment of many diseases such as cancer and type-2 diabetes, thereby improving human health and life expectancy.

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