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Of Mice and Men: The Benefits of Caloric Restriction, Exercise, and Mimetics

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Abstract

During aging there is an increasing imbalance of energy intake and expenditure resulting in obesity, frailty, and metabolic disorders. For decades, research has shown that caloric restriction (CR) and exercise can postpone detrimental aspects of aging. These two interventions invoke a similar physiological signature involving pathways associated with stress responses and mitochondrial homeostasis. Nonetheless, CR is able to delay aging processes that result in an increase of both mean and maximum lifespan, whereas exercise primarily increases healthspan. Due to the strict dietary regime necessary to achieve the beneficial effects of CR, most studies to date have focused on rodents and non-human primates. As a consequence, there is vast interest in the development of compounds such as resveratrol, metformin and rapamycin that would activate the same metabolic- and stress-response pathways induced by these interventions without actually restricting caloric intake. Therefore the scope of this review is to (*i*) describe the benefits of CR and exercise in healthy individuals, (*ii*) discuss the role of these interventions in the diseased state, and (*iii*) examine some of the promising pharmacological alternatives such as CR- and exercise-mimetics.

Keywords

Caloric restriction; Exercise; Aging; Mimetic; Healthspan; Metabolic disorder

1. Introduction

> “The only things certain in life are death and taxes.” – Benjamin Franklin

While taxes may be unavoidable, researchers throughout the world are focused on developing ways to increase lifespan and postpone death. Such research is emerging at the start of an expanding older population. According to the Administration on Aging, the U.S. population of persons age 65 years or older is expected to grow from 12.4% in 2000 to 19%

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in 2030, roughly equal to 72.1 million individuals (http://www.aoa.gov/aoaroot/aging_statistics/index.aspx, 2011). While advances in healthcare, nutrition, and technology have resulted in increased lifespan, such beneficial effects have not necessarily translated into improved healthspan, defined as the number of healthy, fully functional years attained before the onset of disease. In 2011, it is estimated that approximately one in three adults is obese (http://www.cdc.gov/obesity/data/adult.html, 2011). Alarmingly, both obesity and aging are major risk factors for several diseases such as cardiovascular disease, diabetes, and even some cancers. While increased caloric intake and decreased physical activity may lead to these disorders, caloric restriction (CR) and exercise have been shown to delay these age-related diseases. In addition, since most individuals would be unable to commit to such a rigorous dietary program, novel research is focusing on developing CR mimetics in order to achieve the benefits of CR without decreasing food intake. This review will first describe the benefits of CR and exercise in healthy individuals. Secondly, we turn to evidence for such interventions in the diseased state. We will conclude by discussing some of the promising pharmacological alternatives such as CR- and exercise-mimetics.

2. Caloric Restriction and Exercise in the Healthy State

The aging processes threaten to steal an individual s sense of self by targeting their motility and independence. For many decades, scientists have been trying to evade these processes through various interventions in the hopes of finding the Fountain of Youth. Two possible, and well-known, interventions include CR and exercise. This section of the review will briefly focus on the effects of CR and/or exercise on both lifespan and healthspan, covering studies from mice to men.

2.1. Caloric Restriction

CR, defined as a decrease of 30% to 60% *ad libitum* feeding without malnutrition, has long been shown to increase lifespan. The first evidence that CR extends mean and maximum lifespan was published in 1935 by McCay *et al.* (McCay et al., 1989). Since then, numerous studies have reported that lifelong CR, initiated early in life, extends mean and maximum lifespan and delays age-associated diseases in a variety of short lived species(Weindruch and Walford, 1988). Importantly, the age of onset for CR alters its effects as CR initiated in adult life also extended maximum lifespan in mice, although to a lesser degree (Weindruch and Walford, 1982). The mechanisms underlying CR-induced life extension are still not known, although several hypotheses have been proposed including inflammatory processes, oxidative damage, mitochondrial dysfunction, apoptosis, and body fat composition (see (Masoro, 2009) for an extensive review). Previous reports (Erdos et al., 2007; Fontana et al., 2007a; Holloszy and Schechtman, 1991; Jiang et al., 2010; Kim et al., 2008; Lee and Skerrett, 2001; Seo et al., 2006; Wohlgemuth et al., 2010) have documented the beneficial effects of CR on biomarkers of aging across species. Despite this evidence, the question remains whether CR will also act to retard aging and disease in higher species such as non-human primates and humans.

Two ongoing longitudinal studies are investigating the benefits of long-term CR on longevity and disease in non-human primates: one at the National Institute on Aging (NIA) and one at the University of Wisconsin (Colman et al., 2009; Mattison et al., 2003). A recent report by Colman *et al.* (Colman et al., 2009) shows a benefit of CR in reducing age-related mortality and disease in rhesus monkeys. However, when all deaths (age and non-age related causes) were included, the effect of CR on overall mortality did not reach statistical significance at this point, although a decreasing trend was observed. Currently, the survival data from aged monkeys in the NIA study are still ongoing (Mattison et al., 2003), and may take several years before any irrefutable evidence of CR on longevity becomes available.

While longevity data are still inconclusive at this time, preliminary evidence from both studies suggest that long-term CR in rhesus monkeys exhibit many similar benefits as observed in rodents. Some of these beneficial effects include lower overall abdominal adiposity (Colman et al., 1999), improved insulin sensitivity and lipid/lipoprotein profiles (Kemnitz et al., 1994; Lane et al., 1999), decreased body temperature (Lane et al., 1996), and decreased triiodothyronine concentrations (Roth et al., 2002). Moreover, the same beneficial effects in rhesus monkeys were observed in short-term studies of CR initiated later in life (Weindruch et al., 1986). Collectively, these findings indicate improved health status and thus a reduced risk for diabetes, cardiovascular disease and cancer in monkeys under a CR regimen.

Several reports of naturally-induced CR indicate that such a diet may also have beneficial effects on human longevity. A study among Spanish nursing home residents undergoing long-term alternate day feeding regimen led to decreased morbidity and mortality (Stunkard, 1976; Vallejo, 1957). In addition, a study on the inhabitants of Okinawa, who followed a low-calorie diet over a prolonged period of time had an extended lifespan, and more importantly, an increased healthspan compared to the rest of the Japanese population (Kagawa, 1978). Other evidence comes from the Biopshere II study in which an involuntary, unplanned severe CR was associated with many physiological, hematological, hormonal, and biochemical parameters that resemble those observed in rodents and non-human primates (Holloszy, 1988; Samorajski et al., 1985). This compelling evidence suggests that CR may lead to an increased lifespan in humans.

While the previous work has demonstrated the benefits of CR under naturally-occurring circumstances, such practices would be difficult since many populations today are faced with an excess of food. Interestingly, in a study by Weindruch *et al.* (Weindruch et al., 1986), it was shown that lifespan is inversely proportional to the degree of CR. However, 30–60% CR is not achievable in most humans, especially in the elderly. Vigorous CR interventions in humans may result in some adverse health effects such as osteoporosis, functional disability, infertility, and amenorrhea (for a review see (Dirks and Leeuwenburgh, 2006). Therefore, more studies have begun investigating the health benefits of alternative diet regimens such as moderate/mild CR and intermittent feeding, whereby animals receive every-other-day (EOD) feeding. Holloszy and colleagues (Holloszy et al., 1985) have shown that 8% CR increased mean lifespan without affecting maximum lifespan. This data could be interpreted that even an 8% CR affects health-related outcomes without affecting the basic aging process. Similar beneficial effects of EOD feeding on health and longevity have been observed, although interspecies differences exist (Holloszy, 1988; Ingram, 1987; Pekkanen et al., 1987; Samorajski et al., 1985). This EOD regimen is attractive to most people because it does not require a reduction in caloric intake to achieve the same beneficial effects as CR. One question that may never be answered, however, is whether or not CR will extend lifespan in humans. With a large proportion of today s population choosing unhealthy lifestyles including poor nutrition and sedentariness, the onset of many metabolic diseases is occurring at earlier ages. Therefore, whether or not researchers truly can extend lifespan seems irrelevant if there is not an overall simultaneous extension of healthspan.

2.2. Exercise

While CR increases lifespan, studies support more of a beneficial role for exercise on healthspan. In rodents, exercise improves mean lifespan compared with *ad libitum*-fed controls without increasing their maximum longevity (Holloszy, 1988; Holloszy et al., 1985; Samorajski et al., 1985). Similarly, high physical activity fails to prolong maximum lifespan in humans (Pekkanen et al., 1987). Although CR and exercise have similar effects, clearly

disparities exist between these two interventions, with potential molecular mechanisms excellently reviewed by Huffman (Huffman, 2010).

Despite not altering lifespan, regularly performed moderate exercise will delay certain age-associated changes and protect against several metabolic disorders (Warburton et al., 2006). Previous research has shown that exercise is associated with greater benefits than CR, or vice versa. The most noticeable health benefits of exercise over CR are maintenance of aerobic capacity, muscle mass and muscle strength, and an improved bone health (Fontana et al., 2007a; Lee and Skerrett, 2001). As a consequence, regularly performed exercise has a stronger impact particularly in cardiovascular disease, diabetes and osteoporosis. Therefore, as pointed out by Huffman *et al.* (Huffman et al., 2008), the effect of exercise may be more pronounced in humans, who perish more from cardiovascular disease, than in animal models that primarily die of renal disease or cancers. Additionally, as aging is associated with a decline in physical activity, regular physical activity plays an essential role in the elderly by lessening disability and prolonging independent living (see review(Nicklas et al., 2009). Taken together, these findings provide compelling evidence that regularly performed exercise is associated with an improved quality of life, without slowing the aging process. Conversely, despite the many favorable changes associated with exercise, several reports by Fontana and colleagues (Fontana et al., 2006a; Fontana et al., 2006b; Fontana et al., 2007a) indicate that, compared to exercise, long-term CR in humans led to enhanced improvements in several biomarkers related to aging. Likewise, a study by Huffman *et al.* (Huffman et al., 2008) provided evidence that exercise is not able to fully mimic the beneficial changes associated with CR in mice. Based on the provided data above, it seems that both interventions are associated with certain distinctive health benefits. Therefore, a combination of CR and exercise may maximize the health benefits in healthy individuals.

Important to note is that despite the well-documented beneficial effects of exercise, a controversy exists as to whether vigorous exercise should be recommended, especially in the elderly. Evidence from observational studies has shown that the intensity of physical activity is inversely and linearly associated with mortality (Lee and Skerrett, 2001). Therefore, a greater understanding as to what dose, duration, and type of physical activity confers the best health benefits is of major importance to human health.

2.3. Caloric Restriction and Exercise

A study by Holloszy and Schechtman (Holloszy and Schechtman, 1991) showed that the combination of exercise and CR did not prolong maximum lifespan further in male rats compared to those on CR alone. Furthermore, several studies have shown that exercise does not have a synergistic effect on the benefits of CR (Erdos et al., 2007; Huffman et al., 2008; Seo et al., 2006; Wohlgemuth et al., 2010). Nonetheless, there is little evidence that exercise in conjunction with CR provides greater benefits on several biomarkers of health than CR alone. For example, the addition of exercise to mild (8%) lifelong CR led to a greater reduction in serum C-reactive protein (Kim et al., 2008). Moreover, a recent study in rats demonstrated that the combination of CR and exercise enhanced insulin sensitivity in skeletal muscle more than that achieved with each intervention alone (Jiang et al.). The authors are not currently aware of any study that is evaluating the effects of CR to a CR plus exercise intervention in normal-weight healthy individuals. Numerous studies, however, have examined the combination of CR and exercise to CR in overweight and obese individuals and are discussed the section below.

3. Caloric Restriction and Exercise in the Diseased State

There has been a recent increase in the number of metabolic disorders caused by overeating accompanied with a decrease in physical activity (Fontana, 2008) which increases in

prevalence with age (Colman et al., 2009). This energy imbalance leads to chronic metabolic diseases such as obesity, diabetes, and cardiovascular disease (CVD) (Hawley and Holloszy, 2009). The decline in physical activity may also be responsible for changes in body composition with age (Stenholm et al., 2008), such as a decrease in muscle mass with a subsequent increase in adiposity and may in turn lead to sarcopenia (Carter et al., 2011). This section will focus on the effects of calorie restriction and/or exercise on preventing or lessening the risk of these metabolic disorders and sarcopenia in individuals who are either at high risk or already in the diseased state.

3.1. Metabolic Disorders

Individuals who are overweight or obese, having an excessive amount of visceral fat, have an increased risk of mortality (Huffman, 2010), CVD (Huang et al., 2010; Larson-Meyer et al., 2010; Lefevre et al., 2009; Murakami et al., 2007; Nicklas et al., 2009), and type II diabetes (Huang et al., 2010; Scheen, 1998). Moreover, the incidence of obesity increases with age (Nicklas et al., 2009) and is caused by increased intake of nutrient-poor foods combined with a decrease in exercise (Fontana, 2008). Obesity has been shown to be an influential risk factor for reduced health and quality of life in older individuals (Stenholm et al., 2008). Reducing adiposity is the primary treatment for overweight and obese humans (Gaesser et al., 2011) since weight gain plays a major role in development of these diseases. Modest weight loss has been shown to improve metabolic control of type 2 diabetes in obese individuals (Scheen, 1998). Lifestyle interventions such as calorie restriction and exercise have been shown to improve obesity and the associated risk of diseases (see below), yet the question remains, which methods are the safest and most effective to maintain a lower body mass in at-risk humans?

3.1.1. Caloric Restriction and Metabolic Disorders—CR has been shown to decrease adiposity, particularly visceral fat (Ye and Keller, 2010). Visceral fat has been suggested to be the primary indicator of metabolic syndrome (Muzumdar et al., 2008). Decreasing visceral fat by way of CR is associated with an increased mean and maximum lifespan (Muzumdar et al., 2008). Weight loss by CR in obese individuals has been shown to result in decreased risk of CVD and weight loss should be targeted at reducing abdominal fat (Lefevre et al., 2009; Nicklas et al., 2009). Moderate CR reduces or prevents the incidence of obesity, type 2 diabetes, and CVD (Fontana, 2008; Jiang et al., 2010; Omodei and Fontana, 2011). More severe CR has even greater beneficial effects (Fontana, 2008). A short-term CR study in overweight men and women resulted in reduced visceral fat, decreased insulin resistance, lower metabolic rate, body temperature, and oxidative stress (reviewed by (Fontana, 2008). These studies collectively demonstrate that, in addition to the healthy state, CR has similar beneficial effects in individuals either at risk for or afflicted by metabolic disorders.

3.1.2. Exercise and Metabolic Disorders—Regular exercise can prevent obesity and provide beneficial changes in the cardiorespiratory system (Hawley and Holloszy, 2009). Aerobic exercise may be an important regime to reduce adiposity, improve fitness, and decrease the overall risk of mortality (Larson-Meyer et al., 2010). Higher levels of physical activity, especially aerobic exercise, can completely reduce the risk for CVD and type II diabetes that are caused by obesity by reducing total and visceral adiposity (Gaesser, 2007; Huffman, 2010; Lefevre et al., 2009; Nicklas et al., 2009). In support of these findings, Nicklas *et al.* (Nicklas et al., 2009) concluded that changes in visceral adipose tissue of obese women were inversely related to increases in the amount of aerobic exercise.

Exercise is especially important in individuals who are at a higher risk for these metabolic disorders. Fifty to seventy percent of American adults do not exercise regularly because they

are unmotivated to perform physical activity (Hawley and Holloszy, 2009). The percentage of diabetic individuals who participate in regular exercise is even lower than that of the general population (Gaesser, 2007) while they stand to gain the most from this practice. Therefore, the important lesson for individuals is that even moderate levels of exercise can be favorable for improving or reducing the risk of other metabolic disorders and mortality. Gaesser (Gaesser, 2007) suggests that the level and amount of exercise needed to reduce the risk of CVD and diabetes is feasible for those at risk. Similarly, Fontana *et al.* (Fontana et al., 2007b) observed that total and visceral fat reductions can be achieved through exercise if food intake is kept constant. Even though more vigorous activity has greater benefits, moderate exercise may be a suitable way for people with diabetes or CVD to reduce their risk of mortality (Gaesser, 2007). Low-intensity activities, such as walking for 30 minutes a day, are protective against diabetes in individuals who are obese (Laaksonen et al., 2005). This study also found that the total time or energy spent on leisure activities was more important than the intensity of exercise in older, obese individuals.

3.1.3. Caloric Restriction and Exercise on Metabolic Disorders—As discussed above, weight loss is the ultimate treatment for those at risk for diabetes and CVD, particularly the overweight/obese population. Both CR and exercise induce weight loss and improve risk factors as well as decrease the risk of mortality. It would therefore seem plausible that combining the two interventions provide greater effects; however, this is not always the case.

Recent studies have compared the effects of CR and/or exercise in overweight and obese humans. Lefevre *et al.* (Lefevre et al., 2009) saw a more favorable, yet not statistically significant, improvement in reducing the risk of CVD in a 10-year study of overweight subjects on CR in combination with exercise. Similarly, in a short-term CR study for 6 months, overweight subjects in the combined interventions group had the greatest improvements in insulin sensitivity and cardiometabolic health (Larson-Meyer et al., 2010). Additionally, in obese humans, CR, exercise, and resulting weight loss can improve insulin sensitivity, yet the effects of the addition of exercise on this improvement is still debated (Larson-Meyer et al., 2006). In another study, the combination of both interventions did not confer additional reductions in CVD risk factors in comparison to the same amount of weight loss by CR alone (Nicklas et al., 2009). These authors proposed that weight loss is the most important component of reducing risk factors and therefore surpasses any effects of exercise. Furthermore, they state that exercise in conjunction with dieting may result in a greater negative energy balance leading to increased total and abdominal fat loss than dieting alone, although their controlled experimental setting did not include the effects of exercise on a CR regime. On the contrary, exercise has been shown to have weight-loss independent effects on reducing the risk of metabolic disorders as well (Gaesser et al., 2011; Huffman, 2010). These studies collectively suggest that a combination of the two lifestyle interventions appears to offer more beneficial effects at reducing risk factors while improving mortality in those at risk and unmotivated to participate in more intense levels of diet and exercise.

3.2. Sarcopenia

Sarcopenia is defined as the age-associated loss of muscle strength and function (Lauretani et al., 2003). Sarcopenia, a chronic disease, can lead to frailty and a high rate of disability in the elderly population (Glass and Roubenoff, 2010; Lauretani et al., 2003; Morley et al., 2010). Approximately 3–8% of skeletal muscle mass is lost each year after the age of 30 in humans (Colman et al., 2008). Results from the InCHIANTI study revealed that the decline in skeletal muscle is more severe in men than in women (Lauretani et al., 2003). In addition, the effects of sarcopenia worsen in those who are obese (Morley et al., 2010) due to too little

muscle mass relative to body mass (Stenholm et al., 2008). This has recently been termed sarcopenic obesity, meaning obesity combined with low muscle mass (Stenholm et al., 2008). The effects of CR and exercise have been studied in the sarcopenic condition (Carter et al., 2007). Although the exact cause of sarcopenia remains unknown, the only currently known methods to delay sarcopenia are by increasing exercise or altering the aging process (Colman et al., 2008).

3.2.1. Caloric Restriction and Sarcopenia—Although unable to prevent sarcopenia, lifelong CR has been shown to slow the onset as well as the severity of sarcopenia (Carter et al., 2011). Even moderate CR (8%) has been shown to attenuate many of the age-related changes in skeletal muscle (Carter et al., 2011; Sakuma and Yamaguchi, 2010). McKiernan *et al.* (McKiernan et al., 2004) observed that in rats, CR can decrease the severity of sarcopenia compared to *ad libitum* controls. Similarly, the onset of sarcopenia was delayed in rhesus monkeys on a CR diet (Colman et al., 2008).

Despite these beneficial effects, there is still debate over whether CR is a reasonable intervention in the elderly. While CR does reduce body mass, an issue in sarcopenic obesity, the decrease in fat-free mass that occurs with weight loss can be an issue in older individuals (Wohlgemuth et al., 2010). Even very low levels of CR can result in a significant loss of muscle mass (Carter et al., 2007). Conversely, CR was able to retain muscle mass throughout a 6 year study in rhesus monkeys (McKiernan et al., 2011) and did not reduce muscle strength and function in overweight humans (Larson-Meyer et al., 2010).

3.2.2. Exercise and Sarcopenia—It is well-established that regular exercise can provide many positive changes in skeletal muscle (Hawley and Holloszy, 2009) and reduce the risk of sarcopenia in humans (Huffman, 2010). Exercise, in particular resistance training, is the only currently proven treatment to reverse or prevent muscle wasting (Glass and Roubenoff, 2010). This differs from metabolic disorders where aerobic exercise seems to be more important in mediating risk factors. Resistance exercise imparts its beneficial effects by increasing protein synthesis and muscle hypertrophy in order to increase muscle strength at any age. It may also reverse the progression of sarcopenia as well as decrease the risk of frailty in the elderly population (Jones et al., 2009; Lauretani et al., 2003)

Exercise has also been shown to stimulate mitochondrial biogenesis within the muscle (Hawley and Holloszy, 2009). This process can be induced by a single bout of exercise and is maintained by regular and repeated exercise (Hawley and Holloszy, 2009). Mitochondrial biogenesis is of particular importance in the diseased state because mitochondrial dysfunction has been linked to insulin resistance in skeletal muscle and type II diabetes (Hawley and Holloszy, 2009). Diabetics also have an increased loss of muscle strength and quality (Stenholm et al., 2008). Exercise in overweight, obese, or diabetic individuals can affect not only those at-risk but also their offspring (Kelley et al., 2002). Exercise, therefore, is crucial to delay the onset of sarcopenia in at-risk individuals as well as to improve muscle quality and lower the chances of these disorders in any offspring.

3.2.3. Caloric Restriction and Exercise on Sarcopenia—Since the combination of CR and exercise may be detrimental to frail, elderly individuals, no present studies have investigated the addition of exercise and CR to CR alone in this population. Research has shown that the combination of this treatment is beneficial to those with sarcopenic obesity. Short-term studies in older adults have shown that reducing body mass by way of CR and exercise can improve health and lessen the decline in physical performance that is associated with increasing age (Carter et al., 2007). Exercise combined with diet-induced weight loss can improve muscle in terms of mass, strength, and aerobic capacity (Huffman, 2010). This is in agreement with two studies (reviewed by (Stenholm et al., 2008) showing that dieting

and exercise in older obese humans improved muscle strength and quality as well as decreasing adiposity. Wohlgemuth *et al.* (Wohlgemuth et al., 2010) observed improved muscle health and function, most likely due to activation of cellular control mechanisms, in overweight, older individuals. In support of these findings, Kim *et al.* (Kim et al., 2008) recommended lifelong mild CR combined with regular exercise in order to combat sarcopenia.

4. Alternative Interventions

While CR offers numerous benefits to both lifespan and healthspan, it is unlikely that most people would adopt and maintain such a rigorous dietary program. Therefore, there is vast interest in the development of compounds that would activate the same metabolic- and stress-response pathways induced by CR without lowering food intake, particularly in mid- to late-life stages. Such compounds include pharmaceuticals, nutraceuticals, and hormones, while omitting practices such as stomach stapling or appetite suppressants (Ingram et al., 2004; Ingram et al., 2006). This section of the review will briefly cover three of the most studied CR mimetics (resveratrol, metformin, and rapamycin) and their use in combination with an exercise regime, as well as the potential for exercise mimetics.

4.1. CR mimetic: Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene) is a naturally-occurring polyphenolic compound present mainly in the skin of grapes (Baur et al., 2006). Originally identified in 2003 (Howitz et al., 2003), resveratrol has since been shown to induce similar changes in gene expression patterns as CR in the liver, skeletal muscle, heart, neocortex, and adipose tissues (Barger et al., 2008; Pearson et al., 2008). Consistent with the lifespan-extending effects of CR, resveratrol increased lifespan by 18–56% in *Saccharomyces cerevisae* (Howitz et al., 2003), *Caenorhabditis elegans* (Wood et al., 2004), *Drosophila melanogaster* (Bauer et al., 2004), and the short-lived fish *Nothobranchius furzeri* (Valenzano et al., 2006). However, these findings are a point of contention as others have failed to observe such effects (Bass et al., 2007; Kaeberlein et al., 2005), and resveratrol has not yet been shown to increase lifespan in a mammalian model on a standard diet (Pearson et al., 2008). One potential explanation for such discrepancies is that the beneficial effects of this compound may require metabolic stress to achieve its lifespan-extending properties (Mouchiroud et al., 2010). For example, resveratrol did increase survival of mice on high-fat diets and animals on an EOD regimen independent of weight loss (Pearson et al., 2008).

Numerous studies have demonstrated the ability of resveratrol to reverse many high fat diet-induced pathologies, including insulin resistance, dyslipidemia, and cardiovascular dysfunction (Baur et al., 2006; Lagouge et al., 2006; Sun et al., 2007). Indeed, this polyphenolic compound has been shown to improve glucose tolerance in rats with type II diabetes, as well as increase glucose transport in skeletal muscle (Barger et al., 2008; Chi et al., 2007; Deng et al., 2008; Park et al., 2007; Su et al., 2006). Specifically, Chi *et al.* (Chi et al., 2007) found that resveratrol increased expression of the glucose transporter GLUT4 in the soleus of diabetic rats but had no effect in the muscles of healthy rats. Such findings further suggest a need for high-fat conditions in order to elicit the true beneficial effects of this compound (Dirks Naylor, 2009).

Resveratrol elicits these beneficial effects by primarily targeting the stress signaling pathways where it has been reported to activate or inhibit over 15 various enzymes (Pirola and Frojdo, 2008). Two of the most common pathways involve sirtuins and AMPK (Mouchiroud et al., 2010; Sauve, 2009). Having been originally identified in an assay for sirtuin activators (Howitz et al., 2003), resveratrol has been shown to activate SIRT1 (Baur et al., 2006; Borra et al., 2005), as well as several other sirtuin-family members (Schirmer et

al., 2011). Whether or not resveratrol stimulates sirtuins directly is debatable (Kaeberlein, 2010; Pacholec et al., 2010) and has instead been suggested to act indirectly through AMPK (Beher et al., 2009; Suchankova et al., 2009; Um et al., 2010). Indeed, SIRT1 has been shown to be activated by AMPK (Canto et al., 2009), and resveratrol failed to protect AMPK$\alpha^{-/-}$ mice from high-fat diet-induced obesity (Um et al., 2010). Further studies are clearly needed to elucidate the exact tissue-specific molecular target of resveratrol in order to determine how this proposed CR mimetic is truly having such beneficial effects (Pearson et al., 2008).

4.1.1. Resveratrol and Exercise—Recently, several studies have indicated that the beneficial effects of exercise may be further enhanced with resveratrol supplementation, specifically in skeletal muscle. The combination of exercise and resveratrol has been shown to attenuate age-related decreases in muscle force. In a model of aging, senescence-accelerated prone mice placed on a 12 week exercise regime with resveratrol supplementation exhibited increases in running endurance capacity, oxygen consumption, and mitochondrial function compared to those on exercise alone (Murase et al., 2009). The authors pointed out that since resveratrol and exercise share many of the same pathways, it is difficult to elucidate which effects are due solely to resveratrol (Murase et al., 2009). However, increased muscular endurance, muscle strength, and mitochondrial biogenesis were also observed following resveratrol treatment in mice on a high fat diet compared to controls (Baur et al., 2006; Lagouge et al., 2006).

These beneficial effects may be due to the antioxidant properties of this compound. Indeed, resveratrol supplementation decreased oxidant production and oxidative damage following short-term isometric exercise in both young and old healthy mice (Ryan et al., 2010). Additionally, resveratrol alleviated oxidative stress while preserving fast-twitch fiber contractile function when given to middle-aged mice (Jackson et al., 2011). In addition to exercise-induced oxidative damage, resveratrol also had protective effects against such damage in the skeletal muscle due to mechanical unloading (Momken et al., 2011), ischemia and reperfusion injury (Dirks Naylor, 2009), and in a mouse model of Duchenne muscular dystrophy (Hori et al., 2011). Several *in vitro* studies have shown resveratrol also elicits beneficial effects through the inhibition of protein degradation and atrophy of skeletal muscle fibers (Busquets et al., 2007; Russell et al., 2006; Wyke et al., 2004; Wyke and Tisdale, 2006), as well as through increasing muscle precursor cell proliferation (Rathbone et al., 2009). However, there is debate if such effects occur *in vivo*, as a recent study found that resveratrol supplementation failed to prevent sarcopenia or improve muscle force compared to controls (Jackson et al., 2011).

4.2. CR mimetic: Rapamycin

Rapamycin was originally identified in 1975 as an antibiotic secreted from the bacteria *Streptomyces hygroscopicus* isolated from soil on the island Rapa Nui, whereby it received its name (Vezina et al., 1975). Today, rapamycin and derivatives are used clinically as immunosuppressants during graft transplantations and cancer treatments (Mouchiroud et al., 2010). In addition, rapamycin has also been shown to increase lifespan in yeast, flies, nematodes and rodents (Miller et al., 2011; Stanfel et al., 2009). Furthermore, rapamycin given in late age has increased lifespan in both male and female mice by 9 and 14%, respectively (Harrison et al., 2009; Miller et al., 2011). The beneficial effects of rapamycin are presumably achieved through its inhibition of the mammalian target of rapamycin, (mTOR). mTOR is a central regulator of various metabolic processes including nutrient and stress sensing, protein synthesis, and cell survival, and has been extensively reviewed elsewhere (Evans et al., 2011).

4.2.1. Rapamycin and Exercise—While inhibiting the mTOR pathway may be beneficial for increasing lifespan of an organism as a whole, similar inhibition may have detrimental effects on individual tissues, particularly skeletal muscle. The mTOR pathway is stimulated by exercise and has been shown to stimulate myoblast differentiation and myocyte hypertrophy ultimately leading to myogenesis (Park et al., 2005). Conversely, skeletal muscle mTOR signaling decreases with age and is highly correlated with atrophy (Paturi et al., 2010). Therefore, inhibition of mTOR via rapamycin would presumably block the benefits of exercise in skeletal muscle. Indeed, several studies have observed such effects. Kubica *et al.* (Kubica et al., 2005) found that rapamycin treatment prior to resistance-exercise prevented protein synthesis in the gastrocnemius muscle of rats. A separate study found similar results in that rapamycin treatment for ten days significantly reduced stretching-induced longitudinal muscle growth in the rat soleus muscle (Aoki et al., 2006). Moreover, rapamycin treatment in humans inhibited muscle protein synthesis following acute contraction-induced exercise (Drummond et al., 2009). Rapamycin did, however, have beneficial effects in a mouse model of Duchenne muscular dysptrophy where treated mice had significantly less muscle fiber necrosis, presumably from decreased immune cell infiltration (Eghtesad et al., 2011). Collectively, while rapamycin may be beneficial as an immunosuppressant for the treatment of various pathologies and in extending lifespan, it may have deleterious effects on healthy individuals.

4.3. CR mimetic: Metformin

Metformin belongs to the biguanides class of drugs and is widely used for the treatment of type II diabetes (Mouchiroud et al., 2010). Several studies have demonstrated that metformin enhances insulin s action, thereby increasing whole-body insulin sensitivity by 10–30% (Eriksson et al., 2007; Musi et al., 2002; Stumvoll et al., 1995). Specifically, metformin decreases glucose production in the liver, increases insulin-dependent glucose uptake in peripheral tissues, and promotes the usage of fatty acids (Bailey and Turner, 1996). Metformin has also recently emerged as a potential anti-cancer agent (Dowling et al., 2011), as well as a CR mimetic (Ingram et al., 2006; Mouchiroud et al., 2010). Interestingly, mice placed on either CR or metformin had similar changes in the gene expression profiles of their liver (Dhahbi et al., 2005). Much like CR, several studies have found metformin to increase lifespan in *C. elegans* (Onken and Driscoll, 2010) and several mouse models (Anisimov et al., 2005; Anisimov et al., 2008; Anisimov et al., 2011; Anisimov et al., 2010), while having no significant effect in a recent rat study (Smith et al., 2010). Moreover, metformin treatment has been shown to increase survival in individuals with type II diabetes and CVD (Eurich et al., 2005; Scarpello, 2003).

Although research is advancing on the physiological benefits of metformin, the exact molecular target of this compound remains unknown. Several proposed targets include activation of mitochondrial complex I of the electron transport chain (El-Mir et al., 2000), AMPK (Musi et al., 2002; Zhou et al., 2001), and SIRT1 (Mouchiroud et al., 2010). Alternatively, metformin has recently been reported to inhibit mTOR (Kalender et al., 2010), thereby suggesting a potential overlap in the signaling pathways induced by both metformin and rapamycin.

4.3.1. Metformin and Exercise—Though beneficial in itself, the combination of metformin with exercise does not appear to offer any synergistic effects in either glucose metabolism or myogenesis. Indeed, numerous studies have demonstrated the beneficial effects of metformin and exercise individually. Both exercise and metformin treatments on their own result in decreased food intake, body weight, and insulin concentrations in both rats (Borst and Snellen, 2001) and db/db mice (Tang and Reed, 2001). However, the combination of metformin treatment with an exercise regime disappointingly fails to elicit

any further advantages. Smith *et al.* (Smith et al., 2007) found that Zucker rats on a high-fat diet given metformin and on an exercise regime had no further protection from developing hyperglycemia than those on exercise alone. In individuals with type II diabetes, metformin failed to alter whole-body insulin sensitivity or glucose uptake in resting or exercised skeletal muscle (Hallsten et al., 2002). Moreover, a recent study demonstrated that metformin treatment may actually attenuate the beneficial effects of exercise in insulin-resistant individuals (Sharoff et al., 2010). Such a combination increased fat oxidation (Boule et al., 2011; Sharoff et al., 2010), heart rate, and plasma lactate levels (Boule et al., 2011), while having no effect on muscle glucose uptake or insulin signaling (Hallsten et al., 2002; Karlsson et al., 2005). Metformin in combination with exercise, however, may have collective effects on blood flow, which may in turn increase insulin sensitivity (Holten et al., 2004; Horowitz, 2007). While both metformin and exercise stimulate glucose transport in muscle, this has been proposed to occur via separate molecular mechanisms (Sajan et al., 2010). Therefore, the clinical application of combining metformin treatments with exercise requires further investigation.

4.4. Exercise Mimetics

With all of the long-known health benefits of exercise, it is intriguing to speculate on the possibility of mimicking such effects using pharmacological interventions without necessarily having to increase physical activity. Several potential targets of these exercise mimetics (EMs) include AMPK, calcium and calcium/calmodulin-dependent protein kinase II, heat shock proteins, nuclear factor kappa B, and the myokine interleukin 6 amongst others (Carey and Kingwell, 2009; Hawley and Holloszy, 2009). However, the very notion of EMs is an area of intense debate (Booth and Laye, 2009; Goodyear, 2008). For example, 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR) increases muscle mitochondria and running endurance through its activation on AMPK (Narkar et al., 2008). However, it is not a feasible EM for chronic use as AICAR has also been shown to inhibit muscle protein synthesis (Hawley and Holloszy, 2009). These authors have also pointed out that such increases in mitochondria do not alter energy expenditure alone and must be combined with exercise in order to burn energy (Hawley and Holloszy, 2009). Moreover, there are numerous health benefits of exercise beyond those related to skeletal muscle, including improving conditions such as dementia, osteoarthritis, and certain cancers (Carey and Kingwell, 2009). Taken together, creating a true EM that can replicate the all-encompassing health benefits of exercise may prove to be extremely challenging.

5. Conclusions

Faced with an ever-increasing aging population in the middle of an obesity epidemic, the need for interventions to combat age- and obesity-associated diseases has never been greater. Of particular interest, CR and exercise are two interventions that have consistently received the most attention. CR is currently the only intervention known to increase maximum lifespan, demonstrated primarily in rodents and lower species with promising outcomes in non-human primates. Alternatively, both CR and exercise commonly extend healthspan across species. The true benefits of these regimens depend on many factors including age, physical activity, and disease state. It is therefore highly unlikely that any general guidelines would be universally adopted. However, with encouraging results from CR mimetic studies, the next generation may actually be able to have their cake and eat it too!

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HIGHLIGHTS

- Caloric restriction increases mean and maximum lifespan in the healthy state
- Exercise increase healthspan in healthy individuals
- CR and exercise reduce the risk of metabolic disorders and sarcopenia
- CR mimetics and exercise do not produce synergistic benefits
- The feasibility and efficacy of exercise mimetics is debatable