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Review

Caloric restriction in humans: Potential pitfalls and health concerns

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Abstract

To date, the only intervention that has consistently been shown to slow the rate of aging, and to increase mean and maximum lifespan in short-lived species, is life-long calorie restriction. It is yet unclear whether long-term calorie restriction in longer lived species (i.e. primates and humans) will have a similar effect. In humans, several studies investigating short-term calorie restriction or ''weight loss'' programs suggest beneficial outcomes on parameters of cardiovascular disease. Studies on long-term calorie restriction are performed on a self-selected group of human subjects and show similar effects. However, few studies are currently investigating the quality of life and potential pitfalls of long-term calorie restriction in humans. It is likely that some of the physiological and psychological effects of caloric restriction that occur in animals may impact the human life very differently. For certain, calorie restriction has a plethora of health benefits in mammals, such as a reduction in age-related diseases such as cancer. However, despite the ''magic'' of CR, this intervention in humans may present itself with a number of health concerns, which may not be applicable to or impact the life of experimental animals, but may do so in humans. These potential pitfalls and ''side effects'' are not clearly addressed in the literature and will be a focus of this review.

Keywords: Caloric restriction; Potential pitfalls; Health

1. Introduction

Caloric restriction (CR) is the only non-genetic intervention that has consistently shown to slow the intrinsic rate of aging in mammals. Caloric restriction was first shown to increase medium and maximum lifespan in 1935 (McCay et al., 1935). However, not until relatively recently did the excitement in the scientific arena for the discovery of a ''fountain of youth'' lead to an explosion of data describing the various genetic, biochemical and physiological effects of CR in search of its anti-aging mechanism.

Caloric restriction refers to the reduction in caloric intake while maintaining essential nutrient requirements. Traditionally, experimental mammalian models of caloric restriction involve a reduction in caloric intake by ~40% of the ad libitum diet throughout the lifespan of the animal, which results in a 30–40% increase in maximum lifespan (Weindruch et al., 1986). Rodents, various strains of rats and mice, are the most commonly used animal model in which much of the current literature is based upon. Ongoing studies involving caloric restriction in non-human primates are accumulating data and thus far support the life-extending physiological effects as shown in rodents (Kemnitz et al., 1994; Lane et al., 1995, 1996).

As no surprise, there are currently no well-controlled long-term studies showing the effects of CR in humans. Although scarce, data concerning the short-term effects in humans have shown health benefits (Fontana et al., 2004; Walford et al., 1999; Weyer et al., 2000). However, despite the overwhelming data supporting health benefits and slowing of the aging process by CR in mammalian animal models, it may be likely that long-term CR in humans will fall short of the expectations as our ''fountain of youth''. It is likely that some of the physiological and psychological effects of caloric restriction that occur in animals may impact the human life very differently. Others believe that a maximum genetic life-span ceiling exists in humans (Viidik, 1999).

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2. Physiologic and biochemical effects of caloric restriction

Aside from slowing the intrinsic rate of aging, long-term CR provides many health benefits. First, it prevents many of the age-related diseases, including the top two killers of the United States population, cardiovascular disease and cancers. Moreover, CR provides protection against diabetes, neurodegenerative diseases, and auto-immune disorders (Bronson and Lipman, 1991; Roe et al., 1995; Weindruch et al., 1986). Prevention of such diseases would have a tremendous impact not only by extending the medium lifespan, but also by enhancing the quality of life and at the same time reducing healthcare costs.

The extension of lifespan and the prevention of disease are secondary to the hormonal, physiological and biochemical adaptations that occur in response to CR. First, CR invokes a variety of hormonal alterations. In general, insulin levels, and activities of the thyroid, gonadotropic and somatotropic axes decline while that of the hypothalamus–pituitary–adrenal axis is enhanced (Chacon et al., 2004; Herlihy et al., 1990; Sabatino et al., 1991; Zhu et al., 2004). Secondly, CR also alters a variety of physiological parameters. In response to the energy deficit, experimental animals experience a significant decrease in both fat mass and lean body mass. Muscle mass is significantly reduced, however, the rate of loss of function and mass/body weight that occurs with age is attenuated (Aspnes et al., 1997; Dirks and Leeuwenburgh, 2004; Payne et al., 2003). Metabolic rate may decrease transiently in the short-term, but studies indicate that in the long-term the metabolic rate per kg lean body mass is similar to that of ad libitum fed rodents (Selman et al., 2005). Body temperature and systolic and diastolic blood pressure decreases (Duffy et al., 1989; Hunt et al., 2004). Sympathetic activity is also reduced (Kushiro et al., 1991). Animals that undergo CR are more spontaneously active and have superior cognitive abilities compared to their ad libitum counterparts (Bellush et al., 1996; Means et al., 1993; Yu et al., 1985). Lastly, several biochemical and molecular adaptations occur with long-term caloric restriction. Blood glucose and lipid profiles are improved. Oxidant production and oxidative damage to macromolecules are reduced (Drew et al., 2003; Leeuwenburgh et al., 1997; Yu, 1996). Caloric restriction appears to prevent many of the changes in gene expression that occur with aging (Lee et al., 1999, 2000, 2002). Caloric restriction alters gene expression to favor expression of genes involved in cell repair, protein synthesis and turnover, stress resistance, and glucose metabolism (Lee et al., 1999, 2000). Genes involved with oxidative stress and inflammation are down-regulated (Lee et al., 1999, 2000). In short, the decline in cellular function that occurs with age is attenuated by CR.

Most of what is known thus far about the life-prolonging effects of CR is based upon experimental rodent models. To explore the effects of CR on higher longer lived mammals, experiments using non-human primates are currently underway. Although it will be several decades before the effects of life-long CR on longevity will be discerned, the physiological and biochemical adaptations observed thus far are consistent with the life-prolonging adaptations in rodents (Ingram et al., 2001; Kemnitz et al., 1994; Lane et al., 1996, 2002; Roth et al., 2002; Verdery et al., 1997).

3. Caloric restriction in humans

Since the physiological and biochemical effects of CR in non-human primates are comparable to those in rodents, the possibility exists that caloric restriction also extends the medium and maximum lifespan of humans. Currently, data describing the effects of CR in humans are extremely limited (Fontana et al., 2004; Walford et al., 1992, 1999, 2002). Due to the anticipated difficulties of adhering to this relatively rigorous intervention and the length of the human lifespan, there are no well-controlled long-term studies and most likely will not be in the foreseeable future. However, insights into the effects of long-term CR in humans come from observations of the Okinawan population (Heilbronn and Ravussin, 2003; Kagawa, 1978). Furthermore, data describing the short-term effects of CR in humans have recently been published (Fontana et al., 2004; Walford et al., 1992, 1999, 2002).

The Okinawan population is renowned for their reduced morbidity and mortality having the greatest percentage of centenarians anywhere in the world (Heilbronn and Ravussin, 2003; Kagawa, 1978). Compared to Americans, the mortality rate of Okinawans between the age of 60 and 64 years is 50% lower. The death rates due to heart disease, stroke, and cancer is approximately 30–40% lower compared to the rest of Japan and even more so compared to the United States. Why do Okinawans have the longest disability-free life expectancy in the world? The answer is thought to be within their diet. The Okinawans consume a nutrient-dense diet lower in calories compared to the rest of Japan by 20% and the United States by ~40%. The diet consists mainly of vegetables, grains, fruits, soy, seaweed, and fish. Their diet mimics the caloric restriction interventions imposed on experimental animals and appears to also mimic the effects of the CR diet in animals. However, none of the Okinawans have achieved the maximum life-span recorded by the French woman Jeanne Calment (122 years), which would maybe suggest that CR in humans can only extend mean lifespan as seen in the Okinawans. The longest lived Japanese human (the second longest lived human and longest lived male) was a man named Shigechiyo Izumi, who died in 1986 at the age of 120.

Other experiments suggesting beneficial effects on health were obtained during the Biosphere 2 experiments. Biosphere 2 is a closed ecological space located in the deserts of Arizona. In 1991, eight individuals (four females and four males) entered the biosphere for 2 years without the intention of being subjects of their own caloric restriction study. Due to unexpected problems in the growth of crops, the crew members had limited access to food over the span of 2 years. Actual caloric intake by crew members was approximately 30% lower than anticipated upon entering the biosphere. Physiological and biochemical measurements were assessed over the time span spent inside the biosphere, while crew members experienced caloric restriction, as well as 18 months after exiting the biosphere and returning to

their normal diets (Weyer et al., 2000; Walford et al., 1992, 1999, 2002). Short-term caloric restriction of the crew members invoked a decline in metabolic rate, body temperature, and systolic and diastolic blood pressure. Blood glucose, insulin, and thyroid hormone levels were also reduced. In summary, the physiological and biochemical alterations that the biospherians experienced are similar to those of caloric restricted rodents and non-human primates.

The Caloric Restriction Society (CRS) consists of a group of individuals who practice caloric restriction with optimum nutrition (CRON). Fontana et al. reported the effects of long-term caloric restriction on atherosclerotic risk factors (Fontana et al., 2004). The subjects of the study were 18 volunteers that were members of the Caloric Restriction Society (CRONies) and have been practicing the diet for 3–15 years. The CRONies consumed 1112–1958 kcal/day while the age- and height-matched controls consumed 1976–3537 kcal/day. Classical signs of CR adaptations were evident in the CRONies, showing significantly lower blood glucose levels, insulin levels, and blood pressure. Lipid profiles of the CR group were significantly healthier than the height-matched controls. Specifically, total cholesterol, LDL, and triglycerides were all reduced and HDL was elevated compared to controls. Moreover, C-reactive protein, a robust marker of systemic inflammation and therefore a risk factor for atherosclerosis, was also reduced. These data suggest that individuals practicing CR have a reduced risk for atherosclerosis. Several new short-term calorie restriction studies have recently started at Washington University School of Medicine, Tufts University, Pennington Biomedical Research Center's, and Duke sponsored by the National Institute on Aging. Using various designs of calorie restriction, these studies referred to as CALERIE are designed to test the effect of calorie restriction on health and markers of longevity.

Currently, the data describing the effects of CR in humans are scarce. The published reports suggest that CR in humans may have similar life-extending properties to those in experimental animals. Signs of CR efficacy that occur in animals, such as reduced blood glucose, insulin, body temperature, and blood pressure, also occur in humans. For certain, CR has a plethora of health benefits in all mammals tested as well as in humans. However, despite the ''magic'' of CR, this intervention in humans may present a number of health concerns, which may not be applicable to or impact the life of experimental animals, but may do so in humans. These ''side effects'' and potential pitfalls are not clearly addressed in the literature.

4. Health concerns of caloric restriction in humans

As the numerous benefits of caloric restriction are published in the literature and publicized in the news, the likelihood of eager individuals taking on this regimen to reap the life-extending benefits increases. The ''classical'' regimen typically used experimentally in animals and, therefore, most commonly publicized is caloric restriction to the degree of ~40% of the ad libitum diet. In general, the greater the level of caloric restriction without causing malnutrition, the more beneficial it is. Concern arises when individuals take on such an extreme level of caloric restriction, similar to what most often is described in the experimental literature, resulting in excessive loss of fat mass and muscle mass. Excessive weight loss can lead to health complications. Validity of such a concern has arisen with the advent of the Caloric Restriction Society (CRS), by members who themselves are practicing a regimen of caloric restriction.

Looking at the CRS volunteers who participated in the study by Fontana et al., the average body mass index (BMI) was 19.6 ± 1.9 kg/m^2 (range was 16.5–22.8 kg/m^2) with total body fat as $6.7 \pm 4\%$ (Fontana et al., 2004). The Dietary Guidelines for Americans 2005, published by the Department of Health and Human Services (HHS) and the Department of Agriculture (USDA), defines a healthy BMI as 19–25 kg/m^2. A BMI less than 18.5 kg/m^2 is considered underweight which could lead to serious health complications. Depending on age and fitness status, the healthy range for body fat composition for men is 5–25% and for women is 16–38%. Body fat below these ranges is considered inadequate and can be associated with elevated health risks. The mean BMI and percent body fat in the CRONies are in the ''healthy'' range, however, some subjects do indeed fall into the high risk category (Fontana et al., 2004).

4.1. Physiological symptoms associated with caloric restriction in humans

Some symptoms that individuals partaking in the CR lifestyle may experience include hypotension, loss of libido, menstrual irregularities, infertility, bone thinning and osteoporosis, cold sensitivity, loss of strength and stamina, slower wound healing, and psychological conditions such as depression, emotional deadening, and irritability. These are some of the cautions and hazards listed on the CRS website (www.caloricrestriction.org) for those interested in beginning a CR regimen.

Characteristically, CR causes a significant drop in blood pressure. Systolic blood pressure fell from 108 to 88 mmHg and diastolic blood pressure from 77 to 54 mmHg within several months of initiation of caloric restriction in the Biospherians (Walford et al., 1999). It was also reported that after approximately 1 year of caloric restriction, by some CRONies, that SBP decreased by ~20 mmHg and DBP decreased by ~11 mmHg (Fontana et al., 2004). At the time of publication, the SBP and DBP of these individuals averaged 97 and 59 mmHg, respectively (Fontana et al., 2004). The cause for the decline in blood pressure upon initiation of CR is not completely clear, although decreased sympathetic nervous system stimulation, increased vagal stimulation, and decreased leptin signaling appear to contribute (Kushiro et al., 1991; Swoap, 2001). Hypotension and a blunted orthostatic reflex are of concern due to the resulting lightheadedness or dizziness upon standing. If severe enough, one can experience syncope and could injure him/herself during a fall.

Body fat is necessary and essential for production of sex hormones, insulation of vital organs, and regulation of body

temperature. The excessive loss of body fat and the concomitant decline in sex steroids can lead to loss of libido in both sexes and menstrual irregularities, such as amenorrhea, and infertility in females (Morgan, 1999; Morgan et al., 1999). Moreover, women with a low BMI are at greater risk for preterm delivery and birth of low birth-weight infants (Allen et al., 1994). Therefore, CR should not be practiced by women prior to or during pregnancy.

Low estrogen levels, as can be experienced during CR, can also contribute to bone thinning and the development of osteoporosis. The decline in estrogen levels in post-menopausal women and the associated likelihood of developing osteoporosis is testament of the concern in individual undergoing CR (Felson et al., 1993a,b; Michaelsson et al., 1996). In fact, one in two women will experience an osteoporosis related fracture in her life-time, which is most likely to occur after menopause (Sasser et al., 2005). In severe cases of osteoporosis the bones can be fragile to the point that muscle contraction during daily activities can cause a fracture. The associated fear of fracture, the pain experienced with fractures, and the rehabilitation time will impact quality of life.

Cold sensitivity experienced by caloric restriction practitioners may be due to multiple factors. First, body temperature decreases with CR. Body temperature is maintained by a balance between heat loss and metabolic heat production. Animal studies have shown that in response to starvation, the body temperature drops in a regulated manner to conserve energy (Sakurada et al., 2000). The drop in body temperature appears to be due to a decrease in the threshold for activation of thermogenesis. Secondly, lack of fat stores that serve as insulation and preserve heat loss may contribute to cold sensitivity when exposed to colder temperatures (Florez-Duquet and McDonald, 1998). Lastly, the loss of muscle mass during CR equates to less metabolically active tissue. Shivering thermogenesis in skeletal muscle is important for maintaining body temperature and is estimated to provide up to one-third of the total heat production during cold exposure (Florez-Duquet and McDonald, 1998). Individuals with less muscle mass may have a reduced ability to generate heat via shivering thermogenesis, although a direct link has yet to be established (Florez-Duquet and McDonald, 1998). For these reasons individuals who practice a CR regimen may have cold sensitivity and a higher risk for hypothermia, which can lead to stroke, myocardial fibrillation or death. In emergency situations, when one is unexpectedly exposed to cold environments for extended periods of time, individuals who engage in long-term caloric restriction may be less likely to survive compared to someone with a greater body weight and body fat. Moreover, less adipose tissue equates to less energy reserves in the body. The length of time that a person can survive during times of starvation is highly correlated with the amount of adipose stores. This would be pertinent in emergency situations when survival is threatened by starvation. These concerns may be most applicable to individuals who participate in sports and recreation which expose them to high risk environments, such as mountain climbing, backpacking, mountain biking, skiing, or sailing.

Caloric restriction results in the loss of muscle mass until a new set-point is reached which is in equilibrium with the energy intake. Although caloric restriction has the beneficial effects of attenuating the loss of muscle mass with age, the initial loss of mass may be significant and impact the strength and stamina of an individual. Exercise intolerance can be a consequence which may be experienced while engaging in activities of daily living and/or recreational activities. In addition, muscular strength is highly predictive of disability and all-cause mortality (Metter et al., 2002; Rantanen et al., 1999). Rantanan et al. found that healthy men ranging in age between 45 and 68 years old with the lowest handgrip strength had the highest risk of disability and experienced functional limitations 25 years later (Rantanen et al., 1999). It is suggested that good muscle strength in midlife may protect individuals from disability in old age by providing a greater safety margin above the threshold of disability. Acute illness and surgery are two examples where physical deconditioning can occur. With already low muscle mass and reserve capacity due to the CR lifestyle, functional disability is a valid concern under such conditions.

Slower wound healing is another ‘‘side effect’’ of CR. Caloric restriction is associated with decreased collagen biosynthesis and decreased proliferation of cells (Reiser et al., 1995). Changes in the levels of growth factors, hormones, and other mitogens in response to dietary restriction may be the underlying mechanism for impaired wound healing (Reed et al., 1996). Of interest is the observation that wound repair is enhanced, compared to ad libitum counterparts, in caloric restricted mice that have been re-fed their ad libitum diet 4 weeks prior to injury. The authors conclude that long-term caloric restriction results in preservation of proliferative capacity with age and the ability to augment synthesis of extracellular matrix proteins and trophic factors in response to tissue injury. However, an adequate source of nutrients must be provided to demonstrate this ability (Reed et al., 1996). Therefore, it may be beneficial for those individuals practicing CR who experience blunted wound healing to increase caloric intake in times of injury. Future studies are required to test this hypothesis.

Walford et al. reported the blood levels of lipophilic toxicants, insecticides, pollutants, and their derivatives, in two crew members of the Biosphere 2 undergoing caloric restriction (Walford et al., 1999). With rapid and substantial weight loss, the blood levels of DDE (dichlorodiphenyltrichloroethane) and total PCB (polychlorinated biphenyls) load rose and, upon return to a normal diet, returned to near baseline levels. Hence, rapid weight loss should be done so with caution. Lipid soluble toxins can be taken up and stored in adipose tissue. With the onset of lipolysis during weight loss, these toxins are released into the blood stream. If released into the blood at a faster rate than they are cleared, the levels of these compounds can become toxic, altering normal physiologic function of various organs. Some of the acute effects of these toxins are sweating, headache, and nausea, while higher doses can result in convulsions (Longnecker et al., 1997). Slower weight loss may protect against a sudden and dramatic rise of harmful toxins in the blood.

4.2. Psychological symptoms associated with caloric restriction in humans

In 1950, Keys et al. published the results of the Minnesota Starvation Study in which 36 physically and psychologically healthy men underwent semi-starvation (50% caloric restriction diet) for 6 months (Keys et al., 1950). Many of the volunteers experienced some kind of psychological change during the semi-starvation period. These include a dramatic increase in the preoccupation with food, constant hunger, binge eating, emotional deadening and/or depression, mood swings, irritability, anxiety, and social isolation.

Members of the Caloric Restriction Society have noted many of the listed psychological effects of a semi-starvation diet. Similar psychological disturbances are also characteristic in patients suffering from anorexia nervosa. Some scientists who study depressive symptoms in anorexia believe that the symptoms occur secondary to the eating disorder and may involve the somatic effects of low weight and weight loss (Fichter and Pirke, 1995; Halmi, 1995). The results from the Minnesota Starvation Study also suggest that the emotional disturbances experienced among volunteers are secondary to starvation (Keys et al., 1950). The mechanism by which calorie reduction or semi-starvation causes emotional and psychological instability is not known.

Although not all people practicing the CR lifestyle experience these negative side effects, caution is warranted. Due to the limited data available describing the short-term effects of CR and no data yielding long-term effects in humans, a CR lifestyle should be initiated with extreme caution. The potential for the negative side effects exist and, therefore, those undergoing the classical regimen require medical supervision. Aside from the potential side effects, classic CR is difficult for humans to maintain due to the degree of food restriction and the attention given to food selection to assure adequate nutrition. For these reasons, alternatives to classical CR are under investigation.

5. Caloric restriction alternatives for humans

The classical CR regimen, ~40% reduction in caloric intake, is an unlikely reality for most humans to undertake in order to gain the health and life-extending benefits that CR has to offer. Scientists are investigating the health benefits of CR regimens of lesser degrees which will be more attainable for humans. Most notably, scientists are excited over the future reality of developing a CR mimetic, in which a pill will extend the same benefits as a CR lifestyle.

5.1. Alternative caloric restriction regimens

Alternative diet regimens may provide an easier intervention for humans to sustain while still experiencing the health and longevity benefits that the classical regimen offers. Two of these regimens include daily restriction of calories to a lesser degree, such as 8–25% rather than 40%, and also a regimen of every-other-day feeding (EOD). Recent findings from our laboratory show that 8% CR already has beneficial effects on specific biochemical and inflammatory biomarkers shown to decrease with 40% CR. Weindruch et al. investigated the effects of varying degrees of CR on health and longevity in rodents (Weindruch et al., 1986). They found that CR of all degrees tested, 25, 55, and 65% of the ad libitum diet, conferred improved health and longevity over ad libitum fed control mice. It appears that the greater degree of CR, without inducing malnutrition and starvation, the greater the effects on health and longevity of the mice. Although a lesser degree of CR may not maximize the potential benefits, restriction to a lesser degree is an intervention that is much more feasible for humans to maintain for the long-term.

A regimen of EOD is a second diet regimen that may be an alternative to classical CR. EOD feeding involves a day of fasting followed by a day of ad libitum feeding. Studies have shown that EOD feeding in rodents can confer the same health and longevity benefits as a daily CR regimen (Anson et al., 2003; Goodrick et al., 1990). Even more, the EOD feeding regimen does not appear to require a significant reduction in caloric intake in order to produce the same benefits. Mice on an EOD feeding program eat approximately twice as much the day after fasting as the ad libitum fed mice. Therefore, the average weekly caloric intake of both groups is similar (Anson et al., 2003). This suggests that the state of fasting rather than the reduction in caloric intake may be an important factor in slowing the intrinsic rate of aging. The fasted state likely signals a cellular stress response, which seems to optimize cell signaling and cellular resistance to cell death (Dirks and Leeuwenburgh, 2004; Payne et al., 2003).

5.2. Caloric restriction mimetics

The National Institute on Aging (NIA) developed a research program to investigate CR mimetics (Ingram et al., 2004). The objective of the program is to develop an intervention that produces the same prolongevity effects that CR provides, but without reducing caloric intake or inhibiting food intake. Possible CR mimetics may be nutraceuticals, pharmaceuticals, hormones, or genetic manipulations, but would not include interventions involving appetite suppression or procedures such as stomach stapling. These mimetics developed by the NIA will most likely target a metabolic pathway that is involved in mediating the effects of CR (Ingram et al., 2004).

Because CR characteristically reduces blood glucose and insulin levels and increases insulin sensitivity, a CR mimetic may likely target the glucose metabolism and/or insulin signaling pathways. Metformin is a possible CR mimetic under investigation. Metformin is a drug currently used to treat type II diabetes and functions to reduce blood glucose levels by inhibiting gluconeogenesis in the liver and improving insulin sensitivity (Kirpichnikov et al., 2002). Longevity studies are underway to examine the effects of metformin (Ingram et al., 2004). Other candidates under investigation are iodoacetate acid, an inhibitor of glycolysis, the thiazolidinediones, agonists for peroxisome proliferators activated receptors, and inhibitors of IGF-1 signaling (Guo et al., 2001; Oliver et al., 2001).

6. Conclusions

Caloric restriction is the only non-genetic intervention that consistently slows the intrinsic rate of aging in mammals. The classic regimen of CR most often used in experimental animal models is a ∼40% reduction in caloric intake, as compared to the ad libitum diet, while maintaining all essential nutrients. The health and longevity benefits of such a diet regimen are numerous, however, is not without potential negative side effects applicable to the human life. These include hypotension, loss of libido, menstrual irregularities, infertility, bone thinning and osteoporosis, cold sensitivity, loss of strength and stamina, slower wound healing, and psychological conditions such as depression, emotional deadening, and irritability. Because the long-term effects of CR in humans is not yet known precautions should be taken before engaging in such a severe CR regimen. The CR regimen classically used experimentally may not be feasible for most humans. Alternatives to the classic CR regimen are currently being investigated. Caloric restriction regimens that are less severe in nature have health benefits and therefore may positively impact an individual's life, however, the ability to slow the intrinsic rate of aging in rodents appears to be reduced with the lesser degree of CR. Development of a CR mimetic may be promising in providing the same health benefits and slowing of the aging process as a rigorous CR regimen, while circumventing the need to reduce food and calorie intake.

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