Caloric restriction and its mimetics

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Caloric restriction is the most reliable intervention to prevent age-related disorders and extend lifespan. The reduction of calories by 10-30% compared to an ad libitum diet is known to extend the longevity of various species from yeast to rodents. The underlying mechanisms by which the benefits of caloric restriction occur have not yet been clearly defined. However, many studies are being conducted in an attempt to elucidate these mechanisms, and there are indications that the benefits of caloric restriction are related to alteration of the metabolic rate and the accumulation of reactive oxygen species. During molecular signaling, insulin/insulin-like growth factor signaling, target of rapamycin pathway, adenosine monophosphate-activated protein kinase signaling, and Sirtuin are focused as underlying pathways that mediate the benefits of caloric restriction. Here, we will review the current status of caloric restriction. [BMB Reports 2013; 46(4): 181-187]

INTRODUCTION

Everyone desires a long and healthy life, and many researchers have investigated methods to overcome and retard the aging process. The most well defined intervention of retarding aging is caloric restriction. Caloric restriction, also known as dietary restriction, is the reduction of food intake without malnutrition. Experimentally, caloric restriction means a reduction in calorie intake by 10-30% when compared to an ad libitum diet (1). Lifespan extension in response to caloric restriction is thought to be caused by a decreased rate of increase in age-specific mortality (2). It is widely believed that caloric restriction delays the onset of age-related decline in many species (1), as well as the incidence of age-related diseases such as cancer, diabetes, atherosclerosis, cardiovascular disease, and neurodegenerative diseases. Caloric restriction affects the behavior, animal physiology, and metabolic activities such as modulation of hyperglycemia and hyperinsulinemia, as well as increases insulin sensitivity (3).

Reductions of protein source in the diet without any changes in calorie level have been shown to have similar effects as caloric restriction (4). Furthermore, restriction of individual amino acids has been shown to induce lifespan extension in some species, especially methionine restriction (5). Moreover, the restriction of tryptophan is believed to have a positive effect on longevity (6). Thus, several researchers have stated that this phenomenon occurs as a result of dietary restriction, not caloric restriction. However, other studies have indicated that protein and or methionine restriction is not involved in the caloric restriction-induced lifespan extension (2).

HISTORY OF CALORIC RESTRICTION STUDIES

The first experimental evidence of the effects of food restriction on lifespan was provided by Osborne et al. (7). In the early 1900s, they reported that the restriction of food intake of rats retarded their growth, but prolonged their lifespan. However, their study did not get much attention since Robert and Ray reported the results to show the correlation of longevity to growth rate of mice after three years (8). The most noted study of the effects of caloric restriction was conducted by 1935 by McCay et al. (9), who showed that restriction of food intake by 40% from the age of weaning extended lifespan of rat by up to two times. Their findings were confirmed by a series of experiments conducted by Walford and Weindruch using mice in 1986 (10). Weindruch reported that mice brought up under caloric restriction lived longer than a control group fed ad libitum, and that they also showed improved external appearance and physical conditions, as well as retardation of the onset of age-related diseases (10). To date, the effects of caloric restriction on lifespan and health had been demonstrated in many model animals from yeast to mammals.

MODEL ANIMALS FOR CALORIC RESTRICTION: FROM YEAST TO PRIMATES

The effects of caloric restriction on longevity and health have been reproducibly investigated in a wide range of laboratory animals, yeast, worms, fruit flies, and rodents, as well as some wild animals including cows and dogs (1). In addition, investigations of caloric restriction on non-human primates has been conducted in the last few decades, as have studies of caloric restriction on humans based on epidemiological data.
and volunteer studies.

**Yeast**

Saccaromyces cerevisiae, a single-celled budding yeast, is an excellent experimental model for the discovery of fundamental mechanisms associated with aging and genetic screening for mechanisms of longevity effects of caloric restriction (11). Caloric restriction of *S. cerevisiae* is performed via the reduction of glucose in growth medium. The limitation of glucose availability via growth in low-dose glucose medium (0.5% glucose) has been shown to extend the replicative lifespan of yeast (12). In addition, yeast with a mutation of the Hxtp gene, which is a sensor for glucose, lived longer than controls, further indicating that glucose limitation extends yeast lifespan (12). However, despite its usefulness, the yeast model system has a great weakness in that it is a unicellular organism that is very dissimilar to humans.

**Nematodes**

Nematodes (Caenorhabditis elegans) are the simplest experimental model animal among multicellular organisms, allowing investigations of intercellular and tissue changes in response to caloric restriction. Studies have shown that the reduction of their food source (*E. coli*) can extend the lifespan of nematodes (13). Dissimilar to the mammalian model system, the effects of caloric restriction on the lifespan of worms increases as the restriction increases to starvation. In the absence of bacteria, the lifespan of worms was reproducibly increased by up to 150% (14). The medium utilized for the *C. elegans* model system is well defined, allowing investigation of the roles of individual nutrients on caloric restriction benefits. In addition, the *C. elegans* model system is useful for identification of mechanisms of caloric restriction since it has a relatively shorter lifespan than other multicellular model systems as well as a great deal of known mutants related to lifespan.

**Fruit flies**

One of the most fascinating model systems for investigation of gerontology is the fruit fly, *Drosophila melanogaster*, which has a high similarity to human disease-related genes, as well as a relatively short lifespan (approximately 60-80 days). The relationship of the response to the dose of caloric restriction has been well established in *D. melanogaster*. In studies of *D. melanogaster*, the restriction of food is generally performed via the dilution of nutrients (especially yeast as a protein source). It seems that diet quality, not calorie per se, is important regulator of lifespan after caloric restriction at least in *Drosophila* since yeast restriction and carbohydrate restriction had different effect on lifespan (15). Recent studies have shown that the balance of protein to non-protein energy ingested is the key determinant of lifespan in *Drosophila* (16).

**Rodents**

The rodent model system was the first system investigated for benefits of caloric restriction on lifespan (17). Rodent models including rats and mice have a high similarity to human diseases and metabolism, making them the most practical. Caloric restriction interventions of rodents were first performed via the reduction of food supplemented daily, but the alternative protocol of alternate-day fasting or intermittent fasting was later developed (18). The alternate-day fasting intervention was confirmed to have beneficial effects such reduced insulin sensitivity, diabetes, and body weight, as well as extended lifespan (19).

**Non-human primates**

The beneficial effects of caloric restriction on non-human primates, especially rhesus monkeys (*Macaca Mulatta*), have been investigated by three independent groups, the National Institute of Aging (NIA), the Wisconsin National Primate Research Center (WNPRC), and the University of Maryland. At the University of Maryland, Hansen focused on obesity and diabetes in rhesus monkeys using short-term caloric restriction. She found that caloric restriction had a beneficial effect on body weight, insulin sensitivity, and diabetes (20, 21). The effects of caloric restriction on non-human primates longevity was investigated in two independent 20-year longitudinal adult-onset studies in rhesus monkeys (22, 23). In 2009, WNPRC reported their long-term study begun in 1989, which showed that caloric restriction extended the median lifespan of rhesus monkeys and reduced the onset of age-related diseases (22). Although their study was not completely finished, this report suggested that the benefits of caloric restriction on longevity are evolutionally conserved and controlled by conserved mechanisms. However, in 2012, NIA published another study about the effects of caloric restriction on rhesus monkey lifespan (23). Their study, which began in 1987, showed results that were somewhat different from those reported by the WNPRC. Although it was also ongoing study that showed beneficial effects of caloric restriction on age-related diseases, the young onset caloric restriction monkeys did not show advantages associated with age-related mortalities when compared to *ad libitum* monkeys. These opposing results seem to be caused by differences in the method of diet supplementation, the amount of calories provided to control animals, and/or the genetic background of the experimental animals. Nevertheless, the positive results from studies of non-human primates suggest that restriction of food intake can help humans have longer and healthier lives.

**Humans**

Owing to ethical and experimental limitations, investigations of human caloric restriction have not been actively conducted. As a result, studies of the benefits of caloric restriction on humans have primarily been restricted to epidemiological studies. However, many people follow food restrictions for religious or regional reasons. Studies of the effects of observance of Ramadan, during which time Muslims do not intake any