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Regulation of metabolic health and aging by nutrient-sensitive signaling pathways

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ABSTRACT

All organisms need to be capable of adapting to changes in the availability and composition of nutrients. Over 75 years ago, researchers discovered that a calorie restricted (CR) diet could significantly extend the lifespan of rats, and since then a CR diet has been shown to increase lifespan and healthspan in model organisms ranging from yeast to non-human primates. In this review, we discuss the effects of a CR diet on metabolism and healthspan, and highlight emerging evidence that suggests that dietary composition – the precise macronutrients that compose the diet – may be just as important as caloric content. In particular, we discuss recent evidence that suggests protein quality may influence metabolic health. Finally, we discuss key metabolic pathways which may influence the response to CR diets and altered macronutrient composition. Understanding the molecular mechanisms responsible for the effects of CR and dietary composition on health and longevity may allow the design of novel therapeutic approaches to age-related diseases.

1. Calorie restriction promotes health and longevity

Calorie restriction (CR), a dietary intervention in which calories are reduced while maintaining adequate levels of micronutrients, was first discovered to extend the lifespan of rats more than 75 years ago (McCay et al., 1935). Since that time, a CR diet has been shown to extend lifespan in many model organisms including yeast, worms, flies, rodents, and non-human primates (Colman et al., 2014; Greer and Brunet, 2009; Lin et al., 2000; Rogina and Helfand, 2004; Weindruch et al., 1986). The precise degree of restriction, as well as the precise macronutrient composition of the CR regimen utilized, that maximizes lifespan extension may vary between individuals and species (Mair et al., 2005; Piper et al., 2005). A recent study of a 40% CR diet – typically utilized in mouse studies of CR – across 41 strains of recombinant inbred mice found a range of responses including strains with decreased lifespan, and it has been proposed that the response to CR and/or the optimal degree of restriction to promote longevity may vary according to genotype (Liao et al., 2010; Mitchell et al., 2016). While some have argued that the beneficial effects of CR in laboratory animals is an effect of overfeeding in the lab, CR extends maximum lifespan and robustly inhibits cancer in wild-type mice (Harper et al., 2006).

The specific mechanisms by which CR extends lifespan and promotes health is unknown, but as the gold standard for anti-aging interventions, understanding the molecular and physiological mechanisms that underlie the effects of CR has been a priority of researchers for many years. Understanding the mechanisms that underlie the beneficial effects of a CR diet may enable the creation of dietary or pharmaceutical interventions that will permit those incapable of adhering to a CR diet to achieve some of the same benefits to health and longevity. The physiological effects of CR have been extensively cataloged; some of the changes which are believed to be beneficial include reduced inflammation (Chung et al., 2001), reduced oxidative stress (Sohal and Weindruch, 1996), altered neuroendocrine and sympathetic nervous system function, reduced energy expenditure, and improved metabolic flexibility (Bordone and Guarente, 2005; Heilbronn and Ravussin, 2003). CR also alters metabolism at the transcriptional level, and several studies show that CR can reverse many of the transcriptional changes associated with aging (Lee et al., 1999; Park et al.,

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2009; Pearson et al., 2008; Weindruch et al., 2001). Importantly, CR has been shown to not only extend lifespan, but also to improve healthspan, with animals on CR diets showing decreased rates of cancer, cardiovascular disease, and diabetes (Berrigan et al., 2002; Colman et al., 2014; Lamming and Anderson, 2014). A CR diet also promotes cognition in mouse models of neurodegeneration and Alzheimer's disease (Graff et al., 2013; Halagappa et al., 2007).

Ongoing studies of CR in non-human primates suggest that CR promotes longevity and prevents age associated diseases such as cancer, type 2 diabetes, cardiovascular disease, brain atrophy, and osteoporosis (Colman et al., 2014; Cruzen and Colman, 2009; Mattison et al., 2012b). CR studies performed in non-human primates also show improved metabolic parameters, including increased insulin sensitivity and glucose tolerance as well as reduced energy expenditure, similar to their rodent counterparts (Kemnitz, 2011). While study design, husbandry, and dietary composition appear to impact the effect of CR on the longevity of primates (Colman et al., 2014), CR clearly has a dramatic effect upon the prevalence and severity of age-related diseases (Colman et al., 2009; Mattison et al., 2012a). These studies suggest that the fundamental mechanisms engaged by CR are preserved all the way from yeast to primates (Colman and Anderson, 2011; Fontana and Partridge, 2015).

While the benefit of a CR diet to human lifespan is unknown, the physiological and metabolic effects of CR in humans appear to be similar to those observed in non-human primates. Humans who consumed a low calorie, nutrient dense diet for approximately two years in Biosphere 2 showed physiologic, hematologic, hormonal, and biochemical changes resembling those of rodents and monkeys on such diets (Walford et al., 2002). More recently, a randomized clinical trial of a 25% CR diet in non-obese adults was shown to result in significant weight loss, primarily due to loss of adiposity through decreased visceral fat (Fontana et al., 2016b). Other studies on the effect of a CR diet on humans has demonstrated that CR can improve age-associated changes in blood pressure, systemic inflammation, and myocardial fibrosis (Meyer et al., 2006), protect against atherosclerosis (Fontana et al., 2004), and reduce cardiovascular disease instance and risk (Cruzen and Colman, 2009). Similar to rodents and non-human primates placed on a CR diet, humans placed on a CR diet also have increased levels of adiponectin and improved insulin sensitivity (Fontana et al., 2009). Given these favorable effects, while the jury remains out on the effect of a CR diet on human lifespan, it appears very likely that a CR diet has the potential to improve healthspan, and perhaps prevent or delay many age-associated diseases.

While CR diets will likely prove effective in preventing age-related disease, they are difficult to sustain for all but a handful of individuals. There is therefore great interest in developing dietary strategies that are easier to follow that mimic the beneficial effects of a CR diet. One of the most popularly researched and implemented CR mimetic dietary strategies is feeding intermittently – either restricting the time of day during which feeding is permitted, or fasting intermittently. As similar dietary regimens have been followed by many for religious reasons for centuries or millennia, they may be more sustainable. The cellular responses to fasting are similar to CR but include reduced oxidative damage, improved energy metabolism, and overall protection. Physiologically, fasting can improve longevity and prevent against many diseases such as diabetes, heart disease, cancers, obesity, hypertension, asthma, rheumatoid arthritis, and neurodegeneration (Longo and Mattson, 2014). This may occur through a shift to fat and ketone metabolism during a fast, as well as through adaptive changes to stress and repair of cellular damage (Mattson et al., 2014). Restricting feeding to four short time periods per day can significantly extend the lifespan of rats (Deerberg et al., 1990), and in mice limiting food access to an eight hour window each day can improve metabolic disease even in consumption of diabetogenic diets (Chaix et al., 2014). However, human data on the benefits of time-restricted feeding suggests that the benefits of time-restricted feeding may depend on the exact composition of the diet (Mattson et al., 2014), and thus it is not clear that this type of dietary intervention will promote healthy aging in humans, or if CR mimetics will be as effective as they are in model organisms.

2. Dietary composition – when is a calorie not just a calorie?

Unfortunately, while a CR diet may be an effective method in reducing age-associated diseases and possibly extending lifespan, even a slight reduction in caloric intake or occasional fasting may be difficult in present-day Western society, in which we are surrounded by cheap and readily available calories and struggling with obesity. Intriguingly, despite significant interest in the biological mechanisms engaged by CR, until recently it has been unclear what macronutrients in a CR diet are responsible for its beneficial effects. While CR regimens typically decrease protein, fat, and carbohydrates, research suggests the reduced consumption of these macronutrients may not contribute equally to CR's benefits.

Many of the first experiments which investigated the effect of restricting individual macronutrients, particularly protein, on rat lifespan observed varied results (Weindruch and Walford, 1988). In retrospect, these difficulties may have been due to a combination of uncertainty regarding the exact nutritional needs of rats, and the use of dietary protein from different sources with varying amino acid composition. These problems began to be resolved in the 1980s, and experiments using Fisher 344 rats determined that restriction of dietary fat in the context of an isocaloric diet did not extend lifespan, but that the source of dietary protein greatly impacted lifespan (Iwasaki et al., 1988a, b). More recent experiments conducted in *Drosophila melanogaster* have shown that restriction of either dietary sugar or yeast will extend lifespan, but that calorie-for-calorie, restriction of yeast has a much greater impact than restriction of sugar (Mair et al., 2005). Another *Drosophila* study showed that essential amino acid balance changes can reverse the effects of DR, even though calorie level is restricted (Grandison et al., 2009).

Since these initial experiments, dietary protein has been revealed as a key determinant of the effects of a CR diet on rodent metabolism and lifespan. In a series of experiments during the last decade, a nutritional Geometric Framework approach was used to analyze the lifespan of first *Drosophila* and more recently C57BL/6J mice fed isocaloric diets with many possible ratios of protein, fat, and carbohydrates (Lee et al., 2008; Solon-Biet et al., 2014). This approach takes into account that in diet studies, shifting ratios in diet always affects at least two macronutrients, and may affect the influence of the third. The Geometric Framework therefore permits the consideration of altered macronutrient ratios and total energy intake in their full spectrum. In *Drosophila*, this approach was used to determine the lifespan of over 1000 flies fed one of 28 diets with varying concentrations of sugar and yeast, and Lee and colleagues determined that “lifespan declined from the maximum as protein intake increased and as carbohydrate intake fell” (Lee et al., 2008). Similarly, a recent study determined the lifespan of C57BL/6J mice placed on one of 25 different diets with varying concentrations of protein, carbohydrates, and fat, and determined that mice fed a low protein diet lived the longest, with mice fed a low protein, high carbohydrate diet living the very longest (Solon-Biet et al., 2014). Importantly, this study also found that CR in the context of high protein did not extend lifespan. Further work by Solon-Biet and colleagues demonstrated that low protein, high carbohydrate diets produce metabolic benefits comparable to CR with respect to blood