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Nutrition modulation of human aging: The calorie restriction paradigm

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ABSTRACT

Globally, the aging population is growing rapidly, creating an urgent need to attenuate age-related health conditions, including metabolic disease and disability. A promising strategy for healthy aging based on consistently positive results from studies with a variety of species, including non-human primates (NHP), is calorie restriction (CR), or the restriction of energy intake while maintaining intake of essential nutrients. The burgeoning evidence for this approach in humans is reviewed and the major study to date to address this question, CALERIE (Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy), is described. CALERIE findings indicate the feasibility of CR in non-obese humans, confirm observations in NHP, and are consistent with improvements in disease risk reduction and potential anti-aging effects. Finally, the mechanisms of CR in humans are reviewed which sums up the fact that evolutionarily conserved mechanisms mediate the anti-aging effects of CR. Overall, the prospect for further research in both NHP and humans is highly encouraging.

1. Introduction

Aging is inevitable and an integral part of human life, and is associated with multiple physiological, metabolic, hormonal, immune and neurocognitive changes (Lamberts et al., 1997; Roberts and Rosenberg, 2006; Tosato et al., 2007) that collectively contribute to the development of age-related metabolic disease and physical disabilities. Remarkable improvements in life expectancy, in part the result of medical advances that have significantly decreased mortality from communicable diseases, have resulted in an unprecedented growth of the population of older adults (WHO, 2011). However, non-communicable diseases, including diabetes, heart disease, cancer, stroke, and Alzheimer's are now the leading cause of morbidity and mortality worldwide (WHO, 2011). A critical need is therefore to improve healthspan, i.e., to reduce illness, disability and dependency during the aging process. Interventions that have the potential to reduce disease risk and facilitate retention of health, productivity, independence, and quality of life through the aging years are therefore greatly sought after and merit scientific investigation.

2. The calorie restriction paradigm

Over the past several decades, the anti-aging researchers have identified and tested several nutritional, life-style and pharmacological interventions known to improve health and longevity. Calorie restriction (CR) is the only nutrition intervention that, based on strong and consistent evidence in a variety of non-human species, is now widely recognized as a highly promising strategy to delay the onset and progression of age-related metabolic diseases (Roth et al., 2001) and extend lifespan (Fontana et al., 2010). CR is the restriction of habitual caloric intake without a reduction in essential nutrients. CR is prescribed or practiced with the primary aim of attenuating or delaying the onset of physiological and metabolic effects of aging and associated disabilities. McCay et al. were the first to show CR effects on age related disease risk reduction and extension of lifespan based on findings in rats (McCay et al., 1935). Similar beneficial effects have been subsequently demonstrated in various animal models, including yeast, flies, worms, fish, and in mammals (Anderson and Weindruch, 2012). However, human studies have been limited due to the feasibility issues of

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implementing an appropriately timed intervention with follow-up for the course of the lengthy human lifespan.

3. CR is a relevant delayed aging model in primates

Non-human primates (NHP), owing to their high genetic and physiological similarity to humans, serve as an excellent model to test the translatability of CR in humans (Gibbs et al., 2007). In addition, nonhuman primate models also offer the convenience of tightly controlled experimental conditions and less complicated implementation of a uniform study protocol, not to mention the cost efficiency. Small-animal studies suggest that no single causal pathway or mechanism by which CR attenuates disease risk and improves markers of longevity, instead indicating that the benefits of CR are realized via a complex interplay of biological changes that are both synergistic and mutually non-exclusive. However, reduced metabolic rate, lower energy expenditure, and reduced core-body temperature have been implicated as responses to CR in both rodents and NHP (Lane et al., 1996). The net effect of these physiologic changes is a reduction in oxidative stress-induced cellular damage and improvements in markers of inflammation and immune function; these outcomes are widely captured in CR studies and serve as markers for assessing the benefits of CR in humans. Newer mechanisms have been identified and are discussed in section 6 of this review.

The establishment of the first two prospective studies in NHPs, one at the National Institute on Aging (NIA) in 1987, and a second at the University of Wisconsin's National Primate Research Center (WNPRC) in 1989 marked an important milestone in laying the foundation for bridging animal and human CR research. The description of the NIA and WNPRC cohorts and major findings, including key similarities and differences between the two studies, have been detailed elsewhere (Cava and Fontana, 2013; Kemnitz, 2011; Mattison et al., 2003, 2017). Most notably, compelling evidence for the beneficial effects of CR on healthspan has been clearly demonstrated in both of the NHP cohorts for a variety of physiological outcomes, including a lower body fat, favorable changes in lipid profile, improved insulin sensitivity and glucose tolerance, and lower incidence of cancer, type 2 diabetes and cardio-vascular disease (Anderson and Weindruch, 2012; Colman and Anderson, 2011; Colman et al., 1998, 1999, 2009, 2014; Edwards et al., 1998, 2001; Gresl et al., 2001; Lane et al., 1992, 1999; Mattison et al., 2017, 2003, 2012; Ramsey et al., 2000; Roth et al., 2001, 2002b). Although lifespan effects are not entirely consistent in the two NHP cohorts due to the differences in study design and time of onset of CR (Mattison et al., 2017), the positive effects of CR on healthspan is largely consistent and highly encouraging. In summary, CR studies in NHP not only validated the findings from smaller animals, but also reinforced the scientific priority for conducting randomized controlled trials (RCT) in humans.

4. Population studies suggest that CR may be conserved in humans

In parallel to the emerging positive findings of the benefits of CR from ongoing studies in NHPs, findings from direct observation of human populations who fit the CR paradigm likewise suggest that CR may improve healthspan and promote longevity in humans. These data therefore provided evidence for the potential feasibility of conducting CR intervention studies in humans. Examples of such studies are described below.

The Okinawa Centenarian Study (http://www.okicent.org/index.html) is an ongoing population-based study of centenarians and select elderly (>65 years of age) from the Japanese prefecture of Okinawa, whose caloric intake is historically documented as being lower than age matched elders in other regions of the world including mainland Japan (Willcox et al., 2006a, 2007). These Okinawan elders reported consumption of a reduced calorie but nutrient dense diet since their younger ages. Compared to relevant reference elderly populations from around the world, the Okinawan elders exhibited less metabolic damage, better cardiovascular health (low plasma homocysteine levels), fewer hormone related cancers, a lower prevalence of osteoporosis and dementia, increased physical activity, fewer menopause-related problems, and higher sex hormone levels (Arakawa et al., 2005; Willcox et al., 2006b).

The Biosphere experiment in 1991, in which eight adults (four female and four male) were sealed inside a self-contained ecological space (Biosphere 2), accidentally resulted in reduced food production and therefore lower energy consumption by the crew members. While it was planned that they would produce and consume energy in excess of 2500 kcal per person per day for 2 years, during seven-eighths of the 2 year period the crew consumed only 1750–2100 kcal/d via a nutrient-rich diet of vegetables, fruits, nuts, grains, and legumes, with small amounts of dairy, eggs, and meat. They also consumed vitamin and mineral supplements consisting of vitamin B12, folic acid, vitamin D, Vitamin E and ascorbic acid (Walford et al., 2002). The men lost 19% of their body mass while the women lost 13%. Both men and women experienced decreases in systolic blood pressure of 25% and diastolic blood pressure of 22%. In addition, there were favorable changes in hematology (e.g. white blood cell count decreased by 31%), hormonal levels (e.g., insulin decreased by 42%; tri-iodothyronine (T_3) decreased by 19%), and biochemical parameters (e.g., blood sugar decreased by 21%; cholesterol decreased by 30%) (Walford et al., 2002).

There is also evidence of positive effects from a study of CR Society members (http://www.crsociety.org/), a group of voluntary practitioners of CR. A comparison of CR Society members with age- and gender-matched subjects eating typical Western diets found that CR members were consuming approximately 800 fewer kcal per day and had a significantly lower mean body fat mass, core body temperature, blood pressure, and T_3 level; as well as lower blood levels of inflammatory markers, namely, tumor necrosis factor alpha (TNF-α), high sensitivity C-reactive protein (hsCRP) and transforming growth factor-1-beta (TGF1-β). They also had lower total testosterone and free androgen indices but higher levels of sex hormone binding globulins (Cangemi et al., 2010; Meyer et al., 2006).

In sum, the collective evidence from available human CR observational and population studies strongly and consistently favors improvements in potential markers of health and longevity and supports the investigation of CR effects in humans using a Randomized Controlled Trial (RCT). Further, examining the benefits of CR on healthspan is a logical focus for human CR intervention studies.

5. Clinical trials of CR in humans

A CR study in humans that parallels the studies in NHP and are long enough to study survival effects would be both premature and impractical. A medium-term study of sustained CR that could provide valuable information of potential human effects including feasibility, safety, evidence for mechanistic paralles from animal studies, risk factors for age-related conditions and markers of longevity was considered as a rational first step and practical approach. Accordingly, the primary research questions were a) is CR feasible and safe in humans? b) does CR have the same beneficial effects in humans as in animal models, e.g., reduced rate of biological aging, enhanced immune function, reduced oxidative