METABOLIC ADAPTATIONS TO TWO-YEAR CALORIC RESTRICTION

A. SPECIFIC AIMS

Caloric restriction (CR) from birth or during adult life in rodents and lower species prolongs life. Measurement of surrogate markers of longevity suggests that this may be the case in primates as well. The mechanism(s) responsible, and whether this is the case for humans is unknown. CR is associated with several well-known changes in metabolism, including lowering of the metabolic rate. It is unknown which, if any, of these adaptations might be responsible for extending maximum life span. One intriguing hypothesis is that CR lessens the oxidative damage and repair of vital tissues by reducing energy flux and metabolism. CR results in loss of weight and tissues, and lowers the rate of metabolism. A portion of this is the result of the reduced energy intake itself, and another portion is due to the decline in size of the metabolizing mass. Whether there is also a "metabolic adaptation," defined here as a reduction of metabolic rate that is out of proportion to the decreased size of the respiring mass is a subject of continued debate.

We will test for this, and in addition, if the expected decline in metabolic rate (whether or not proportionate to the respiring mass) that follows CR is associated with reduced oxidative stress in tissues, and risk factors for age-related metabolic diseases, including cardiovascular disease and type 2 diabetes. In addition, we will test if combining physical activity (PA) and CR to produce the same caloric deficit alters the adaptations caused by CR alone. As part of these investigations, we will assess the expression of genes involved in energy metabolism and oxidative stress that are known to be associated with longevity in "lower" organisms.

This proposal is in response to an RFA to test if chronic CR, as it does in rodents and "lower" species and possibly in non-human primates, improves surrogate markers of longevity in humans, and therefore might extend the maximum life span. Thus, this is mainly a descriptive undertaking. However, we also propose to test several interesting hypotheses. These are stated below and listed in Table 1.

Hypothesis A. Chronic CR (resulting in loss of weight and maintenance of energy balance at a new lower body mass) is associated with several metabolic adaptations, including lower absolute and relative rates of energy expenditure, lower body temperature, and evidence of lower tissue oxidative stress.

Aims: Measure and compare for difference:

A1) Energy expenditure (free living, sedentary 24-h, resting, exercise efficiency), and body temperature.

A2) DNA, protein and lipid oxidative damage.

Hypothesis B. Chronic CR improves surrogate markers (risk factors) for chronic diseases, including cardiovascular disease and type-2 diabetes. These adaptations are the same whether the energy deficit is produced by combining PA and CR or by CR alone.

Aims: Measure and compare for difference:

B1) CVD risk factors (BP, lipid profile, hemostasis factors, homocysteine, endothelial function, and markers of inflammation).

B2) Type 2 diabetes risk factors. (Insulin action and secretion)

Hypothesis C. Chronic CR dampens the activity of the neuroendocrine axes, and lowers SNS activity, potentially by decreased leptin signaling. These adaptations are less pronounced when the same energy deficit is achieved by combining PA and CR.

Aims: Measure and compare for difference:

C1) Hypothalamic neuroendocrine function (thyroid, adrenal, and somatotrophic axes), and diurnal rhythm of leptin.

C2) SNS activity

Hypothesis D. Chronic CR is associated with adaptations in the expression of genes involved in aging, including those related to oxidative stress, energy metabolism (carbohydrate, lipid and protein), and longevity.

Aim D: Measure for differences in the expression of candidate genes in skeletal muscle and adipose tissue.

Hypothesis E. Psychophysiologic outcomes are improved when the energy deficit is produced by combining PA and CR compared to CR alone.

Aim E: Measure for differences in weight loss, compliance, rate of drop out, quality of life (QOL), mood, cognitive function, fitness & strength, reaction times, physical activity & food records, and risk of developing an eating disorder.