The diet restriction paradigm: a brief review of the effects of every-other-day feeding

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Abstract

It has been known since the early 1900s that restriction of dietary intake relative to the ad libitum (AL) level increases stress resistance, cancer resistance, and longevity in many species. Studies investigating these phenomena have used three paradigms for dietary restriction. In the first, the AL intake of a control group is measured, and an experimental group is fed less than that amount in a specified proportion, e.g., 40%. In the second, food is provided AL to both the control and experimental groups; however, the experimental group is subjected to periods of fasting. Recent studies using this paradigm provide food every other day (EOD). Both of these paradigms have been in use since the early 1900s. A third paradigm that combines them was developed in the early 1970s: one or more days of fasting separate the provision of a limited amount of food. It was assumed for many years that the physiological responses to these paradigms were due exclusively to a net decrease in energy intake. Recently, however, it was found that some species and strains of laboratory animals, when fed AL every other day, are capable of gorging so that their net weekly intake is not greatly decreased. Despite having only a small deficit in energy intake relative to control levels, however, these animals experience enhanced longevity and stress resistance in comparison to AL controls as much as in animals enduring daily restriction of diet. These observations warrant renewed interest in this paradigm and suggest that comparisons of the paradigms and their effects can be used to determine which factors are critical to the beneficial effects of caloric restriction.

Many species age more quickly with an ad libitum food intake than with one that is restricted, and the mechanism underlying this effect remains unidentified

The effects of dietary restriction [more commonly known as caloric restriction (CR)] on longevity and resistance to environmental stress were first noted in studies of cancer and malnutrition

The discovery that caloric intake strongly influences the rate of aging was not made in one step. It arose gradually out of two independent fields of research: the influence of dietary intake on cancer and the effect of malnutrition early in life on growth, reproduction, and adult health. The work, which gave rise to what is now one of the most intense areas of interest in the field of biogerontology, was begun early in the 20th century. For example, one of the earliest studies on the role of dietary intake on cancer was led by Rous (1914), whose group published a study in 1914 which showed that reducing food intake reduced cancer incidence in rodents (Rous 1914). Enormous volumes of research have since supported and elaborated on this finding. Around the same time (1915), a study on juvenile malnutrition which influenced the biogerontological
field was published by Osborne et al. (1915). In it, they described the resumption of growth after a long period of arrested development induced by a restricted food supply (Osborne et al. 1915). They concluded that CR during youth delayed maturation and extended life span. CR also slows the rate of aging even when begun after maturation is complete, but this was not completely proven until 1982 (Weindruch and Walford 1982).

The role of energy intake in the CR effect is accepted, but whether it is a direct or indirect role is controversial

The correlation between reduced food intake and increased life span did not demonstrate that caloric restriction was the causative factor. The initial hypotheses concerning the effects focused on individual macro- and micronutrients. However, evidence that decreased consumption of dietary energy was responsible, rather than decreased intake of any specific nutrient, began to accumulate. An early study of importance in this regard was conducted in 1937. Growth, life span, and body size were measured in rats in response to fat and carbohydrate intake. Restriction of either macronutrient led to life span extension (McCay et al. 1937). Several objections to these findings can be considered. Fat, for example, is hardly a homogenous substance, and omega-6, trans-hydrogenated, or fully saturated fatty acids consumed in excess might well shorten the life span of a “control” group. The glycemic index of the carbohydrate content could be a variable as could food palatability if ad libitum (AL) controls ate enough to become obese. Throughout the ensuing years, each of these variables and others have been manipulated without changing the outcome of the experiment. Invariably, it has been the limitation of energy consumed that has been considered as the primary variable for the increased life span observed in these protocols. (For a brief but useful and interesting review, see Masoro 2003.)

A summary of the various hypotheses proposed to explain the role of energy intake on life span was recently provided (Masoro 2003). Masoro lists the following: (1) the oxidative damage attenuation hypothesis, (2) the alteration of the glucose–insulin system hypothesis, (3) the alteration of the growth hormone-IGF-1 axis hypothesis, and (4) the hormesis hypothesis. The first postulates that oxidative damage has a major influence on the rate of aging, and that CR decreases the levels of such damage. In turn, these decreases are proposed to be either a direct effect of decreased energy flow through the system, or an indirect effect due to alteration of metabolic pathways involved in repair and in free radical scavenging. The second is based on the strong correlation between decreases in average blood glucose and insulin levels with increases in life span in response to CR. This involvement of insulin and glucose in life span mediation has been hypothesized to be due to either direct changes in levels of damage (for example, lowered glucose would lead to decreased rates of spontaneous, nonenzymatic glycation of macromolecules) or to a programmed response to lowered insulin levels. The third hypothesis is based on the observation that genetic changes which decrease IGF-1 or growth hormone (GH) result in increased longevity, and that levels of these hormones are decreased in CR animals (although the fact that CR has an additive effect on life span extension when imposed on animals with genetically lowered IGF-1 or GH levels suggests the presence of separate mechanisms; Bartke et al. 2001). Here, a coordinated response to changes in hormone levels is thought to lead to changes in cell proliferation and death, as well as in other parameters influencing life span. Finally, the hormesis hypothesis suggests that a decrease in caloric intake induces a coordinated activation of pathways necessary to survival without food, thus leading to increased damage prevention and repair.

These hypothesized mechanisms underlying the effects of CR remain unproven. Despite their number and variety, they can be divided into two general classes. One class postulates that decreased energy availability leads to direct alterations in energy metabolism. The other class, in contrast, postulates that the difference between actual and desired intake, rather than the absolute caloric intake, leads to a programmed physiological response. Both postulates result in enhanced stress resistance, cancer resistance, and increased longevity.

Animals that gorge avoid a net energy deficit, but still benefit from intermittent fasting: this finding supports hypotheses postulating an indirect role for energy intake in the CR effect and suggests a new line of experimentation

Studies seeking to investigate the effects of CR can be classified according to the paradigm of restriction used. Three paradigms are in common use. In the first, the AL intake of a control group is measured,