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Review

Benefits of short-term dietary restriction in mammals

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ABSTRACT

Dietary or calorie restriction (DR, CR), defined as reduced food intake without malnutrition, imparts many benefits in model organisms. Extended longevity is the most popularized benefit but the least clinically relevant due to the requirement for long-term food restriction. DR also promotes stress resistance and metabolic fitness. Emerging data in experimental models and in humans indicate that these benefits occur rapidly upon initiation of DR, suggesting potential clinical relevance. Here we review data on the ability of short-term DR to induce beneficial effects on clinically relevant endpoints including surgical stress, inflammation, chemotherapy and insulin resistance. The encouraging results obtained in these preclinical and clinical studies, and the general lack of mechanistic understanding, both strongly suggest the need for further research in this emerging area.

1. Introduction

Dietary or calorie restriction (DR, CR), defined as reduced food intake without malnutrition, is a potent intervention that increases lifespan and decreases incidence and severity of age-related disease in numerous model organisms from single-celled yeast to fruit flies to non-human primates (Speakman and Mitchell, 2011). In addition to these aging-related endpoints, DR also improves metabolic fitness including glucose homeostasis, insulin sensitivity, serum lipid profiles and blood pressure, and improves resistance to a variety of acute oxidative stressors (Speakman and Mitchell, 2011).

After the early 20th century reports of DR's beneficial actions regarding cancer and longevity in rodents, hypotheses as to its mechanism of action focused on accumulated effects of reduced oxidative stress over time (Gredilla and Barja, 2005). An important implication of this viewpoint was that benefits of DR take a long time to accrue. Because long-term voluntary food restriction is impractical for most people, this made DR by dietary means (as opposed to pharmacological means in the form of DR mimetics) of little practical clinical value.

In the 21st century, it came with some surprise that near maximal changes in mortality rates could be achieved within days of food restriction in fruit flies (Mair et al., 2003). In mice, 40% CR initiated in 19 month old mice significantly increases lifespan and decreases the rate of age-associated mortality within 8 weeks. Changes in liver gene expression similar to those observed upon long-term CR occur in as little as 2 weeks (Dhahbi et al., 2004).

The idea of a rapid response to DR runs counter to the idea of accrual of benefits (for example, a reduction in steady state levels of oxidized macromolecules) being important for the onset of benefits. Instead, it supports the hormesis hypothesis of DR action focused on adaptive changes to the mild stress of food deprivation (Sinclair, 2005). Although the molecular nature of the "mild stress" associated with food restriction is not well defined, it may involve at least a temporary increase in oxidative free radical production driving pleiotropic adaptations in energy metabolism, stress resistance, and in multicellular organisms, immune function (Hine and Mitchell, 2012).

While the relative importance of these DR-dependent adaptations to increased lifespan/healthspan remains unclear, the speed at which these changes in immunological or metabolic fitness can occur is becoming readily apparent. This realization set the stage to ask which of the many known benefits of DR in mammals may also be realized within clinically relevant time frames. In this review, we will highlight existing evidence for short-term benefits of DR against clinically relevant endpoints. We will focus on planned stressful events with the most immediate translational potential, including elective surgery and chemotherapy. What little is currently known about underlying mechanisms will also be summarized. We begin with a definition of terms.

2. What is short-term DR?

The term DR is itself loosely defined, and its execution in experimental mammals varies widely among laboratories with respect to composition of diet, severity of restriction and timing of meals. For example, DR can consist of once daily or thrice weekly feeding over a range of restricted food amounts (Weindruch et al., 1986). Every-other-day

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(EOD) fasting is an alternate method of DR consisting of alternating days of ad libitum feeding and fasting generally resulting in reduced overall food consumption. DR is sometimes referred to as CR, implying the mechanistic importance of reduced calorie intake (Masoro, 2003). When food is restricted, calories and nutrients are both reduced proportionately, yet the relative contribution of calorie vs. nutrient restriction remains unresolved. Total protein restriction and restriction of an individual essential amino acid such as methionine can both lead to organismal adaptations and functional benefits reminiscent of DR, but without enforced calorie restriction (Miller et al., 2005; Pamplona and Barja, 2006). In this review, DR is defined broadly enough to include each of these dietary interventions, without implying a shared underlying mechanism among them.

In the context of DR, "short-term" and "long-term" also lack rigorous definitions in the experimental literature. Long-term DR in rodents is often associated with lifespan studies lasting years. Short-term DR, on the other hand, is used in conjunction with different experimental endpoints and ranges from days to months. For example, 3 days of 100% DR (water-only fasting) and 1 month of 30% DR both result in similar functional protection against renal ischemia reperfusion injury in mice (Mitchell et al., 2010). However, this does not imply that these two short-term DR regimens work by the same mechanism, or that either necessarily shares a mechanistic basis with long-term DR.

How then best to define "short-term DR?" With an eye toward clinical translation, we first considered setting an upper limit on the period of time that would be considered practical for a given clinical application, for example preconditioning prior to surgery or chemotherapy. However, what is considered practical is likely to depend on a number of variables including the severity of food restriction, motivation of the patient and his/her doctor, and evidence of potential benefit. Each of these variables is either currently unknown or difficult to ascertain. A different way to define short-term DR would be to equate it to a measurable biological phenomenon. In rodents, for example, the initial response to DR involves weight loss. At sustainable levels of DR such as 30%, initial weight loss is typically followed by a slight rebound before a new weight set point is established (Koubova and Guarente, 2003). Short-term DR could thus correspond to this period of time in which animals lose weight after initiation of food restriction but prior to rebound or weight maintenance (Fig. 1).

Nonetheless, given the dearth of reports fitting this narrow biological definition of short-term DR, we instead took a practical approach and focused on the shortest reported DR periods available for a given experimental endpoint with potential clinical translation. Thus, our definition of "short-term" here ranges from one day to several months. However, in most cases the experiments highlighted in this review were not designed to find the minimum time of onset of benefits, so the potential clearly exists for shorter DR periods to demonstrate clinical relevance.

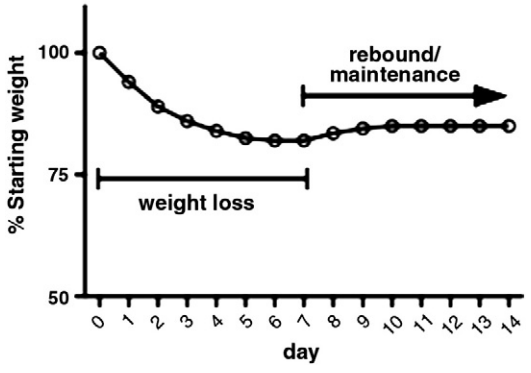

Fig. 1. Model for weight change characteristics upon initiation of DR.

3. Protection from ischemia reperfusion injury and other surgical stressors in experimental models

3.1. Dietary preconditioning

Surgery is inherently stressful. Incision, tissue dissection, cauterization and temporary stoppage of blood flow (ischemia followed by reperfusion) are standard techniques that engender local and systemic inflammatory as well as sympathetic nervous responses. Ischemic injury can also occur as an unintended consequence of vasoconstriction and/or arterial plaque rupture, resulting in such perioperative complications as heart attack or stroke (Mitchell et al., 2013).

The use of long-term DR as a preconditioning method to protect against stress, associated directly or indirectly with elective surgery, was first reported in a rat model of myocardial infarction. Twelve months of 40% daily food restriction reduces inflammation and infarct size associated with occlusion of the coronary artery (Chandrasekar et al., 2001). Three months of DR also protects against neuronal damage induced by occlusion of the middle cerebral artery (Yu and Mattson, 1999) and other types of neuronal stressors, including MPTP toxicity (Duan and Mattson, 1999). While these examples provided proof-of-principle that DR can lend protection in clinically relevant models, the long duration of the preconditioning period precluded any immediate practical translation to the clinic.

The first study to look specifically at the timing of onset of benefits of DR against surgical stress used models of ischemia reperfusion injury to the kidney and liver in mice (Mitchell et al., 2010). Two–four weeks of 30% DR or 1–3 days of 100% DR (water-only fasting) both ameliorate organ damage and dysfunction. Protection against death associated with renal failure is significantly reduced by as little as an overnight fast, while protection against organ dysfunction by fasting is dose dependent up to at least 3 days. Mechanistically, protection correlates with improved insulin sensitivity, reduced expression of insulin-like growth factor (IGF)-1, and increased expression of cytoprotective genes including hemeoxygenase 1 and components of the glutathione detoxification system (Mitchell et al., 2010).

While this was the first study to place fasting in a mechanistic framework shared by DR with regard to protection from ischemic injury, it was by no means the first to show benefits of fasting in the context of clinically relevant models of surgical stress. Early studies in a rat model of focal brain ischemia showed that 48 h of fasting prior to onset of injury reduces edema and neuronal necrosis in the striatum, neocortex and hippocampus (Marie et al., 1990). Mechanistically, utilization of ketone bodies was postulated to minimize lactic acidosis and its maladaptive neuropathological symptoms including seizures and mortality. In an isolated, perfused heart model of ischemia in rats, a 16 h fast protects against damage, measured by the release of cellular enzymes, and promotes functional recovery of heart rate and cardiac output following 15 min of total ischemia (Schneider and Taegtmeyer, 1991). In a rat model of liver transplantation following warm or cold ischemia, fasting of the donor animal for up to 4 days reduces organ damage and increases survival of the recipient for up to one week after transplantation. Interestingly, protection from warm ischemia by fasting increases in a dose dependent fashion for up to at least 3 days, while protection from cold ischemia is significant only after 4 days of fasting, consistent with a threshold-based model of protection (Sumimoto et al., 1993).

Although diets lacking essential macronutrients such as protein are incompatible with long-term survival, they can be used for up to 2 weeks to probe the nutritional basis of short-term DR. Two recent studies point to protein/essential amino acid deprivation as sufficient to induce protection from renal and/or hepatic ischemia reperfusion injury without restricting overall calorie intake. In one study, calories were supplied to mice for 3 days exclusively in the form of a saturated glucose solution (Verweij et al., 2011a). In the other study, mice had ad libitum access to chow lacking protein or a single essential amino acid (tryptophan) for 6–14 days (Peng et al., 2012). Both

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