Beneficial Effects of Mild Stress (Hormetic Effects):
Dietary Restriction and Health

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Abstract Hormesis is defined as a dose-response phenomenon characterized by low-dose stimulation and high-dose inhibition, and has been recognized as representing an overcompensation for mild environmental stress. The beneficial effects of mild stress on aging and longevity have been studied for many years. In experimental animals, mild dietary stress (dietary restriction, DR) without malnutrition delays most age-related physiological changes, and extends maximum and average lifespan. Animal studies have also demonstrated that DR can prevent or lessen the severity of cancer, stroke, coronary heart disease, autoimmune disease, allergy, Parkinson's disease and Alzheimer's disease. The effects of DR are considered to result from hormetic mechanisms. These effects were reported by means of various DR regimens, such as caloric restriction, total-nutrient restriction, alternate-day fasting, and short-term fasting. Mild dietary stress, including restriction of amount or frequency of intake, is the essence of DR. For more than 99% of their history, humans lived as hunter-gatherers and adapted to restrictions in their food supply. On the other hand, an oversufficiency of food for many today has resulted in the current global epidemic of obesity and obesity-related diseases. DR may be used, therefore, as a novel approach for therapeutic intervention in several diseases, when detailed information about effects of mild dietary stress on human health is obtained from clinical trials. *J Physiol Anthropol 29(4): 127–132, 2010* http://www.jstage.jst.go.jp/browse/jpa2 [DOI: 10.2114/jpa2.29.127]

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Dietary Restriction (DR) and Hormesis

The hormetic dose-response model is the most common and fundamental in the biological and biomedical sciences (Calabrese, 2008b). Hormesis is defined as a dose-response phenomenon characterized by low-dose stimulation and high-dose inhibition. This dose-response curve typically appears as an inverted U-shape or J-shape (Calabrese, 2008ab). Hormesis represents an overcompensation for mild environmental stress (Calabrese, 2001) and is the mechanism for adaptive responses to low doses of harmful environmental stimuli (Calabrese, 2008a). These harmful conditions include not only toxic substances, but also any environmental stimulus with potentially deleterious consequences for the organism, such as an increase or decrease in temperature. A stimulus that induces a beneficial hormetic response is called a mild stress (Le Bourg, 2009). Mild stress appears to slightly increase lifespan and to increase resistance to some stresses (Le Bourg, 2009).

Mild dietary stress (dietary restriction, DR) without malnutrition delays most age-related physiological changes and extends maximum and average lifespan in experimental animals (Weindruch and Sohal, 1997; Frame et al., 1998). The first evidence in rodents was reported by McCay et al. in 1935 (McCay et al., 1935). Since then, similar observations have been made in various species, including fish (Comfort, 1963), flies (Partridge et al., 1987), worms (Klass, 1977), and yeast (Lin et al., 2000). More recently, DR was reported to extend lifespan and increase disease resistance in primates (Colman et al., 2009). Lifespan extension by DR may occur in humans as well. In addition to lifespan extension, animal studies have demonstrated numerous beneficial effects of long-term DR. Long-term DR can prevent or lessen the severity of spontaneously occurring (Chen et al., 1990), chemically-induced (Birt et al., 1999), and radiation-induced neoplasia (Yoshida et al., 1997) in experimental animals. Chronic DR also reduces ischemic brain damage (Yu and Mattson, 1999) and protects the heart from ischemic injury (Ahmet et al., 2005). Furthermore, DR inhibits the development of autoimmune disease in several strains of mice (Kubo et al., 1992), and delays the onset and progression of spontaneous (Fan et al., 2001) and chemically-induced (Nakamura et al., 2004) allergic dermatitis. DR also increases resistance to neurotoxins in experimental models relevant to Parkinson's disease and Alzheimer's disease (Mattson et al., 2003). The DR-related increase in lifespan and protection against various diseases is likely mediated, in part, by hormetic mechanisms (Mattson, 2008).

Dietary Restriction (DR): Size or Frequency?

These beneficial effects of DR were reported using various regimens in experimental animals. One DR regimen, chronic energy intake restriction, is performed by restricting daily total calorie intake using defined diets (Johnson et al., 1986; Chen et al., 1990) and is also called calorie restriction. Long-term total-nutrient restriction is a method that restricts total daily nutrient intake (Lueker et al., 1956). In total-nutrient restriction, the amount of food provided is adjusted daily to represent 60–80% of the food consumption of paired animals fed ad libitum (AL) (Fan et al., 2001). In general experimental studies, food is provided once daily. When DR animals are provided with food, they eat all of it within approximately 1 hour. After that, animals have no access to food and are under fasting conditions for the next 23 hours (Kouda et al., 2009).

Another DR regimen is alternate-day fasting (also called "intermittent fasting" or "every-other-day fasting"), in which animals alternate between days where they are fed AL and days of fasting (Goodrick et al., 1990). In this regimen, mice subjected to alternate-day fasting consume essentially the same amount of food in a 48-h period as those fed AL and eat roughly twice as much as AL-fed mice on days they can access food (Anson et al., 2003). There is no difference in body weight between alternate-day fasting mice and AL-fed mice (Anson et al., 2003). Thus, alternate-day fasting is a restriction in the frequency of food consumption, but not the amount of food consumption. Shorter periods of DR are also effective in protecting against environmental stress. For example, two days of water-only fasting induces differential stress resistance against oxidative stress in mice (Raffaghello et al., 2008) and suppresses chemically induced allergy in mice (Nakamura et al., 2001).

Hormetic Mechanisms of Dietary Restriction (DR)

In mild dietary stress, both the amount and frequency increase lifespan and protect against various diseases, in part, by hormetic mechanisms that increase cellular stress resistance (Mattson, 2008). One of the hormetic mechanisms contributing to the beneficial effects of DR is an increase in *SIRT1* mRNA expression (Heilbronn et al., 2005a). *SIRT1* is a key regulator of many cellular defenses that allow survival in response to stress (Motta et al., 2004). The increased longevity induced by DR in yeast requires the activation of *Sir2p*, the homolog of mammalian *SIRT1* (Lin et al., 2000). DR promotes mammalian cell survival by inducing *SIRT1* (Cohen et al., 2004). It has been reported that three weeks of alternate-day fasting significantly increases expression of *SIRT1* in nonobese humans (Heilbronn et al., 2005a).

Increased levels of heat shock proteins (HSPs) by DR are considered another hormetic mechanism (Mattson, 2008). HSPs are stress proteins present in cells of all organisms, where they function as chaperones and play a crucial role in protecting cells from stress. HSPs are classified based on their molecular weight (e.g., hsp10, hsp40, hsp60, hsp70, hsp90) (Li and Srivastava, 2004). Caloric restriction has been reported to reverse the age-related decline in the induction of hsp70 transcription in rat hepatocytes (Heydari et al., 1993), and alternate-day fasting increases levels of Hsp70 protein in rat cortical synaptosomes (Guo et al., 2000).

It has been suggested that persistent glycolysis is deleterious due to the generation of methylglyoxal (Hipkiss, 2006). Methylglyoxal is formed predominantly from glycolytic intermediates, and rapidly glycates proteins and damages mitochondria. In a general DR regimen, food is provided once daily. When DR animals are provided with food, they eat all of it within approximately 1 hour. After that, animals are under fasting conditions for the next 23 hours (Kouda et al., 2009). Daily restricted animals are glycolytic for the first 12 hours after feeding and then obtain energy from fat metabolism during the subsequent 12 hours (Kouda et al., 2009), and glycolysis is suppressed (McCarter and Palmer, 1992). Consequently, it can be argued that the beneficial effects of DR are derived partly from the suppression of glycolysis (Hipkiss, 2006).

Humans and Obesity

Today, there are two serious problems concerning diet and health. The first is malnutrition (marasmus) due to serious food shortage. The second is obesity from overeating. The human lineage diverged from that of chimpanzees about 6 to 7 million years ago (Brunet et al., 2002). For more than 99% of its history, most humans lived as hunter-gatherers. They adapted to restrictions in their food supply (Zimmet and Thomas, 2003). In contrast, many people living in today's modern technological society can obtain more than enough food. The adoption of a regular intake of high-calorie foods has resulted in the current global epidemic of obesity (Zimmet and Thomas, 2003). Dietary patterns shift rapidly, particularly in the developing world, resulting in major shifts in obesity globally (Popkin and Gordon-Larsen, 2004).

Feeding Frequency and Obesity

Our ancestors could not eat three meals every day. They consumed meals much less frequently, and often consumed one large meal per day or went for several days without food. Thus, they were adapted to intermittent fasting and intermittent AL feeding (Mattson, 2005).

Despite the lack of strong scientific evidence, health care professionals believe that consuming smaller meals more frequently is healthier than consuming larger meals less frequently (Mattson, 2005). Indeed, several epidemiological studies have reported an inverse relationship between high meal frequency and obesity. However, a recent review of epidemiological studies concluded that the evidence is at best very weak, and almost certainly represents an artifact (Bellisle et al., 1997). Consistent with this, one randomized controlled

trial reported that meal frequency and a period of fasting have no major impact on energy intake in obese patients (Taylor and Garrow, 2001). Several important errors in the epidemiological studies have also been reported. The most important issue is dietary under-reporting in overweight people. Discrepancies between self-reported and actual caloric intake in overweight people can lead to artifacts in the results (Livingstone et al., 1990; Lichtman et al., 1992). The validity of meal frequency estimates in epidemiological studies is also very weak at best (Mattson, 2005).

Many observational studies report that breakfast frequency is inversely associated with obesity and chronic disease. Breakfast is considered the most important meal of the day. Most health care professionals believe, therefore, that skipping breakfast is a risk factor for obesity. However, this conclusion has important limitations. It has been reported that skipping breakfast demonstrates no substantial or significant association with mortality after multivariate adjustment (Wingard et al., 1982), and that the average total energy intake is significantly lower in children who skipped breakfast than children who consumed breakfast (Nicklas et al., 1993). Thus, not all studies associate skipping breakfast with obesity. Recently, one systematic review concluded that many observation studies have important limitations, that there are only four relatively small and short-term randomized trials, and that these studies concluded mixed results (Timlin and Pereira, 2007). Thus, the relationship between breakfast consumption and body weight is not well established (Rampersaud et al., 2005). To conclude an association between breakfast frequency and health, more well-designed work, such as randomized controlled studies or cross-over studies, is required in the future.

Intermittent Fasting in Humans

Fasting is obligatory for all healthy adult Muslims during the month of Ramadan. Ramadan fasting is intermittent, because food and water intake is permissible from sunset to dawn (Al Suwaidi et al., 2004). Body weight decreases slightly during this month. Ramadan fasting has been shown to reduce low-density lipoprotein (LDL) levels and increase high-density lipoprotein (HDL) levels (Lamri-Senhadji et al., 2009). The increase of HDL and apoprotein A1, and the decrease in LDL that occur with fasting can be beneficial for the cardiovascular system (Adlouni et al., 1997; Roky et al., 2004). The effects of alternate-day fasting in humans have also been reported: nonobese participants fasted from midnight to the subsequent midnight on alternating days for 22 days and lost 2.5% of their initial body weight and 4.1% of their initial fat mass (Heilbronn et al., 2005b).

Dietary Restriction (DR) for Future Clinical Use

Animal studies have shown that DR can prevent or lessen the severity of cancer (Chen et al., 1990), stroke (Yu and Mattson, 1999), coronary heart disease (Ahmet et al., 2005),

autoimmune disease (Kubo et al., 1992), allergy (Nakamura et al., 2004), and Parkinson's disease and Alzheimer's disease (Mattson et al., 2003). Thus, evidence is now strong for the association between DR and disease protection in experimental animals. However, there is a substantial shortage of information concerning the usefulness of DR as clinical therapy and disease prevention in humans. It is known that obesity in humans is related to diseases such as coronary heart disease, cancer, atherosclerosis, hypertension, and diabetes mellitus. DR is considered essential in clinical therapy for the prevention of obesity. On the other hand, evidence of the beneficial effects on human health is weak, except for obesity-related diseases. Recent epidemiological studies indicate that individuals with a low daily caloric intake have a reduced risk for Parkinson's disease (Logroscino et al., 1996) and Alzheimer's disease (Luchsinger et al., 1999). These epidemiological studies are consistent with the results of animal studies. Concerning inflammatory disease, a relationship between asthma and obesity has been suggested in several epidemiological studies (Story, 2007). In a clinical study, a low-energy diet reduced inflammatory symptoms and oxidative damage in patients with atopic dermatitis (Kouda et al., 2000). A case of a patient with atopic dermatitis and repeated one day fasting has also been reported (Nakamura et al., 2003). Furthermore, rapid and sustained beneficial effects of alternate-day calorie restriction in overweight adults with asthma have been recently reported (Johnson et al., 2007). These beneficial effects on allergic disease are consistent with the results of an animal study (Fan et al., 2001). Fasting (Kjeldsen-Kragh et al., 1991) and a low-energy diet (Iwashige et al., 2004) have been reported to be effective treatments for patients with rheumatoid arthritis. The effect of fasting was assessed in a randomized, single-blind controlled trial (Kjeldsen-Kragh et al., 1991). This beneficial effect on autoimmune disease is also consistent with the results of an animal study (Kubo et al., 1992). However, to demonstrate an evidence of clinical use, there are still few data about the DR and human inflammatory disease. Numerous well-designed clinical studies, such as randomized controlled studies or cross-over studies, are needed to obtain detailed information about the effects of mild dietary stress and human health.

Conclusions

In experimental animals, the beneficial effects of DR without malnutrition on disease prevention and lifespan extension have been studied for many years. Mild dietary stress, including restriction of amount or frequency of intake, is the essence of DR (hormetic effects). Lifespan extension by DR may occur in humans as well. DR may be used, therefore, as a novel approach for therapeutic intervention in several diseases, when detailed information about the effects of mild dietary stress on human health is obtained from clinical trials.

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