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The Effect Of Diet Variation On Health And Longevity In Humans And Model Organisms

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Abstract: ***Human longevity is a complex process that is affected by both environmental and genetic factors and interactions between them. Lifespan of any organism can be extended by reduction in diet taken. This is known as dietary restriction (DR), and that extension of lifespan by it is evolutionary conserved in organisms including yeast, insects, and mammals. The insulin/IGF like signaling (IIS) pathway has diverse function in all multicellular organisms, including body growth regulation and life span. For alteration in life span & body growth, dietary nutrients play a major role. Considerable interest has been shown in the ability of caloric restriction (CR) to improve multiple parameters of health and to extend lifespan. CR is the reduction of caloric intake - typically by 20 - 40% of ad libitum consumption - while maintaining adequate nutrient intake. Several alternatives to CR exist. Dietary restriction (DR) - restriction of one or more components of intake (typically macronutrients) with minimal to no reduction in total caloric intake - is another alternative to CR. Many religions incorporate one or more forms of food restriction. Although these facts carry the implication that the mechanisms of DR are also evolutionary conserved, extension of life span could be a case of evolutionary convergence, with different underlying mechanisms in different taxa. Furthermore, extension of lifespan by different methods of DR in the same organism may operate through different mechanisms. These topics remain unresolved because of the very fact that the mechanism of DR is unknown. Given these uncertainties, it is essential that work on the mechanism of DR is not clouded by imprecise description of methods or by technical problems.***

Keywords: Dietary restriction, Health, Longevity and Drosophila.

I. INTRODUCTION

Scientists have long been interested in what can be done to lengthen life span and to reduce the impact of age-related diseases. One area of research relates to nutrition. Food is a source of nourishment as well as delight, comfort, fuel and protection. However, in many people inappropriate choices in diets lead to metabolic imbalances, thereby enhancing the risk of diseases such as food allergies and intolerances, gastrointestinal disorders as well as atherosclerosis, obesity, type 2 diabetes, hypertension and inflammatory diseases. The genetic and phenotypic variation among humans is so wide that a diet that might be optimal for one individual could predispose another to disease. Although this fact has become increasingly evident as public health agencies attempt to address diseases stemming from metabolic dysregulation, the scientific knowledge necessary to generalize or better, to personalize, diets is far from being established.

The major energy resource of animals is fat, stored as triacylglycerols (TAG). TAG is deposited in intracellular lipid droplets of specialized organs like mammalian adipose tissue or fat body in *Drosophila*. These organs, together with the digestive tract and the central nervous system form an integrated molecular communication network that ensures

lifelong integrity of energy homeostasis in response to environmental variations by adjusting the organismal fat storage level to a genetically determined setpoint. Chronic imbalance of energy homeostasis contributes to the pathogenesis of obesity in mammals including human.

Environmental factors such as diet have a huge impact on longevity. Reducing levels of food by 30—50% has been shown to significantly extend lifespan and reduce age–related diseases in mice and rats. This led to the theory of Caloric Restriction (CR) – that by manipulating the nutrition of the organism, and limiting the access to or availability of calories, we can induce a lifespan extension phenotype in a wide range of organisms. Dietary restriction extends lifespan in species as diverse as yeast (Jiang *et al*., 2000), nematode worms (Braeckman *et al*., 2001), and flies (Pletcher *et al*., 2002), and it is the most powerful modulator of the aging process known in mammals (Masoro, 2005). With a few exceptions, dietary restriction has been applied in flies by concomitant manipulation of both sucrose and yeast (Pletcher *et al*., 2005) or by modulation of yeast at a single level of sucrose (Mair *et al*., 2005; Min & Tatar, 2006b). The integrative nature and opposing effects of dietary sugar and yeast suggest the possibility that the two dietary components may modulate lifespan and physiology through distinct mechanisms. Modulation of longevity by manipulation of dietary yeast does not require the transcription factor FOXO (Giannakou *et al*., 2008; Min *et al*., 2008), while components of the TOR pathway may be important.

So alterations in dietary sugar, yeast, or both modulate normal lifespan and physiology in *Drosophila melanogaster* in a manner that is significantly independent of their caloric content. Carbohydrates enhanced consumption in flies, while increased protein intake seemed to induce satiation. Alterations in ingestion alone, however, were not sufficient to compensate for the patterns of increased TAG and protein accumulation, both of which were dependent on diet composition.

Severely unbalanced diets appear to induce disease-like pathological states. For example, flies maintained on high sugar diets were generally obese even when they consumed a modest number of calories. They also displayed a shorter than expected lifespan and reduced fecundity, suggesting that longevity can be modulated by diet under non starvation conditions without necessarily increasing reproduction. Yeast-rich diets suppressed feeding and overall caloric intake, yet they also resulted in reduced lifespan. These flies were highly fecund indicating that a high protein diet is not overtly toxic.

Dietary conditions had significant impact on age-associated changes in physiology. Under most circumstances, the body composition of aging flies tended to remain relatively constant, with protein and fat levels holding steady or modestly decreasing throughout life (Johnson & Butterworth, 1985). Transcriptional changes with age in these conditions support the notions that extremely old flies experience moderate to severe starvation and that aging in *Drosophila* is accompanied by a loss in metabolic efficiency, feeding rate, or both (Pletcher *et al*., 2005). Flies exposed to a high-glycemic (sugar) diet exhibited enhanced fat storage when young and significant age-associated obesity including an age-dependent increase in TAG levels of up to 200–300%, which appeared to result from a combination of physiological and behavioral changes. The complex effects that nutritional components have on body composition, behavior, and lifespan in flies provide a broad perspective for investigating the mechanisms of dietary restriction.

II. DIETARY COMPOSITION INFLUENCES AGE-DEPENDENT OBESITY IN DROSOPHILA ALTERS LONGIVITY

The impact of diet on human health has a strong age-dependent component, as alterations in physiology lead to increased accumulation and redistribution of adipose tissue and enhanced risk of cardiovascular and other aging-related diseases (Chumlea *et al*., 2002). Having observed deleterious effects on lifespan associated with consumption of unbalanced diets, these diets induce long-term changes in overall TAG levels. Due to practical considerations, we were unable to measure age-dependent changes dietary regimes. We therefore chose the most extreme treatments and subjected flies to a 3 × 3 matrix of varied sugar and yeast concentrations throughout their lifespan (yeast and sugar concentrations of 2.5 g·dL–1, 10 g·dL–1, and 40 g·dL–1). Females were harvested after 13, 26, 40, and 52 or 56 days of age. TAG and protein levels were measured as previously described. The most striking age-dependent pattern was observed in flies maintained in high-sugar diets, where the propensity for fat storage was magnified by age. While normal-to-low-nutrient concentrations resulted in a roughly constant loss of TAG with age, flies maintained on a sucrose-rich diet (2.5 g·dL–1 yeast/ 40 g·dL–1 sugar) exhibited nearly twofold increase in TAG stores at 13 days of age and a further twofold increase by 40 days (Figure 1). This effect contrasts with that previously observed (and replicated here) in dietary restriction experiments by food dilution where flies maintained on a balanced diet experienced age-induced weight and TAG loss (Johnson & Butterworth, 1985). Very old flies (52 or 56 days of age) lost significant amounts of TAG during the latter part of their lives, even on the pro-obesity diets, during a time when they also tend to lose body weight (Bross *et al*., 2005).

The total energy available from food consumption is directed by nutrient-dependent signaling mechanisms into three sinks: (i) *reproduction*, (ii) *somatic maintenance*, and (iii) *energy storage*. Dietary yeast promotes reproduction and inhibits TAG storage, while dietary sugar inhibits egg-laying and promotes adiposity. It is well established that increased reproduction limits lifespan. While the impact of adiposity *per se* on aging is currently of some debate, diversion of substantial resources to either reproduction or storage limits their availability for programs of somatic maintenance. In low-protein/high-carbohydrate diets, overconsumption is driven by strict regulation of protein levels, reproduction is strongly suppressed, and the absence of cues from dietary yeast activates storage programs. Flies become obese and short-lived (Fig. 1A). In high-protein/low-carbohydrate diets, dietary yeast stimulates high levels of reproduction, while reduced carbohydrates inhibits storage and de-represses reproduction, which draws the majority of resources away from maintenance. Flies are very lean but also short-lived

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(Fig. 1B). The addition of carbohydrates to this diet – which essentially *adds* caloric value – *increases* lifespan by suppressing reproduction, promoting moderate levels of storage, and freeing resources for somatic maintenance.

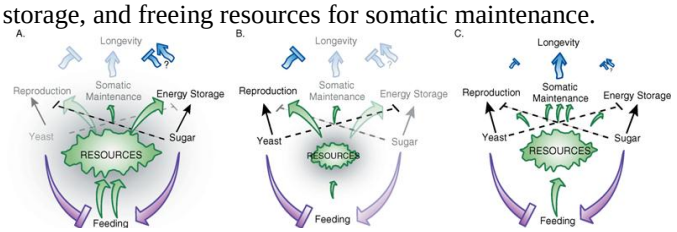

Figure 1

Figure 1. Dietary components may influence life strategies through their energetic and signaling characteristics. We propose a working model whereby the total energy available to an animal may be diverted towards reproduction, somatic maintenance and/or storage processes. Each of these three energy decisions interacts and harbors an inherent physiological impact on the organism that determines lifespan. Although both yeast and sugar consumption increase the total resources available, cues from high yeast diets drive reproduction and suppress mechanisms of somatic maintenance while cues from high sugar diets preferentially drive energy storage.

(A) In a low-yeast/high-sugar environment resources are strongly diverted towards energy storage, resulting in obesity and reduced longevity.

(B) In a high-yeast/low-sugar environment, reproduction is simultaneously stimulated (high protein) and de-repressed (low sugar), resulting in very high levels of reproduction that leave few resources for somatic maintenance.

(C) Lifespan is optimized on a balanced diet as the interaction between cues from each dietary component maintain energy balance allowing sufficient resources for reproduction, energy storage, and somatic maintenance.

III. FOOD DILUTION(DR) REDUCES THE REPRODUCTION(FECUNDITY) IN FLIES

If egg-laying increases with food supply, then it is reasonable to deduce that nutrient intake is increased. In combination with lifespan, egg-laying can indicate if food toxicity might be the cause of lifespan shortening, the argument being that if a fly does not increase its egg-laying for nutrient level increases that decrease lifespan, the food may be having a general toxic effect. For DR therefore, each increase in nutrient concentration that leads to a reduction in lifespan should be accompanied by an elevation in daily and lifetime fecundity (Figure 2). At the very least, this ensures that dietary types that are used for DR do result in increased nutrition over the range tested. A further test for food toxicity could be made using behaviour assays such as negative geotaxis [34] on young flies. Since the quality of industrially produced yeasts is dependent on the production method and seasonal quality of the feedstock, it is important that laboratories empirically determine whether they are working with yeast that is not toxic to flies. Unfortunately, not all studies have taken this precaution For instance, some work on the effects of dietary lipids on lifespan was performed without any simultaneous measure of egg laying or activity, thus making it impossible to know if increased food supply was in fact associated with increased nutrition, or if the short lifespans associated with elevated lipid supply were due to a nutritional effect or instead due to toxicity of the lipid sources added.

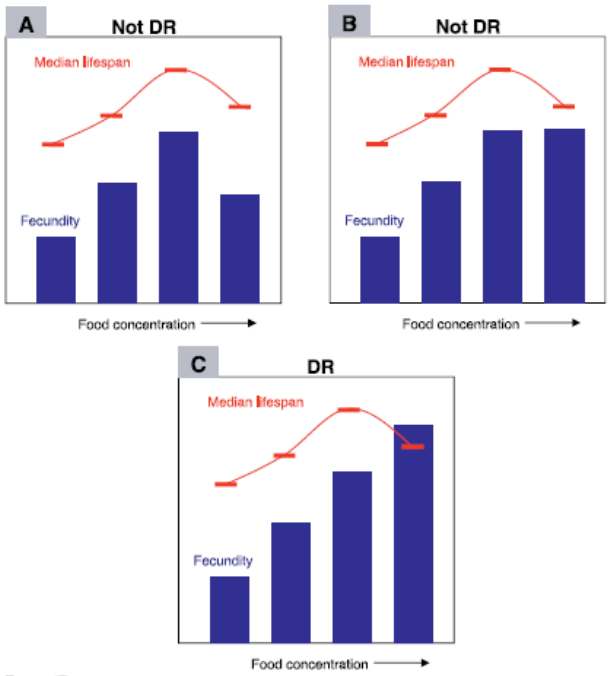

Figure 2

Figure 2. The Responses of Lifespan and Fecundity to Food Concentration That Is Required for DR Studies in *Drosophila* As food concentration increases from starvation, lifespan should increase to a peak at DR, from which it declines due to a nutrient-dependent effect of ‘‘high’’ food. If fecundity decreases (Figure 2A) or is unchanged (Figure 2B) by the nutrient increase that decreases lifespan, the most likely explanation for shortened lifespan is toxicity. To minimize the possibility that food toxicity is the explanation for the lifespan shortening at high food concentrations, it is important that daily and lifetime fecundity increase for the increases in food concentrations that decrease lifespan (Figure 2C).

IV. HIGH-SUGAR FEEDING RESULTED IN INSULIN RESISTANCE

As a first step towards identifying the cause of hyperglycemia in high-sugar-fed larvae, two phenotypes that are dependent on insulin signaling: developmental rate and larval size are examined (Chen et al., 1996; Bohni et al., 1999; Shingleton et al., 2005). In the fly life cycle, larvae hatch from eggs and eat continuously, stopping only to molt twice after first instar (L1) and second instar (L2) stages. At 5-6 days after egg laying, third instar (L3) larvae leave the food and ‘wander’ as they prepare to undergo metamorphosis into the adult fly. Despite eating more calories, wild-type wandering L3 larvae raised on high-sugar, or highfat or high-protein diets were reduced in size, with the greatest decrease in size observed for the high-sugar-fed animals. Adults reared on high-sugar food were also smaller than those reared on control food (data not shown). The decreases in both size and rate of larval development of the high-sugar-reared animals

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resembled those observed in mutations that reduced insulin receptor activity (Chen et al., 1996; Shingleton et al., 2005) or in IPC-ablated flies (Rulifson et al., 2002). Strikingly, high-sugar feeding resulted in a dramatic delay of 3-5 days in larval developmental rate when compared with those reared on control food. For the delay in the rate of development, the carbohydrate requirement was not strict, because glucose, fructose and maltose all produced similar results; supplementary material. Of note, the disaccharides were present at half the osmolarity of the monosaccharides (1.0 vs 2.0 M), and thus the osmolarity of the food probably did not contribute to the delays observed on high sugar. To confirm that the phenotypes observed in larvae reared on elevated sucrose concentrations were not due to protein deficiency, we restored the protein composition of the diet to provide the same amount of protein per animal. This did not rescue any sugar-induced phenotypes. Of the high-calorie diets, high-sugar feeding had the most striking effects on hyperglycemia, larval size and developmental rate, and we focused on this diet for the remainder of our studies. Except where noted, wandering L3 larvae were used to examine persistent physiological changes resulting from the high-sugar diet. At this stage, larvae have reached maximal size and are no longer feeding. Both insulin-deficient and insulin-resistant *Drosophila* exhibit growth defects, because the insulin signaling pathway serves both insulin- and IGF-like functions in the fly (Baker and Thummel, 2007). We examined whether high-sugar feeding led to either insulin deficiency or peripheral insulin resistance. To assess IPC integrity, we raised *DILP2-GAL4, UAS-GFP Drosophila* on control or high-sugar food. No significant change in the number or morphology of IPCs was observed. However, expression of multiple genes encoding DILPs increased after chronic highsugar feeding, suggesting that larvae attempted to compensate for the increased glycemic load by increasing DILP levels. Because insulin secretion by IPCs has been shown to be controlled by diet (Geminard et al., 2009), we evaluated the levels of circulating DILP using *DILP2-GAL4, UAS-DILP2-FLAG* larvae.

Increased levels of FLAG-tagged DILP2 were found in the hemolymph of high-sugar-reared larvae compared with larvae raised on control food. These data demonstrated that the hemolymph of high-sugar-reared larvae was not insulin deficient, and suggested that a central defect upon high-sugar feeding was peripheral insulin resistance.

V. CALORIC RESTRICTION AND HUMANS

It is difficult to definitively answer whether or not CR prolongs human life because of the ethical and logistical mitations of research design. Rather than measuring longevity directly, most human CR studies measure biomarkers correlated with longevity. Collectively, these studies have noted favorable changes in multifarious biomarkers, particularly those related to cardiovascular and glucoregulatory function.

Numerous studies have found that CR improves cardiovascular and glucoregulatory health. Specifically, CR may reduce the risk of cardiovascular disease by lowering total cholesterol, triglycerides, blood pressure, and carotid intima-media thickness. CR also has been shown to attenuate the age-related decline in diastolic function. Regarding glucoregulatory health, circulating insulin and glucose levels decrease - while insulin sensitivity increases - following a period of CR. CR has also been shown to attenuate oxidative stress, a condition thought to contribute to aging and disease. In addition, enhanced verbal memory performance has been reported in elderly individuals on a CR regimen as assessed by the Rey Auditory Verbal Learning Task. Unfortunately, CR does not appear to retard the age-related loss of bone and muscle mass.

VI. RELIGIOUS FASTING AND HUMANS

Several religions place one or more of the following restrictions on food consumption: 1) the types of foods permitted for consumption in general or during particular times of the year; 2) the time of day when food consumption is permitted; and 3) food preparation [34]. These types of restrictions can either persist year-round or be active only during special fasting periods. Fasting has various advantages for body. Body uses quite a bit of energy to digest food, and when fasting this energy become obtainable for further uses. In the fasting state, the body cleanses for dead cells, damaged tissues, fatty deposits, eruptions, all of which are burned for energy or barred as waste. The elimination of these obstructions restores the immune system functionality and metabolic process to an optimum state. Fasting restores good digestion and elimination, and peristaltic action is quickened. Fasting allows a deep, physiological rest of the digestive organs, and the energy saved goes into self-healing and self-repairing. By eliminating obstructions, by cleansing, detoxification, and purifying the intestines, the blood, and the cells, we can overcome many of our physical ills as well as get a boost in energy. Fasting not only removes obstructions and helps the body to heal itself; it is also rejuvenating and life-extending. These resulting benefits can have lasting affects in your mental and emotional health.

VII. OVERALL SUMMARY AND CONCLUSIONS

CR has been demonstrated to extend the maximal lifespan of a diverse group of species. This extension of life is maximized when: 1) the magnitude of CR is elevated to the highest possible value before inducing malnutrition and 2) the duration of CR is maximized. Animals on CR regimens exhibit a variety of improvements in overall health in general and cardiovascular health in particular. Unfortunately, the likelihood of discovering whether or not CR extends human life is rather remote due to the ethical and logistical limitations of research design. The optimal magnitude and duration of CR for humans will also likely never be known for the same reason. Nonetheless, many human CR studies have noted favorable changes in biomarkers related to cardiovascular and glucoregulatory function, which likely relate to quality of life and may relate to longevity.

This paper has touched on some of the numerous methods of restricting dietary intake. Whether one chooses to restrict energy intake daily, fast every other day, restrict intake of a particular macronutrient, or fast for religious purposes, I hope that this study can serve as a valuable tool to understanding the ability of dietary modification to improve overall health and the quality of life. Furthermore, I hope that this information will fuel the development of new ideas and research studies focused on investigating the health benefits of caloric and dietary restriction.

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