PHYSIOLOGY

Dietary Restriction in Long-Lived Dwarf Flies

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Interventions that slow down aging provide invaluable insights into its causes. But do they act upon common underlying mechanisms? Recent work with a long-lived mutant mouse, the Ames dwarf, showed that its life-span could be further extended by another intervention, dietary restriction, in which food intake was restricted to about 70% of voluntary levels (*1*). This finding was taken to demonstrate that the Ames mutation and dietary restriction slow aging by different mechanisms, because the Ames mutation and dietary restriction do not mask each other's effect on life-span. Using the fruit fly *Drosophila*, we show here that (i) slowing of aging by a mutation in an insulin/insulin-like growth factor (IGF)–like signaling (IIS) pathway and by dietary restriction occurs by overlapping mechanisms and (ii) life-span must be maximized by at least one of the interventions under investigation for a proper test of the hypothesis that the mechanisms of life-span extension differ.

Mutations that reduce IIS extend life-span in the nematode worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster* (*2*). The *chico*^{1} mutation in the IIS pathway in *Drosophila* produces dwarf, long-lived females at normal nutrition (*3*). Dietary restriction slows aging in organisms ranging from yeast to mammals (*4*), probably including primates (*5*). In rodents, extension of life-span by dietary restriction has been suggested to be attributable to reduced caloric intake. Dietary restriction by food dilution slows aging in *Drosophila*, with life-span of wild-type females increasing to a peak under dietary restriction as the food is diluted and then dropping with further dilution, presumably as a result of starvation (*6*). At least part of the response may be attributable to dilution of yeast in the diet (*7*). If *chico*^{1} extends life-span by an overlapping mechanism with dietary restriction, then we would expect the relation between life-span and nutrition to be different in *chico*^{1} and control flies. *chico*^{1} flies should behave as though they are already to some extent subjected to dietary restriction. They should therefore be more prone than controls to starvation at low levels of nutrition. At the food dilution that maximizes control life-span, *chico*^{1} flies would be malnourished and less long-lived. Life-span of *chico*^{1} females should peak at a higher food concentration than that of controls does, and at this and higher food concentrations, the *chico*^{1} females should be longer lived than controls.

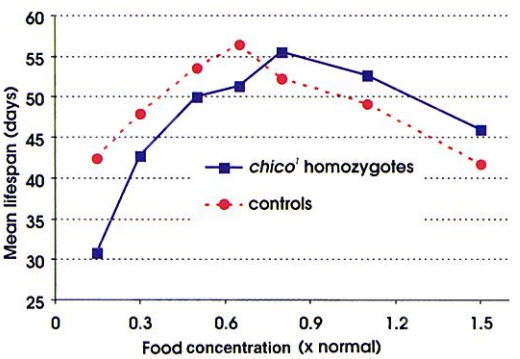

Fig. 1. Interaction between dietary restriction by food dilution and reduced IIS in the determination of mean life-span. *chico*^{1} was back-crossed six times into the Dahomey genetic background. Females were reared at standard low density on normal (1.0 times normal) food, collected as virgins, maintained at 10 adults per vial, and transferred to fresh vials and scored for deaths every 2 to 3 days.

We therefore measured the life-span of *chico*^{1} and control flies over a range of food concentrations (Fig. 1). As predicted, the relation between life-span and food concentration was right-shifted in the *chico*^{1} females. Control and *chico*^{1} females showed similar peak life-spans under dietary restriction, but the food concentrations at which these were achieved were different, with *chico*^{1} females peaking on 0.8 times food and controls on 0.65 times food. This shows that *chico*^{1} did not extend life-span beyond the maximum that can be achieved by dietary restriction alone and that, for maximization of life-span, *chico*^{1} flies required a higher level of nutrients than did controls. At the food concentration that maximized wild-type life-span (times 0.65), *chico*^{1} females were significantly shorter lived ($P = 0.0236$, log rank test). At all food concentrations below 0.65, *chico*^{1} females were significantly shorter lived than controls, whereas at all concentrations above 0.8, they were significantly longer lived ($P < 0.001$ in all cases). Taken together, these results demonstrate that *chico*^{1} induces a state equivalent to submaximal, dietary restriction–induced slowing of aging. These two pervasive interventions that slow aging therefore act through overlapping mechanisms.

Had we not maximized life-span by dietary restriction in these experiments, we could have reached an incorrect conclusion. For instance, the life-span of *chico*^{1} females is extended by dietary restriction in the 0.85 to 1.5 range of food concentrations, as was the life-span of the Ames dwarf mice by dietary restriction (*1*). However, this finding taken alone does not lead to the conclusion that these two interventions act by nonoverlapping mechanisms. If life-span has not been maximized by one intervention, then a further increase in life-span may be seen when the other is added, even if they do operate through overlapping mechanisms.

The nature of the mechanisms by which *chico*^{1} acts like dietary restriction requires further analysis. The mutation may reduce nutrient sensing, food uptake, or nutrient uptake in target tissues. Alternatively, reduced IIS and dietary restriction may interact in determination of life-span because they both alter some common downstream process. Identifying the common pathways at work should do much to increase our understanding of the pervasive amelioration of the aging process by these two interventions.

References

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