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Action of food restriction in delaying the aging process

(longevity/metabolic rate/lifetime caloric expenditure/life prolongation)

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ABSTRACT **Food restriction has long been known to prolong life in rodents, and recent studies have shown it to have antiaging effects in regard to a variety of physiologic and pathologic processes. It has been suggested that these actions of food restriction relate to the reduction of metabolic rate per unit of body mass brought about by this dietary regimen. Data are presented in this report showing that food restriction can have a marked life-prolonging action in rats without reducing caloric intake per gram of body weight. Moreover, the food-restricted rats consumed a greater number of calories per gram of body weight during their lifetimes than did the rats fed ad lib, yet they lived longer. Thus, the data in this report do not support the concept that food restriction slows the rate of aging by decreasing the metabolic rate.**

In his 1977 review surveying life-prolonging experimental procedures, Sacher (1) concluded that the well-established life-prolonging antiaging action of food restriction in rodents is due to a reduction in the rate of metabolism per unit of body mass. Sacher based this conclusion on an analysis of data from a study performed by Ross (2) in which rats were provided five different dietary regimens resulting in caloric intakes ranging from 18 to 75 kcal/day. The average survival times varied among groups (ranging from 780 to 990 days) and were found to be inversely correlated with the daily caloric intake of the rat. However, when Sacher (1) calculated total caloric intake during the life span per gram of body weight, he found that it was almost the same for each of the five dietary regimens; the average was 102 kcal/g of body weight, and none of the means for the five dietary groups differed from the average by more than 4.5%. Thus, the lifetime caloric consumption per gram of body weight was nearly constant; this indicates that food restriction prolongs life by increasing the time required to reach this total.

Research just completed in our laboratory on the effects of food restriction on specific pathogen-free male Fischer 344 rats does not support the conclusion of Sacher regarding the basis of the life-prolonging action of food restriction. In our study, food restriction markedly prolonged the length of life, slowed the progression of age-related disease, and delayed age-related physiological deterioration but did not influence caloric intake per gram of body weight in the manner predicted by Sacher. The details of our research in regard to longevity and age-related disease have been published elsewhere (3), and the data on the effects of food restriction on age-related physiological deterioration have been recently reviewed (4). The data on the relationship between food restriction and total life-span caloric intake per gram of body weight are the subject of this report.

MATERIALS AND METHODS

Male, specific pathogen-free Fischer 344 weanling rats (28 days old), purchased from Charles River Breeding Laboratories, were singly housed in bonneted cages in our barrier facility. For the first 2 weeks, all rats were fed ad lib a semisynthetic diet with a caloric composition of 21% protein/57% carbohydrate/22% fat; a detailed description of this diet has been published elsewhere (5). At age 6 weeks, 230 rats were randomly selected for the longevity study; 115 (called group A) continued to be fed ad lib, and 115 (called group R) were fed ≈60% of the mean amount of diet consumed by the group A population. Both groups were fed the diet of the composition just described with the exception that the vitamin concentration was increased in the diet for the group R rats in order to provide both groups the same vitamin intake.

The amount of food eaten by the group A rats was measured for 3 or 4 days in rotating groups of 40 rats; thus, the weekly food consumption of group A rats was calculated from the data obtained on 80 group A rats. On the basis of this calculation, the group R rats were fed 60% of the intake of the group A rats, in daily allotments.

The specific pathogen-free status of the rat population maintained in the barrier facility was monitored in the following manner. Sera from eight rats sacrificed immediately after arrival and from five rats during the first year of the study were submitted to Microbiological Associates (Walkersville, MD) for the serologic detection of rat and mouse viruses. Fresh tissues from the same rats were also submitted for identification of *Mycoplasma pulmonis* with PPLO agar. Fixed lung tissue from both sacrificed rats and those dying spontaneously were examined for lesions, particularly those that might be caused by *Mycoplasma pulmonis*. In addition, a broad survey of microbiological contamination was carried out on a weekly basis; culture swabs were made on equipment, cages, bonnets, food, and drinking devices, to detect fungi, aerobic bacteria, and anaerobic organisms. The findings of these tests indicate that the specific pathogen-free state was maintained and that the rats were free of *Mycoplasma pulmonis* infection.

RESULTS

The detailed results of the longevity study, which have been published elsewhere (3), can be summarized as follows: the mean, median, and maximum length of life of the group A rats expressed in days were 701 ± 10, 714, and 963, respectively, and of the group R rats were 986 ± 25, 1,047, and 1,435, respectively.

Table 1 contains the data on food intake by the group A and group R rats from age 6 weeks until the mean length of life for each group. The striking finding is that beyond age 3 months, group R rats consume as much or more food per gram of body weight as do group A rats. Although the data in Table 1 are terminated at the mean length of life, this represents almost all of the life span of all of the rats because of the rectangular shape of the survival curves of group A and group R rats (3). Indeed, extending the analysis to the 90% mortality/10% survival point does not change the nature of the results.

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Table 1. Food intake from age 6 weeks to the end of the mean length of life of groups A and R rats*

Age range, mo	Rats fed ad lib (group A)			Rats fed restricted diet (group R)		
	Mean food intake,† kcal/day	Mean body wt,‡ g	Food intake/ g body wt, kcal/g/day	Food intake, kcal/day	Mean body wt,‡ g	Food intake/ g body wt, kcal/g/day
1½–2	41.4	142	0.29	26.2	109	0.24
2–3	47.6	216	0.22	28.3	132	0.21
3–4	49.6	284	0.17	28.7	164	0.18
4–5	44.7	325	0.14	29.1	187	0.16
5–6	53.3	353	0.15	30.8	203	0.15
6–7	52.5	376	0.14	30.8	215	0.14
7–8	57.0	393	0.15	33.6	221	0.15
8–9	55.4	410	0.14	33.2	228	0.15
9–10	56.2	427	0.13	34.0	234	0.15
10–11	54.1	444	0.12	34.4	241	0.14
11–12	59.0	460	0.13	34.0	247	0.14
12–13	64.0	475	0.13	34.9	253	0.14
13–14	58.6	489	0.12	34.9	258	0.14
14–15	63.1	503	0.13	35.3	263	0.13
15–16	62.3	517	0.12	36.1	268	0.13
16–17	63.1	531	0.12	36.5	274	0.13
17–18	66.0	545	0.12	37.3	279	0.13
18–19	65.6	544	0.12	38.1	284	0.13
19–20	66.4	530	0.13	39.0	288	0.14
20–21	64.0	516	0.12	39.0	292	0.13
21–22	60.3	502	0.12	39.0	297	0.13
22–23	59.4	488	0.12	39.0	301	0.13
23–24	—	—	—	39.0	306	0.13
24–25	—	—	—	39.0	308	0.13
25–26	—	—	—	39.0	308	0.13
26–27	—	—	—	39.0	308	0.13
27–28	—	—	—	39.0	308	0.13
28–29	—	—	—	39.0	308	0.13
29–30	—	—	—	39.0	308	0.13
30–31	—	—	—	39.0	305	0.13
31–32	—	—	—	39.0	299	0.13
32–33	—	—	—	39.0	292	0.13

* The number of group A rats was 115 at 1.5 mo, 114 at 6 mo, 114 at 12 mo, 102 at 18 mo, and 64 at the end of the mean length of life (701 days); the number of group R rats was 115 at 1.5 mo, 115 at 6 mo, 110 at 12 mo, 105 at 18 mo, 98 at 24 mo, 81 at 30 mo, and 69 at the end of the mean length of life (986 days).

† Mean food intake for group A rats was determined as follows: Food intake was measured for 3 or 4 days in rotating groups of 40 rats. This measurement was made continuously throughout the month. The mean monthly food intake per rat was calculated from the data collected in this way during that month.

‡ Mean body weight (wt) was assumed to change in a linear fashion between 1.5 and 2 mo, 2 and 3 mo, 3 and 4 mo, 4 and 6 mo, 6 and 12 mo, 12 and 18 mo, 18 and 24 mo, 24 and 30 mo, and 30 and 36 mo. Random checks of the raw data establish this assumption to be sufficiently correct for our purposes.

Body fat averaged 15% of body weight in group A rats and 10% of body weight in group R rats during the time spans recorded in Table 1 (5). Calculations based on these data show that group A and group R rats have almost the same food intake per gram of lean body mass.

Because the rate of caloric intake per gram of body weight is the same in group A and group R rats, similar lifetime caloric intakes per gram of body weight would not be expected. Indeed, calculation of caloric intake per gram of body weight per lifetime (based on the mean length of life for each group but excluding the first 6 weeks of life, when both groups have similar weights and caloric intakes) yielded a value of 91.5 kcal for group A and 133.5 kcal for group R rats.

DISCUSSION

The concept of Sacher (1) that food restriction prolongs life by reducing metabolic rate per unit of body mass was based on a reduced rate of food intake per gram of body weight of the food-restricted rats and similar life span caloric intakes per gram of body weight for rats fed ad lib or restricted diets. To draw such a conclusion, Sacher (1) assumed that most of the caloric materials ingested by the rats was absorbed and almost totally utilized as fuel. The validity of this assumption is difficult to establish unequivocally. In our study, it appears to be sufficiently valid for this assessment to be made because: (*i*) calculations based on weight gain, body fat content, and food intake between age 6 weeks and the remainder of the mean length of life indicate that <3% of the calories ingested are stored by group A and group R rats; and (*ii*) when rats are fed semisynthetic diets with compositions like that fed in our study, almost all of the ingested caloric materials are absorbed (6).

Food restriction in our study did not cause a reduction in caloric intake per gram of body weight. Moreover, the restricted rats in our study consumed a greater number of calories per gram of body weight during their lifetime than did the rats fed ad lib, yet they lived longer. Therefore, our data do not support the concept that food restriction slows the rate of aging

by decreasing the rate of energy metabolism.

There are several possible reasons for the discrepancy between our findings and those of Sacher (1). First, Sacher may have made an inappropriate choice of data from the Ross paper (2) for his calculations because a different choice of data (and to our way of thinking, a more logical one) would have yielded results similar to ours. The basic problem resides in the fact that the paper of Ross, like those of others (7–10), was not designed to provide data for this kind of calculation. Moreover, even though Sacher found the lifetime energy intake per gram of body weight to be similar for each of the dietary regimens used by Ross, he did note that the data suggested the possibility of a positive correlation between this parameter and longevity. Another possible factor relates to the use of two different strains of rat (the Sprague–Dawley strain in the Ross study and the Fischer 344 in ours). Sprague–Dawley rats fed ad lib tend to become obese, whereas Fischer strain rats remain lean (11); this difference could greatly influence the results when expressed per gram of body weight because food-restricted rats of both strains are likely to be similarly lean. Finally, the study of Ross involved very severe restriction of calories (≅25% of the ad lib intake), whereas our study used a moderate restriction (≅60% of the ad lib intake), and this could be responsible for the difference in results.

Although our findings indicate that the total rate of fuel flux per gram of body weight is probably not the basis for the antiaging action of food restriction, they do not rule out a metabolic basis for this life-prolonging regimen. For example, food restriction may well influence the quantitative distribution of fuel use amongst different tissues or metabolic pathways, or both; its antiaging effect may relate to such action. Indeed, it is almost certain that food restriction is coupled to the aging process by metabolic events, but total fuel flux per gram of body weight appears not to be an obligatory component of this coupling.

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