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Source of Dietary Carbohydrate Affects Life Span of Fischer 344 Rats Independent of Caloric Restriction

Carol M. Murtagh-Mark,[1] Karen M. Reiser,[2] Robert Harris, Jr.,[3] and Roger B. McDonald[1]

Departments of [1]Nutrition, [2]Medicine, and [3]Veterinary Pathology, University of California, Davis.

Previous investigations suggest that increased life span of calorie-restricted rodents is a function of caloric intake rather than the macro- or micronutrient composition of the diet. However, the dietary source of carbohydrate has not been widely investigated. We hypothesized that the dietary carbohydrate source may affect the life span of rats independent of caloric restriction. This hypothesis was tested in male Fischer 344 rats fed ad libitum or restricted to 60% of ad libitum, an isocaloric diet containing 14% protein, 10% fat, and 66% sucrose or cornstarch. Body weights of the ad libitum- and restricted-fed sucrose rats were consistently greater throughout the experimental period compared to diet-matched animals. Food intake did not differ significantly. The survival curves of ad libitum starch- vs sucrose-fed rats were significantly different. That is, the mean, median and upper 10th percentile survival were significantly greater in the ad libitum starch- vs sucrose-fed rats (mean life span: cornstarch-fed, 720 ± 23 days; sucrose-fed, 659 ± 19 days). Calorie-restricted starch-fed rats had poorer early life survival, and no significant increase in mean life span compared to ad libitum cornstarch-fed animals (726 vs 720 days). These animals did, however, have the greatest upper 10th percentile survival of all four experimental groups. Mean life span of calorie-restricted sucrose-fed rats was significantly greater than that of all other groups (890 ± 18 days). The differences in survival rates between sucrose- and cornstarch-fed animals could not be attributed to the effects of carbohydrate source on body weight, energy absorption, or on the timing and severity of the pathological lesions normally associated with aging and/or caloric restriction in this species. These data support the hypothesis that the dietary source of carbohydrate, i.e., sucrose vs cornstarch, can significantly affect life span independently of caloric intake.

SEVERAL investigations have established that caloric restriction increases the life span of rodents (Snyder, 1989). Although the mechanism(s) responsible for the increase in life span of calorie-restricted animals has yet to be elucidated, it has been generally accepted that life span enhancement is related to caloric density rather than the nutrient composition of the diet (Masoro et al., 1991). For example, reduction in the percent fat and mineral component of diets given to ad libitum-fed rats does not significantly affect life span (Iwasaki et al., 1988). Yu et al. (1985) observed that, while lowering the protein content of the diet in ad libitum-fed rats slightly increased median and maximal life span, the effect was enhanced when combined with caloric restriction. Few investigations, however, have focused on the effect that altering the dietary source of carbohydrate may have on longevity.

To our knowledge, only one study has reported the effects of feeding dietary sucrose on life span. In an investigation designed to study the long-term effects of sucrose on taste preference and food intake patterns, Smith and Wilson (1989) reported that male F344 rats fed a chow diet ad libitum and provided sucrose in the drinking water (0.062, 0.125, 0.25, 0.50, and 1.0 M) did not have significantly different life spans compared to rats given chow and water without sucrose. However, some aspects of the diet and feeding protocol used by Smith and Wilson (1989) limit the interpretation of their data and their conclusions concerning the effects of sucrose on life span. First, the source of complex carbohydrate (i.e., wheat, corn, barley, etc.) used in chow diets can vary considerably among batches, and thus the type of starch eaten by these rats was not controlled. This is an important consideration because intestinal absorption rates of dietary starches are not equivalent (Gray, 1992). Second, the combination of chow feeding and sucrose-supplemented water provided a diet with varying degrees of caloric density. In order to effectively evaluate the effect of sucrose vs other types of carbohydrates on life span, the diets should be isocaloric.

In other long-term feeding studies, ad libitum feeding of dietary sucrose has been observed to markedly increase the incidence of renal basement membrane and retinal vasculature pathology (Cohen and Rosenmann, 1971; Papachristodoulou and Heath, 1977; Dyer et al., 1991). These pathological lesions are, in some respects, similar to the renal and retinal lesions found in the aging male F344 rat. Based on these data, we postulated that a lifetime of feeding diets high in sucrose content might, in fact, be associated with a decreased life span in comparison to other carbohydrate sources. We specifically hypothesized that a lifetime of feeding dietary sucrose vs cornstarch will accelerate the development of pathological lesions, most notably renal pathology, and hence shorten life span.

The purpose of the investigation presented here was to evaluate the interaction between varying the source of dietary carbohydrate and caloric restriction on longevity in male F344 rats. To this end, we measured survival rates of male F344 rats fed ad libitum or 60% of ad libitum an isocaloric diet containing either sucrose or cornstarch as its carbohydrate source. In addition, bioavailable energy of the diets, pathological lesions in rats dying spontaneously, and probable cause of death were evaluated.

Materials and Methods

Animals and animal care. — Approximately 180 male inbred F344 rats age 21 days were obtained from Harlan

Sprague Dawley Laboratory (Indianapolis, IN). On arrival, the rats were placed into laminar flow units (Duo-Flo, Lab Products, Maywood, NJ) that provided clean air by precirculation through high-efficiency particle filters. Rats were housed individually in wire bottom hanging cages (20 × 25 × 18 cm) and maintained on a 12:12 light:dark cycle (lights on at 0600 h, off at 1800 h) at a room temperature of 25°–26 °C and 50% humidity. Distilled, autoclaved water acidified to pH 3.5 was provided ad libitum. A detailed description of procedures for maintenance of the barrier facility is reported elsewhere (McDonald et al., 1988). A rat was chosen randomly from the colony (at approximately 2–3 month intervals until month 24 of the experiment), and euthanized; a systematic necropsy was then performed to determine possible gross lesions resulting from environmental contamination. Sera from these sentinel rats were monitored for murine virus antibodies and mycoplasma. All findings were negative.

Diet and feeding protocol. — All rats were allowed ad libitum access to a semi-purified diet containing, by weight, 66.7% cornstarch, 6.4% hydrogenated oil, and 17.5% casein (Table 1: Growth) for 16 weeks. Then, approximately 45 animals per group were assigned to one of four diet treatments (Table 1): sucrose ad libitum; sucrose restricted; cornstarch ad libitum; and cornstarch restricted. Animals were assigned to their respective diet groups such that initial mean body weights did not differ among groups. Animals assigned to the restricted diets were given daily 60% of the mean caloric intake of their diet-matched ad libitum-fed rats. The four diets were isocaloric (as determined by bomb calorimetry).

Food intake of the ad libitum sucrose- and cornstarch-fed groups (n = 10 per diet group) was evaluated one week prior to start of caloric restriction, one week after initiation of caloric restriction, and periodically between weeks 30 and 90. In addition, food intake of the entire colony of ad libitum-fed rats was determined during week 45. Average daily food intake was calculated from measurements performed for 5 consecutive days. Although there was some variation in food intake of the ad libitum-fed groups (during the fifth week of the experimental protocol, average food intake of the ad libitum-fed rats increased by approximately 0.8 g; the amount fed to the calorie-restricted rats was adjusted accordingly), food intake did not differ significantly between the cornstarch- and sucrose-fed animals throughout the investigation, nor was the sample group's food intake significantly different from the entire population. The average daily food intake was 15.0 ± 3.0 g for the ad libitum sucrose-fed rats and 14.7 ± 2.3 g for the ad libitum cornstarch-fed animals, during weeks 30–90.

Histopathology analysis. — Rats were observed at 12-hour intervals, and animals that died spontaneously or killed when grossly morbid were necropsied immediately or refrigerated for a brief period before necropsy. Rats were examined grossly, and lesions and condition of the carcass and organs were recorded. The following tissues were routinely collected in 10% neutral buffered formalin for subsequent staining with hematoxylin and eosin: brain, Hardarian gland, lung, heart, spleen, stomach, pancreas, small intestine, kidney, adrenal gland, urinary bladder, prostate gland, testicle, and sections of triceps and quadriceps skeletal muscle. In addition, tumors and other abnormal tissue observed during necropsy were collected and prepared for analysis.

Histopathology was performed on all tissues collected during necropsy. We did not observe significant differences in any tissue due to the source of dietary carbohydrate. Differences were limited to those between ad libitum- and calorie-restricted rats. Because these lesions have been thoroughly described previously (Maeda et al., 1985; Boorman et al., 1990), we have limited our presentation of pathological lesion to a few representative tissues. A subjective grading system was applied to quantify the severity of certain common degenerative changes in the kidney, heart, and pancreas. The severity of chronic degenerative nephropathy was graded into four categories: no significant degeneration, 0; mild degeneration, 1; moderate degeneration, 2; and severe degeneration, 3. Degeneration was defined as the spontaneous renal disease of the Fischer 344 rat, also known as chronic progressive nephrosis. Spontaneous degenerative myocardial disease was graded on a scale similar to degenerative lesions in the kidney. Pancreatic fibrosis and inflammation were also graded on a four-scale system. Other notable pathological lesions and probable cause of death are described.

Table 1. Composition of Experimental Diets (g/100 g Diet)

Component	Growth Ad Libitum	Sucrose Ad Libitum	Sucrose Restricted	Cornstarch Ad Libitum	Cornstarch Restricted
Sucrose	0.0	66.7	63.7	0	0
Cornstarch	66.7	0	0	66.7	63.7
Casein	17.5	13.9	13.9	13.9	13.9
Hydrogenated oil[a]	6.4	10.0	10.0	10.0	10.0
α-Cellulose	1.8	1.8	1.8	1.8	1.8
Vitamin mix[b]	1.5	1.5	2.1	1.5	2.1
Salt mix[b]	6.0	6.0	8.4	6.0	8.4
DL-Methionine	0.04	0.04	0.05	0.04	0.05
Gross Energy (kcal•g^{-1})	4.3	4.2	4.2	4.2	4.1

[a]Crisco, Procter and Gamble, Cincinnati, OH.

[b]Vitamin and Salt mix contents were previously described (McDonald, 1990). The Growth diet was provided ad libitum to all animals between weeks 4 and 16. Gross energy content of the diet (kcal•g^{-1}) was determined by bomb calorimetry.

Calculation of bioavailable energy of the diet. — Although the diets given to the rats were isocaloric, body weights were found to be significantly higher in sucrose-fed rats (see Results), suggesting possible differences between cornstarch- and sucrose-fed animals in the amount of energy absorbed. In order to evaluate this possibility, we conducted another study, after completing the longevity study, designed to investigate the bioavailable energy content of cornstarch and sucrose diets during ad libitum and restricted feeding. Bioavailable energy of the diet was defined as the difference between the gross energy content of the diet and amount of kcal available for absorption. Briefly, male F344 rats (n = 20) aged 6 months were fed, ad libitum, a diet containing, by weight, 13% protein, 10% fat, 33% cornstarch, and 33% sucrose (all other nutrients were provided as described in Table 1, Growth) for 3 weeks. Energy content of this diet was 4.3 kcal/g (determined by bomb calorimetry). The bioavailable energy of the diet was determined by placing the rats in specially designed metabolic cages that allowed for accurate measurement of food and water intake, and urine and fecal output. Animals were maintained in these cages for 7 consecutive days. Food intake and fecal output were measured daily. Following the 7 days in the metabolic cages, the animals were returned to their normal housing and remained on this diet for one more week. Then, the rats were assigned to one of four diet treatments (n = 5 rats/group) as described above (see Diet and Feeding Protocol). Food intake and fecal output were determined for 2 weeks in the metabolic cages, and then the rats were returned to their normal housing for two additional weeks. After 4 weeks (total) on these diets, the bioavailable energy was again determined for 13 consecutive days. Because there was no difference in bioavailable energy among the groups or any of the collection periods, only the average values for the final week of evaluation are presented.

The energy content of the lyophilized feces and diet was determined by bomb calorimetry. Energy absorbed (kcal) was calculated as the difference between the total amount of energy intake and energy excretion in the feces.

Statistics. — Possible differences in survival (median and percentile groups) between the groups were analyzed through the nonparametric procedure Kaplan-Meir test to determine if the groups came from the same distribution. Survival means were compared by one-way analysis of variance (ANOVA).

Repeated measures ANOVA was used to determine possible differences in means of body weights. Differences in the main effects were determined by one-way ANOVA with post hoc comparison utilizing Scheffé's test. The difference in slope of the body weight was determined through regression analysis and comparison of the slope through a modified t-test. Comparison of means from food intake, and energy absorption was performed by one-way ANOVA as stated above. Differences were considered significant at $p < .05$.

RESULTS

Body weight. — Repeated measures ANOVA indicated a significant effect of diet on body weight (Figure 1). Rats fed

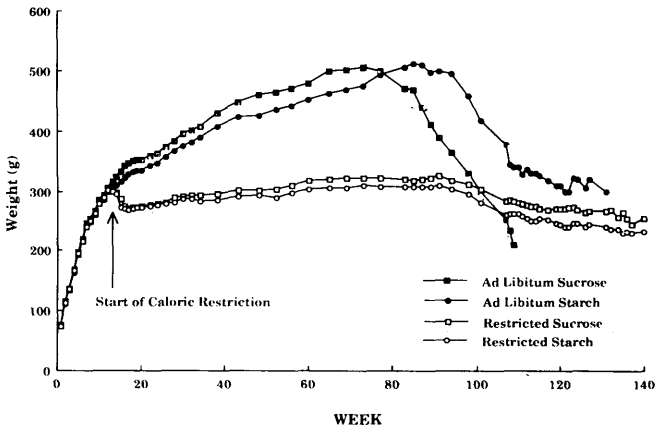

Figure 1. Mean body weights of F344 rats fed a diet containing either 66% sucrose or cornstarch. For ease of reading, standard error bars have been omitted. Standard error was generally between 1–3% of the mean in all groups.

sucrose diets either ad libitum or restricted to 60% of ad libitum had, in general, significantly greater body weights than those of the cornstarch-fed rats. By one-way ANOVA and post hoc tests, the first significant difference in body weight between the ad libitum sucrose- and cornstarch-fed rats occurred one week after the diet switch from growth to experimental (sucrose, 315 ± 4, cornstarch 306 ± 3). In contrast, a significant difference in body weight of the restricted cornstarch-fed vs restricted sucrose-fed rats was observed approximately 16 weeks after the start of caloric restriction. The slopes of the regression line for body weight (used as a measure for rate of weight gain) of ad libitum sucrose-fed vs cornstarch-fed rats did not differ significantly between weeks 18 and 70 (t = .633). However, the slope of regression line for body weight between weeks 16 and 18 was significantly steeper in the ad libitum sucrose-fed animals compared to rats fed cornstarch (t = 3.71).

The maximal body weights attained by ad libitum sucrose- and cornstarch-fed rats did not differ significantly (ad libitum sucrose-fed, 506 ± 7.0 g; ad libitum cornstarch-fed, 510 ± 6.0). However, maximal body weight of the cornstarch-fed rats was achieved at 83% of this group's median life span as compared to 72% of the median life span for sucrose-fed animals.

Maximal body weight regressed against day of death was not significant within any of the four diet treatments; i.e., there were no correlations between body weight and life span. (Figure 2: Because the slopes of the regression line were not significantly different between the two ad libitum and two restricted groups, regressions are presented only for combined data.)

Survival analysis. — The survival curves of ad libitum cornstarch-fed vs ad libitum sucrose-fed rats were significantly different (Figure 3). This reflected significantly greater mean, median, and upper 10th percentile survival of the ad libitum cornstarch-fed rats compared to feeding-matched sucrose rats (Table 2). Maximal life span, but not mean or median life span, was significantly increased in

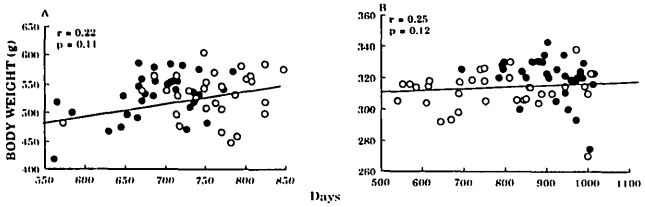

Figure 2. Regression analysis of body weight to day of death in (**A**) ad libitum- and (**B**) restricted-fed rats. Open circles are cornstarch-fed and closed circles are sucrose-fed rats. Because the slopes of the regression lines were not significantly different between the two ad libitum-fed or the two restricted-fed groups, data for each diet treatment were combined.

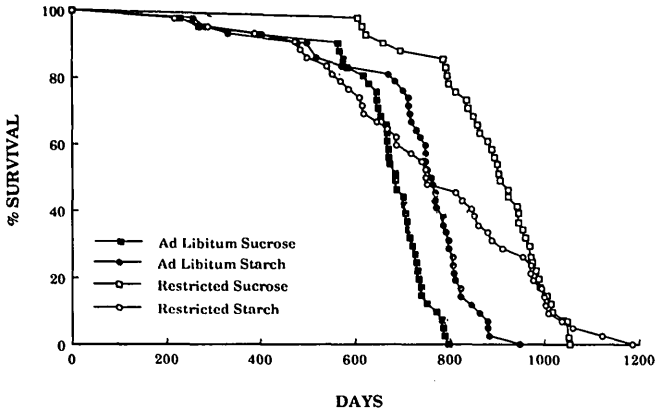

Figure 3. Survival curves for ad libitum- and caloric restricted-fed male F344 rats.

Table 2. Survival Characteristic (in Days) of F344 Rats

Diet Group	Mean ± *SE* (Range)	Median	Percentile Lower 10th	Percentile Upper 10th
Ad libitum sucrose	659 ± 19[a]	685[a]	533[a]	777[a]
n = 41	(224 – 799)			
Restricted sucrose	890 ± 18[b]	906[c]	680[b]	1013[b]
n = 42	(606 – 1051)			
Ad libitum cornstarch	720 ± 23[b]	762[b]	491[ac]	855[c]
n = 41	(258 – 948)			
Restricted cornstarch	726 ± 31[b]	749[ab]	482[c]	1095[d]
n = 42	(218 – 1150)			

Note: Within a column, values sharing a common letter superscript do not differ significantly ($p < .05$).

restricted cornstarch- vs restricted sucrose-fed animals. Mean and median life span did not differ in these two groups. The upper 10th percentile survival was significantly greater in restricted cornstarch- vs restricted sucrose-fed rats, and the three longest lived rats were in the restricted cornstarch-fed group. Restricted- and ad libitum cornstarch-fed rats had significantly poorer early life survival as indicated by the lower 10th percentile survival compared to their sucrose-fed counterparts.

Calorie-restricted sucrose-fed rats had significantly greater mean, median, and maximal life span compared to ad libitum-fed animals. However, calorie restriction only increased maximal life span and not mean or median life span in cornstarch-fed rats.

Histopathology. — Histopathology analysis on 15 separate tissues revealed no significant differences due to source of dietary carbohydrate. That is, the timing and severity of the pathological lesions were those normally associated with aging and/or caloric restriction in this species (Maeda et al., 1985; Boorman et al., 1990). The primary cause of death (where probable cause was evident from hematoxylin and eosin stain sections) in the ad libitum-fed rats was renal failure (Table 3) resulting from severe chronic degenerative nephropathy (Table 4). Chronic degenerative nephropathy was virtually absent in the calorie-restricted animals. The severity of cardiac myopathopy tended to be greater in the ad libitum-fed groups. Tumors were observed in all groups, ranging from benign subcutaneous fibromas to malignant carcinomas; the incidence of these tumors did not differ significantly among the dietary groups or from previously reported data. Intestinal blockage (hairballs) was present in all groups with restricted cornstarch-fed rats showing the highest occurrence. Although it is likely that intestinal blockage (i.e., hairballs) resulted in the death of some of the animals, a causal relationship could not be determined from the gross necropsy.

Energy absorption and bioavailability of energy in the diet. — There were no significant differences among the dietary groups with respect to fecal energy, energy absorbed, percent energy absorbed, or bioavailable energy of the diets (Table 5).

DISCUSSION

This study was designed to investigate whether the source of dietary carbohydrate could influence life span independently of caloric intake. To this end, we compared the effects of diets containing cornstarch or sucrose on the life span of F344 rats fed either ad libitum, or restricted to 60% of ad libitum. As expected, caloric restriction extended maximal life span in both carbohydrate groups. We also observed that, as we had hypothesized, carbohydrate source affected mean, median, and maximum life span independently of caloric restriction. Although maximum life span was highest in the calorie-restricted cornstarch-fed rats, a surprising finding was that the calorie-restricted sucrose-fed animals had the highest mean and median life spans. That is, calorie-restricted rats whose diets contained cornstarch as the carbohydrate source did not have the well-characterized increase in median life span expected of restricted-fed animals. What mechanisms might be responsible for the observation that the life span of rats fed sucrose differed from that of rats fed cornstarch, independent of caloric intake? We considered a number of possible causes.

We first investigated the possibility that bioavailable energy of sucrose differed from that of cornstarch, a plausible explanation given that body weights of sucrose-fed rats were significantly higher than those of cornstarch-fed rats, despite the fact that food intake was similar and the diets were isocaloric (Figure 1). Furthermore, other investigators have

shown that glucose derived from cornstarch is less readily absorbed than glucose derived from sucrose (Gray, 1992). A decrease in absorption by cornstarch-fed rats would be equivalent to caloric restriction, possibly accounting for their increased life span, at least in ad libitum-fed animals.

Table 3. Probable Cause* of Death and Incidence of Intestinal Blockage (Hairballs) in F344 Rats Dying Spontaneously

Cause of Death	Sucrose Ad Libitum (n = 41)	Cornstarch Ad Libitum (n = 41)	Sucrose Restricted (n = 42)	Cornstarch Restricted (n = 42)
Renal failure	23	20	2	1
Cardiac failure	—	2	4	2
Cancer (all types)	3	4	2	4
Mononuclear cell leukemia	1	2	1	2
Unknown	14	13	33	33
Intestinal blockage	2	7	7	23

*Probable cause was determined from hematoxylin and eosin stained sections.

Table 4. Lesions of Kidney, Heart, and Pancreas in Rats Dying Spontaneously

Lesion Grade	Sucrose Ad Libitum	Cornstarch Ad Libitum	Sucrose Restricted	Cornstarch Restricted
Kidney				
0	0 (2.7)	2 (5.1)	13 (36.1)	23 (57.5)
1	2 (5.5)	6 (15.3)	18 (50.0)	16 (45.0)
2	9 (25.0)	10 (25.6)	4 (11.1)	1 (2.5)
3	24 (66.6)	21 (53.8)	1 (2.7)	0 (0)
Heart				
0	13 (37.1)	10 (25.6)	11 (30.5)	15 (37.5)
1	6 (17.1)	17 (43.6)	19 (52.1)	18 (45.0)
2	16 (45.7)	12 (30.7)	4 (11.1)	5 (12.5)
3	0 (0)	0 (0)	2 (5.5)	2 (5.0)
Pancreas				
0	27 (79.4)	29 (74.3)	22 (61.1)	30 (75.0)
1	4 (11.7)	8 (20.5)	11 (30.5)	8 (40.0)
2	2 (5.8)	2 (5.1)	3 (8.3)	2 (5.0)
3	1 (2.9)	0 (0)	0 (0)	0 (0)

Notes: Values are the number and (percentage) of rats with lesions. Lesions were graded on a 0–3 scale with 3 being the most severe. See text for definition of grading system. Severe autolysis occurred in some tissue, making analysis impossible.

However, as shown in Table 5, the percent absorption and bioavailable energy were identical for sucrose and cornstarch.

We next hypothesized that the differences in survival among the dietary groups were related to the observed alterations in body weights, consistent with McCay's hypothesis that the life span of rodents is inversely related to body mass (McCay et al., 1935, 1939). Rats fed sucrose diets ad libitum or calorie restricted had, in general, significantly greater body weights than those of the cornstarch-fed rats (Figure 1). The mechanism(s) accounting for the differences in body weights of rats fed these two carbohydrates is unclear, but they most likely reflect differences in their post-absorptive metabolism. For example, there are several reports describing increased lipogenesis of rats and humans fed fructose and/or sucrose vs other carbohydrates (see review, Mayes, 1993). Others have suggested differences in the thermic effect of food between sucrose/fructose and starch (Tappy and Jequier, 1993). Regardless, we did not observe a significant correlation between body weight and life span in rats fed sucrose or cornstarch, whether they were fed ad libitum or were calorie-restricted (Figure 3). That is, the current data suggest that body weight was not the factor accounting for differences in life span among the dietary groups.

Histopathologic analyses were performed on 15 tissues in order to determine if differences in survival rates could be accounted for by differences in the timing, location, or severity of pathological lesions. In addition to these tissues, tumors and other abnormal tissues observed during necropsy were collected and prepared for analysis. Differences between ad libitum-fed animals and calorie-restricted animals were consistent with the literature (Maeda et al., 1985; Boorman et al., 1990). That is, the primary detectable cause of death in ad libitum-fed rats, regardless of carbohydrate source, was renal failure resulting from severe chronic degenerative nephropathy (Table 4). We did not observe significant differences in pathological lesions in any tissue due to the source of dietary carbohydrate. Although there was a trend for sucrose-fed animals to have a higher percentage of grade 3 kidney lesions in the ad libitum-fed group, and a higher percentage of grade 1 and 2 kidney lesions in the calorie-restricted group as compared with restricted cornstarch-fed animals, the differences in frequency distribution of lesion grades were not statistically significant. There were no differences in cause of death between sucrose- and cornstarch-fed animals in either restricted or ad libitum groups.

Table 5. Food Intake, Percent Energy Absorption (mean ± SE), and Bioavailable Energy of the Diet (mean) in Rats Fed Cornstarch or Sucrose

	Sucrose Ad Libitum	Cornstarch Ad Libitum	Sucrose Restricted	Cornstarch Restricted
Food intake (kcal)	56.7 ± 3.1[a]	49.4 ± 2.1[a]	35.4 ± 0.3[b]	35.2 ± 0.5[b]
Fecal energy (kcal)	2.6 ± 0.2	2.3 ± 0.2	2.1 ± 0.1	2.0 ± 0.3
Energy absorption (kcal)	54.1 ± 3.1[a]	47.1 ± 2.2[a]	33.3 ± 0.2[b]	33.2 ± 0.1[b]
Percent absorption	95.3 ± 0.2	95.3 ± 0.3	94.0 ± 0.2	94.4 ± 0.7
Bioavailable energy (kcal•g^{-1})	3.99	4.04	3.94	3.90

Note: Within a row, values sharing or without a superscript do not differ significantly ($p < .05$).

Finally, we considered the possibility that differences in life span between sucrose-fed and cornstarch-fed rats might reflect changes in the regulation of glucose homeostasis. This speculation was based on studies reporting age-related alterations in glucose tolerance, insulin resistance, and blood glucose levels (Defronzo, 1979; Reaven, 1979; Reaven et al., 1983; Wright et al., 1983). However, such mechanisms are unlikely to account for the differences in life span observed in our study. We have documented in earlier studies that neither age nor the source of dietary carbohydrate has a significant impact on glucose homeostasis in the F344 rat (McDonald, 1990; Eiffert et al., 1991, 1993; Hara et al., 1992). For example, we did not observe significant differences in intravenous glucose tolerance among 6-, 12-, and 26-mo-old male F344 rats fed cornstarch or sucrose for 4 months (Hara et al., 1992). Similarly, we have not detected age- or diet-related differences in blood glucose levels (Hara et al., 1992; Eiffert et al., 1993), skeletal muscle insulin receptor number and function (Eiffert et al., 1991), or insulin-stimulated glucose uptake of perfused hindlimbs (Eiffert et al., 1993).

Given that we have eliminated factors such as differences in body weight, energy absorption, pathological lesions, and regulation of glucose homeostasis as possible explanations for the differences observed in life span between sucrose- and cornstarch-fed rats, what other possible mechanisms might underlie our observations? We believe that the differences in life span may reflect fundamental differences in metabolism occurring at the cellular and molecular level. This speculation is based in part on preliminary studies (Reiser, 1994) in which we observed that pentosidine, an advanced glycation product whose formation is increased under conditions of increased oxidative stress (Reiser, 1991), was decreased in calorie-restricted sucrose-fed rats relative to ad libitum sucrose-fed rats, while no such differences were observed between ad libitum-fed and calorie-restricted cornstarch-fed rats. Thus, although the underlying mechanism accounting for the difference in life span among various carbohydrates has yet to be elucidated, we speculate that dietary sucrose and cornstarch may have different effects through an interaction between advanced glycation and oxidative stress. This suggestion is consistent with recent reviews describing the many pathways by which oxidation and glycation, separately and together, are capable of affecting virtually every aspect of homeostasis, ranging from functioning of subcellular organelles through multisystem physiological processes (Sohal and Allen, 1990; Kristal and Yu, 1992). Indeed, the impact on overall homeostasis of the complex feedback loops that exist between nonenzymatic glycation and free radical generation (Wolff and Dean, 1987; Hicks et al., 1989; Mullarkey et al., 1990; Baynes, 1991; Reiser, 1991) have only recently been appreciated. Although the role of dietary carbohydrate sources in affecting these pathways in vivo has yet to be fully clarified, there is considerable evidence that different carbohydrates have very different effects on nonenzymatic glycation pathways that may play an important role in glycation-oxidation interactions (McPherson et al., 1987; Suarez, 1989; Dyer et al., 1991; Grandhee and Monnier, 1991; Nagaraj et al., 1994).

In light of the potential importance of dietary carbohydrates affecting the complex interactions between glycation and oxidation, surprisingly few long-term dietary studies have been conducted. Longer-term studies (6–18 months) have documented that in certain strains of rats, sucrose diets result in retinopathy and nephropathy not found in rats fed cornstarch (Cohen and Rosenmann, 1971; Papachristodoulou and Heath, 1977; Dyer et al., 1991). It should be noted that all of the studies in which ad libitum sucrose, but not ad libitum cornstarch, resulted in nephropathy utilized an albino rat strain (Sabra HUS strain) that appears to have an abnormality of carbohydrate metabolism (Cohen and Rosenmann, 1970); hence, these studies are not directly relevant to studies of the effects of sucrose on F344 rats. To our knowledge, no such studies have been conducted in F344 rats. In a more recent study, Boot-Handford and Heath (1980) provided evidence that fructose is the pathogenic component responsible for the development of retinopathy in Wistar rats fed sucrose ad libitum. However, the precise mechanism is unclear: Heath and Hamlett (1976) showed that there were no differences in retinal levels of glucose, sorbitol, or fructose in sucrose-fed animals as compared with cornstarch-fed animals.

In summary, then, the data presented in this study suggest that the dietary source of carbohydrate, i.e., sucrose vs cornstarch, can significantly affect the life span of F344 rats independently of caloric intake. Furthermore, we did not observe an increase in median or mean life span of male F344 rats provided diets containing cornstarch as the carbohydrate source and restricted to 60% of rats fed ad libitum cornstarch — a surprising finding given the significant amount of literature describing, almost universally, that dietary restriction increases median life span of rodents. The mechanism by which sucrose and cornstarch may have differential effects on life span remains to be elucidated. We have, however, eliminated factors such as differences in body weight, energy absorption, pathological lesions, or regulation of glucose homeostasis as possible explanations for the differences observed in life span. Based on preliminary data on pentosidine and fluorophore accumulation, as well as on data on Maillard product accumulation in previous studies of caloric restriction, we hypothesize that specific dietary carbohydrates may affect life span through their influence on cumulative glyco-oxidative damage. While few inferences can be drawn from the literature regarding the long-term effects of sucrose and other sugars on life span, some studies suggest that it is the fructose component, rather than the glucose component, that may potentially play a role in altered oxidative stress.

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Address correspondence to Dr. Roger B. McDonald, Department of Nutrition, University of California, Davis, CA 95616.

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