Effect of voluntary exercise on longevity of rats

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HOLLOSZY, JOHN O., E. K. SMITH, M. VINING, AND S. ADAMS. *Effect of voluntary exercise on longevity of rats.* J. Appl. Physiol. 59(3): 826–831, 1985.—The purpose of this study was to obtain information regarding the effects of exercise on longevity in rats. The exercise used was voluntary activity wheel running. The runners gradually decreased their running from ~4 to ~1 mile/day as they aged from 9 to 30 mo. The runners lived slightly but significantly longer than sedentary freely eating controls and sedentary pair-fed controls (1,012 ± 138 vs. 923 ± 160 and 928 ± 186 days) but significantly less long than food-restricted paired-weight sedentary controls (1,113 ± 150 days). Although the exercise improved survival, it did not result in an extension of life-span. In contrast, the food-restricted paired-weight sedentary rats showed a true increase in life-span. The paired-weight rats also had a significantly reduced incidence of malignancies compared with the other three groups. However, there was no significant difference between the runners and the freely eating or pair-fed sedentary controls in the cause of death. These results provide evidence that exercise improves survival but does not result in an extension of life-span in rats.

activity wheel running; exercise and body weight; food restriction; life-span

A NUMBER OF ADAPTATIONS to endurance exercise in rats run counter to the changes in structure and function that occur with aging (5, 20, 27, 28). Laboratory rats are usually confined to cages that markedly restrict their physical activity and are provided with food ad libitum. This is an abnormal situation that generally results in development of obesity (17, 20). It therefore seemed possible that exercise might increase survival time in the laboratory rat either by *1*) counteracting some of the deterioration in structure and function associated with aging, resulting in a true increase in longevity, or *2*) countering deleterious effects of overeating combined with a sedentary lifestyle and improving survival without an increase in life-span. On the other hand, it has been postulated that life-span is inversely related to energy expenditure, and if this is correct, exercise might, by increasing the "rate-of-living," shorten survival (6, 8, 13, 21, 25).

As available information regarding the effect of exercise on longevity in rats was sparse and inconclusive (2, 7, 22, 26), we performed this study to provide information regarding the effect of exercise on longevity in healthy rats.

METHODS

Male specific-pathogen-free Long-Evans rats aged 3 mo were obtained from Charles River. Five percent of the animals, selected at random, were killed and necropsied; cultures were obtained on their respiratory tracts, tympanic bullae and gastrointestinal contents, and serum was examined for titers of antibodies against pathogenic viruses and mycoplasma. The remaining animals were kept in quarantine until it was determined that the necropsied rats were pathogen free. The animals were housed in a temperature- and light-controlled animal room with its own ventilation system, with 15 air exchanges per hour, 100% intake and 100% exhaust (no recirculation), in a facility in which no other rodents were housed. No additional rats were placed in this room after the aging study was begun. To avoid the danger of introducing infections into the aging rat colony, the people who entered the room to care for the animals did not work with other rodents or in areas where they were exposed to other rodents. The room was lighted between 0700 and 1900 h and maintained at a temperature between 18 and 20°C. The rats were fed a diet of Purina chow and water.

Some of the animals in the aging rat colony were used in studies of the effects of voluntary exercise on longevity. The present paper deals only with the exercising and control rats in the longevity study. The rats assigned to the longevity study were not subjected to any experimental treatment other than voluntary exercise or food restriction and were permitted to die of natural causes. At 6 mo of age, animals were randomly assigned to a voluntary exercise group (32 rats), a sedentary freely eating group (54 rats), or a paired-weight group whose food intake was restricted to keep their body weights the same as those of the runners (54 rats). The sedentary rats were housed in stainless steel cages measuring 7 × 14 × 8 in. The voluntary runners were housed in 7 × 14 × 8 in. stainless steel cages to which were attached running wheels, 44 in. in circumference, that the rats had free access to. The running wheels were fitted with counters that recorded the number of revolutions made by the wheels. The stainless steel running wheels with cages were custom-built for us by Wahmann Co. (Baltimore, MD).

Seven of the rats initially assigned to the voluntary runner group showed no interest in running and were replaced after 2 wk with rats that were willing to run. The rats that would not run were randomly assigned to the control or experimental group of a different study (of the effect of cold stress on longevity). After the first 3 wk the runners were running 2–7 miles/day, and with this amount of exercise, their body weights stabilized

between 350 and 420 g on ad libitum food intake. After ~4–6 mo the voluntary runners appeared to lose interest in running and would abruptly and markedly reduce the distance they ran. We discovered that if we gave the runners slightly less food than they were eating ad libitum, so that there was a period during the day in which they were without food, this reversed the decrease in their running. Because it was essential to the purpose of the study that the rats continue to exercise, we made the decision to decrease each runner's food intake, by ~8% below its ad libitum intake, at the time that it became evident that the animal was markedly reducing its running. By age 12 mo all but one of the 32 runners were on the slightly restricted intake.

Food restriction can increase life-span in rats. Therefore, to control for the runners' slightly restricted food intake, a group of paired weight controls, i.e., rats that had been food restricted to keep their weights in the same range as those of the runners from age 6 mo on, were converted to pair-fed controls at age 12 mo. These animals were given the same average amount of food as eaten by the runners. Eighteen animals for this new pair-fed control group came from the original group of paired-weight controls for the longevity study, and an additional 12 were transferred from paired-weight control groups from parallel studies (of the effects of aging and exercise on a number of physiological variables). Thus, beginning at age 12 mo there were 36 paired-weight controls and 30 pair-fed controls for the voluntary runners in the longevity study.

In the case of the freely eating sedentary control rats, food intake was measured daily for 1 wk/mo for 10 rats; the animals' food intake measurements were rotated, i.e., the first 10 rats during the first month, the next 10 rats in the next month, and so forth. In the case of the runners and the paired-weight and pair-fed control groups, which were given premeasured amounts of food, any remaining, i.e., uneaten, food was weighed.

A detailed necropsy was performed on all the rats in the longevity study except for the few in which autolysis was too far advanced at the time their death was discovered. Unless otherwise specified, results are expressed as means ± SD. Least-squares linear regression analysis was used to evaluate the relationships between body weight and longevity in the freely eating sedentary controls and between distance run and longevity in the voluntary runners. To determine the statistical significance of differences in survival between the groups of rats, we used the Generalized Wilcoxon (Breslow) test (4). The significance of differences in the cause of death was evaluated using the χ^2 test. Statistics were performed using the Statistical Analysis System of the SAS Institute, Inc., Cary, NC (1).

RESULTS

Running performance. During their first 3 wk in the running wheels the voluntary runners increased their running to between 2 and 7 miles/day. After 4–6 mo, the voluntary runners appeared to lose interest in running and would abruptly and markedly reduce the distance they ran if given continued free access to food. As described in METHODS, we discovered that slightly reducing the runners' food intake to ~92% of what they were eating ad libitum reversed this abrupt decrease in running. By age 12 mo all but one of the 32 runners were on the slightly restricted food intake. Since the animals reduced their running at different times and as the decrease in running was reversed in 1–2 wk, the abrupt transient reduction is not evident in the graph of the average distances run per week by the voluntary runners in the longevity study (Fig. 1). From 7 to 9 mo of age, the rats ran an average of 4.1 ± 2.4 miles/day. As shown in Fig. 1, the rats' average daily running decreased gradually from ~4 to 1 mile/day as they aged from 9 to 30 mo. There were considerable differences between rats in the amount of running performed, as illustrated by the two extremes in Fig. 1. (The distances that a rat ran during the last 3 mo of its life were not included in the averages in Fig. 1 to avoid the period of terminal illness.)

There was no significant correlation between longevity and the average distance run per week during the period between 9 and 21 mo; e.g., for the 9th mo $r = 0.28$ ($P = 0.12$), and for the 18th mo $r = 0.023$ ($P = 0.90$).

Body weights and food intakes (Fig. 2, Table 1). At the start of the longevity study when the rats were 6 mo old, their average body weight was 332 ± 16 g. By 10 mo of age the voluntary runners' body weights had stabilized in the 360- to 420-g range on an ad libitum food intake. The slight reduction in food intake required to keep the voluntary runners running did not affect their average body weight, probably as a result of the progressive decrease in the amount of exercise performed (Fig. 1). Both the freely eating sedentary controls and the runners showed a gradual decline in food intake as they aged (Table 1); between the ages of 10 and 24 mo the decrease in food intake amounted to ~10% ($P < 0.01$). Despite this decline in food intake the freely eating sedentary rats continued to gain weight up to ~26 mo of age (Fig. 2). Although the runners were on a slightly restricted food intake, it was evident that their voluntary food intake was decreasing, as they would no longer eat all the food given to them and had to undergo further reductions in the amount of food given them in order to keep them at ~92% of their ad libitum intake.

Beginning at about 26 mo of age, the sedentary freely eating animals began to lose weight, with a decline in average weight of the group from roughly 600 to 500 g between 26 and 32 mo of age (Fig. 2). This decline was due to loss of weight by the surviving animals rather than to a longer survival of smaller animals. There was no significant relationship between longevity and body weight in the freely eating sedentary group; the correlation coefficient between weight at age 12 mo and age at death was −0.10 ($P = 0.48$); for weight at age 18 mo and age of death $r = 0.14$ ($P = 0.32$). The weight loss was gradual and occurred while the rats still appeared healthy; it did not appear to represent weight loss due to terminal illness. (Weights during the last 2 mo of life are not included in the averages in Fig. 2.) The pair-fed sedentary controls showed a gradual increase in weight of about 80 g over the 12-mo period after they were

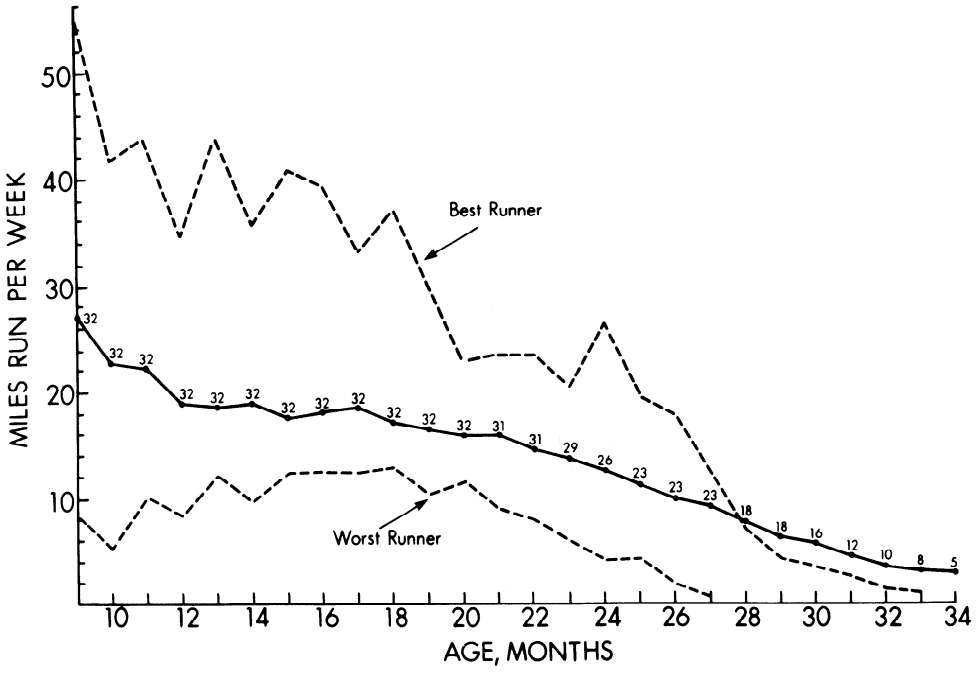

FIG. 1. Decline with age in average distance run per week. Number of rats surviving at each time point is shown above line.

FIG. 2. Average body weights of rats in 4 groups.

TABLE 1. *Food intake*

Age Period, mo	Group			
	Freely eating sedentary	Runners	Paired-weight sedentary	Pair-fed sedentary
	Food intake, g			
9–12	26.9±3.3	25.8±2.4	17.6±0.7	
13–18	26.5±2.9	24.4±1.5	17.9±0.9	23.8±0.8
19–24	24.2±3.4	23.1±1.8	17.7±0.8	22.0±0.8
25–28	23.2±3.8	22.1±1.6	17.6±0.6	21.4±0.7
29–32	20.6±2.2	21.3±1.4	17.2±1.0	20.3±1.1

Values are means ± SD.

converted from paired weight to pair fed; unlike the freely eating sedentary group, the pair-fed controls showed no decline in body weight after age 26 mo.

Survival patterns (*Fig. 3, Table 2*). The paired weight sedentary rats, whose food intake was restricted to keep their body weights in the same range as the runners', ate approximately two-thirds as much food as the freely eating sedentary controls during the first year of the study. Thereafter, the degree of food restriction relative to the freely eating animals decreased as the latter group voluntarily reduced their food intake; for the period of the study from 9 to 32 mo of age, the paired-weight group ate ~28% less than the freely eating groups. This reduced food intake was associated with a 20% increase in average life-span (of the paired-weight group compared with the freely eating controls). The increase in longevity was evident both in a later age of onset of mortality and in a longer life-span of the oldest paired-weight rats (Fig. 3, Table 2). Although the runners' body weights were in the

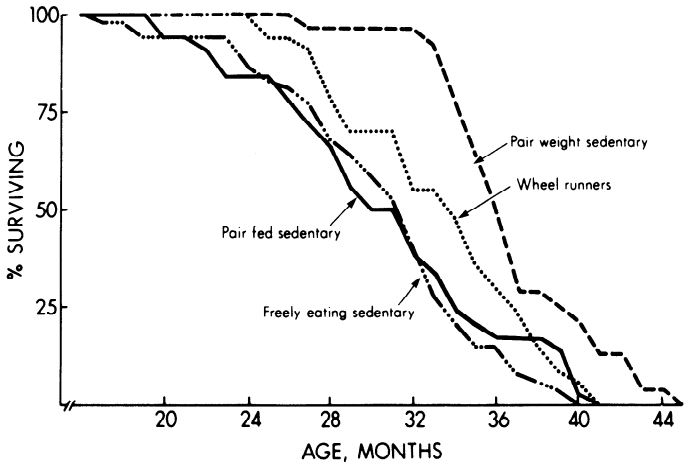

FIG. 3. Survival curves for 4 groups.

TABLE 2. *Longevity of the four groups*

Group	*n*	Age at Death, days	Median Age at Death, days	Age of 3 Oldest Rats, days
Paired-weight sedentary	36	1,113±150*	1,100	1,317±23
Voluntary runners	32	1,012±138†	1,041	1,220±11
Pair-fed sedentary	30	928±186‡	961	1,212±18
Freely eating sedentary	54	923±160	956	1,209±19

Age at death and age of 3 oldest rats are means ± SD. * Paired weight vs. pair-fed sedentary, $P < 0.01$; vs. freely eating sedentary, $P < 0.01$. † Runners vs. paired weight, $P < 0.02$; vs. freely eating sedentary, $P < 0.02$. ‡ Pair-fed sedentary vs. runners, $P < 0.05$; vs. freely eating sedentary, NS.

same range as those of the paired-weight sedentary rats, their life-span was significantly shorter. This difference was evident throughout the range of the mortality curve (Fig. 3) and is reflected in the range of age at death, which was 735–1,229 days for the runners and 801–1,344 days for the paired-weight controls.

The runners had a significantly better survival than the freely eating sedentary controls; this difference in longevity was modest, being 89 days (~10%) for average length of life and 85 days (~9%) for median length of life. The runners also lived slightly longer, an average of 9%, than the pair-fed sedentary controls. A comparison of the longevity of the freely eating sedentary animals with that of the pair-fed sedentary controls provides evidence that the slight food restriction (Table 1) required to keep the voluntary runners running was not sufficient in itself to increase longevity, as there was no significant difference in life span between these two groups.

Cause of death (*Table 3*). There were no significant differences between the runners and the freely eating sedentary or pair-fed sedentary rats in the cause of death (Table 3) or in the incidence of the major pathological processes responsible for mortality in rats (data not shown); this provides evidence that voluntary exercise does not influence the development of these disease processes. On the other hand, the food restriction to which the paired-weight rats were subjected was sufficient to result in a significant protection against the development of malignancies. As a consequence, a larger proportion of the paired-weight animals survived sufficiently long to succumb to the chronic nephropathy that most older rats develop (16).

TABLE 3. *Cause of death*

Group	No. Necropsied	Cause of Death: Renal disease		Neoplasia		Cardiovascular		Other	
		n	%	*n*	%	*n*	%	*n*	%
Paired-weight sedentary	34	23*	67.6	7*	20.6	2	5.9	2	5.9
Voluntary runners	30	9	30.0	15	50.0	3	10.0	3	10.0
Pair-fed sedentary	29	12	41.4	13	44.8	2	6.9	2	6.9
Freely eating sedentary	46	19	41.3	23	50.0	3	6.5	1	2.2

* Paired-weight vs. other 3 groups, $P < 0.01$.

DISCUSSION

The results of this study provide evidence that rats that perform voluntary exercise have a slightly but significantly longer average survival than sedentary freely eating or pair-fed rats. We tentatively interpret our results to indicate that exercise results in improved survival without slowing of the aging process or an increase in life-span. This interpretation is based on the findings that *1*) the oldest runners (1,208, 1,223, 1,229 days) were similar in age to the oldest pair-fed (1,194, 1,210, 1,231 days) and freely eating (1,187, 1,215, 1,225 days) rats, and *2*) there was no significant difference in the incidence of the pathological processes responsible for mortality between these groups. Thus it appears that exercise may counteract deleterious effects of a sedentary life combined with overeating and thus allow a larger proportion of the animals to attain old age without slowing the aging process per se. This is in contrast to severe food restriction, which results in an increase of life-span in rats (cf. Refs. 3, 18, 19, 23, 24, 30).

The degree of food restriction required to keep the paired-weight sedentary rats' body weight in the same range as that of the runners was relatively mild compared with that used in most of the studies on the life-prolonging effect of reduced food intake. Food intake was usually restricted to 40–60% of ad libitum consumption in studies in which food restriction resulted in a marked increase in longevity (3, 18, 19, 23, 24, 30); in the present study, the paired weight control rats ate ~72% as much food per day as the freely eating controls. Even this degree of food restriction was sufficient to result in a 20% increase in average age at death and a true increase in life-span. The latter is evidenced by the finding that the oldest rats in the paired-weight group were more than 3 mo older than the oldest rats in the other three groups, and 20% lived longer than the oldest rat in the other groups.

These findings and conclusions appear to be in partial disagreement with the results of a study by Goodrick (10) published while the present study was in progress. Goodrick (10) found that male rats given access to running wheels lived, on the average, 4 mo longer, while female runners lived 3 mo longer than sedentary controls. Although the absolute increase in survival was roughly similar, Goodrick's voluntary runners, in contrast to

ours, appeared to have an increase in life-span, such as is seen with food restriction. This was evidenced by the finding that the oldest runners were roughly 3 mo older than the oldest sedentary controls (10). It is not possible on the basis of available information to explain this difference between our and Goodrick's results. However, there were major differences in study design and findings. One major difference is that Goodrick's sedentary freely eating male Wistar rats had an average survival of only 631 days and half of his control rats were dead by age 21 mo. This seems a short life-span for ad libitum fed male Wistar rats, which normally have an average life-span of about 750 days (14). It is therefore difficult to accept the conclusion that the voluntary running retarded the aging process (10); instead it may have partially protected against disease processes that began to kill them at the relatively early age of 17–18 mo. Possibly of relevance to this question is the finding by Goodrick et al. (11), in other studies, that rats housed in voluntary running wheels, fed every other day to reduce their food intake, lived longer than ad libitum-fed rats (10) but did not live as long (14 wk less) as sedentary rats fed every other day (12). This finding would appear to argue against the interpretation that exercise slows the aging process.

In an earlier study Retzlaff et al. (22) reported that 10 min of daily running at 11.5 m/min markedly increased mean survival and maximum life-span in Sprague-Dawley rats. The results of this study are difficult to interpret because of the extremely short life-span, only 474 days, of the sedentary control male rats, and 605 days for the runners. Although the Sprague-Dawley strain is short lived, their normal life expectancy when fed ad libitum is at least 2 yr (14). Other unusual findings were that the runners were heavier than the sedentary controls and that the peak body weight of the sedentary ad libitum-fed male rats was only 401 g.

Food restriction, i.e., underfeeding, is the only procedure that has clearly been proved effective in markedly prolonging life-span of a species of mammal. This effect was first demonstrated in rats by McCay et al. (18, 19) and confirmed in rats (3, 23, 24, 30) and mice (9, 29) by other investigators. The effects of underfeeding in rodents appear to represent a true slowing of the rate of aging, with an increase in maximum life-span (3, 18, 19, 23, 24, 30), maintenance of immune system function at a "younger" level (9, 29), and a lower incidence of a wide variety of neoplasms (3, 9, 19, 29). One of the major hypotheses that has been proposed to explain this slowing of aging is that underfeeding results in a persistence of "growth potential" in rodents (18, 19). The body size of food-restricted rats stabilizes far below that attained in rats fed ad libitum, and because the epiphyses close late in life in rats, they retain the ability to grow in response to increased food intake until late in life (18, 19).

Certain reptiles and fish grow in proportion to their food supply and retain the capacity to grow as long as they live; their rate of aging appears to be inversely proportional to their rate of growth (15). It has been postulated that a similar mechanism may be operative in food-restricted rats (18, 19). A finding in the present study that may have importance relative to this question is that growth was retarded to a similar extent in the exercising rats and the sedentary paired-weight (food-restricted) animals. Thus the runners also retained growth potential. The findings that the runners *1*) showed a significantly shorter survival than the paired-weight animals and, in contrast to the sedentary paired weight rats, *2*) did not have an increase in maximal life-span (i.e., age at which the oldest rats died) and *3*) did not have a reduced incidence of malignancies, despite a similar retardation of weight gain, may be evidence against the "growth potential" hypothesis.

A second mechanism that has been suggested to play a role in the greater longevity of food-restricted rats relates to their low body fat content (17). According to this hypothesis, the prevention of obesity and the associated metabolic abnormalities, such as decreased glucose tolerance and insulin resistance, may account for the greater longevity of underfed animals. We have found in parallel studies that the voluntary runners have a slightly lower body fat content than the paired-weight sedentary controls (unpublished observations). This finding argues against the hypothesis that reduced body fat stores are responsible for slowing aging in food-restricted animals. On the other hand, our findings are compatible with the hypothesis that exercise, by protecting against deleterious effects of obesity, improves survival and enables more rats to attain old age but without an extension of life-span. Food restriction clearly does something more.

An alternative possibility is that growth retardation with maintenance of growth potential and prevention of obesity do slow aging in the rat but that these, and possibly other, beneficial effects are counteracted by a deleterious effect of exercise, possibly due to increased free radical damage associated with elevated rates of O_2 utilization (6, 8, 13). Therefore, although our results are encouraging in that, contrary to the early reports of Benedict and Sherman (2) and Slonaker (26), they show that exercise slightly prolongs, instead of shortening, survival of healthy rats, they do not rule out the possibility, which requires further study, that exercise may also have deleterious effects due to an increased rate-of-living (6, 8, 13, 21, 25).

In conclusion, the results of this study provide evidence that exercise improves survival of rats (i.e., more attain old age) but, in contrast to food restriction, does not result in an extension of life-span.

This research was supported by Research Grant AG-00425 from the National Institute of Aging.

Received 22 February 1985; accepted in final form 9 April 1985.

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