Exercise and Food Restriction in Rats[1,2]

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ABSTRACT A number of studies have shown that exercised rats live longer than sedentary freely eating controls. There is disagreement regarding whether exercise results in extension of maximal life span. However, in two studies of the effect of voluntary wheel running on longevity of male specific-pathogen–free Long-Evans rats it was found that, although the runners had a longer average survival than sedentary freely eating controls, they did not have an increase in maximal life span. This is in contrast to the effect of food restriction. Sedentary rats that were food restricted to keep their body weights in the same range as those of the runners lived longer than the runners and showed an extension of life span. When exercise, in the form of voluntary wheel running was combined with food restriction (~30% below ad libitum), the runners had an increased mortality rate over the first ~50% of their mortality curve up to age ~900 d. However, in those food-restricted runners that survived past ~900 d survival became similar to that of food-restricted sedentary controls, with a similar increase in maximal life span. Thus, although exercise has a deleterious effect on food-restricted rats, it does not counteract the increase in maximal life span induced by food restriction. J. Nutr. 122:774–777, 1992.

INDEXING KEY WORDS:

• *exercise* • *food restriction* • *longevity* • *rats*

Early studies on the effects of exercise on the longevity of rats gave conflicting results that are difficult to interpret. Nonpathogen free rats were used in these studies, and chronic infections may have affected their outcomes. Slonaker (1), who probably conducted the first study on the effects of exercise on longevity, found that rats given access to voluntary running wheels died earlier than sedentary controls. Benedict and Sherman (2) also found that exercise shortened the survival of rats. In subsequent studies by Retzlaff et al. (3) and Edington et al. (4), exercise increased the longevity of rats if the exercise was begun at an early age. In both of these studies the amount of exercise, walking at 11.5 m/min for 10 min (3) or at 10 m/min for 20 min (4) per day, was minimal and would not be expected to result in physiological or anatomical adaptations (5, 6). In the study by Retzlaff et al. (3) the rats were abnormally short-lived, with an average longevity of only 474 d for the sedentary rats.

Goodrick (7), in a study on the effects of voluntary wheel running on longevity of Wistar rats, found that male runners lived an average of 4 mo longer and that female runners lived an average of 3 mo longer than sedentary freely eating controls. In this study, the exercise resulted in an increase in maximal life span, such as occurs with food restriction of rats, with the oldest runners living ~3 mo longer than the oldest controls (7).

Two studies on specific-pathogen–free male Long-Evans rats confirmed that exercise results in improved survival (8, 9). As in Goodrick's (7) study, voluntary wheel running was the form of exercise. Young freely eating male rats that are given access to running wheels generally run 4.8–8.1 km/24 h. However, after a few months they usually lose interest in running and markedly decrease the distance that they run. This reduction in running is prevented by giving the rats slightly less food than they eat when fed ad libitum so that they run out of food during the night. Therefore, to keep them exercising, the runners' food intake was decreased to ~92% of their ad libitum intake at the time when they abruptly reduced their running, usually between 8 and 11 mo of age (8, 9).

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In the first study (8), there were four groups: a freely eating sedentary group, wheel runners, sedentary rats that were food restricted to keep their body weights in the same range as those of the wheel runners and a pair-fed sedentary group that was given the same average amount of food as the runners after the runners were restricted to 92% of ad libitum intake.

Although the 8% food restriction reversed the abrupt decrease in running, it did not prevent a progressive decline in running from ~6.4 km/24 h at age 9 mo to ~1.6 km at age 30 mo. Exercising male rats do not increase their food intake to compensate for the increased energy expenditure. As a result, the food intake of the runners when they were fed ad libitum was the same as that of the freely eating sedentary controls. The freely eating sedentary rats attained a maximal body weight of ~600 g. By age 10 mo, the runners' body weights had stabilized at ~400 g. The small reduction in food intake required to keep them running did not affect the runners' body weights significantly, probably as a result of the progressive decline in running activity. The paired-weight sedentary rats, whose food intake was restricted to keep their body weights the same as those of the runners, ate ~30% less food per day than the freely eating sedentary rats. As in many previous studies (10–20), food restriction resulted in a significant increase in longevity. The paired-weight sedentary rats' average age at death was 1113 ± 150 d compared with 923 ± 160 d for the sedentary freely eating group. As in previous studies of the effect of food restriction (10–20), this improved survival was due to a later onset of mortality and an increase in maximal life span (8).

The average length of life of the runners was 1012 ± 138 d, which was significantly longer than that of the freely eating sedentary controls. However, the runners' survival was significantly shorter than that of the food-restricted paired-weight controls, even though the two groups had the same degree of growth retardation. In contrast to the finding of Goodrick (7) the runners had no increase in maximal longevity. The reason for this major difference between the results of Goodrick's (7) study and our (8, 9) studies is not clear. The pair-fed sedentary rats that, like the runners, had their food intake restricted by 8% had an average survival (928 ± 186 d) similar to that of the freely eating sedentary rats, showing that this minimal degree of food restriction is not sufficient to improve survival.

Pathological examination showed that the causes of death were similar in the runners and the sedentary freely eating and pair-fed rats (8). This is in contrast to the food-restricted paired-weight controls, which had a significantly reduced incidence of malignancies (8), a finding consistent with the results of previous studies of food restriction (10, 11, 13, 16).

It has variously been hypothesized that food restriction increases maximal longevity by retarding growth (10), protecting against obesity (11) and decreasing availability of energy for cell proliferation with a shift in physiological state from cell proliferation and reproduction to maintenance/repair pathways (19, 20). The male wheel runners in our first study did not increase their food intake to compensate for the increase in energy expenditure caused by the exercise. As a result they had a decreased availability of energy for cell proliferation, resulting in growth retardation. However, in contrast to the food-restricted paired-weight sedentary rats, which had the same decrease in the availability of energy for cell proliferation and growth, the runners had no increase in maximal longevity (8). This finding raises the possibility that decreased availability of energy for cell proliferation and growth does not cause an increase in longevity, and that food restriction extends maximal life span by another mechanism. It also raised the possibility that exercise might have a deleterious effect that partially counters a life-extending effect of decreased availability of energy.

If food restriction extends maximal longevity by some mechanism other than decreased availability of energy for cell proliferation, and if exercise and food restriction improve survival by different mechanisms, one would expect their combined effects to result in at least as great an improvement in longevity as food restriction alone. On the other hand, if exercise has a deleterious effect that counters a life-prolonging effect of decreased availability of energy for cell proliferation and growth, exercise should prevent the improvement in maximal longevity induced by food restriction. In this context, a second study was performed to examine the combined effects of exercise and food restriction on longevity of male rats (9). As in the first study (8), wheel running improved average length of life without increasing maximal life span (**Fig. 1**). Paired-weight controls, food-restricted (~30% below ad libitum intake) to weigh the same as the runners, showed increases in both average and maximal life span. Food-restricted runners, whose intake was restricted to the

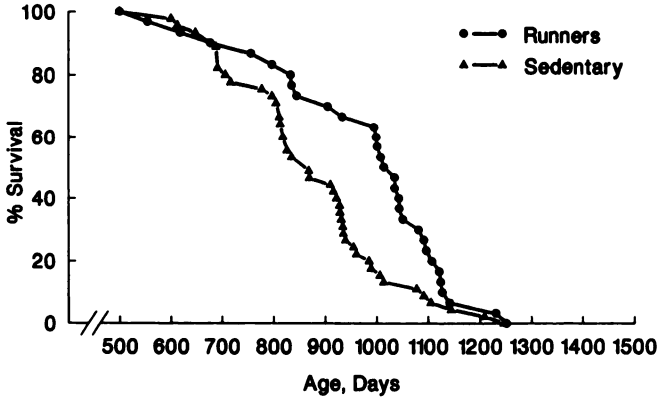

FIGURE 1 Effect of voluntary wheel running on longevity of male Long-Evans rats. (Adapted with permission from ref. 9).

same extent (~30%) had an increased mortality rate over the first ~50% of their mortality curve up to ~900 d of age compared with food-restricted sedentary rats (**Fig. 2**) and also compared with the other group of runners shown in Figure 1. However, after age ~900 d the food-restricted runners' survival became similar to that of the food-restricted sedentary groups, with a comparable increase in maximal life span (Fig. 2). Thus, the exercise did not counteract the increase in maximal life span induced by food restriction. There were two sedentary food-restricted groups in this study, one group, with which the food-restricted runners were pair-fed, ate ~70% of ad libitum, whereas the second group, which was paired-weight with the food-restricted runners, ate ~55% of ad libitum. Somewhat surprisingly, the more severe food restriction did not result in a statistically significantly greater improvement in survival than the more modest food restriction (Fig. 2). The finding of a deleterious effect of exercise in food-restricted rats is in keeping with the results of an earlier study by Goodrick et al. (21), who found that voluntary wheel-running rats that were food restricted by every other day feeding died an average of 14 wk earlier than similarly food-restricted sedentary rats. These results are consistent with the report by Skalicky et al. (22) that exercise reduced the beneficial effects of food restriction on a number of biological measurements in aging rats.

Evaluation of the results of the study of the effects of exercise in combination with food restriction is complicated by the food-restricted runners' increased mortality during the first half of their mortality curve (Fig. 2) and by the lack of information regarding the causes for the higher mortality because of the inability to obtain necropsy data due to funding cuts. Nevertheless, a number of conclusions seem reasonable on the basis of the available information. The finding that the food-restricted runners that survived past ~900 d showed as great an increase in maximal life span as the food-restricted sedentary rats shows that exercise does not counteract the extension of life span by food restriction. Exercise alone, without food restriction, causes a decreased availability of energy for cell proliferation and growth in male rats but does not increase maximal life span (8, 9). This finding provides evidence that decreased availability of energy for cell proliferation and growth does not increase maximal life span. Instead, it favors the interpretation that extension of life span by food restriction is mediated by decreased intake or metabolism of food per se (possibly by decreased formation of toxins and/or carcinogens, and/or decreased accumulation of waste products), not by decreased availability of energy for cell proliferation. Finally, it seems clear, although the mechanism is not known, that exercise has a deleterious effect on food-restricted rats (9, 21, 22).

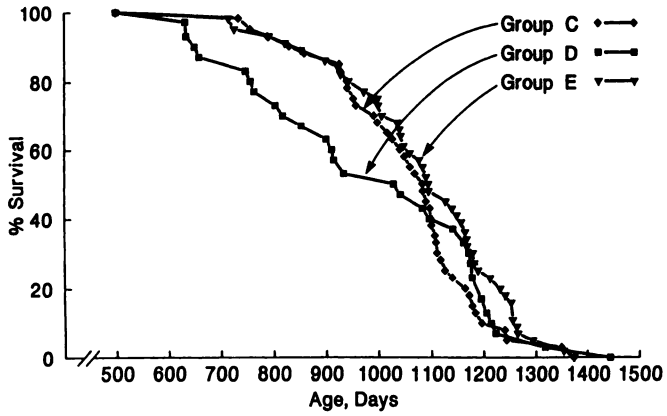

FIGURE 2 Effect of exercise on survival of food-restricted rats. Group D are voluntary wheel runners food restricted to ~70% of ad libitum intake. Group C are sedentary rats that were pair-fed with the runners in Group D. Group E are sedentary rats that were food restricted (to ~55% of ad libitum intake) to keep their body weights in the same range as those of the runners in Group D. (Adapted with permission from ref. 9).

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