Exercise Training Has a Long-Lasting Effect on Prevention of Non–Insulin-Dependent Diabetes Mellitus in Otsuka-Long-Evans-Tokushima Fatty Rats

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Exercise training has been shown to be effective in preventing the development of non–insulin-dependent diabetes mellitus (NIDDM) in a model rat (Otsuka-Long-Evans-Tokushima Fatty [OLETF]). For determination of how long a preventive effect of exercise training against the development of NIDDM lasts in this model, six male OLETF rats each were assigned to training (1) for a whole experimental period, from 7 to 28 weeks of age (E—E); (2) for the first half of the period, from 7 to 15 weeks of age (E—S); and (3) for the second half of the period, from 16 to 28 weeks of age (S—E). In addition, eight male OLETF rats were given no exercise during the experimental period (S—S). At 28 weeks of age, E—E, E—S, S—E, and S—S rats, weighed averages of 514, 542, 557, and 669 g and had abdominal fat deposits of 13.9, 21.3, 38.2, and 76.0 g, respectively. At 28 weeks of age, the cumulative incidence of NIDDM in S—S was 100%, while none of the trained rats were diabetic. The glucose infusion rate (GIR) during a hyperinsulinemic euglycemic clamp test, an index of insulin sensitivity, in the E—E group was significantly greater than that in the S—S group. The values in the E—S and S—E groups were slightly, but not significantly, less than that in the E—E group. Morphologic studies on the pancreas of E—E rats and S—E rats showed minimal changes of islets, whereas sections of islets from E—S rats appeared slightly enlarged and fibrotic, although significantly less than those of islets of S—S rats. These results demonstrate that the preventive effect of exercise training against the development of NIDDM lasts for at least 3 months after the cessation of exercise in this model.

THE BENEFICIAL EFFECTS of exercise training, such as increase in insulin sensitivity resulting in insulin sparing and changes in the plasma levels of insulin, glucagon, and ctecholamine are reported to last several days at the longest after stopping exercise.[1-5] This short-lasting beneficial effect of exercise was observed after strenuous short-term physical training in terms of insulin sensitivity evaluated by in vivo glucose disposal by the euglycemic clamp technique, blood glucose levels relative to plasma insulin concentrations during oral glucose tolerance tests (OGTT)[5] or intravenous glucose tolerance tests (IVGTT),[3] and the insulin-binding capacities of erythrocytes[1] or monocytes.[5] However, there has been no prospective study on the preventive effect of exercise training on the development of non–insulin-dependent diabetes mellitus (NIDDM) and its duration after stopping exercise in humans, and only a few retrospective reports on its effect.[6-9] A prospective study on this problem in humans is difficult, but such studies can be performed in animal models. In previous studies in a model animal with NIDDM, the Otsuka-Long-Evans-Tokushima Fatty (OLETF) rat, we found that exercise training even once a week is effective for preventing the development of diabetes mellitus and morphologic alterations of the pancreatic islets.[10,11] In the present study, we used this animal model to clarify how long this beneficial effect of exercise lasts after stopping exercise.

MATERIALS AND METHODS

Animals and Experimental Design

A spontaneously diabetic rat with polyuria, polydipsia, and slight obesity was discovered in 1983 in an outbred colony of Long-Evans rats that had been purchased from Charles River Canada in 1983 and subsequently maintained at the Tokushima Research Institute, Otsuka Pharmaceutical Co, Tokushima, Japan. By 20 generations of selective breeding, the diabetic strain, OLETF, was established in 1990. According to Kawano et al,[12] the cumulative incidence of diabetes in male rats of this strain is 81.2% at 10 months of age. Twenty-six male OLETF rats were obtained from the Tokushima Research Institute, Otsuka Pharmaceutical Co and maintained in our animal facilities under specific pathogen-free conditions (Institute for Animal Experimentation, The University of Tokushima, Tokushima, Japan), where the temperature (21 ± 2°C), humidity (55% ± 5%), lighting (7:00 AM to 7:00 PM), and air conditioning are all controlled. The animals were supplied with standard rat chow (Oriental Yeast, Tokyo, Japan) and tap water ad libitum.

Experiments were performed on 7-week-old OLETF rats at the beginning of the study. The rats were randomly divided into four groups of six rats each or eight rats in a sedentary group. The exercised groups were assigned to exercise training throughout the whole period (E—E), for the first half of the period, from 7 to 15 weeks of age (E—S) or for the second half of the period, from 16 to 28 weeks of age (S—E), respectively. The sedentary group (S—S) was given no exercise training during the experimental period (Fig 1). For training, rats were placed individually in wire-mesh cages of 36 × 36 × 27 cm with an exercise wheel (Meiko, Tokyo, Japan) and were allowed to run at their own pace. The number of revolutions of the wheel per day was recorded with a cyclometer attached to the axis of the wheel as a measure of running activity. Sedentary rats were maintained individually in conventional plastic cages of 36 × 26 × 20 cm. Trained rats were maintained in the same manner as sedentary rats when they were not engaged in exercise training. Food consumptions in 24-hour periods and body weights of test animals were measured once per week. The running activity of rats in cages with an exercise wheel was recorded every day.

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Submitted May 1, 1995; accepted August 4, 1995.

Supported by grants from the Ministry of Education Science and Culture of Japan and for a 5-Year Project for Exploration of the Pathogenesis of Diabetes Mellitus from Otsuka Pharmaceutical Co, Tokushima, Japan.

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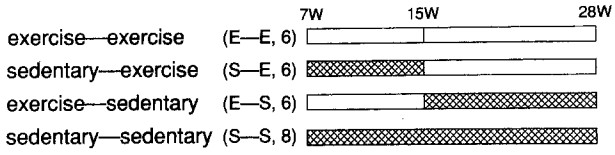

Fig 1. Experimental designs. Rats were allowed to exercise throughout the whole period (E—E), or the first half (E—S) or the second half (S—E) of the period, or were kept sedentary (S—S). The trained groups each consisted of 6 male OLETF rats kept individually in cages with an exercise wheel. The sedentary rats were 8 male OLETF rats kept 2 or 3 to a conventional cage. When not engaged in exercise training, trained rats were maintained in the same manner as sedentary rats. (□) exercise; (▩) sedentary.

OGTT

At 16, 20, 24, and 28 weeks of age, the OGTT was performed on rats at least 24 hours after their last food consumption. Two grams of glucose (500 g/L) per kg body weight was administered orally, and blood was taken from a tail vein without anesthesia at −15, 0, 30, 60, and 120 minutes for measurement of plasma glucose levels and at 0, 60, and 120 minutes for measurement of plasma insulin levels. Rats were defined as diabetic when their peak blood glucose level was ≥ 16.7 mmol/L and their 120-minute blood glucose level was ≥ 11.1 mmol/L.

Measurement of In Vivo Glucose Disposal by Euglycemic Clamp Studies

Insulin-mediated whole-body glucose uptake was measured in anesthetized rats using a euglycemic clamp[13] 2 weeks after the last OGTT. Rats were anesthetized by intraperitoneal injection of pentobarbital (50 mg · kg^{-1}) and catheters were inserted into the jugular and femoral veins at least 24 hours after their last food consumption. Rats received an infusion of insulin at 70 pmol · kg^{-1} · min^{-1} for 1 hour. Infusion of a variable amount of 100-g/L glucose solution was started at time 0 and adjusted to clamp the plasma concentration at approximately 6.1 mmol/L. Plasma samples for determination of glucose levels were obtained at 2- to 5-minute intervals for 60 minutes. Then the rats were treated with pentobarbital (60 mg · kg^{-1}), the abdomen quickly opened, blood withdrawn from the aorta for determination of total cholesterol and triglyceride levels, and the pancreas removed for morphologic studies. Data for total-body glucose uptake are shown as mean values of the glucose infusion rate (GIR) during the last 20 minutes.

Determination of Abdominal Fat

All fat pads attached to the wall of the abdominal cavity and to the viscera were collected. After removal of the viscera, the weight of all fat pads, including the epididymal fat pads, was determined.

Assays

Plasma glucose levels were determined by the glucose oxidase method with a Toecho Super from Kyoto Daiichi Kagaku (Kyoto, Japan). Insulin levels were measured with a commercial kit (Daiichi Radioisotope, Tokyo, Japan) with rat insulin (Novo Nordisk, Bagsvaerd, Denmark) as a standard. Total cholesterol and triglyceride levels were measured automatically by enzymatic techniques with a Hitachi autoanalyzer (Type 763; Hitachi, Tokyo, Japan).

Histologic Analyses

Paraffin sections (4 μm) of formalin-fixed pancreata were obtained from widely separated regions of each pancreas and stained with hematoxylin-eosin. At least 20 islets per individual were examined.

Statistical Analysis

Data are expressed as means ± SEM unless otherwise indicated. Significance was determined by analysis of variance, followed by Tukey's test for individual means. The χ^2 test was used for comparing frequencies.

RESULTS

As shown in Fig 2, the mean exercise level of E—E rats increased from 1,428 ± 335 m/d at 7 weeks of age to a peak level of 10,784 ± 1,593 m/d at 11 weeks of age, and then decreased to 3,257 ± 789 m/d at 21 weeks of age and did not change significantly thereafter. The mean daily running distances of E—S and S—E rats were similar to those in the corresponding periods of E—E rats. In general, trained rats consumed more calories than sedentary rats, but it took about 4 weeks for rats to show significant changes in daily food consumption after change from exercise to a sedentary condition or vice versa (Fig 3).

Figure 4 shows the growth curves of the groups. The body weight of S—S rats increased progressively from 258 ± 5.1 g at 7 weeks to 669 ± 10.4 g at 28 weeks of age. Physical training decreased weight gain: at 28 weeks of age, the body weight of rats in the E—E group was 514 ± 13.6 g, which was significantly less than that of rats in the S—S group. The body weight of rats in the S—E group at 20 weeks of age, 4 weeks after commencement of exercise training, was similar to that of rats in the E—E group. The growth curve of rats in the E—S group after 15 weeks of age, when exercise training was discontinued, was similar to that of rats in the E—E group during the corresponding period except for significant differences at three points in the latter half of the period, and the body weight of rats in this E—S group did not increase to that of rats in the S—S group within the experimental period. The amount of fat located in the abdominal cavity was lowest in rats in the E—E group (13.9 ± 1.0 g), and highest in rats in the S—S group (76.0 ± 4.4 g). The amounts of abdominal fat in rats in the S—E and E—S groups were intermediate between those in rats in the E—E and S—S groups, although that in the S—E

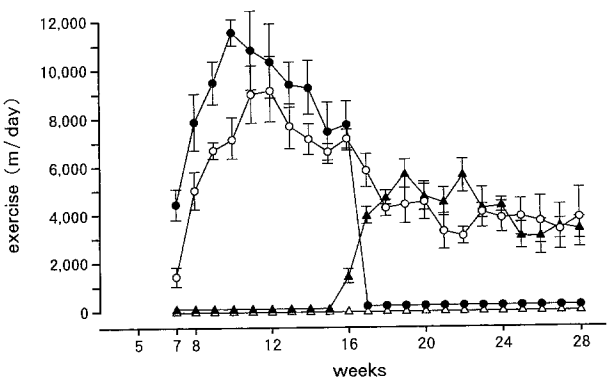

Fig 2. Chronologic changes in exercise of E—E (○), E—S (●), S—E (▲), and S—S (△) rats. Exercised and sedentary rats were the same as for Fig 1. Points and bars represent means ± SEMs.

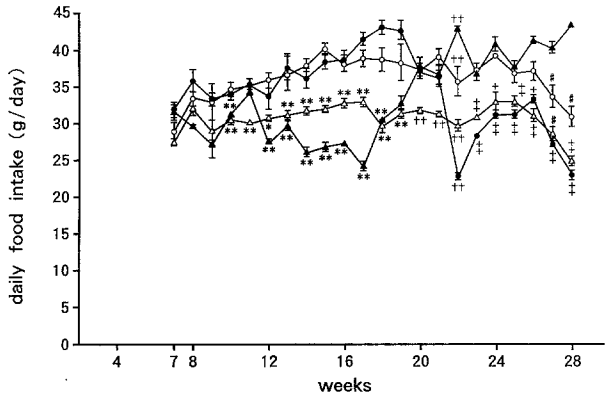

Fig 3. Chronologic changes in daily food intakes of E—E (○), E—S (●), S—E (▲), and S—S (△) rats. Exercised and sedentary rats were the same as for Fig 1. Points and bar represent means ± SEMs. *P < .05 v E—E and E—S rats. **P < .01 v E—E and E—S rats. ††P < .01 v other groups. †P < .05 v E—E and S—E rats. ‡P < .01 v E—E and S—E rats. #P < .01 v S—E rats.

group (21.3 ± 2.5 g) was significantly less than that in the E—S group (38.2 ± 2.7 g).

Plasma Lipid Concentrations

Plasma lipid concentrations of the four groups are listed in Table 1. Plasma cholesterol levels were significantly different in rats in the E—E and S—S groups, and those in rats in the E—S and S—E groups were intermediate. A similar trend was observed in the plasma triglyceride levels, but the value in the S—E group was significantly lower than those in the S—S and E—S groups and similar to that in the E—E group.

Glucose Tolerance and Incidence of Diabetes Mellitus

The chronologic changes in plasma glucose and immunoreactive insulin (IRI) responses to an oral glucose load in the four groups are shown in Fig 5. At 16 weeks of age, the S—S and S—E groups showed significantly higher plasma glucose levels 60 and 120 minutes after an oral glucose load than the E—E and E—S groups. The S—S group also

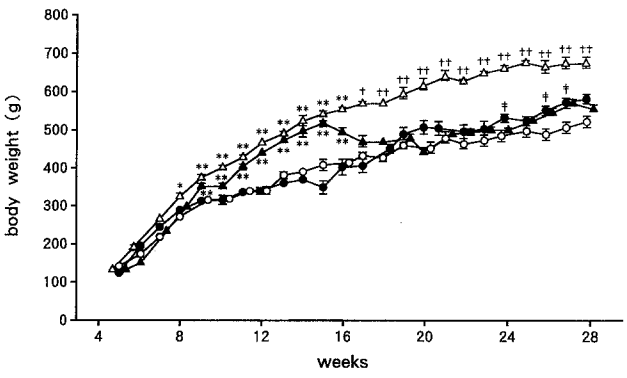

Fig 4. Chronologic changes in body weight of E—E (○), E—S (●), S—E (▲), S—S (△) rats. Exercised and sedentary rats were the same as for Fig 1. Points and bars represent means ± SEMs. *P < .05 v E—E and E—S rats. **P < .01 v E—E and E—S rats. †P < .05 v other groups. ††P < .01 v other groups. QP < .05 v E—E rats.

Table 1. Plasma Concentrations of Total Cholesterol and Triglyceride in Male OLETF Rats Trained for the Whole Experimental Period (E—E), the Second Half (S—E) and the First Half (E—S) of the Period, and Sedentary Male OLETF rats (S—S)

Rat Group	Total Cholesterol (mmol/L)	Triglyceride (mmol/L)
E—E (n = 6)	1.24 ± 0.05*†	0.52 ± 0.12*
S—E (n = 6)	1.79 ± 0.05*	0.74 ±0.09*
E—S (n = 6)	1.79 ± 0.16*‡	2.44 ± 0.41*†‡
S—S (n = 8)	2.77 ± 0.14	3.58 ± 0.27

NOTE. Values are the mean ± SEM for the numbers of animals shown in parentheses.
*P < .01 v S—S.
†P < .05 v S—E.
‡P < .05 v E—E.

showed higher levels at 20, 24, and 28 weeks of age, but the S—E group showed no hyperglycemic response to an oral glucose load at 20, 24, and 28 weeks of age. The plasma glucose levels in the OGTT of the E—S group at 20, 24, and 28 weeks of age were similar to those at 16 weeks of age, showing no deterioration of glucose tolerance during the sedentary period after exercise training for a certain period. According to the criteria for diabetes mellitus based on the plasma glucose level in the OGTT described earlier, at the end of the experiment the incidence of diabetes mellitus was 100% in the S—S group, but zero in the three other groups. Plasma IRI concentrations during the OGTT were significantly higher at at least one point throughout the experiment in the S—S group than those in the other groups at the corresponding points. After 4 weeks of exercise training, the hyperinsulinemia observed at a basal level in the S—E group at 16 weeks of age was ameliorated, but persisted until the end of the experiment. At 28 weeks of age, the plasma IRI concentration of the E—S group was slightly, but not significantly, higher than those of the E—E and S—E groups.

In Vivo Glucose Disposal

Figure 6 shows that insulin-stimulated glucose disposal in vivo was 62% less in the S—S group than in the E—E group (P < .01). The values in the E—S and S—E groups were also slightly, though not significantly, lower than that in the E—E group.

Histologic Findings

Light microscopic findings in random sections through the pancreata of rats in the E—E, S—E, E—S, and S—S groups are shown in Fig 7A, B, C, and D, respectively. Islets of the rat in the S—S group (Fig 7D) are clearly enlarged and have typical alterations. More than half the islets in individual rats were 250 to 500 μm in diameter, and islets greater than 500 μm were observed in seven of eight pancreata of S—S rats (Table 2). Proliferation of connective tissue to various extents was seen in these enlarged islets, in which clusters of endocrine cells were widely separated from each other by transverse bands of connective tissue, resulting in a multinodular appearance. Sections of islets of the E—E group appeared normal except for

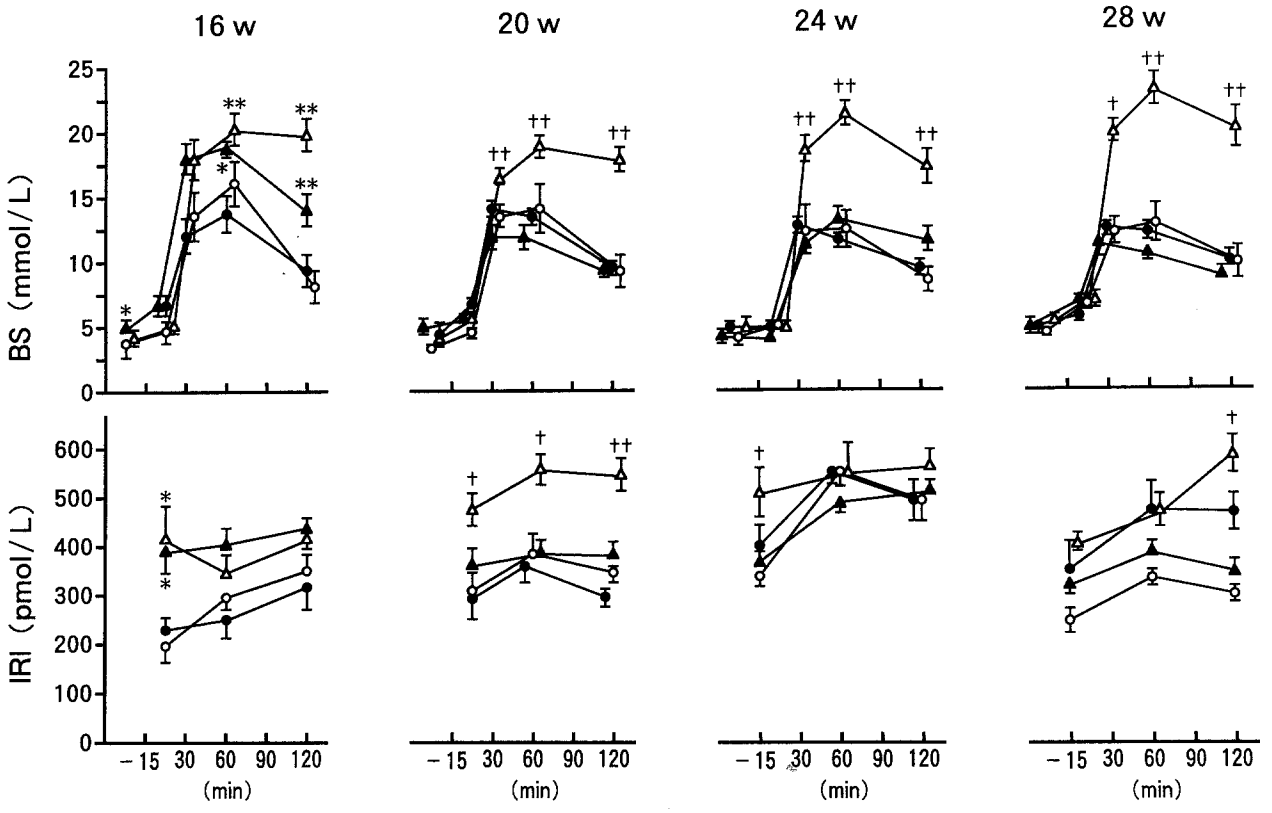

Fig 5. Chronologic changes in plasma glucose (top) and IRI (bottom) responses to an oral glucose load in E—E (○), E—S (●), S—E (▲), and S—S (△) rats. Exercised and sedentary rats were the same for Fig 1. After overnight starvation, 2 g glucose/kg body weight was administered orally. Blood samples were taken from a tail vein without anesthesia. Points and bars represent means ± SEMs. *$P < .05$ v E—E and E—S rats. **$P < .01$ v groups E—E and E—S rats. †$P < .05$ v other groups. ††$P < .01$ v other groups.

being slightly enlarged. Histopathologic alterations in pancreata from the S—E and E—S groups were intermediate between those of the S—S and the E—E groups, although those of the S—E group were more similar to those of the E—E group, and those of the E—S group to those of the S—S group. The frequencies of various degrees of histopathologic changes differed significantly in the various groups ($\chi^2 = 15.4$, $P < .001$ regarding enlargement of islets; $\chi^2 = 37.3$, $P < .001$, regarding increase in connective tissue).

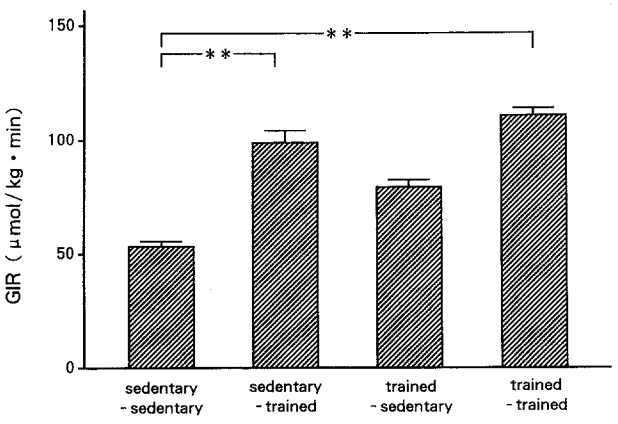

Fig 6. Effects of exercise on insulin-stimulated glucose disposal in vivo in E—E, E—S, and S—S rats. Exercised and sedentary rats were the same as for Fig 1. After overnight starvation, rats were anesthetized and received an infusion of insulin at 70 pmol · kg^{-1} · min/h. Infusion of a 100-g/L glucose solution was adjusted to clamp the plasma glucose concentration at ~6.1 mmol/L. The GIR shown is the mean value in the last 20 minutes. **$P < .01$.

DISCUSSION

In the present study, voluntary exercise training prevented the development of diabetes mellitus in a model rat with NIDDM. This is consistent with previous reports[10,11] and the findings reported by several investigators,[8,9] who clearly showed that increased physical activity was effective in preventing NIDDM in humans. This beneficial effect of exercise was found to persist until the end of the experiment at 28 weeks of age, even when exercise training was stopped at 15 weeks of age. This long-lasting beneficial effect of exercise is not consistent with the results reported by others.[1-5] This difference in the duration of the beneficial effect of exercise was due to a difference in the parameters by which the effect was evaluated. We evaluated the effect of exercise on the development of diabetes mellitus in a model rat with NIDDM, while others evaluated its effect on the actions of insulin in healthy humans. Furthermore, the total amount of exercise was much greater in our animals than in the human subjects, taking body size and life span into consideration.

One finding in our study that apparently did not support the long-lasting effect of exercise on insulin sensitivity after cessation of exercise was that increased peripheral glucose

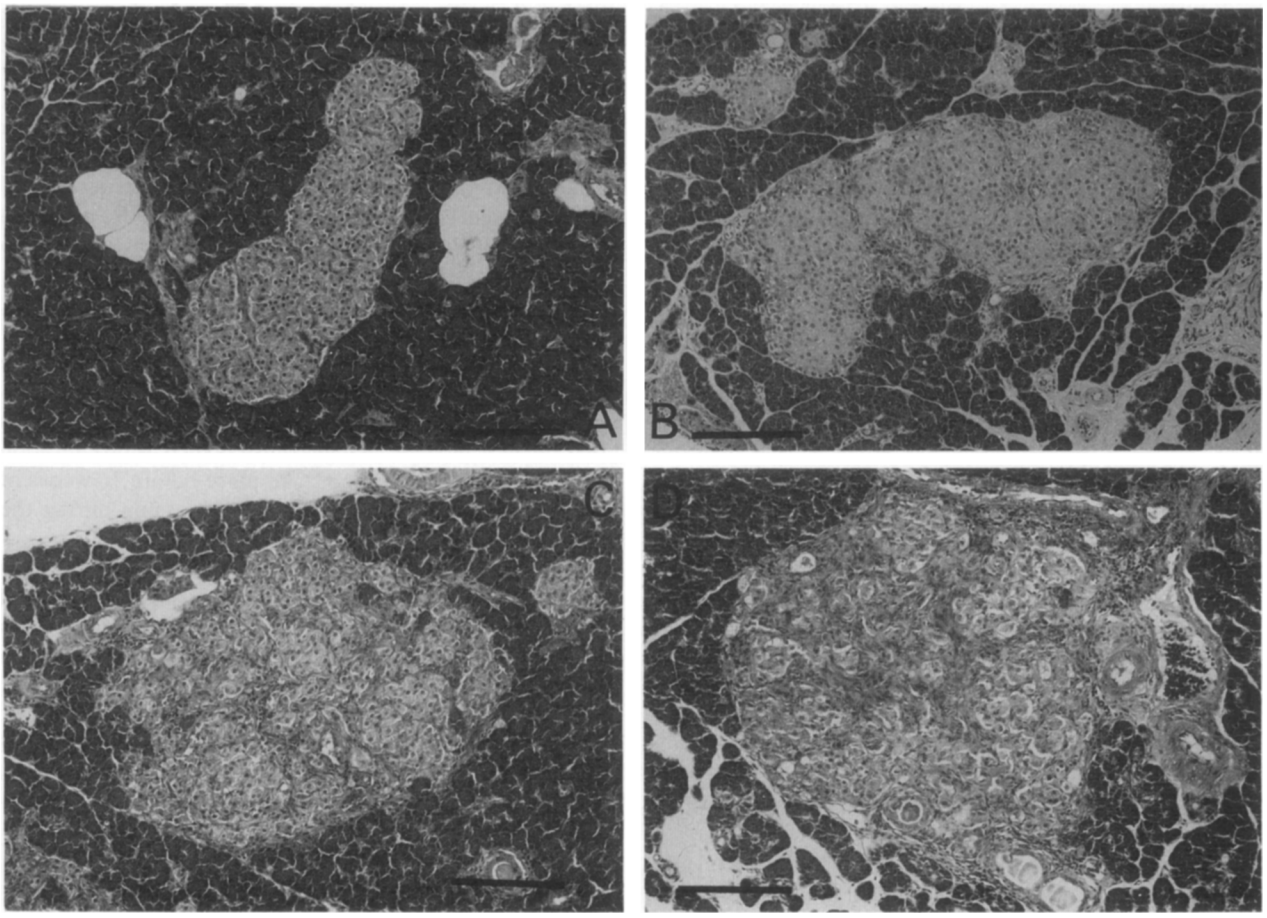

Fig 7. Typical light microscopic features of the islets of (A) E—E, (B) S—E, (C) E—S, and (D) S—S rats. Note the differences in islet sizes and degrees of connective tissue proliferation. Hematoxylin and eosin stain. Original magnification ×160. Bars indicate 100 μm.

utilization during insulin clamp studies, assessed as GIR in the E—S group, was 29% less than that in the E—E group, but not significantly different from the values in the E—E and S—S groups (Fig 3). Insulin sensitivity was investigated 2 weeks after the last OGTT to avoid its aftereffect. Since exercise had been stopped for 2 weeks in the E—E and S—E groups, the GIRs in these groups may have been higher than those observed if they had been measured before the short-lasting enhanced insulin sensitivity decreased after cessation of exercise. If so, the difference between the GIRs of the E—S group and the E—E group might have been statistically significant. When bred in usual conditions, the model rat, OLETF, is insulin-resistant and its GIR is less than that in the nondiabetic control strain, Long-Evans-Tokushima-Otsuka (LETO) rats, from as early as 16 weeks of age.[14] Consequently, exercise training increased insulin sensitivity from a pathologically low level to higher levels in normal rats. This is quite different from the effect of exercise training in increasing insulin sensitivity from a normal to a supranormal level in other studies.[1,2,4] The increased insulin sensitivity decreased to nearly the normal level after cessation of exercise in our experiment as in those of others.[1-5] Thus, we assume that when the body weight was kept within a normal range, insulin sensitivity

Table 2. Variations in Islet Size and Structure in Pancreata From Male OLETF Rats Trained for the Whole Experimental Period (E—E), the Second Half (S—E) and the First Half (E—S) of the Period, and Sedentary Male OLETF Rats (S—S)

	Enlargement of Islet				Increase in Connective Tissue			
Rat Group	−	±	1+	2+	−	±	1+	2+
E—E	1	1	3		2	3		
S—E	1		4	1	2	4		
E—S		1	3	2	1		3	2
S—S			1	7				8

NOTE. Values are numbers of rats that show the indicated degree of histological changes. Islet: −, >95% of 100 to 250 μm diameter; ±, between (−) and (+); +, predominantly (>50%) 150 to 350 μm diameter, those of >500 μm being rare (<2%); ++, predominantly (>50%) 250 to 500 μm diameter, those of >500 μm being frequent (>10%). Connective tissue proliferation: −, no fibrosis; ±, between (−) and (+); +, thin fibrous bundles in >50% of islets; ++, thick fibrous bundles in >50% of islets.

increased to a supranormal level during exercise and decreased to nearly a normal level, but not a pathologically low level, after cessation of exercise in our model rats.

In the E—S group, after cessation of exercise, body weight gain and abdominal fat deposition were less than in the S—S group. Physical activity appears to have an important role in the prevention of NIDDM through its effects in body weight and insulin sensitivity. Taken as a whole, the evidence suggests that in the E—S group, exercise training decreased the occurrence of NIDDM by preventing obesity and/or beneficially altering the distribution of fat,[15] resulting in maintenance of insulin sensitivity at a near normal level.

The E—S group did not gain body weight excessively or become obese after the exercise training period, although they consumed approximately 30% more calories than the S—S group for 4 weeks, from 16 to 20 weeks of age after cessation of exercise training. This might be due to a sharp decline in the daily food intake thereafter. In addition, the prevention of obesity by exercise training during infancy might influence the occurrence of obesity during adulthood, since obesity in infancy is hyperplastic, while that in adulthood is hypertrophic. In the former, the total number of adipose tissue cells in the body is increased and the cells are enlarged, whereas in the latter only the cell size is altered.[16,17] Exercise training during infancy may have a protective effect against the development of obesity by inhibiting excessive deposition of fat in adipocytes and by reducing proliferation of adipocytes.

In the E—S group, the basal plasma IRI level and the response to an oral glucose load tended to be increased in conjunction with normoglycemia at 28 weeks of age, indicating the development of slight insulin insensitivity. As shown in Fig 7 and Table 2, in the E—S group the moderate enlargement of islets was similar to that in the S—E group, but proliferation of connective tissue was greater than in the latter group. In the E—S group, the slight insulin insensitivity during the latter half of the experimental period, as shown by the slightly decreased GIR, indicated that the islets were forced to secrete more insulin to overcome the marginal loss of normal insulin sensitivity. This might have put a stress on the pancreatic β cells, leading to their damage and death and infiltration of connective tissue. The S—E group showed none of the morphopathologic changes observed in the E—S and S—S groups, except slight enlargement of islets, which suggests that the morphologic changes of islets such as proliferation of connective tissue did not take place before 16 weeks of age or were ameliorated by exercise training during the latter half of the experiment.

We conclude from this study that physical activity may have a protective effect against the development of NIDDM by helping to maintain a proper lean to fat balance with respect to body mass for at least 3 months after its cessation in the model OLETF rats with NIDDM. In addition, exercise training during infancy maintained β-cell function. This may be useful for preventing the development of NIDDM for a certain period in adults when causal factors such as inactivity and/or overeating are loaded.

ACKNOWLEDGMENT

We are grateful to Misa Bando for editorial assistance.

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