Pathoetiology and prevention of NIDDM Lessons from the OLETF rat *

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Abstract: The OLETF rat, a genetic model of spontaneous development of NIDDM, exhibits hyperglycemic obesity with hyperinsulinemia and insulin resistance similar to that in humans. It is still unclear whether a defect in the β-cell proliferation per se is the primary pathogenetic event in this model rat. To clarify this matter, we used partially pancreatectomized rats as a model. Male rats of 6 weeks of age were allocated at random to two groups: 70% pancreatectomy (Px) and sham-pancreatectomy (sham). Each group was divided into 4 subgroups by the date of sacrifice after surgery.

Sustained hyperglycemia was evident in the Px OLETF rats after surgery. This was associated with insufficient proliferation of β-cells, characterized by a decrease in β-cell labeling with 5-bromo-2'deoxyuridine in proportion to a decrease in β-cell mass and reduction in insulin content in the remnant pancreas. Administration of nicotinamide, however, ameliorated the sustained hyperglycemia by increasing β-cell proliferation. These findings suggest that OLETF rats have a poor capacity for proliferation of pancreatic β-cells, and that this change may be the critical pathogenetic event prior to the onset of overt diabetes.

OLETF rats following long-term caloric restriction and spontaneous exercise training show normal glucose tolerance accompanied by an increase in GIR as shown by a euglycemic clamp. Both exercise training and caloric restriction normalize the abnormalities in the pancreas such as marked hypertrophy of islets and hyperplasia of connective tissues in islets. It is particularly noteworthy that exercise training significantly elevated the β-cell mass / body weight ratio. This evidence obtained from OLETF rats may be of value when the mechanism of diet and exercise effects on diabetic patients are considered. J. Med. Invest. 46 : 121-129, 1999

Key words **:** *β-cell mass, β-cell proliferation, partial pancreatectomy, nicotinamide, preventive intervention*

INTRODUCTION

Extensive study of the pathophysiology of NIDDM has enabled the identification of two defects, insulin resistance and impaired β-cell function. These two fundamental defects, included in the pathogenesis of NIDDM, are caused by a combination of genetic and environmental factors (1). However, controversy persists concerning which defect can be detected earliest in the course of NIDDM. In prediabetic obese individuals, such as Pima Indians, β-cells can compensate for insulin resistance by sufficiently increasing insulin secretion and enhancing β-cell sensitivity to glucose, but when the β-cell response is inadequate, glucose intolerance becomes apparent (2). According to this view, primary insulin resistance occurs first and results in hyperinsulinemia with several metabolic consequences and ultimately endocrine decompensation (3). No investigative study to gather direct evidence of the primary defect in the endocrine pancreas can be performed on humans, such as Pime Indians who later develop NIDDM. However, animal models do provide an opportunity to study this problem.

Caloric restriction and/or exercise training are

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known to be effective in the therapy of diabetes mellitus for stabilizing glucose homeostasis and improving diabetic control. It is uncertain whether these therapies are effective in preventing diabetes, although several indirect lines of evidence support the concept that they have a protective effect. There is no direct evidence for their preventive effect on the development of NIDDM, since implementing such preventive measures is difficult in humans. However, this possibility can be examined in animal models.

In 1983, a spontaneously diabetic rat with mild obesity was discovered in an out-breeding colony of Long-Evans rats at the Tokushima Research Institute of Otsuka Pharmaceutical Company (Tokushima, Japan). The rat was subsequently maintained and after 20 generations of selective breeding, a diabetic strain, named the Otsuka Long-Evans Tokushima Fatty (OLETF) rat, was established in 1990 (4). The cumulative incidences of diabetes in male rats are 67%, 78%, and 81.2% at 4, 6 and 10 months of age, respectively. On the other hand, the cumulative incidences in female rats, which do not become obese under ordinary feeding, are very low at all ages. A diabetogenic gene (ODB-1) has been reported to be located on the X-chromosome in OLETF rats (5). A control strain, the Long-Evans Tokushima Otsuka (LETO) rat, which originated from the same Long-Evans stock, shows normal responses to an oral glucose tolerance test throughout life.

In this paper, we will review two matters as follows : 1) what is the real pathoetiology of impaired β-cell function in NIDDM, and 2) whether interventions such as caloric restriction and exercise training have preventive effects on the onset and development of NIDDM

1. What is a pathoetiologic event of β-cell dysfunction in NIDDM?

Although various abnormalities in the pancreas of the OLETF rats have been described, their presence may not be sufficient to explain the pancreas, inability to meet the abnormal metabolic demands for insulin to control diabetes when diabetogenic factors are sustained. It would, therefore, be interesting to know if the poor capacity for proliferation of pancreatic β-cells contributes critically to the inability to compensate for an increased insulin demand. To test this hypothesis, we used a partially pancreatectomized rat as a model to determine whether there is a difference in the compensatory capacity of pancreatic β-cell proliferation between OLETF and their diabetes-resistant counterparts, LETO rats, and whether this difference, if any, contributes to impairment of the carbohydrate metabolism. For this purpose, the animals at 6 weeks of age were allocated at random to two groups : 70% Px and sham Px. Each group was divided into four subgroups according to the date of sacrifice after surgery : 3-day, 7-day, 28-day (treated with phlorizin, nicotinamide, or saline), and 91-day. The compensatory capacity of the pancreatic remnant was determined by comparing the changes in blood glucose levels and compensatory proliferation of the pancreatic remnant after surgery.

1) Quantification of extent of pancreatectomy (Px)

The operation for a 70% Px was performed as follows. After an overnight starvation, the animals were anesthetized with ether and given additional ether, if required, during surgery. All pancreatic tissue was removed by gentle abrasion with cotton applicators, except for the anatomically well-definded remnant bordered by the branch of the hepatic portal vein and the first portion of the duodenal loop. The sham operation was performed by disengaging the pancreas from the mesentery and gently rubbing it between the fingers. All operations were performed by one person, whose surgical technique was well controlled, and as a result, the samples of the removed segments from each group gave an expected coefficient variation of 10%. At that time (6 weeks of age), the remnant equivalent of the pancreas (the portion of the pancreas with the same anatomical boundaries as the remnant left in the 70% Px rats) was 30.4±1.0% (n=11) of the total pancreatic weight with 27.8±3.7% (n=6) of the total β-cell mass and 35.6±10.8% (n=5) of the total insulin content in the OLETF rats. For the LETO rats, corresponding values were 30.4±1.3% (n=11), 29.4±3.3% (n=6) and 36.0±2.5% (n=5) of the values for the whole pancreas. No significant difference was noted for any other morphologic characteristics between OLETF and LETO rats.

2) Hyperglycemia

In the OLETF rats, a 70% Px resulted in significant non-fasting hyperglycemia. The blood glucose level began to increase to 9.4±0.9 mmol/l on day 3 after surgery (Fig.1), and remained above 16.7 mmol/l from the sixth day. No sustained hyper-

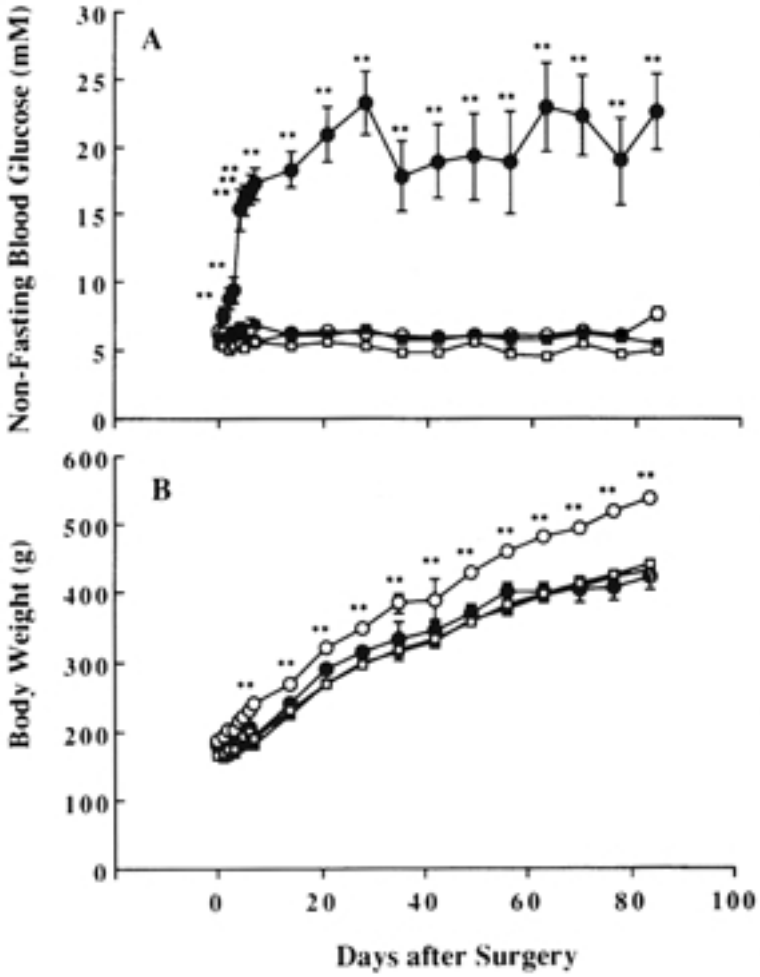

Fig.1. Effects of 70% pancreatectomy on non-fasting blood glucose (A) and body weight (B) of Px OLETF (●), sham OLETF (○), Px LETO (■), and sham LETO (□) rats during the period of observation. Values shown are for all surviving rats in each group, the number of which decreased with time as rats were killed from each subgroup at 3, 7, 28, and 91 days after 70% pancreatectomy. **P<0.01 vs. all other groups.

glycemia was noted in the control LETO rats after surgery. It has been reported that no less than 90% Px would induce hyperglycemia in the normal rodents, except for rats with postprandial hyperglycemia afterm 50% Px and administration of dexamethasone (6), or with minimal chronic hyperglycemia after 60% Px plus 10% sucrose in the drinking water (7). The latter findings may have been due to insufficient compensatory proliferation of residual β-cells to increased insulin demand caused by administration of dexamethasone and 10% sucrose. OLETF rats exhibit insulin resistance at around 12 weeks of age (8), but not at 6 weeks of age or younger, at which age they were used in this study. It has been reported that following a 90% Px in rats, the β-cell mass in the remaining tissue is enhanced 3-to 4-fold within a few weeks, suggesting that β-cells, even in adults, have a far greater capacity to respond to glucose stimulation with compensatory growth by enhanced replication and hypertrophy of individual cell than previously realized (9). Furthermore, hyperglycemia accelerates β-cell mass growth by increasing the number of β-cells undergoing mitosis (10, 11). Therefore, the sustained hyperglycemia observed in the Px OLETF rats very early after surgery would be due to an insufficient adaptive increase in proliferation of β-cells in response to hyperglycemia. To clarify this, we analyzed the pancreatic β-cell proliferative capacity.

3) Defective proliferation in pancreatic β-cells

The reduction in β-cell mass is a critical pathological feature of pancreatic islets in NIDDM. Animal experiments, however, indicate that genetic background is of considerable importance in determining the proliferative response of β-cells to diabetogenic factors leading to a lasting increase in demand for insulin (12, 13). Our findings showed that at each time point (3 days, 7 days, 28 days or 91 days), the remnant equivalents of the sham animals in both OLETF and LETO rats were around 30% of the values for the whole pancreatic weight, suggesting that the relative growth of the remnant equivalent was similar to that of the remainder of the pancreas in the sham rats. It was noted that the remnant tissue weight, as a percentage of the whole pancreatic weight, on day 3 after surgery showed a marked increase in both Px OLETF and LETO rats. The remnant on day 3 after surgery was somewhat edematous (38.3±1.2% of whole pancreatic weight in the OLETF and 41.4 ±1.9% % of whole pancreatic weight in the LETO rats), which may have resulted in a slight overestimation of the tissue weight. Thereafter further increase in growth was detected in the Px LETO rats (36.3±1.5%, 41.0±1.3% and 45.0±3.4% of whole pancreatic weight on days 7, 28, and 91, respectively), while no such growth was detected in the Px OLETF rats ; around 30% of whole pancreatic weight, similar to the values for the sham rats.

As shown in Fig.2-A with in vivo labeling using 5-bromo-2 ˈdeoxyuridine (BrdU), at a dose of 100 mg/kg BW, proliferation of β-cells from the pancreatic remnant was seen during the first 7 days after

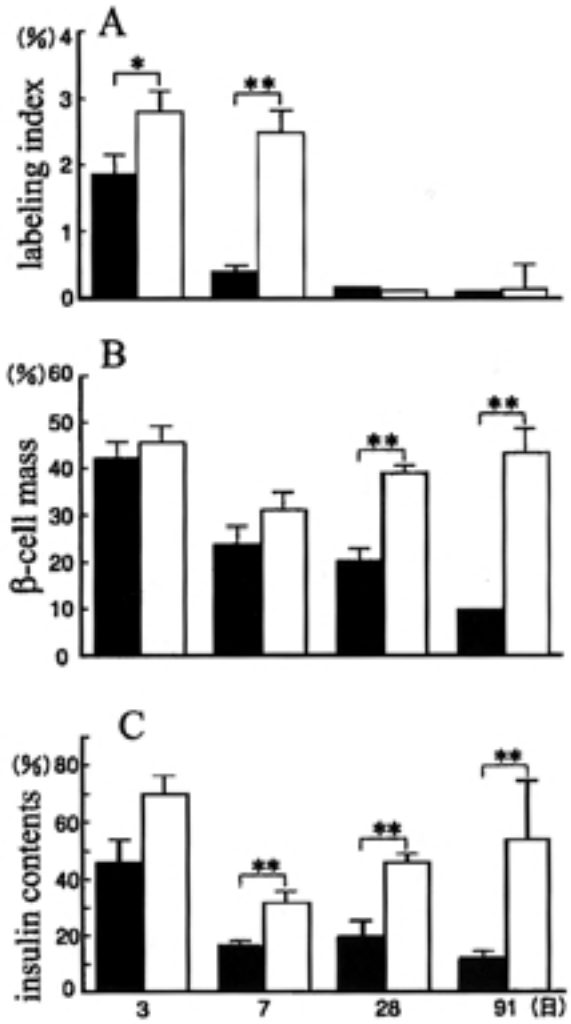

Fig.2. Labeling index (A) with 5-bromo-2'-deoxyuridine, β-cell mass (B) and insulin contents in pancreatic remnant of Px OLETF (■) and Px LETO (□) rats at 3, 7, 28 and 91 days after surgery. *P<0.05, **P<0.01

surgery. The mean labeling index (Li) of β-cells in the sham of both OLETF and LETO rats was higher than that thereafter, because the pancreas was still growing rapidly at that age, but did not subsequently exceed 0.3%/24 hr. However, the mean Li of β-cells in the Px OLETF rats was higher than that in the sham rats on day 3. At 7 days, the mean Li of β-cells was significantly lower in the Px OLETF rats than in the Px LETO rats. On days 28 and 91, the mean Li of β-cells not only in the Px OLETF but also in the Px LETO rats was maintained at a low level similar to that in the sham rats (less than 0.1%/24h). The BrdU-Li of β-cells we obtained suggests that the period crucial for expansion of the β-cell population may be limited to the first 7 days after surgery, which may thus be a critical compensatory period and mark the compensatory function of the latter remnant pancreas.

We used Weibel's point-counting morphometrics (14) to quantitate the absolute β-cell mass, and then calculated the percentage of β-cell mass in the pancreatic remnant to total β-cell mass in whole pancreas from the sham rats. As shown in Fig.2-B, the β-cell mass in the pancreatic remnant of the Px OLETF rats was significantly less than 30% of the total β-cell mass, except on day 3 after surgery, but in the Px LETO, the β-cell mass was significantly higher than the expected value of 30% and reached 45% of the total β-cell mass at 91 days after surgery. Compared with the Px LETO rats, the β-cell mass at each time point, as a percentage of the whole pancreas, showed a progressive decrease in the Px OLETF rats. As a parallel finding (Fig.2-C), the insulin content in the remnant from the Px OLETF rats was significantly less than 30% of the total insulin content, except on day 3 after surgery, but in the Px LETO rats, the increased percentage of insulin content was matched with an increase in β-cell mass, significantly higher than the expected value of 30%, and reached 53.1±20.7% of total insulin content at 91 days after surgery.

The elevated labeling of β-cells synthesizing DNA in the Px LETO rats above that in their sham rats thus provides evidence of an increase in β-cell number or greater β-cell proliferation during the period of observation (15), while decreases in β-cell mass and insulin content in the Px OLETF rats may be a reflection of the smaller number of β-cells, and β-cell degranulation and fibrosis within some islets, which is known to occur with the defect of β-cell proliferation and sustained hyperglycemia (16).

4) Defective β-cell proliferation unaffected by restoration of normoglycemia

Taking account of the hyperglycemic stimulus and a possible effect of glucose toxicity on proliferative activity of β-cells, the animals were injected with phlorizin, 400 mg/kg.body wt. per day, divided into three equal doses at 8 h intervals to ensure continuous, day-long inhibition of renal tubular glucose reabsorption. We used phlorizin not only to eliminate the hyperglycemic stimulus to proliferation of β-cells, but also to avoid any impaired effect of hyperglycemia on β-cell function (17). As expected, the hyperglycemia was normalized with phlorizin, but this insufficient compensatory capacity for β-cell growth was not ameliorated in the Px OLETF rats at 28 days after surgery, suggesting that the abnormality of the proliferative capacity in OLETF rats was unrelated to both the stimulative and toxic effects

of hyperglycemia. It can therefore be concluded that the poor capacity for proliferation of β-cells may be genetically determined.

5) Amelioration of hyperglycemia with increasing β-cell proliferation induced by nicotinamide

To confirm the sustained hyperglycemia as being due to an uncompensated increase in the β-cell mass after surgery, nicotinamide, a potent inhibitor of islet β-cell poly (ADP-ribose) synthase (18-20), at a dose of 350 mg/kg. BW, was given on the third day after surgery, at which time hyperglycemia first became evident in the Px OLETF rats, and was continued until 28 days after surgery. Non-fasting blood glucose levels in the Px OLETF rats were significantly reduced by the administration of nicotinamide. In the Px OLETF rats, non-fasting blood glucose values decreased gradually, and remained at levels that were significantly higher than in the sham rats, but significantly lower than in the saline-treated Px rats, and approached the sham levels at 28 days after surgery. In the nicotinamide-treated Px rats of both strains, it was clear that a considerable increase in the β-cell mass in the Px remnants had occurred (2.8-fold increase in the Px OLETF rats and 1.6-fold increase in the Px LETO rats compared with the saline-treated rats). The findings of the present study provide further support for the presence of a relationship between sustained hyperglycemia and insufficient proliferation of β-cells in the Px OLETF rats, since the augmented proliferate capacity by administration of nicotinamide (350 mg/kg. BW.) manifested as amelioration of the hyperglycemia with a significant decrease in non-fasting blood glucose and increased β-cell mass in the remnant pancreas. The results we obtained with nicotinamide suggest that it specifically stimulates β-cell proliferation in this model rat, because a 3% increase in the remnant tissue weight in both OLETF and LETO rats was accompanied by a far greater increase in the β-cell mass (2.8-fold increase in the Px OLETF and 1.6-fold increase in the Px LETO), as compared with that in the saline-treated counterparts, and the crucial period for expansion of β-cells was consistent with the decrease in blood glucose. Therefore, the failure of β-cell proliferation in the OLETF rats should be a cause of hyperglycemia after a 70% pancreatectomy, rather than an effect.

In conclusion, a 70% pancreatectomy induced sustained non-fasting hyperglycemia in OLETF rats which was associated with a defect in the compensatory proliferation of β-cells. This defect was unaffected by restoration of normoglycemia when phlorizin was used. Administration of nicotinamide ameliorated this sustained hyperglycemia by increasing the β-cell mass in OLETF rats. These findings imply that the pancreatic β-cells are not able to compensate for changes in functional demand, once diabetogenic factors are sustained, but this defect could be ameliorated or improved by administration of nicotinamide, although the predisposed genetic defect in this model rat may impair this capacity for thev β-cell response to proliferation.

2. Are caloric restriction and exercise training effective in preventing diabetes mellitus in the OLETF rats ?

Caloric restriction and/or exercise training ameliorate glucose intolerance in NIDDM. Therefore, to prevent the onset of NIDDM, caloric restriction and exercise training are recommended (21). However, there is no direct evidence for a preventive effect on the onset of NIDDM, since such a study is not possible in humans. Animal models, however, provide an opportunity for such a study.

Using OLETF rats whose cumulative incidence of diabetes mellitus is known to be 80~90% at 24 weeks of age (4), we attempted to determine whether caloric restriction and exercise training have preventive effects on the onset and development of NIDDM.

Preventive effect of the interventions on onset of diabetes

Five weeks old male OLETF rats were assigned to three groups [exercise training, fed ad libitum (Ex) ; sedentary, fed with caloric restriction (CR) ; and sedentary, fed ad libitum (NT) groups]. Animals in the Ex group were placed in individual wire mesh cages with an exercise wheel, and were allowed to run at their own pace. The mean length of the running was 5,243 m / day (22). The CR group was supplied with 70% of the amount of the food consumed by the NT group. The rats of each group were maintained until 24 weeks of age under the conditions described above. At 24 weeks of age, an oral glucose tolerance test (OGTT) was performed and glucose infusion rate (GIR) was measured by a euglycemic clamp within 2 weeks after the OGTT.

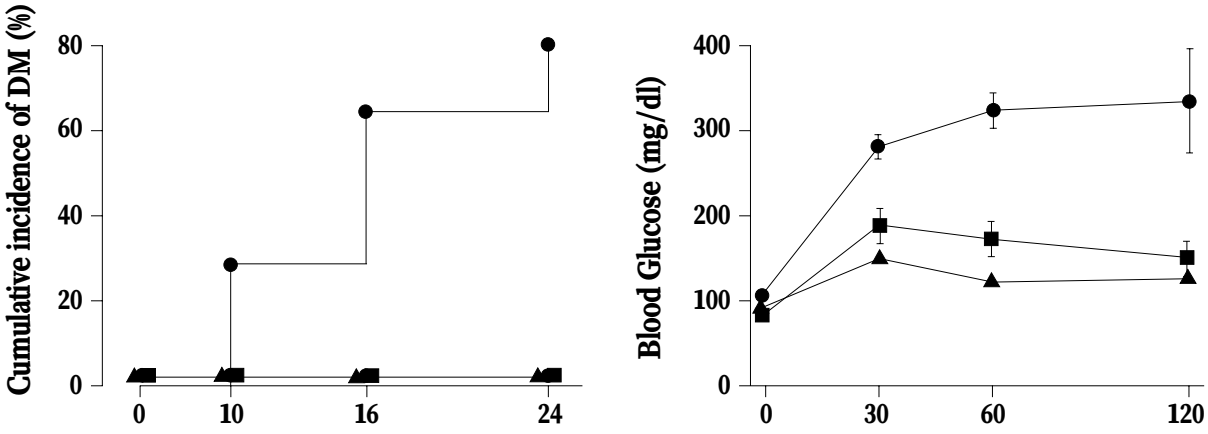

Fig. 3. Incidence of diabetes (left panel) and blood glucose response to oral glucose (right panel) in OLETF rats under caloric restriction and exercise. Diagnosis of diabetes mellitus was made when rat had two criteria as follows after a glucose=(2 g/kg) solution was given per os ; a) a peak level of plasma glucose>16.8 mM, and b) a level of plasma glucose at 120 min>11.2 mM. (●) : sedentary, fed ad libitum, (■) : sedentary, fed with caloric restriction, (▲) : exercise training, fed ad libitum.

1) The cumulative incidence

Fig.3 shows the cumulative incidence of diabetes mellitus (left panel) and the blood glucose responses after OGTT up to 24 weeks of age (right panel). The cumulative incidences of diabetes mellitus in the NT group at 10, 16 and 24 weeks of age were 30, 67 and 78%, respectively, while the cumulative incidences in the Ex and the CR groups remained at 0% throughout the experimental period. The CR group and Ex group showed significantly lower blood glucose levels at 30, 60 and 120 min. after an oral glucose load, as compared to the NT group. Hansen and Bodkin reported similar findings in rhesus monkeys (23), where the effects of sustained caloric restriction and maintenance of normal body composition completely prevented the development of NIDDM or indefinitely delayed its onset.

2) The glucose infusion rate and abdominal fat

Rats received an infusion of insulin at 60~70 pmol/kg per min for 60 min. A variable infusion of 100 g/l glucose solution was started at time 0 and adjusted to clamp the plasma glucose concentration at ~6.1 mM. Plasma samples for determination of glucose were obtained at 2- to 5-min intervals throughout the study. At the end of the 60 min study, the glucose infusion rate (GIR) was calculated.

The GIRs, indexes of insulin resistance, in the CR group (76.4±13.4 mmol/kg•min.) and the Ex group (95.0±6.1 mmol/kg•min.) were significantly greater than that in the NT group (36.1±5.0 mmol/kg•min.), indicating that these interventions ameliorated insulin resistance. The GIRs were inversely related to the weight of abdominal fat. Physical activity and caloric restriction may have a protective effect against the development of NIDDM by aiding the maintenance of a proper lean to fat balance with respect to body mass (22, 24). This was one of the major mechanisms by which the trained or food restricted rats did not become diabetic.

Kissebah has proposed that an increase in the size of the visceral fat deposit is a precursor to increased lipolysis and elevated free fatty acid (FFA) flux and metabolism and to the subsequent overexposure of hepatic and extrahepatic tissues to FFA, which then, in part, promotes aberrations in insulin actions and dynamics. The resultant changes in glucose/insulin homeostasis, lipoprotein metabolism, and vascular events then lead to metabolic morbidities such as glucose intolerance, NIDDM, dyslipidemia, and increased risk for coronary heart disease (25). Therefore, caloric restriction and exercise training are effective in preventing NIDDM, probably as a result of a decreased mass of abdominal fat.

3) The structure of the pancreatic islets

The islet of sedentary OLETF rats fed ad libitum was enlarged and had a multinodular appearance. Clusters of endocrine cells were widely separated from one another by bands of connective tissue.

Due totheir obesity-induced insulin insensitivity, islets are forced to secrete more insulin in order to overcome the loss of normal insulin sensitivity. This may put a stress on the pancreatic β-cells, leading to their damage and death and a concomitant infiltration of connective tissue in the case of the

sedentary rats fed ad libitum.

However, exercise training and caloric restriction resulted in the maintenance of a nearly intact morphological status of the pancreatic islets. Exercise training and caloric restriction help to prevent OLETF rats from becoming obese, resulting in amelioration of insulin resistance, which, in turn, prevents β-cells from overproduction of insulin leading to the damage and death, and infiltration of connective tissue.

Similar beneficial effects of exercise training and caloric restriction were observed in the micro-angio-architecture of the islets. As shown in Fig.4, the glomerulum-like networks of the islet capillaries from the NT rat group were sparse and irregular, while those from the Ex and CR groups had a dense and glomerular appearance similar to that of the normal control, LETO rats. The adequate vascularization of islets may not only require the formation of a dense capillary network to ensure a supply of oxygen to the tissue, but also include the development of a particular micro-angio-architecture, which guarantees the establishment of an intra-islet portal system with core- to -mantle capillary perfusion. Due to an insufficient supply of oxygen and nutrients, the sparse vascularization of the islets observed in the obese sedentary OLETF rats may result in an acceleration of damage and death of β-cells which are vulnerable to overwork stress. Furthermore, alteration of the physiologic core of the islet mantle capillary perfusion (intra-islet portal system) causes dysfunctions of pancreatic endocrine cells, such as the impairment of α-cell responsiveness to glucopenia in these model rats. The α-cells of the Ex group, which had a normal islet micro-angio-architecture as seen in Fig.4, respond normally to glucopenia (26). Thus, exercise training and caloric restriction may be capable of maintaining a capillary network as well as an intact morphology in the islets.

A separate experiment was conducted to study the

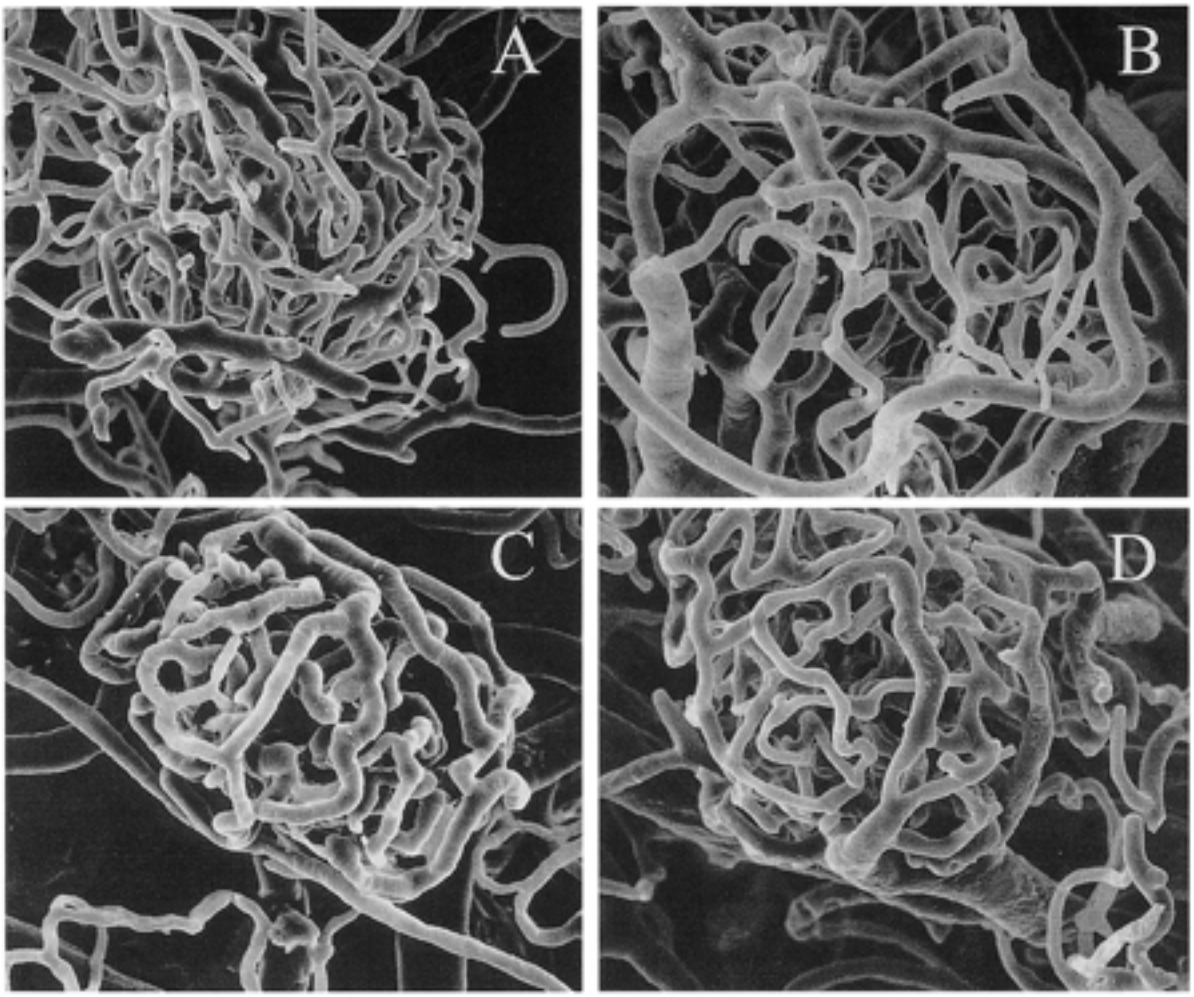

Fig.4. Micro-angio-architecture of islets. A : sedentary, fed ad libitum LETO. B : sedentary, fed ad libitum (NT) OLETF. C : exercise training, fed ad libitum (EX) OLETF. D : sedentary, fed with caloric restriction (CR) OLETF.

effects of caloric restriction and exercise training on the proliferation capacity of β-cells. The sedentary OLETF rats, fed ad libitum until 16 weeks of age, were assigned to three groups ; exercise training, fed ad libitum (Ex), sedentary, fed with 70% restricted calories (CR) and sedentary, fed ad libitum (NT) groups. They were maintained until 20 weeks of age under the conditions described above. At 25 weeks of age, they were sacrified and their pancreatic weight, β-cell mass and insulin contents were measured.

Caloric restriction and exercise training normalized hyperglycemia at 20 weeks of age. The insulin contents in the pancreata of the CR group and the Ex group rats were similarly increased, compared to that of the NT group. The enlarged islet area (17368 ± 2850 mm^2) in the NT group was completely or partially abolished in both the CR (8810 ± 1150 mm^2) and the Ex groups (12947 ± 1040 mm^2). The islet area of each group was not significantly different from that of LETO rats (8439 ± 558 mm^2). These results show that caloric restriction and exercise training are equally effective in preventing a decrease in insulin content in the pancreas and an increase in islet volume. Exercise training clearly increases the pancreatic weight and β-cell mass while caloric restriction does not. Therefore, exercise training appears to be more effective in augmenting the pancreatic β-cell mass, which is decreased in non-intervened OLETF rats.

The mechanisms through which exercise training increases pancreatic weight and β-cell mass are difficult to explain, but several possibilities exist. First, exercise training alone leads to enhanced insulin sensitivity. The GIR in the Ex OLETF group is much higher than that in the NT OLETF group, and nearly the same as that in the LETO group. Such a normalized insulin sensitivity would prevent hyperglycemia," exhaustion "of pancreatic β-cells and consequent cell death, perhaps resulting in increased number of β cells. Second the increased blood flow resulting from exercise supplies sufficient oxygen to the β-cells for regeneration. Unfortunately, at the present time no definitive physiological substances affecting β-cell proliferation have been identified, although several candidates have been proposed (27-30). Further studies will be necessary to identify the substances responsible for β-cell proliferation and to clarify their role in the development of NIDDM and the amelioration of glucose intolerance by exercise training.

As described above, both exercise training and caloric restriction prevented the development of diabetes mellitus in OLETF rats as a result of the amelioration of insulin resistance, although probably through different mechanisms.

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