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

Keywords: β-cell mass, β-cell proliferation, partial pancreatectomy, nicotinamide, preventive intervention
1) Quantification of extent of pancreatectomy (Px)

β-Cell disappearance and β-cell replacement require consideration of the extent of pancreatectomy (Px) as well as the effects of the vascular and peritoneal environments. Since Px is a significant factor in the development of type 2 diabetes, both quantification of extent of pancreatectomy and the rate and extent of β-cell replacement are important in the understanding of the pathogenesis of NIDDM. In the following sections, the quantification of Px is described.

2) Hyperglycemia

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3) Defective proliferation in pancreatic \( \beta \)-cells

Defective proliferation of pancreatic cells is a characteristic feature of chronic pancreatitis. Various factors, including inflammation, oxidative stress, and hormonal alterations, contribute to the defective proliferation of these cells. In chronic pancreatitis, the balance between cell proliferation and apoptosis is disrupted, leading to a decrease in the number of functional pancreatic cells.

The graph above illustrates the changes in non-fasting blood glucose levels and body weight over time post-surgery. The data indicate a significant increase in blood glucose levels and a corresponding decrease in body weight, suggesting a compromised pancreatic function in the study group.

Further studies are needed to elucidate the underlying mechanisms and to develop effective therapeutic strategies to mitigate the adverse effects of chronic pancreatitis on pancreatic cell proliferation.
4) Defective cell proliferation unaffected by restoration of normoglycemia
5) Amelioration of hyperglycemia with increasing β-cell proliferation induced by nicotinamide

As described, the mechanism of action appears to involve the induction of β-cell proliferation by nicotinamide, which leads to an improvement in hyperglycemia. This effect is likely due to the stimulation of β-cell replication and growth, resulting in an increased insulin secretion capacity. The exact mechanism by which nicotinamide promotes β-cell proliferation remains to be fully elucidated, but it is believed to involve the activation of signaling pathways that regulate cell division and differentiation.

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

While caloric restriction and exercise training have been shown to be effective in preventing diabetes mellitus in other models, their efficacy in OLETF rats needs to be evaluated. Caloric restriction may reduce the risk of diabetes by limiting the overall energy intake, thereby preventing obesity and insulin resistance. Exercise training can improve insulin sensitivity and glucose metabolism, which may help prevent the development of diabetes. Further research is needed to determine the optimal strategies for preventing diabetes in OLETF rats.
1) The cumulative incidence

2) The glucose infusion rate and abdominal fat

3) The structure of the pancreatic islets
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