

**Leptin restores the insulinotropic effect of exenatide in a mouse model of type 2
diabetes with increased adiposity induced by streptozotocin and high-fat diet**

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Abstract

Leptin, an adipocyte-derived hormone, has therapeutic potential for treating diabetes and obesity (1-4, 8, 9, 11-15, 17, 18, 22, 25). The glucoregulatory effects of leptin are associated with the reduction of ectopic lipid deposition, which increases with progression of obesity (19, 20, 24). The reduction of ectopic lipid deposition in the pancreas could improve beta-cell function such as glucose-stimulated insulin secretion (GSIS) in rodents and humans (10, 20, 24).

On the other hand, glucagon-like peptide-1 (GLP-1), a hormone released from the L-cells of the intestine, improves glucose metabolism by enhancing GSIS (7). However, in patients with type 2 diabetes, the insulinotropic effect of GLP-1 is substantially reduced associated with impaired beta-cell function (5, 16). Pancreatic lipid deposition increases with progression of obesity and could reduce GSIS (6, 19, 21, 23). Therefore, we speculated that leptin could restore the insulinotropic effect of GLP-1 associated with the reduction of pancreatic lipid deposition and enhance the efficacy of GLP-1 receptor agonists in patients with type 2 diabetes. If this hypothesis is confirmed, we might be able to manage type 2 diabetes more effectively.

In this study, we examined whether leptin could restore the efficacy of exenatide, a GLP-1 receptor agonist, in type 2 diabetes with increased adiposity. We chronically administered leptin (500 $\mu\text{g/kg/day}$) and/or exenatide (20 $\mu\text{g/kg/day}$) for 2 weeks in a mouse model of type 2 diabetes with increased adiposity induced by streptozotocin (STZ) and high-fat diet (HFD) (STZ/HFD mice). The STZ/HFD mice exhibited hyperglycemia, overweight, increased pancreatic triglyceride level, and reduced glucose-stimulated insulin secretion (GSIS); moreover, the insulinotropic effect of exenatide was reduced. However, leptin significantly reduced pancreatic triglyceride level, and adding leptin to exenatide (LEP/EX) remarkably enhanced GSIS. These results suggested that the leptin treatment restored the insulinotropic effect of exenatide in the mice. In addition, LEP/EX reduced food intake, body weight, and triglyceride levels in the skeletal muscle and liver, and corrected hyperglycemia to a greater extent than either monotherapy. The pair-feeding experiment indicated that the marked reduction of pancreatic triglyceride level and enhancement of GSIS by LEP/EX occurred via mechanisms other than calorie restriction. These results suggest that, leptin treatment may restore the insulinotropic effect of exenatide associated with the reduction of pancreatic lipid deposition in type 2 diabetes with increased adiposity.

Combination therapy with leptin and exenatide could be an effective treatment for patients with type 2 diabetes with increased adiposity.

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Contribution statement:

T. S. researched data and wrote the manuscript. T. K. contributed to the discussion and edited the manuscript. D. A., S. K., M.Z., V. M., C. E., M. A., Y. Y., M. N., J. F., and K. H. contributed to the discussion. K. E., N. I., and K. N. contributed to the discussion and reviewed the manuscript.

Disclosures

There are no conflicts of interest, financial or otherwise, are declared by the authors.

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