TITLE:

Leptin restores the insulintropic effect of exenatide in a mouse model of type 2 diabetes with increased adiposity induced by streptozotocin and high-fat diet(Digest_要約)

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CITATION:

Sakai, Takeru. Leptin restores the insulintropic effect of exenatide in a mouse model of type 2 diabetes with increased adiposity induced by streptozotocin and high-fat diet. 京都大学, 2015, 博士(医学)

ISSUE DATE:

2015-01-23

URL:

<https://doi.org/10.14989/doctor.k18683>

RIGHT:

学位規則第9条第2項により要約公開

**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.

Acknowledgments

We thank Mayumi Nagamoto for technical assistance and Yoko Koyama for secretarial assistance.

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.

References

1. **Aotani D, Ebihara K, Sawamoto N, Kusakabe T, Aizawa-Abe M, Kataoka S, Sakai T, Iogawa H, Ebihara C, Fujikura J, Hosoda K, Fukuyama H and Nakao K.** Functional magnetic resonance imaging analysis of food-related brain activity in patients with lipodystrophy undergoing leptin replacement therapy. *J Clin Endocrinol Metab* 97: 3663-3671, 2012.
2. **Ebihara K, Kusakabe T, Hirata M, Masuzaki H, Miyanaga F, Kobayashi N, Tanaka T, Chusho H, Miyazawa T, Hayashi T, Hosoda K, Ogawa Y, DePaoli AM, Fukushima M and Nakao K.** Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. *J Clin Endocrinol Metab* 92: 532-541, 2007.
3. **Ebihara K, Ogawa Y, Masuzaki H, Shintani M, Miyanaga F, Aizawa-Abe M, Hayashi T, Hosoda K, Inoue G, Yoshimasa Y, Gavrillova O, Reitman ML and Nakao K.** Transgenic overexpression of leptin rescues insulin resistance and diabetes in a mouse model of lipodystrophic diabetes. *Diabetes* 50: 1440-1448, 2001.
4. **Kamohara S, Burcelin R, Halaas JL, Friedman JM and Charron MJ.** Acute stimulation of glucose metabolism in mice by leptin treatment. *Nature* 389: 374-377, 1997.
5. **Kjems LL, Holst JJ, Volund A and Madsbad S.** The influence of GLP-1 on glucose-stimulated insulin secretion: effects on beta-cell sensitivity in type 2 and nondiabetic subjects. *Diabetes* 52: 380-386, 2003.
6. **Knop FK, Aaboe K, Vilsboll T, Volund A, Holst JJ, Krarup T and Madsbad S.** Impaired incretin effect and fasting hyperglucagonaemia characterizing type 2 diabetic subjects are early signs of dysmetabolism in obesity. *Diabetes Obes Metab* 14: 500-510, 2012.
7. **Kreymann B, Williams G, Ghatgei MA and Bloom SR.** Glucagon-like peptide-1 7-36: a physiological incretin in man. *Lancet* 2: 8571: 1300-1304, 1987.
8. **Kusakabe T, Ebihara K, Sakai T, Miyamoto L, Aotani D, Yamamoto Y, Yamamoto-Kataoka S, Aizawa-Abe M, Fujikura J, Hosoda K and Nakao K.**

Amylin improves the effect of leptin on insulin sensitivity in leptin-resistant diet-induced obese mice. *Am J Physiol Endocrinol Metab* 302: E924-31, 2012.

9. **Kusakabe T, Tanioka H, Ebihara K, Hirata M, Miyamoto L, Miyanaga F, Hige H, Aotani D, Fujisawa T, Masuzaki H, Hosoda K and Nakao K.** Beneficial effects of leptin on glycaemic and lipid control in a mouse model of type 2 diabetes with increased adiposity induced by streptozotocin and a high-fat diet. *Diabetologia* 52: 675-683, 2009.

10. **Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC and Taylor R.** Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 54: 2506-2514, 2011.

11. **Masuzaki H, Ogawa Y, Aizawa-Abe M, Hosoda K, Suga J, Ebihara K, Satoh N, Iwai H, Inoue G, Nishimura H, Yoshimasa Y and Nakao K.** Glucose metabolism and insulin sensitivity in transgenic mice overexpressing leptin with lethal yellow agouti mutation: usefulness of leptin for the treatment of obesity-associated diabetes. *Diabetes* 48: 1615-1622, 1999.

12. **Miyamoto L, Ebihara K, Kusakabe T, Aotani D, Yamamoto-Kataoka S, Sakai T, Aizawa-Abe M, Yamamoto Y, Fujikura J, Hayashi T, Hosoda K and Nakao K.** Leptin activates hepatic 5'-AMP-activated protein kinase through sympathetic nervous system and alpha1-adrenergic receptor: a potential mechanism for improvement of fatty liver in lipodystrophy by leptin. *J Biol Chem* 287: 40441-40447, 2012.

13. **Miyanaga F, Ogawa Y, Ebihara K, Hidaka S, Tanaka T, Hayashi S, Masuzaki H and Nakao K.** Leptin as an adjunct of insulin therapy in insulin-deficient diabetes. *Diabetologia* 46: 1329-1337, 2003.

14. **Muller TD, Sullivan LM, Habegger K, Yi CX, Kabra D, Grant E, Ottaway N, Krishna R, Holland J, Hembree J, Perez-Tilve D, Pfluger PT, DeGuzman MJ, Siladi ME, Kraynov VS, Axelrod DW, DiMarchi R, Pinkstaff JK and Tschop MH.** Restoration of leptin responsiveness in diet-induced obese mice using an optimized leptin analog in combination with exendin-4 or FGF21. *J Pept Sci* 18: 383-393, 2012.

15. **Naito M, Fujikura J, Ebihara K, Miyanaga F, Yokoi H, Kusakabe T, Yamamoto Y, Son C, Mukoyama M, Hosoda K and Nakao K.** Therapeutic impact of

leptin on diabetes, diabetic complications, and longevity in insulin-deficient diabetic mice. *Diabetes* 60: 2265-2273, 2011.

16. **Nauck M, Stockmann F, Ebert R and Creutzfeldt W.** Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 29: 46-52, 1986.

17. **Ogawa Y, Masuzaki H, Hosoda K, Aizawa-Abe M, Suga J, Suda M, Ebihara K, Iwai H, Matsuoka N, Satoh N, Odaka H, Kasuga H, Fujisawa Y, Inoue G, Nishimura H, Yoshimasa Y and Nakao K.** Increased glucose metabolism and insulin sensitivity in transgenic skinny mice overexpressing leptin. *Diabetes* 48: 1822-1829, 1999.

18. **Perry RJ, Zhang XM, Zhang D, Kumashiro N, Camporez JP, Cline GW, Rothman DL and Shulman GI.** Leptin reverses diabetes by suppression of the hypothalamic-pituitary-adrenal axis. *Nat.Med.* 20: 7: 759-763, 2014.

19. **Saisho Y, Butler AE, Meier JJ, Monchamp T, Allen-Auerbach M, Rizza RA and Butler PC.** Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes. *Clin.Anat.* 20: 8: 933-942, 2007.

20. **Shimabukuro M, Koyama K, Chen G, Wang MY, Trieu F, Lee Y, Newgard CB and Unger RH.** Direct antidiabetic effect of leptin through triglyceride depletion of tissues. *Proc Natl Acad Sci USA* 94: 4637-4641, 1997.

21. **Szczepaniak LS, Victor RG, Mathur R, Nelson MD, Szczepaniak EW, Tyer N, Chen I, Unger RH, Bergman RN and Lingvay I.** Pancreatic steatosis and its relationship to beta-cell dysfunction in humans: racial and ethnic variations. *Diabetes Care* 35: 2377-2383, 2012.

22. **Tanaka T, Hidaka S, Masuzaki H, Yasue S, Minokoshi Y, Ebihara K, Chusho H, Ogawa Y, Toyoda T, Sato K, Miyanaga F, Fujimoto M, Tomita T, Kusakabe T, Kobayashi N, Tanioka H, Hayashi T, Hosoda K, Yoshimatsu H, Sakata T and Nakao K.** Skeletal muscle AMP-activated protein kinase phosphorylation parallels metabolic phenotype in leptin transgenic mice under dietary modification. *Diabetes* 54: 2365-2374, 2005.

23. **Tushuizen ME, Bunck MC, Pouwels PJ, Bontemps S, van Waesberghe JH, Schindhelm RK, Mari A, Heine RJ and Diamant M.** Pancreatic fat content and

beta-cell function in men with and without type 2 diabetes. *Diabetes Care* 30: 2916-2921, 2007.

24. **Wang MY, Koyama K, Shimabukuro M, Mangelsdorf D, Newgard CB and Unger RH.** Overexpression of leptin receptors in pancreatic islets of Zucker diabetic fatty rats restores GLUT-2, glucokinase, and glucose-stimulated insulin secretion. *Proc Natl Acad Sci USA* 95: 11921-11926, 1998.

25. **Wang MY, Chen L, Clark GO, Lee Y, Stevens RD, Ilkayeva OR, Wenner BR, Bain JR, Charron MJ, Newgard CB and Unger RH.** Leptin therapy in insulin-deficient type I diabetes. *Proc.Natl.Acad.Sci.U.S.A.* 107: 4813-4819, 2010.