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A completely novel long-acting GLP-1 receptor agonist, glutazumab

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GLP-1-based drugs have been proposed as a mono- or combined therapy for type 2 diabetes mellitus for the outstanding features, but natural GLP-1 is hardly used in clinic due to its short half-life, while short-acting analogs/receptor agonists have poor compliance in patients for frequent dosing. This study aims to introduce a novel long-acting GLP-1 receptor agonist, which is an antibody fusion protein by linking the human GLP-1 derivative to a humanized GLP-1R antibody via a peptide linker, and to evaluate its anti-diabetic effects and duration. Glutazumab is characterized by receptor binding and reporter gene assay, and its specificity was investigated through addition of exendin (9-39) and Ab1 which were the cognate receptor antagonist and antibody respectively. To evaluate the anti-diabetic effects, glutazumab was studied in diabetic KKAy mice by single dose and repeated doses. The blood glucose, food/water intake, body weight and gastric emptying was measured in the single dose study, while blood glucose, GSP, HbA1c, insulin and lipid were determined in the repeated-dose study. The oral glucose tolerance and hyperglycemic clamp test were performed to assess the β-cell function. In all the experiments, dulaglutide served as a control. Glutazumab significantly binds and activates GLP-1R, while the natural receptor antagonist exendin (9-39) showed no inhibition except in the presence of the antibody Ab1. Single injection of Glutazumab remarkably decreased blood glucose for 3~6 days in normal ICR mice and diabetic KKAy mice. Repeated injections of glutazumab also evidently reduced non-fasting and fasting blood glucose fluctuation, decreased GSP and HbA1c levels, improved impaired oral glucose tolerance and β-cell function and ameliorated the dyslipidemia in diabetic KKAy mice. These results demonstrated that glutazumab is a novel long-acting GLP-1 receptor agonist with excellent anti-diabetic effect in KKAy mice, and suggested that it may be a potential treatment for type 2 diabetes.

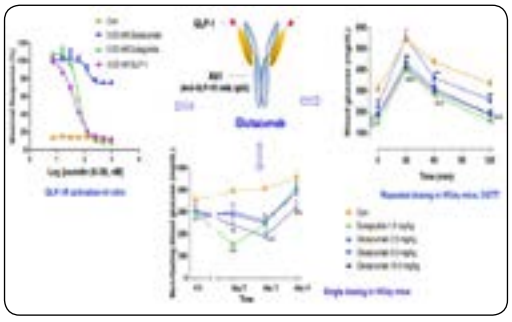

Figure 1: Activation of GLP-1 receptor by glutazumab significantly lowered the blood glucose with a long-lasting during and remarkably improve the impaired oral glucose tolerance in diabetic KKAy mice.

Recent Publications

1. Caina Li, Miaomiao Yang and Xiaofeng Wang, *et al.* (2018) Glutazumab, a novel long-lasting GLP-1/anti-GLP-1R antibody fusion protein, exerts anti-diabetic effects through targeting dual receptor binding sites. Biochemical Pharmacology 150:46-53.
2. Caina Li, Shaocong Hou, Shuainan Liu, *et al.* (2017) The albumin-exendin-4 recombinant protein E2HSA improves glycemic control and β-cell function in spontaneous diabetic KKAy mice. BMC Pharmacology and Toxicology 18(1):48-56.
3. Caina Li, Miaomiao Yang, Guojiang Hou, Yi Huan, *et al.* (2017) A human glucagon-like peptide-1-albumin recombinant protein with prolonged hypoglycemic effect provides efficient and beneficial control of glucose metabolism in diabetic mice. Biol Pharm Bull. 40(9):1399-1408.

4. Guojiang Hou, Caina Li, Yi Huan, *et al.* (2017) The PI3K/Akt1-Foxo1 translocation pathway mediates Exf effects on NIT-1 cell survival. Exp Clin Endocrinol Diabetes 125(10):669-676.
5. Caina Li, Sujuan Sun and Zhufang Shen (2015) Determination of serum acetaminophen based on the diazo reaction and its application in the evaluation of gastric emptying. Acta Pharmaceutica Sinica. 50(5):560-564.

Biography

Caina Li has been engaged in anti-diabetic pharmacology since graduation in 2011. She mainly worked on the pharmacological study of novel GLP-1-based drugs and study mechanism of the occurrence and development of diabetes. Till now, she has completed the pharmacological studies of 3 novel long-acting GLP-1 receptor agonists, Natural Science Foundation of China project and New Teacher Doctoral Fund of Ministry of Education of China. She also created a method for evaluating the gastric emptying in mice based on the diazo reaction, which could significantly reduce the use of animals in the evaluation of gastric emptying.

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