β-cell GLP-1 Receptors Mediate the Action of Exogenous but not Endogenous GLP-1

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Introduction

Oral glucose administration results in increased levels of insulin secretion compared to an intravenous glucose infusion. This phenomenon, termed the incretin effect, has been attributed to gut-derived factors like Glucagon-like peptide-1 (GLP-1) which act on the β-cell to increase insulin secretion. However, GLP-1 is rapidly metabolized before reaching the systemic circulation, raising questions about whether GLP-1 acts directly on β-cell GLP-1 receptors (GLP-1r). GLP-1r exist on other tissues, including in the GI tract, but the contributions of different GLP-1r populations to overall GLP-1 action are not well described. Further clarification of the mechanism of endogenous GLP-1 action is important to fully realize its pharmacologic potential as an antidiabetic agent. We developed lines of mice with global knockout of the GLP-1r and β-cell-specific knockout of the GLP-1r to determine if β-cell GLP-1r are necessary for action of endogenous and exogenous GLP-1.

Methods

Two cohorts of GLP-1r knockout mice were bred using Cre/lox recombination: one with global knockout of GLP-1r, and one with tamoxifen-induced β-cell-specific GLP-1r knockout. Non-knockout littermates were used as controls. Oral and intraperitoneal glucose tolerance tests (OGTT and IPGTT) were performed and response to GLP-1r agonists was assessed on all cohorts. Blood from the tail vein was used to determine glucose and insulin levels.

Results

Mice with global knockout of the GLP-1r had increased glucose excursions during OGTT and IPGTT and failed to respond to a GLP-1r agonist. β-cell GLP-1r knockouts exhibited similar glycemic responses and insulin secretion as controls following oral glucose. After IP glucose, β-cell GLP-1r knockouts cleared glucose better than global GLP-1r knockouts but worse than controls. IP injection of GLP-1 improved glucose tolerance in both control animals and β-cell GLP-1r knockouts, but insulin secretion only increased in the control animals.

Conclusion

The GLP-1r is necessary for normal glucose tolerance and exogenous GLP-1 action. The β-cell GLP-1r appears to mediate IP glucose clearance and is necessary for the insulinotropic effects of GLP-1r agonists. However, the β-cell GLP-1r is not required for normal oral glucose tolerance, suggesting that the incretin effect either does not depend on this population of receptors or that other mechanisms compensate for lack of β-cell GLP-1r signaling after a meal. These results suggest an expanded GLP-1r system that contributes to glucose lowering by more than direct stimulation of β-cells.

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