Science Translational Medicine

Sci Transl Med. 2020 Feb 12;12(530):eaaw9996. doi: 10.1126/scitranslmed.aaw9996.

GLP-1 receptor agonists synergize with DYRK1A inhibitors to potentiate functional human β cell regeneration

Courtney Ackeifi [1], Peng Wang [1], Esra Karakose [1], Jocelyn E Manning Fox [2], Bryan J González [3], Hongtao Liu [1], Jessica Wilson [1], Ethan Swartz [1], Cecilia Berrouet [1], Yansui Li [1], Kunal Kumar [4], Patrick E MacDonald [2], Roberto Sanchez [4], Bernard Thorens [5], Robert DeVita [4], Dirk Homann [1], Dieter Egli [3], Donald K Scott [1], Adolfo Garcia-Ocaña [1], Andrew F Stewart [6]

Affiliations

Affiliations

1 Diabetes, Obesity and Metabolism Institute and Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
2 Department of Pharmacology and Alberta Diabetes Institute, University of Alberta, Edmonton, Alberta T6G 2E1, Canada.
3 Naomi Berrie Diabetes Center and Columbia Stem Cell Center, Columbia University, New York, NY 10032, USA.
4 Department of Pharmacological Sciences, and Drug Discovery Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
5 Center for Integrative Genomics, University of Lausanne, Lausanne 1015, Switzerland.
6 Diabetes, Obesity and Metabolism Institute and Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. andrew.stewart@mssm.edu.

PMID: 32051230 DOI: 10.1126/scitranslmed.aaw9996

Abstract

Glucagon-like peptide-1 receptor (GLP1R) agonists and dipeptidyl peptidase 4 inhibitors are widely prescribed diabetes drugs due to their ability to stimulate insulin secretion from remaining β cells and to reduce caloric intake. Unfortunately, they fail to increase human β cell proliferation. Small-molecule inhibitors of dual-specificity tyrosine-regulated kinase 1A (DYRK1A) are able to induce adult human β cell proliferation, but rates are modest (~2%), and their specificity to β cells is limited. Here, we provide evidence that combining any member of the GLP1R agonist class with any member of the DYRK1A inhibitor class induces a synergistic increase in human β cell replication (5 to 6%) accompanied by an actual increase in numbers of human β cells. GLP1R agonist-DYRK1A inhibitor synergy required combined inhibition of DYRK1A and an increase in cAMP and did not lead to β cell dedifferentiation. These beneficial effects on proliferation were seen in both normal human β cells and β cells derived from individuals with type 2 diabetes. The ability of the GLP1R agonist-DYRK1A inhibitor combination to enhance human β cell proliferation, human insulin secretion, and blood glucose control extended in vivo to studies of human islets transplanted into euglycemic and streptozotocin-diabetic immunodeficient mice. No adverse events were observed in the mouse studies during a 1-week period. Because of the relative β cell specificity of GLP1R agonists, the combination provides an improved, although not complete, degree of human β cell specificity.

Comment in

Two drugs converged in a pancreatic β cell.

Scavuzzo MA, Borowiak M.

Sci Transl Med. 2020 Feb 12;12(530):eaba7359. doi: 10.1126/scitranslmed.aba7359.

PMID: 32051228 Review.

LinkOut – more resources

Full Text Sources

Atypon

Medical

MedlinePlus Health Information