The novel GLP-1-GLP-2 dual agonist ZP-GG-72 increases intestinal growth and improves insulin sensitivity in DIO mice

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Low grade inflammation as observed in Type 2 diabetes, may arise from leakage of bacterial wall components across the intestinal barrier, and is thought to contribute to the disease by reducing insulin sensitivity.

Here we tested the hypothesis that adding GLP-2 agonism, to promote intestinal barrier function and thereby reduce inflammation, to the established beneficial effects of GLP-1 agonism on glycemic control may represent a novel strategy for treating diabetes. The potency of the novel GLP-1-GLP-2 dual agonist, ZP-GG-72 was evaluated by measuring the cAMP levels in recombinant HEK293 cells expressing either human GLP-1 or GLP-2 receptors. The EC50 of the peptide ZP-GG-72 was 0.24 and 0.59 nM on the GLP-1 and GLP-2 receptors, respectively. Pharmacological effects of ZP-GG-72 were investigated in DIO mice dosed subcutaneously and bid for 14 days with vehicle, teduglutide (a GLP-2 analogue, 100 nmol/kg), exendin-4 (10 nmol/kg), or ZP-GG-72 (250, 500 nmol/kg). Data showed that treatment with ZP-GG-72 caused an increase in intestinal weight (A) and improved glycemic control (B, C).

In conclusion, we demonstrated the feasibility of engineering a GLP-1-GLP-2 dual agonist, which displays pharmacological effects in DIO mice. GLP-1-GLP-2 dual agonists may represent a novel paradigm addressing diabetes associated low grade inflammation.