Preclinical Findings with Oral GLP-1 Receptor Agonist TTP273 Reinforce Importance of Neuro-Enteroendocrine Signaling

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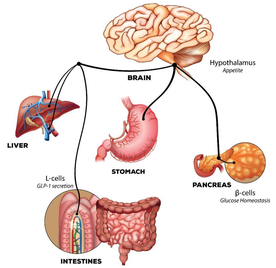
Introduction

GLP-1 is a well-characterized peptide hormone that is secreted by the L-cells of the intestine and activates GLP-1 receptors found throughout the body. Interest in GLP-1 arose from its effects in the pancreas stimulating insulin secretion and decreasing glucagon levels. More recently, additional sites of GLP-1 action, including the gut, have been identified.

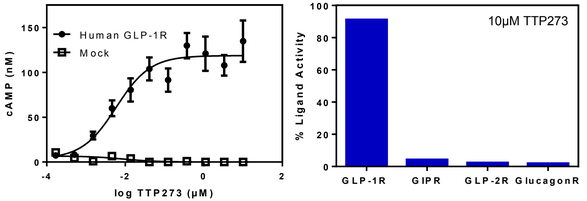
The GLP-1 receptor (GLP-1R) is a well validated target for the treatment of Type 2 Diabetes Mellitus (T2DM) and has recently been shown to be effective as a treatment for weight management in non-diabetic obese and overweight subjects. Injectable GLP-1R agonists are effective in lowering blood glucose and reducing weight and are generally safe and well tolerated except for major side effects related to the GI distress (nausea and vomiting). Oral DPPIV inhibitors that increase GLP-1 levels by preventing its degradation are also effective in lowering blood glucose and are well tolerated, but have little or no effect on weight reduction.

Here we report preclinical characterization of orally bioavailable, specific, non-peptide GLP-1R agonists, TTP3859 and TTP273. A Phase 2 study is currently ongoing to evaluate the effects of TTP273, administered orally, on glycemic control and weight loss in T2DM subjects.



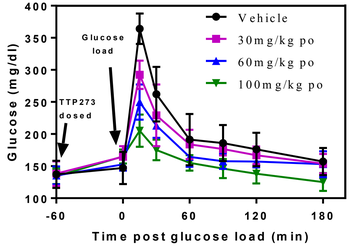
- GLP-1 secretion occurs following nutrient stimulation in the gut lumen (L-cells) where a majority of the peptide is rapidly cleaved by DPP-IV.
- Gut absorption of the remaining peptide promotes systemic activation including activation sensory neurons in the hepatoportal region as well as potential activation of the hypothalamus through direct activation of sensory afferent neurons in the gut.
- Data presented herein suggest oral delivery of TTP273 maintains systemic and CNS effects using mechanisms similar to GLP-1 secretion.

TTP273: Potent and Specific Agonist of the GLP-1 Receptor



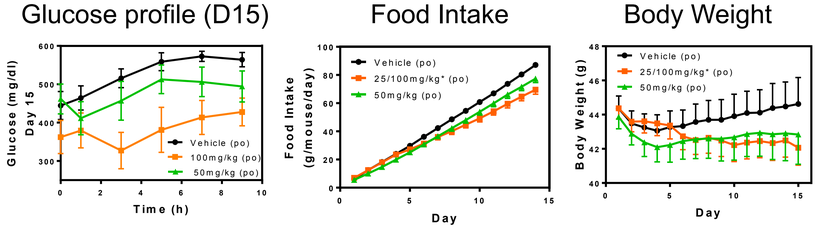
In vitro activity was measured with cAMP response from cells transfected by the indicated receptor (or mock vector) following exposure to receptor ligand or TTP273

TTP273: Dose dependent lowering of glucose following oral GTT in mice



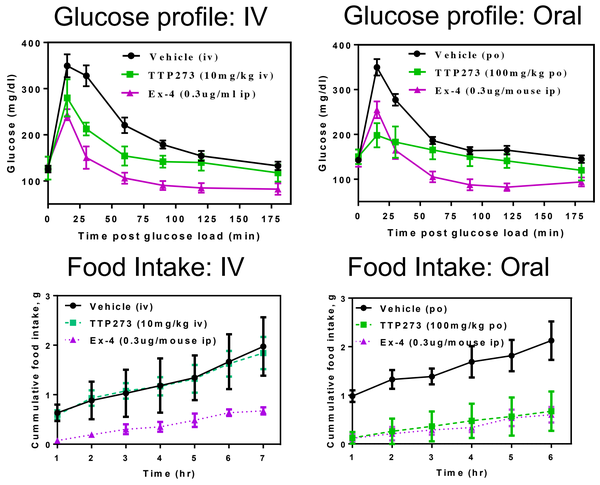
Overnight fasted C57BL/6 mice were dosed with TTP273 or vehicle 1h prior to an oral glucose tolerance test.

14-days of dosing of TTP3859 demonstrate improved glycemic control and reduced food intake and body weight gain in ob/ob Mice



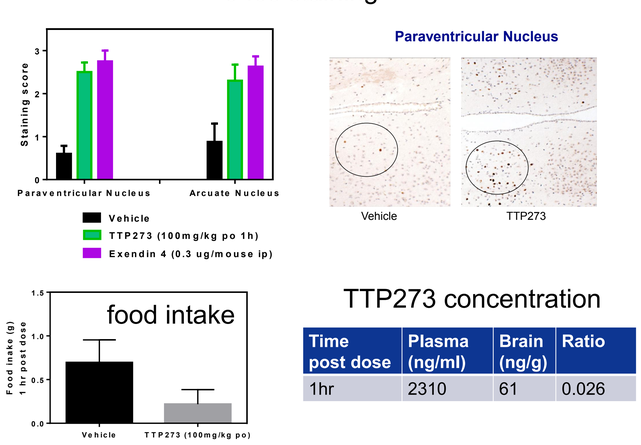
ob/ob mice were dosed for 14 days with either vehicle or 50mg/kg TTP3859 for 14 days or 25mg/kg TTP3859 for 3 days followed by an increase to 100mg/kg for 11 days.

Effect on food intake seems to be mediated by activation of GLP-1R in the hepatoportal region



Animals dosed <u>either</u> orally or intravenously exhibited improved glycemic control following GTT, but <u>ONLY</u> animals dosed <u>orally</u> with TTP273 showed reduction in food intake

Increased *c-fos* staining in the brain suggest that the effect on food intake is mediated by neuro-enteroendocrine signaling



TTP273 concentration

Time post dose	Plasma (ng/ml)	Brain (ng/g)	Ratio
1hr	2310	61	0.026

Food intake and c-fos staining 1 hour post dose suggest signaling through vagus nerve as only negligible amounts of compound are present in the brain

Conclusions

vTv oral small molecules:

- Are potent, specific GLP-1R agonists *in vitro*
- Demonstrate dose dependent reductions of plasma glucose levels *in vivo* following an oral glucose tolerance test (OGTT)
- Have glucose and weight lowering effects following 14 days of dosing in *ob/ob* mice
- Exhibit improved glycemic control following GTT in animals dosed <u>either</u> orally or intravenously
- Show reduction in food intake <u>ONLY</u> in animals dosed <u>orally</u> with TTP273
- Display differential effects depending on route of administration, consistent with GLP-1R activation in the gut promoting satiety through signaling to the brain via the vagus nerve
- Are ***not*** brain penetrant
- Increase *c-fos* staining in the brain