Concomitant oral insulin and exenatide therapies significantly curb postprandial glucose excursions in pigs

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin secretion, and insulin biosynthesis, while inhibiting glucagon secretion and gastric emptying. Taken together with its restorative effect on b-cell sensitivity, GLP-1 and its analogues are suggested to bear therapeutic potential in regulating Type 2 Diabetes Mellitus (T2DM). A combination therapy of insulin and GLP-1 may be of value in simultaneously addressing the multiple metabolic targets of T2DM pathogenesis and in curbing progression of the disease and comorbidities. To assess such a concomitant treatment regimen, fasting pigs were treated with oral insulin (ORMD-0801) and/or oral exenatide (ORMD-0901) capsules thirty minutes prior to caloric intake. Blood glucose concentrations were monitored over the ensuing four hours. Preprandial delivery of ORMD-0901 fully prevented a rise in glucose concentrations following food intake (p=0.002). Similarly ORMD-0801 curbed the glucose excursions observed in nontreated pigs (p=0.086). A sharp, synergistic effect was imparted by simultaneous delivery of both ORMD-0901 and ORMD-0801, as expressed by blood glucose reductions to >50% of mean baseline values, and to concentrations 5.2-fold lower than mean peak values measured in control animals at ~75 min after feeding (p<0.0001). Coadministration of oral insulin and oral exenatide are hereby shown to better control postprandial blood glucose profiles than each drug individually. These favorable effects are proposed to result from improved coverage of a wider range of metabolic pathways stimulated upon food ingestion.

BACKGROUND

- The progressive and multifactorial nature of DM, alongside the failure of long-term monotherapy approaches, call for new therapeutic strategies.
- Anti-DM therapies have been suggested to be most productive when simultaneously focusing on achieving glycemic control, while also addressing the pathophysiological mediators of the disease.
- Oral anti-diabetes substitutes of systemically delivered drugs can impart advanced therapeutic potency, mimic physiological profiles established following their natural release and induce fewer side effects.

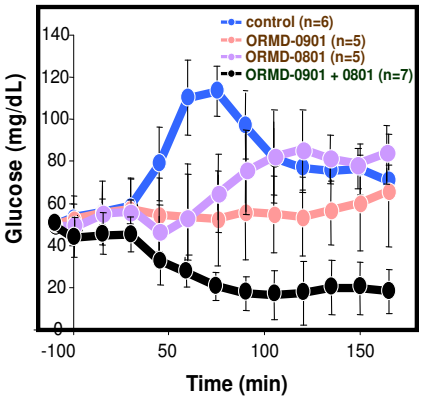
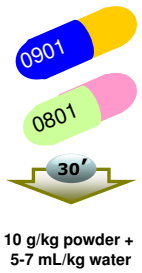


Figure 1. Blood glucose profiles following oral exenatide and oral insulin administration to pigs. Fasting, commercial pigs were treated with ORMD-0901 (150 mg exenatide) and/or ORMD-0801 (8 mg insulin) capsules 30 minutes before caloric intake. Blood samples (1 mL) were periodically drawn throughout the 180-minute observation period to determine glucose concentrations.

METHODS



Fasting animals were anesthetized with isoflurane, administered through a mask before tracheal intubation and hook-up to a respirator (2L O2 per minute and ~5% isoflurane, when required). Pigs were positioned on their left side before entericoated capsules were administered under endoscopic guidance, directly to the duodenum. On test days when both ORMD-0801 and ORMD-0901 were administered, ORMD-0901 was delivered first, followed by the ORMD-0801 capsule within 2-10 minutes. Animals were fed Denkavit powdered milk for piglets (10 g/kg body weight), 30 min after drug administration. Blood samples were periodically drawn from the central line catheter over the 240-min monitoring period for blood glucose monitoring. Piglets were intravenously treated with gentamycin (100 mg/10 kg) after every experiment day to avoid infection. In cases where glucose concentrations dropped below 30 mg/dL, piglets were served commercial pig chowder and glucose concentrations were monitored for an additional 30 minutes thereafter.

RESULTS

Pigs preprandially treated with ORMD-0901, experienced static blood glucose concentrations throughout the 150 minutes following caloric intake (Figure 1). Similarly, ORMD-0801 curbed glucose excursions observed in placebo-treated pigs (Figure 1), but did not fully prevent a rise in blood glucose concentrations throughout the entire monitoring period. A sharp, synergistic effect was observed upon treatment of pigs with both ORMD-0901 and ORMD-0801 30 minutes before caloric intake, when compared to no treatment or to treatment with insulin or exenatide alone (Figure 1; p-value < 0.001). In these cases, glucose excursions were fully avoided and glucose concentrations dropped and remained at a low of >50% below baseline values until the end of the 180-minute monitoring session.

CONCLUSIONS

- Coadministration of oral insulin and oral exenatide capsules provides for tighter regulation of postprandial blood glucose profiles, when compared to oral delivery of each drug alone.
- Their speculated hepato-portal delivery leverage first-pass metabolism to reduce peripheral burdens and consequential adverse effects.
- **The proposed comprehensive therapy calls for further testing to assess its potential in achieving prolonged glycemic control and in blunting disease progression in diabetic patients.**

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