

# Appetite Suppressing Effects of Glucoregulatory Peptides Devoid of Nausea

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**Background:** Few treatments for type 2 diabetes (T2D) and obesity achieve meaningful long-term weight-loss and are often accompanied by nausea and vomiting (affecting ~20-50% of patients). Thus, there is a **critical need** for a new generation of obesity medications that provide glycemic control with enhanced hypophagic response without nausea. Our group has developed and tested two new monomeric chimeric peptides against a novel target for obesity treatment concomitant with T2D in the form of multiple agonism combining the anorectic neuropeptide Y2-receptor (Y2-R), beta-cell protective neuropeptide Y1-receptor (Y1-R), and the glucoregulatory and anorectic glucagon-like peptide 1-receptor (GLP-1R) (**Fig. 1**).

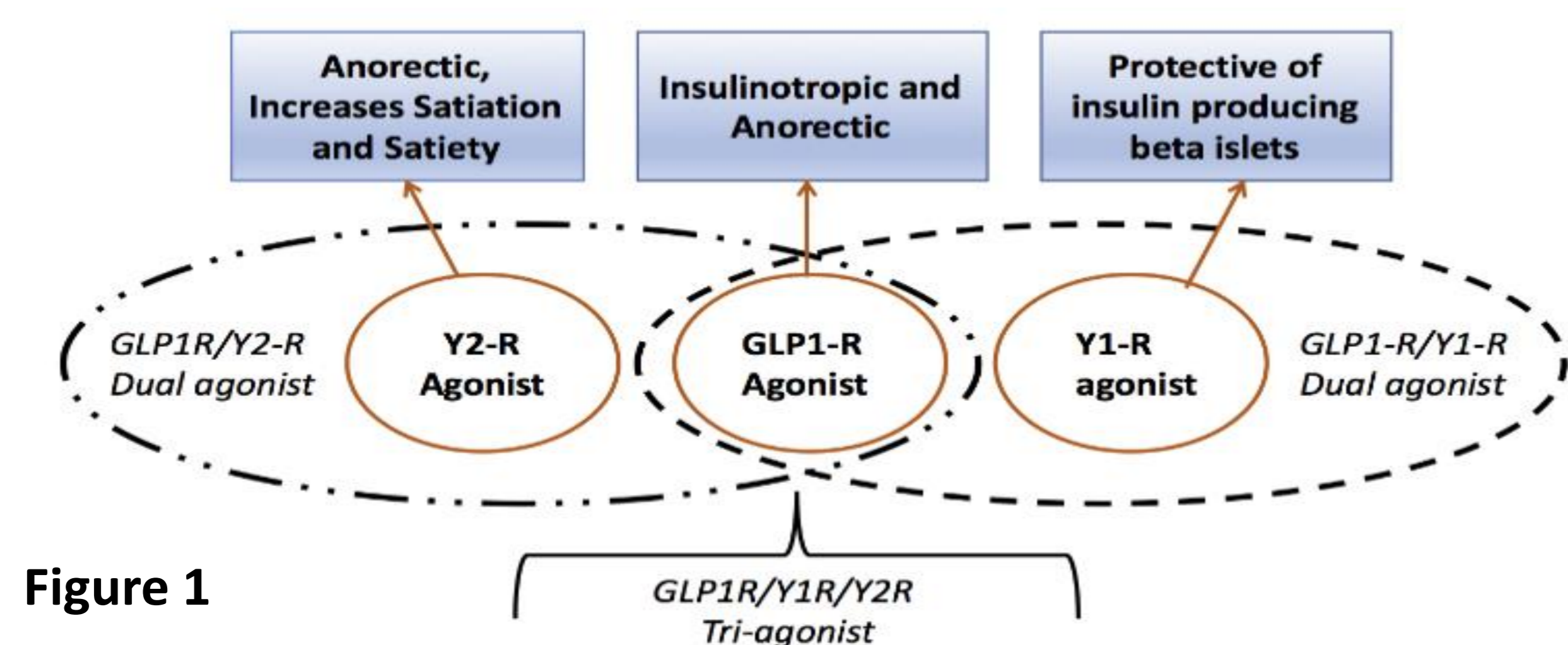


Figure 1

## Methods

Using rational design and in silico modelling based on the GLP-1R agonist (GLP-1RA) exendin-4 (Ex-4) and the Y2-R agonist PYY(3-36), we developed two novel chimeric peptides, **EP44** and **GEP44**. We tested effects of daily injections of these chimeric peptides in adult Sprague-Dawley rats on food intake (FI), body weight (BW) changes, blood glucose levels and kaolin intake, the latter as an indicator of nausea. Furthermore, we tested effects on glucose tolerance in rats and on insulin secretion using explanted rat islets in perfusion chambers (**Fig. 4**).

## Results in Receptor Binding Studies *in vitro*

Both peptides bind and robustly activate the GLP-1R and Y2-R, as assessed by cell-based FRET assays used to screen designed peptides for dose dependent receptor agonism (GLP-1R agonism EC<sub>50</sub>: **EP44** 240 pM, **GEP44** 300 pM, Ex-4 23 pM; Y2-R agonism EC<sub>50</sub>: **EP44** 32 nM, **GEP44** 10 nM, native PYY<sub>3-36</sub> 16 nM).

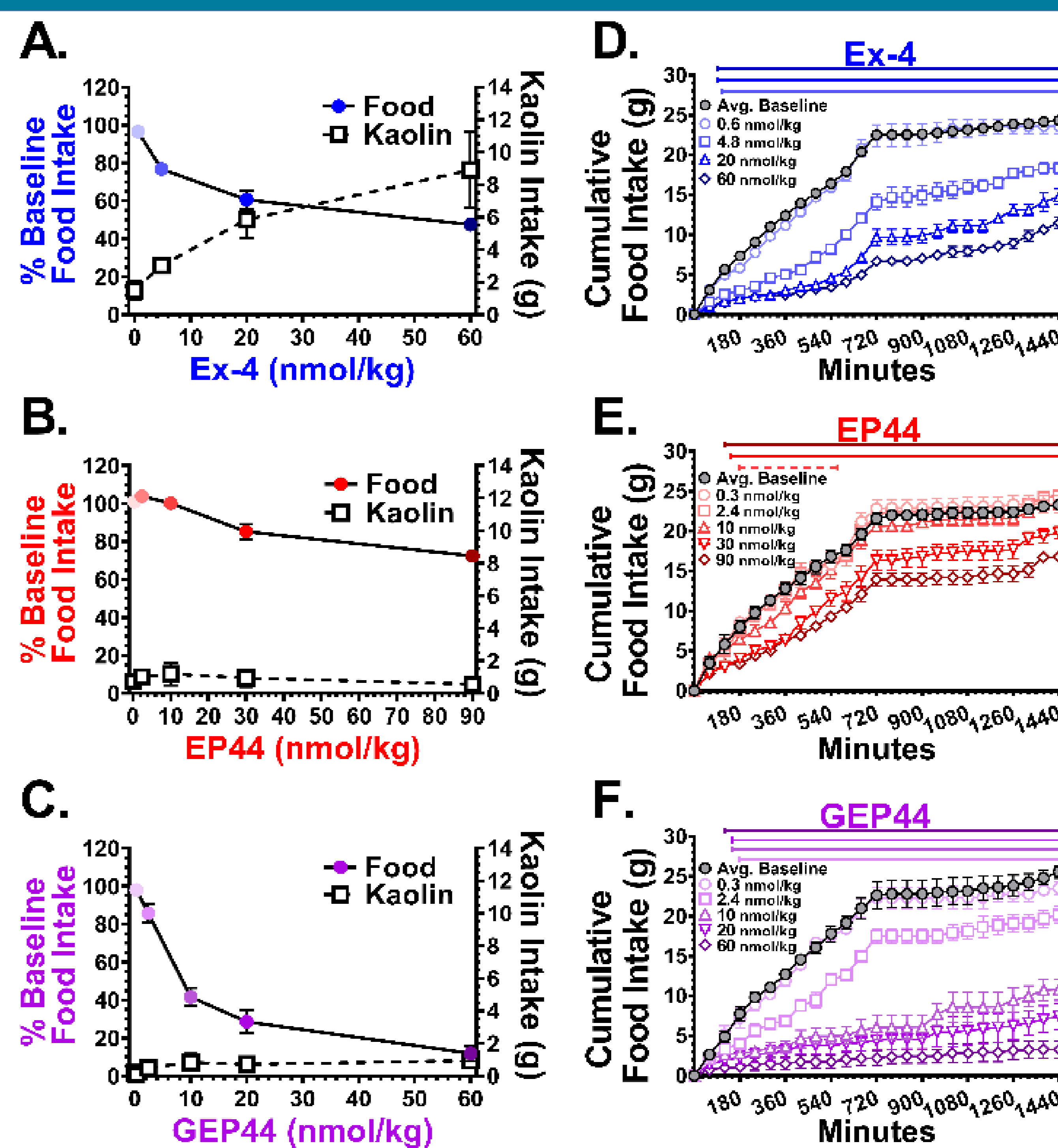
## Results in Rats and Rat Islets

Both peptides reduced FI, with in particular **GEP44** producing profound reduction in FI (**Fig. 2**). Anorectic doses of **EP44** or **GEP44** did not trigger kaolin consumption in treated rats, while in Ex-4 treated rats, kaolin consumption accounted for 28% of total daily solid intake, indicating a clear nausea response. During 11 d of treatment with **GEP44**, FI was consistently reduced resulting in a significantly stronger reduction of BW compared to Ex-4 at the end of treatment (**GEP44** -7.6%, Ex-4 -3.7%). We tested **EP44** on glucose tolerance where it potently reduced blood glucose levels (**Fig. 3**). **EP44** and **GEP44** both also robustly stimulate the insulin secretion rate in rat islet perfusion *in vitro* (**Fig. 4**).

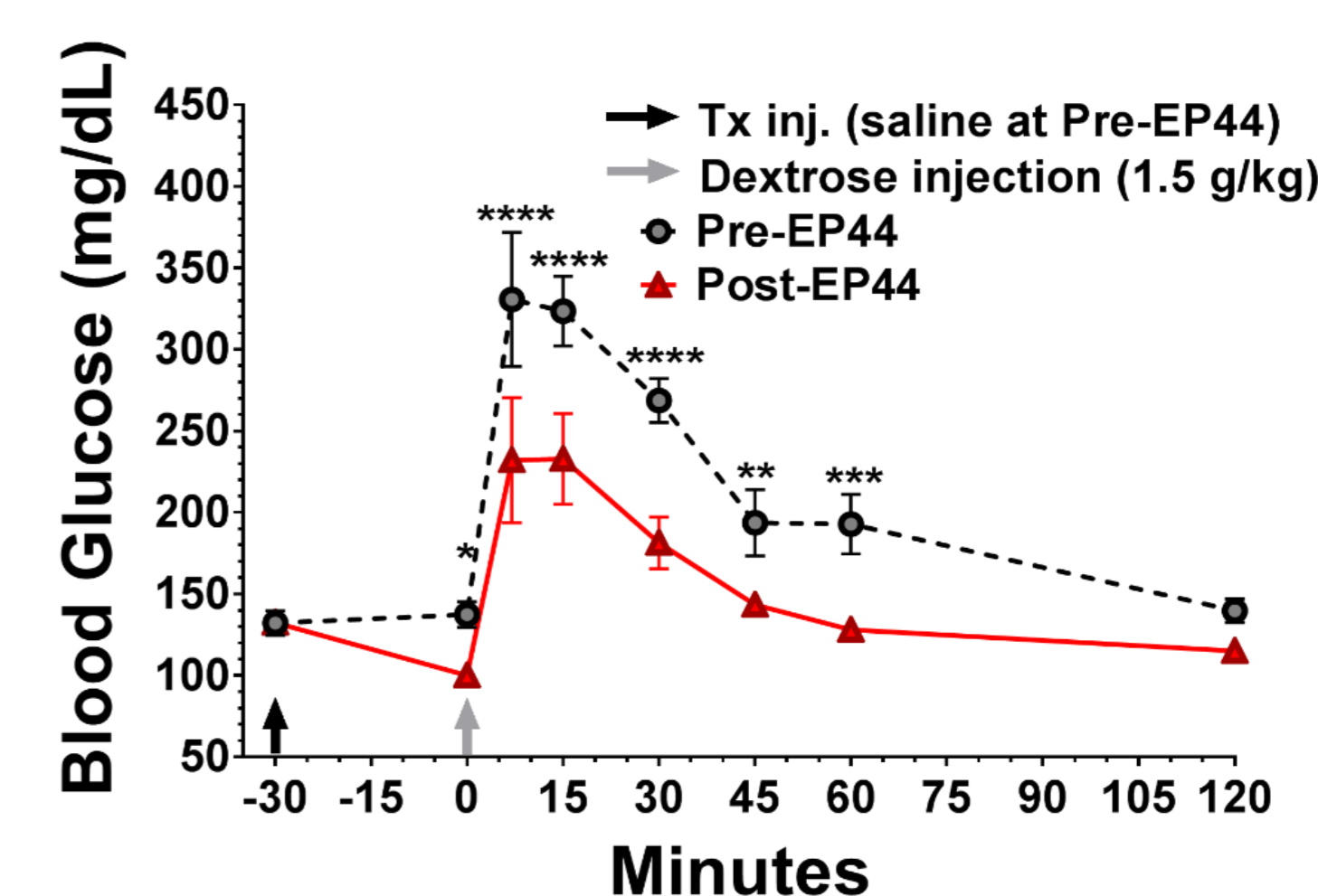
## Conclusion

Utilizing a novel concept of targeting serial anorectic pathways simultaneously with single-small chimeric peptides developed by our group is a new strategy addressing two coexisting conditions, namely obesity and T2D, to safely reduce food intake, body weight and blood glucose levels.

## Results in Rats *in vivo*

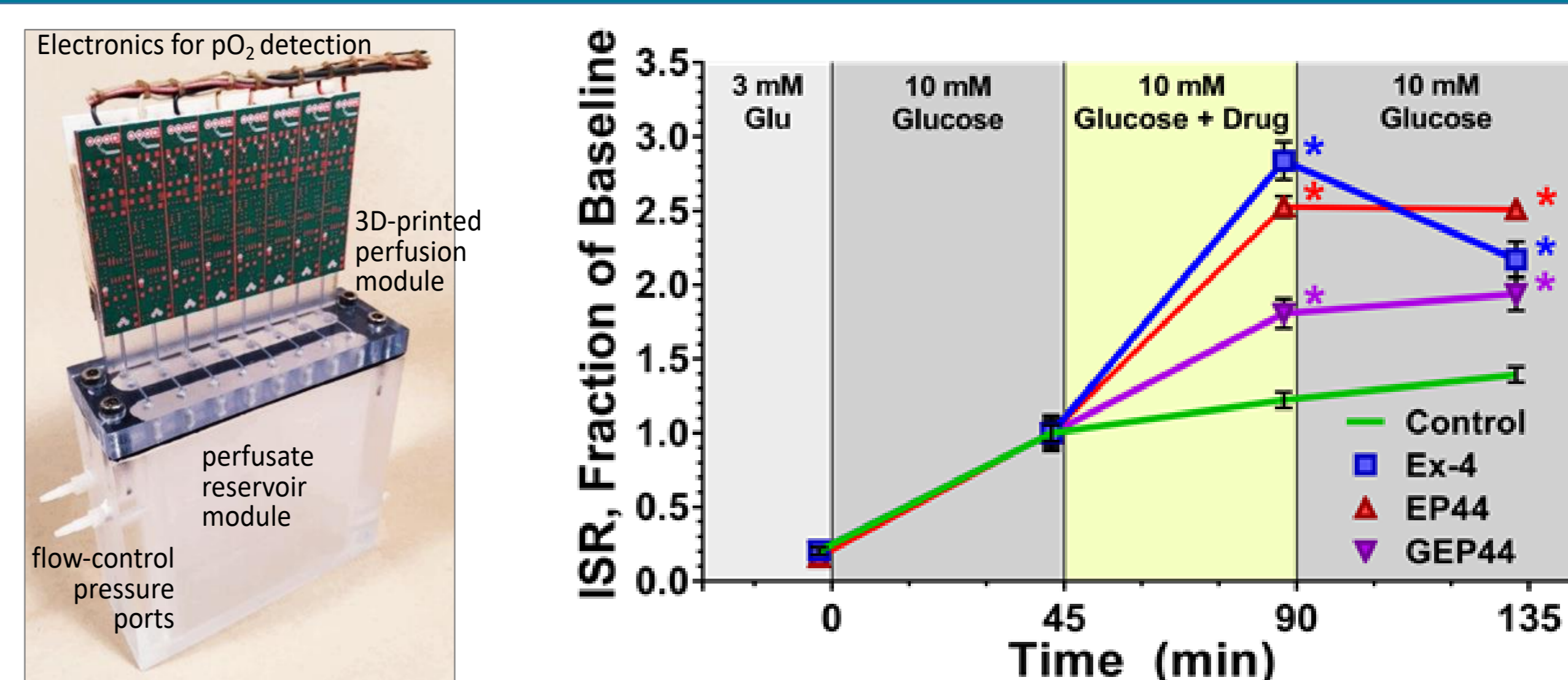


**Figure 2.** Robust reduction of FI in response to **GEP44** without induction of nausea assessed by kaolin intake (C) vs. Ex-4 (A) or EP44 (B). Dose responses of cumulative FI following Ex-4 (D), EP44 (E) and GEP44 (F). Solid lines above graph indicate p<0.001, dotted lines p<0.05.



**Figure 3.** Reduction of fasting and stimulated blood glucose after intraperitoneal glucose injection in obese male rats receiving **EP44** (4 d, 10 nmol/kg/d, n=4) compared to 10 days before drug treatment with saline injections (vehicle).

## Results in Rat Islets *in vitro*



**Figure 4.** Acute effects of Ex-4, **EP44** and **GEP44** exposure and washout on insulin secretion in rat islet cell perfusion *in vitro*. Combined results from two different experiments with each n=6 data points per time point and group. \*p<0.001 vs. control.