GIP receptor antagonist treatment causes weight loss in ovariectomized high fat diet-fed mice

Geke Aline Boer¹, Jenna Hunt¹, Maria Gabe¹, Johanne Windeløv¹, Alexander Sparre-Ulricht², Bolette Hartmann³, Jens Holst¹, and Mette Rosenkilde⁴

¹University of Copenhagen
²Antag Therapeutics ApS
³Novo Nordisk, A/S
⁴University of Copenhagen

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Abstract

Background and purpose The incretin hormone, glucose-dependent insulino-tropic polypeptide (GIP), secreted by the enteroendocrine K-cells in the proximal intestine, may regulate lipid metabolism and adiposity but its exact role in these processes is unclear. Experimental approach We characterized in vitro and in vivo antagonistic properties of a novel GIP analogue, mGIPAnt-1. We further assessed the in vivo pharmacokinetic profile of this antagonist, as well as its ability to affect high-fat diet (HFD)-induced body weight gain in ovariectomized mice during an 8-week treatment period. Key results mGIPAnt-1 showed competitive antagonistic properties to the GIP receptor (GIPR) in vitro as it inhibited GIP-induced cAMP accumulation in COS-7 cells. Furthermore, mGIPAnt-1 was capable of inhibiting GIP-induced glucoregulatory and insulinotropic effects in vivo and has a favourable pharmacokinetic profile with a half-life of 7.2 hours in C57Bl6 female mice. Finally, sub-chronic treatment with mGIPAnt-1 in ovariectomized HFD mice resulted in a reduction of body weight and fat mass. Conclusion and Implications mGIPAnt-1 successfully inhibited acute GIP-induced effects in vitro and in vivo and sub-chronically induces resistance to HFD-induced weight gain in ovariectomized mice. Our results support the development of GIP antagonists for the therapy of obesity.

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A: Mouse GIPR

B: Human GIPR

Log. conc. ligand (M)

% of mouse GIP activation

mGIP
mGIPAnt-1
mGIP(3-30)NH₂
mGIP(3-30)NH₂ + mGIP

Log. conc. ligand (M)

% of human GIP activation

mGIPAnt-1
human GIP
mGIPAnt-1

Note: This is a preprint and has not been peer reviewed. Data may be preliminary.
A

![Graph A](image)

B

![Graph B](image)

C

![Graph C](image)

D

![Graph D](image)

E

![Graph E](image)