

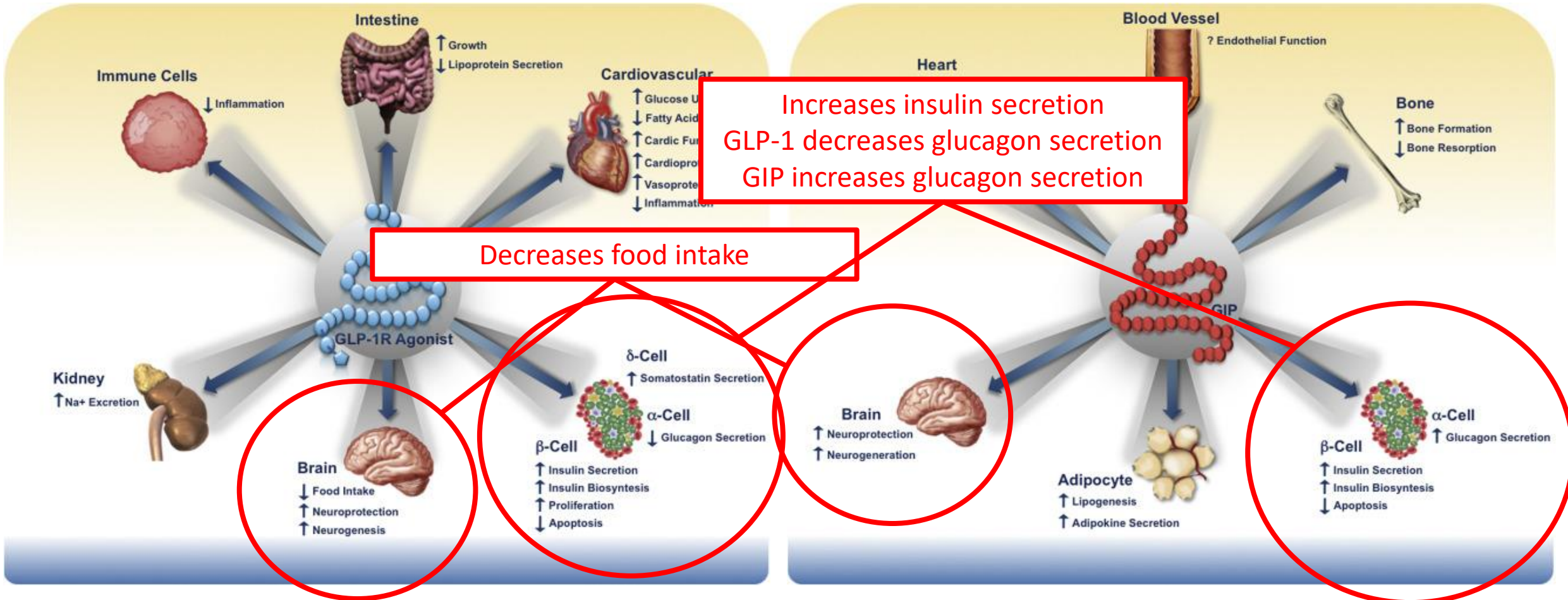
# Fused Incretins – Mechanisms of Action

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WCIRDC  
December 1, 2022

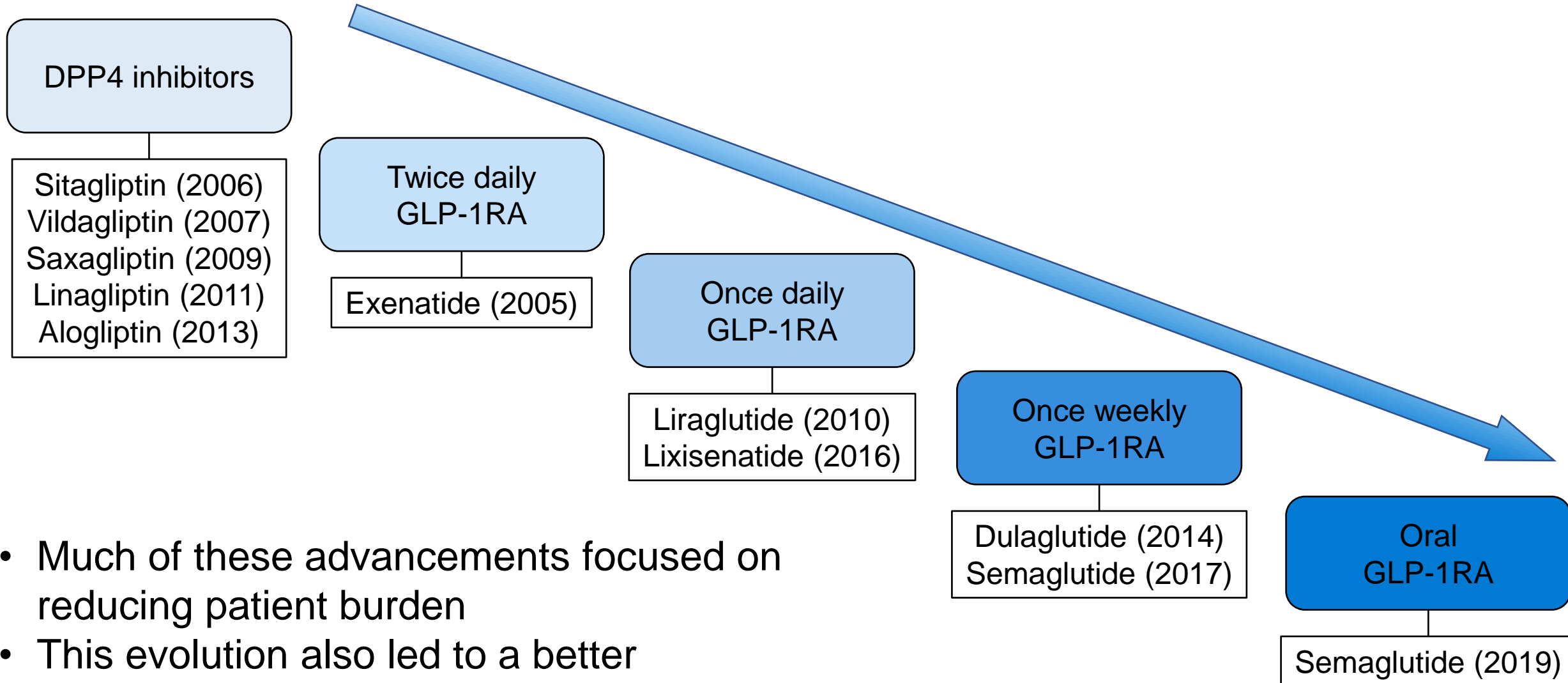
# Incretins are major regulators of metabolism

## GLP-1

## GIP



# The evolution of incretin pharmacology

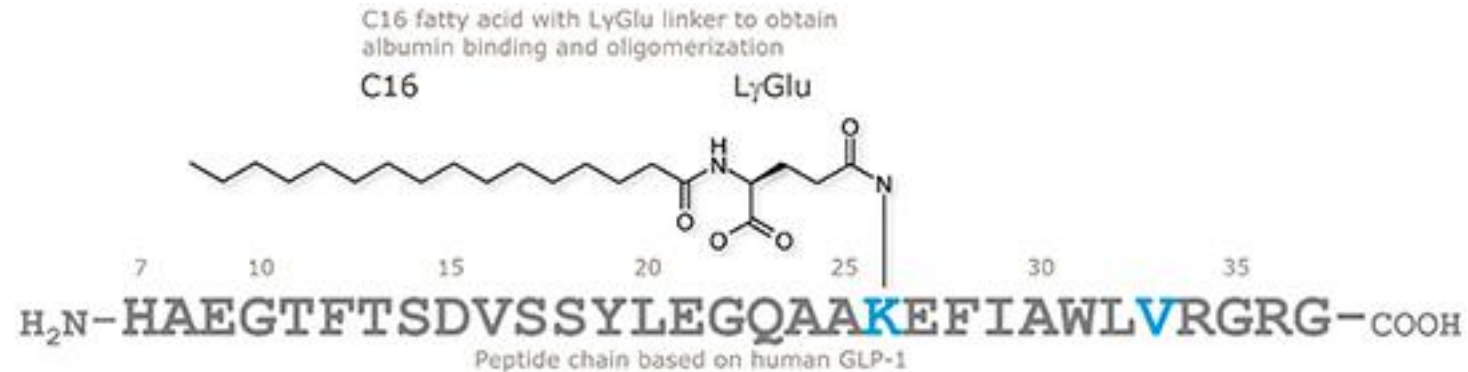


- Much of these advancements focused on reducing patient burden
- This evolution also led to a better understanding of how to increase efficacy

# Not all GLP-1R agonists are the same

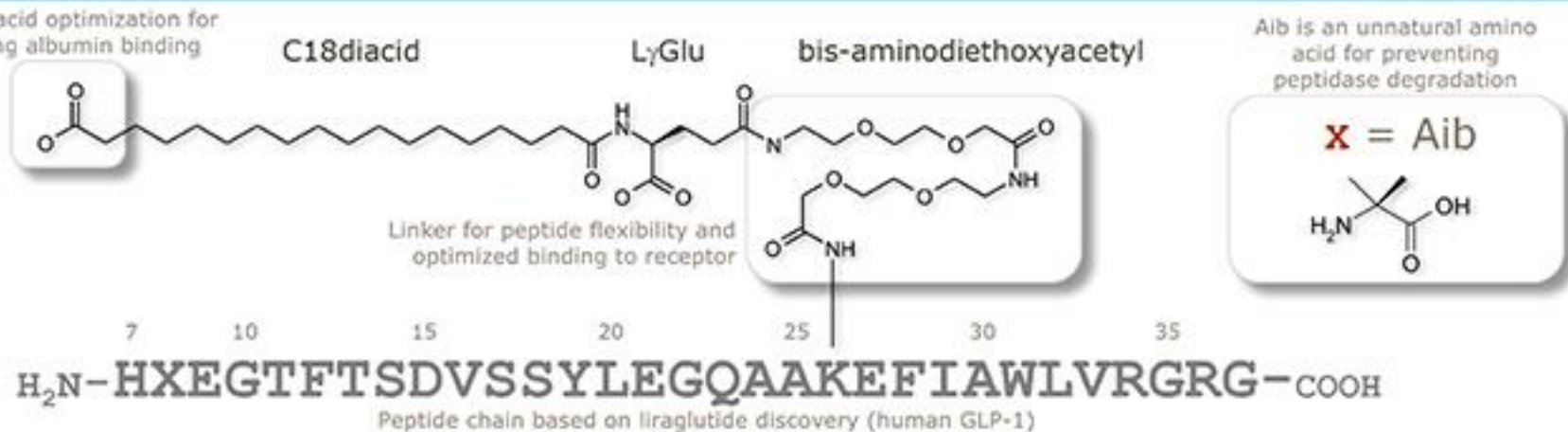
## Liraglutide

6-8% decreases  
in body weight



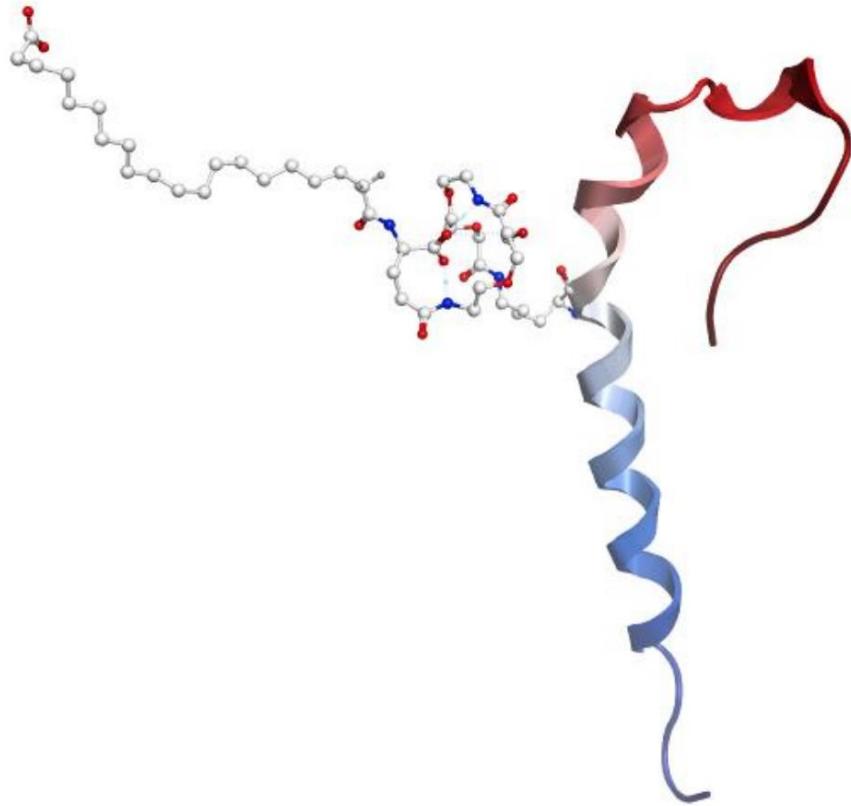
## Semaglutide

10-15% decreases  
in body weight



- Differences in pharmacokinetics?
- Differences in receptor pharmacology?

# Tirzepatide – the first multireceptor agonist in clinic



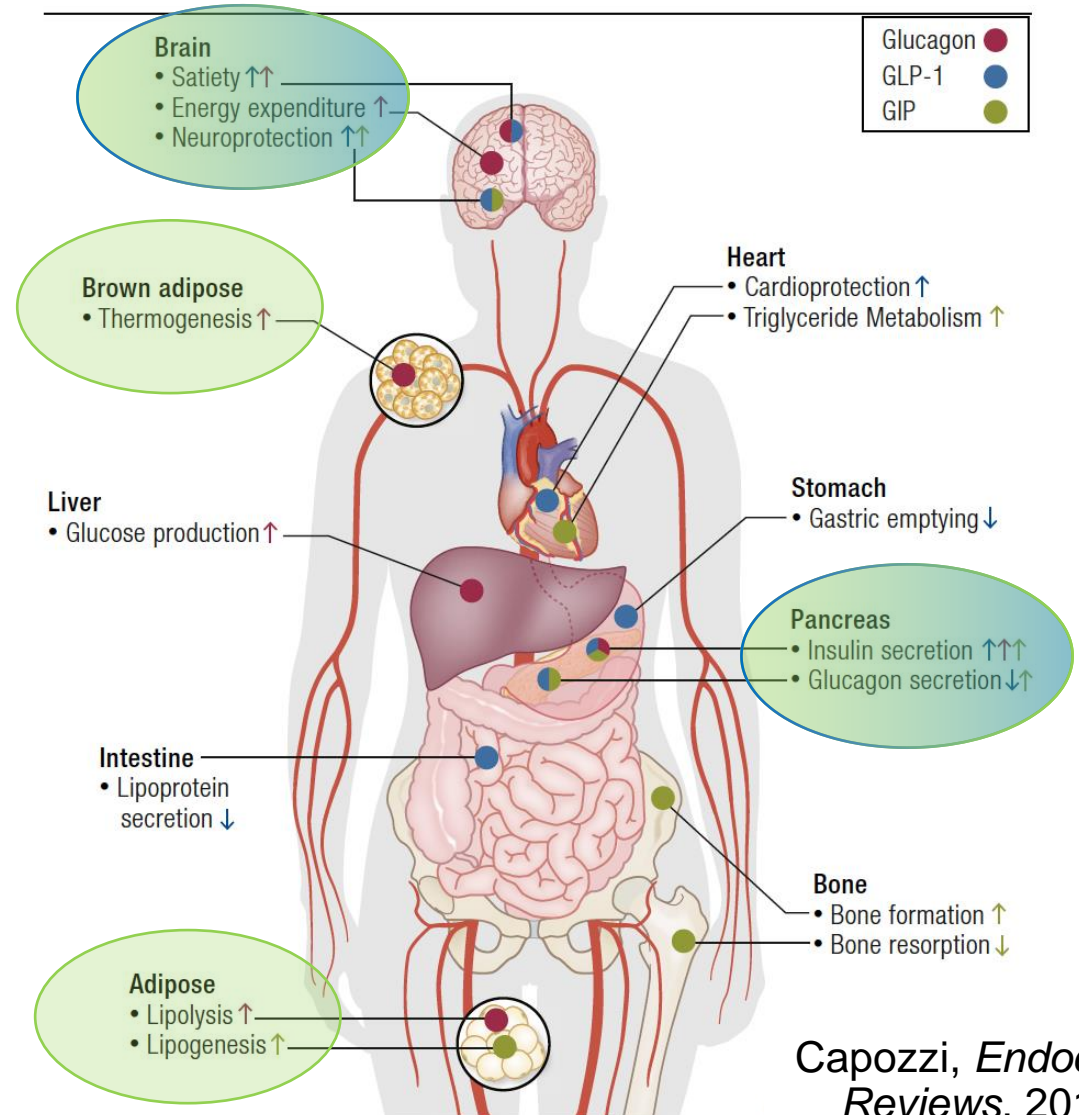
GIPR:GLP-1R co-agonist

- 39 amino acid peptide with activity at both the GIPR and the GLP-1R
- Native GIP sequence with modifications to enable activity at the GLP-1R
- Balanced, full agonist at the GIPR; unbalance, partial agonist at the GLP-1R
- FDA approval in 2022 for treatment of T2D

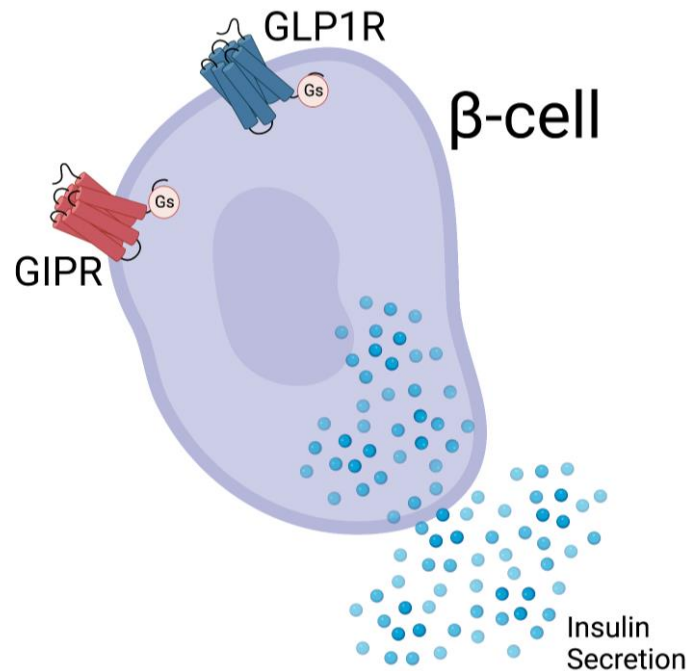
# How could GIPR add to GLP-1R?

## Hypotheses:

1. Engaging more cell types  
i.e. GIPR +, GLP-1R - cells



# Incretin receptors in beta-cells



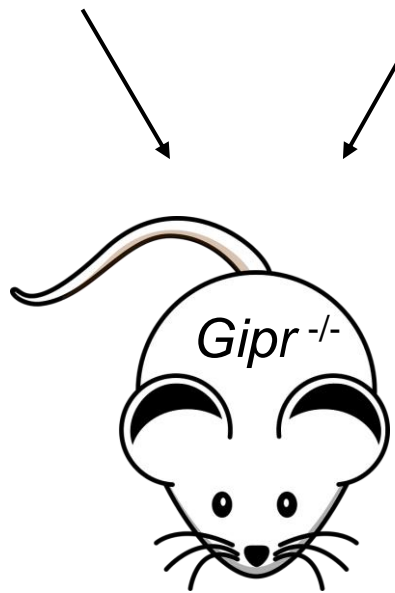
- Beta-cells express both incretin receptors
- Incretin receptors in beta-cells account for the majority of postprandial insulin secretion
- The activity of the receptors are additive for insulin secretion
- Acute insulin secretion is directly proportional to the level of receptor agonism

We can use glucose tolerance and insulin secretion to determine if the GIPR activity of tirzepatide matters

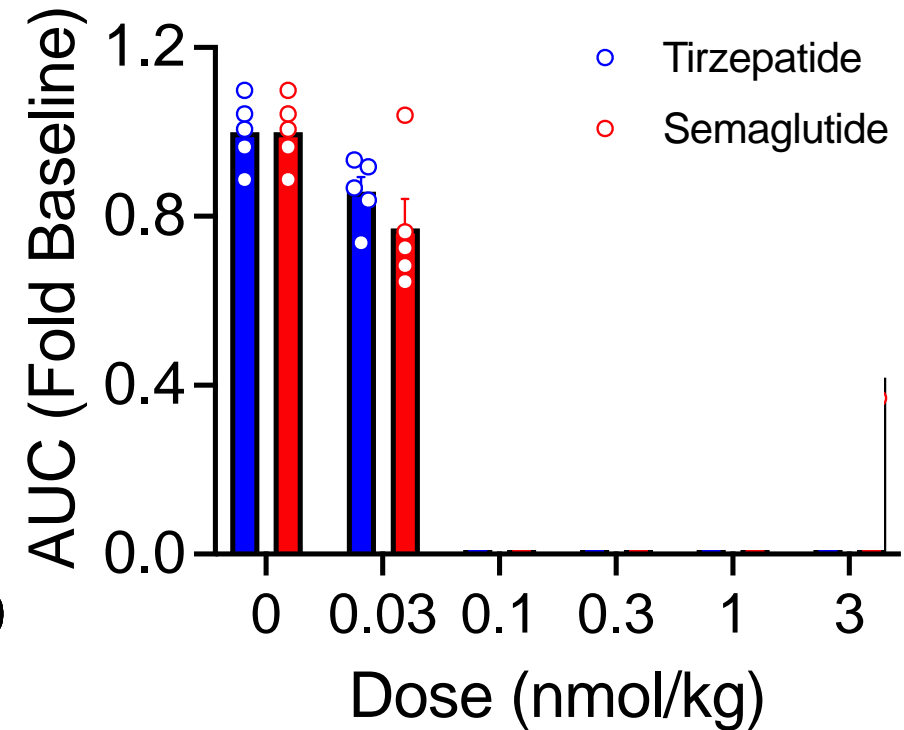
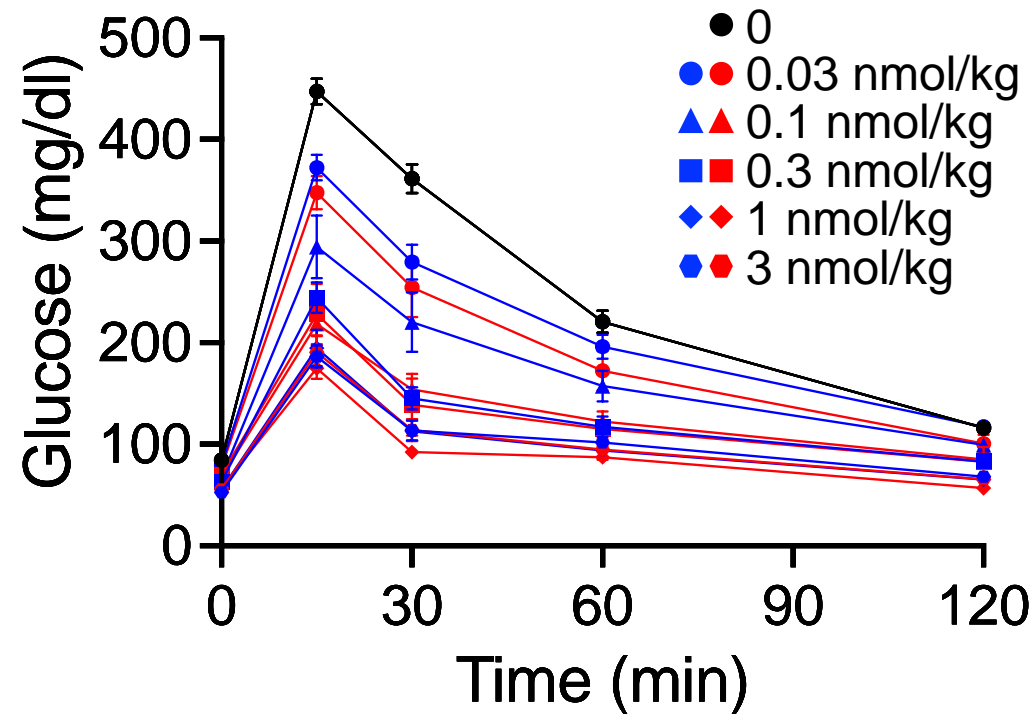
# Do *Gipr*<sup>-/-</sup> mice lower glucose in response to tirzepatide?

Tirzepatide

Semaglutide



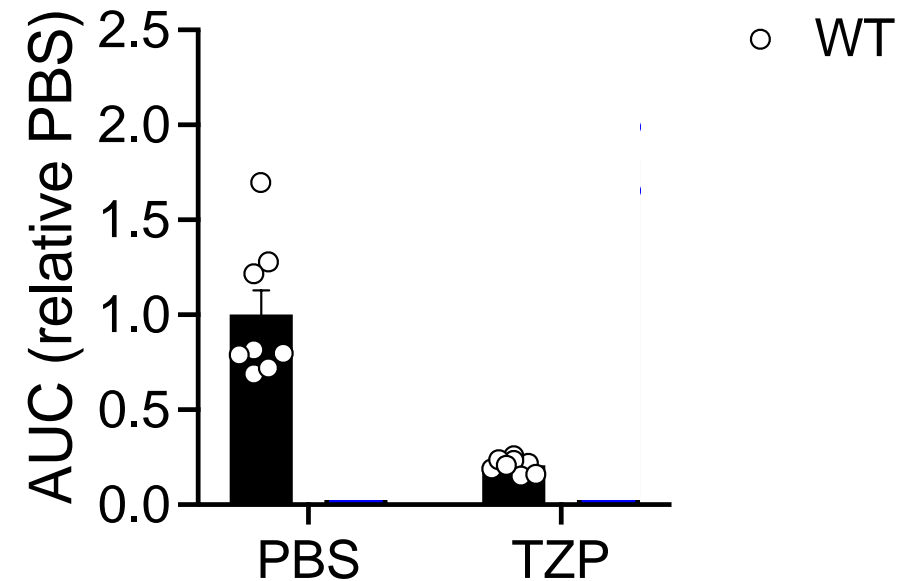
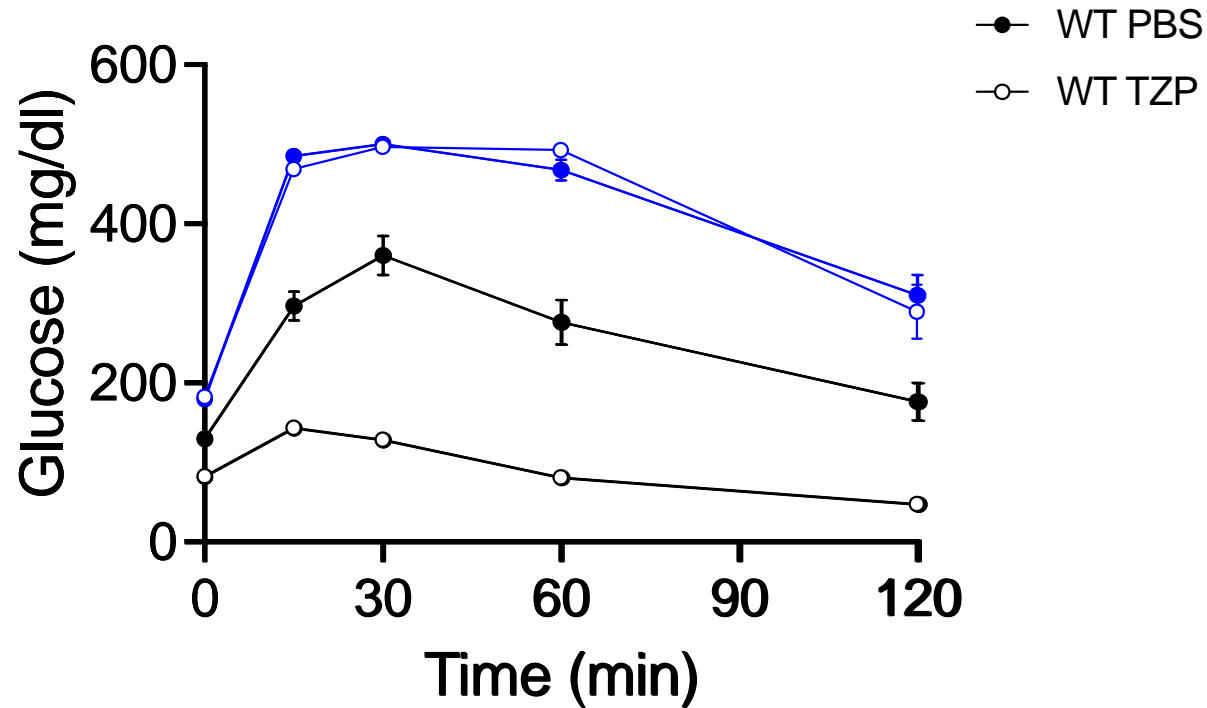
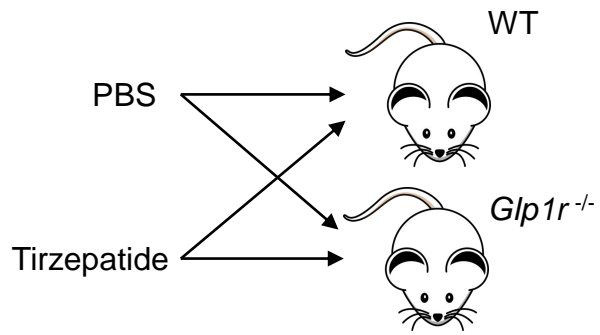
## Tirzepatide vs Semaglutide



Loss of GIPR signaling does not impact the glucose lowering of tirzepatide



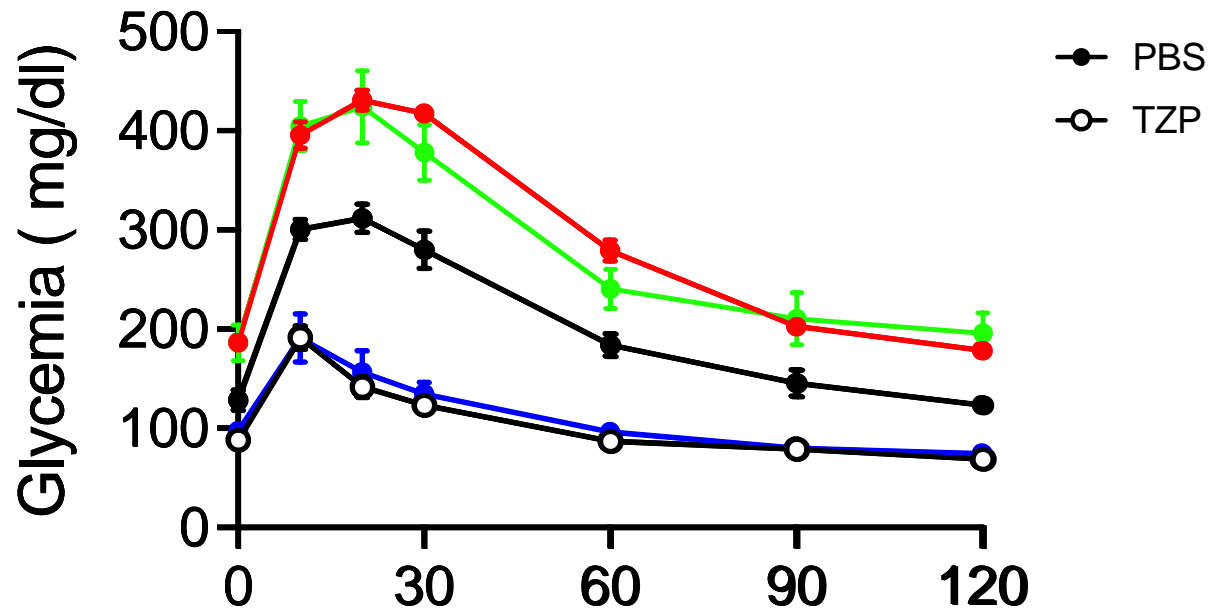
# Do *Glp1r* $-/-$ mice lower glucose in response to tirzepatide?



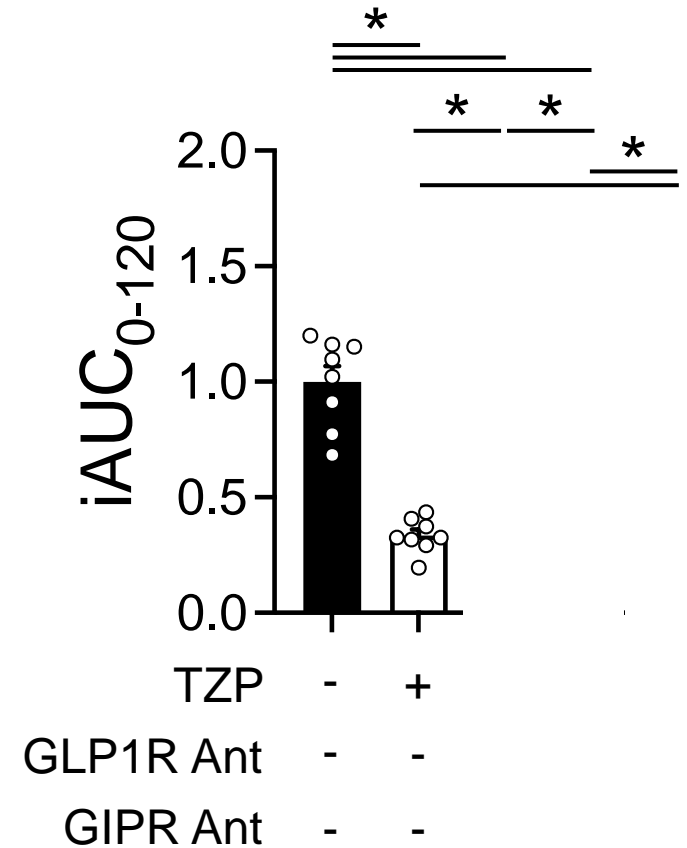
Loss of GLP-1R signaling prevents glucose lowering by tirzepatide

# How does pharmacological antagonism impact tirzepatide?

## IPGTT

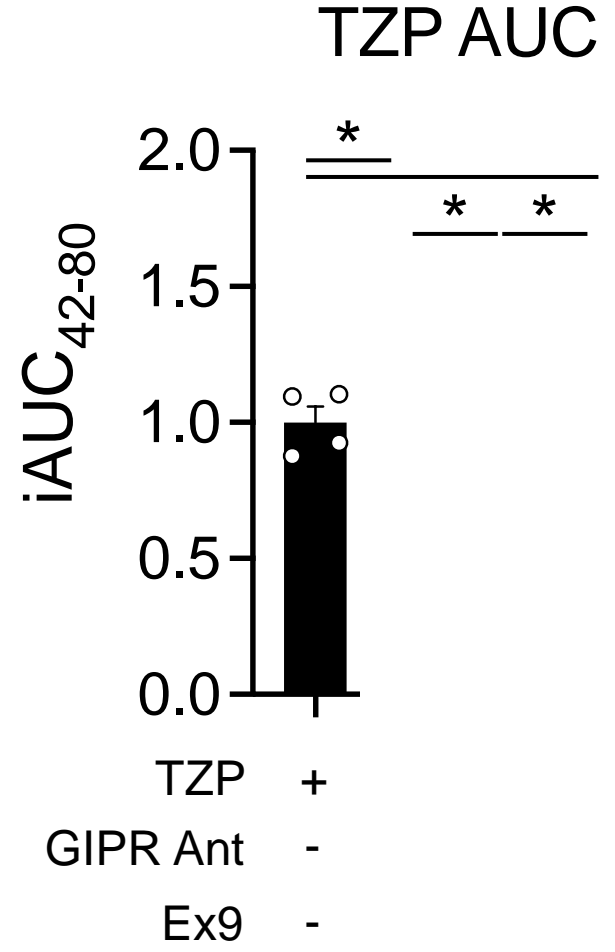
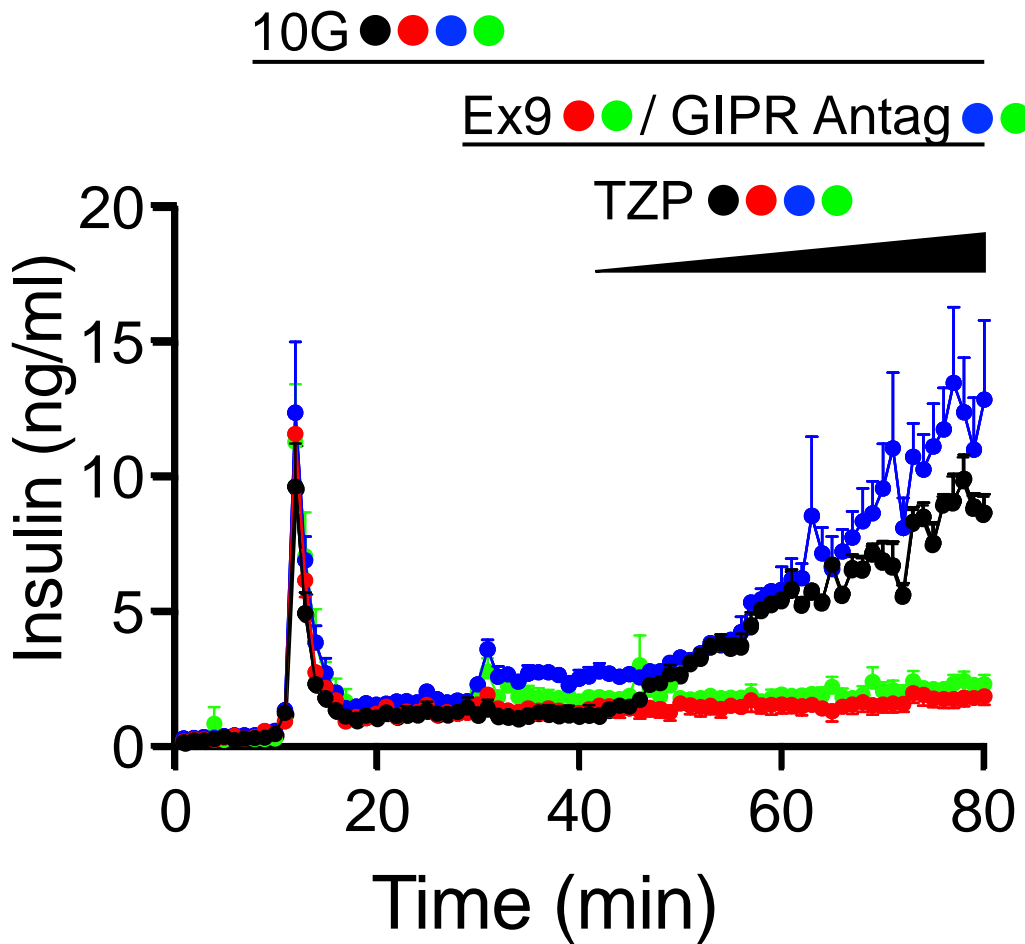
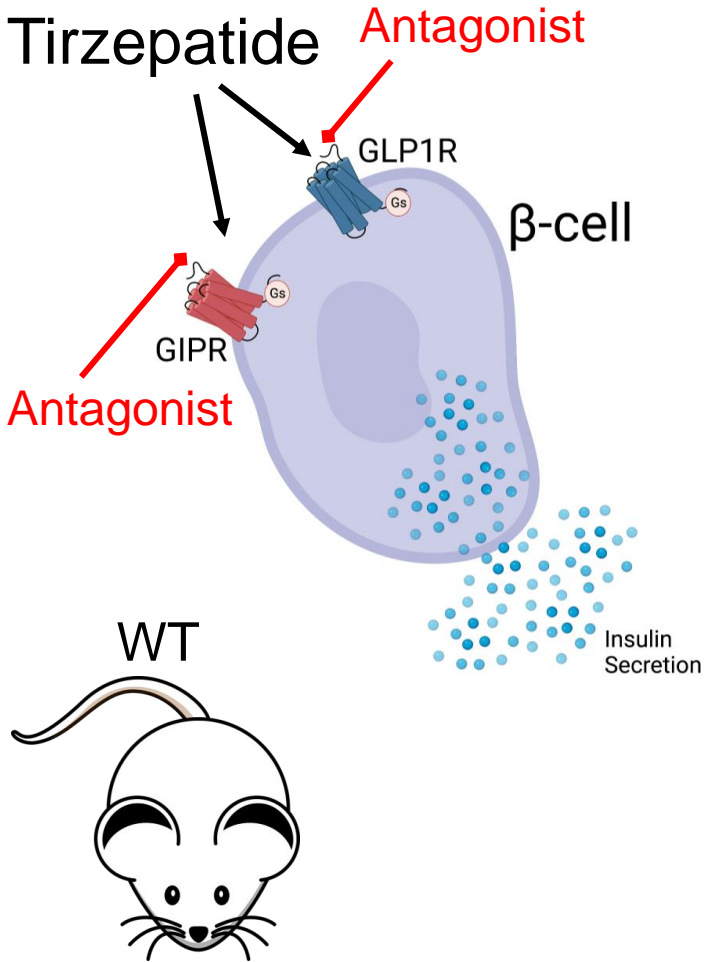


## iAUC



GLP-1R, but not GIPR signaling is required for the glucose lowering by tirzepatide

# What is the impact of incretin receptor antagonism on tirzepatide-stimulated insulin secretion?

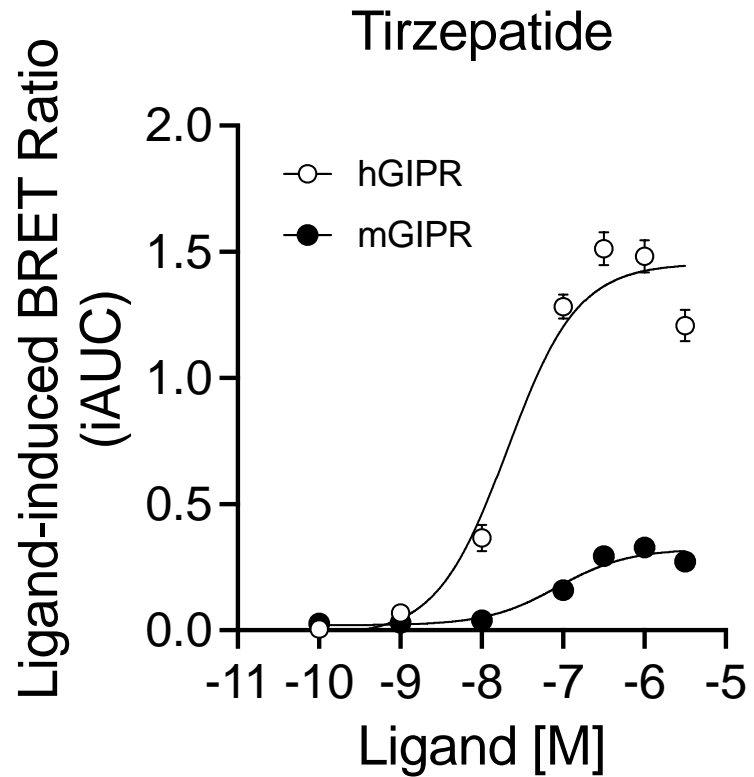


Antagonism of the GIPR in mice in vivo and in mouse islets ex vivo does not alter tirzepatide-stimulated insulin secretion

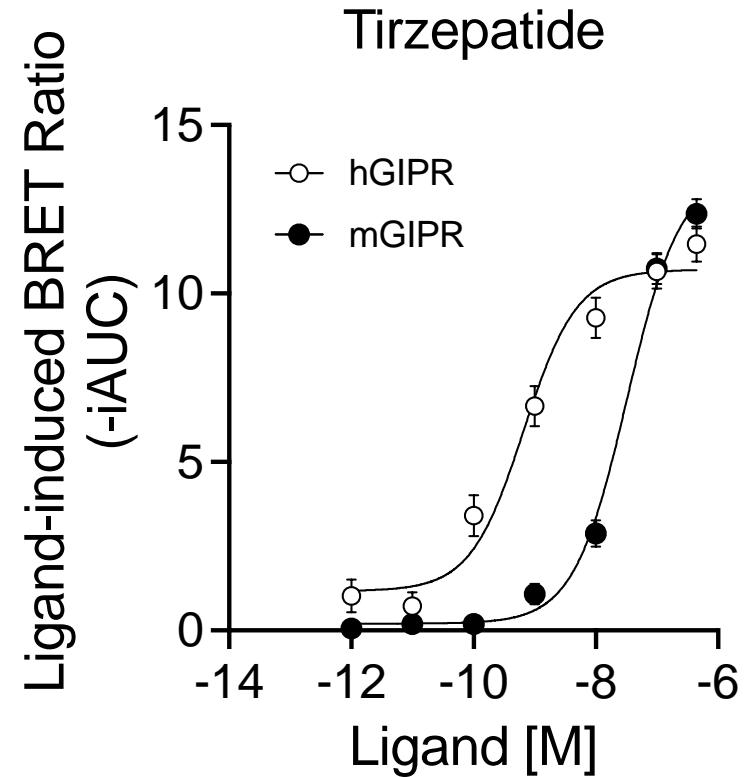
Does this mean tirzepatide really is just a super GLP-1R agonist?

# Tirzepatide has reduced potency at the mGIPR

Gs recruitment



cAMP

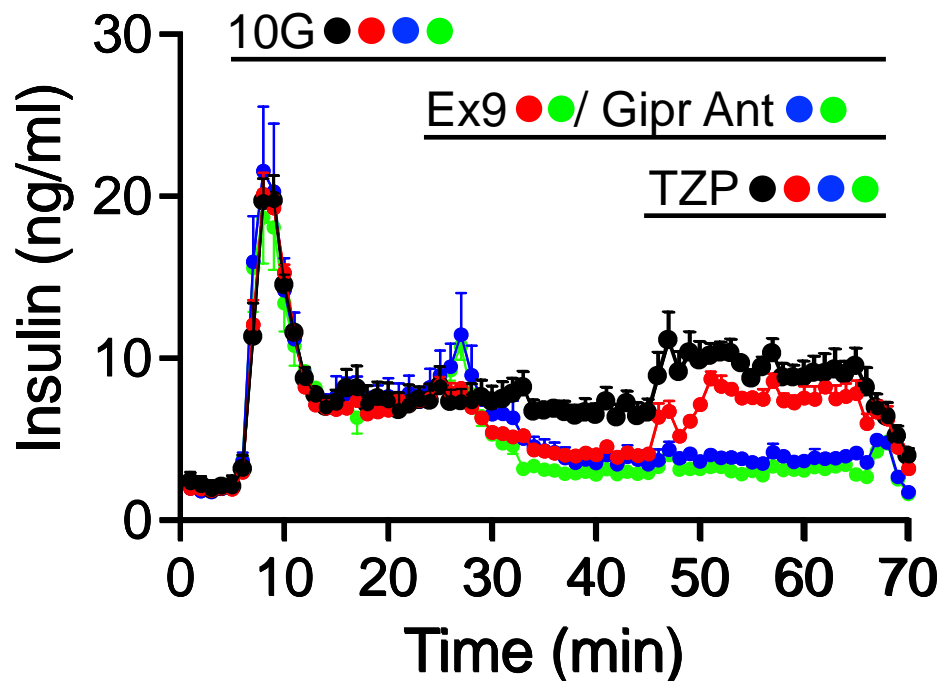


Tirzepatide was designed to target the human incretin receptors – so why study mice?

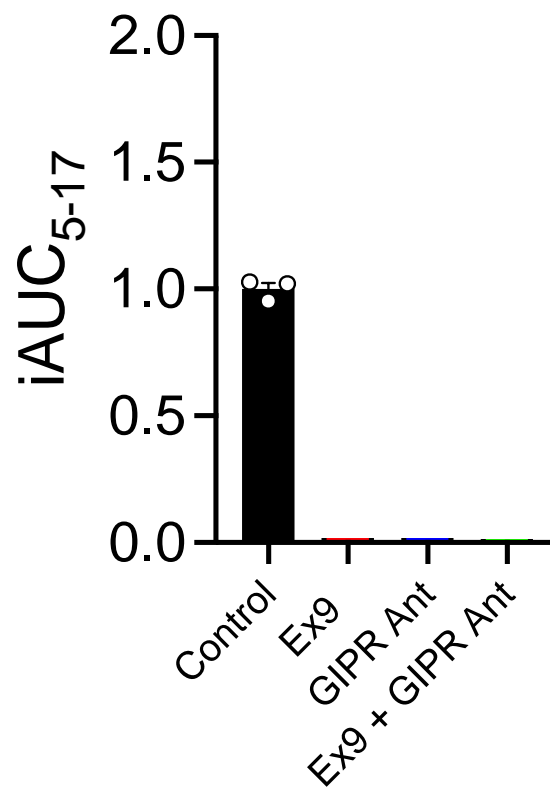
# Does GIPR contribute to tirzepatide activity in human islets?

● Control

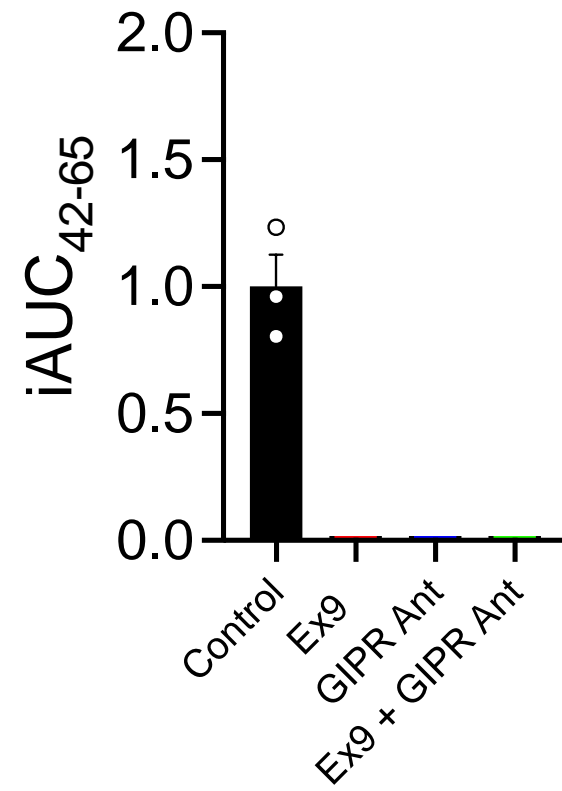
## S1472



## Glucose



## TZP



GIPR signaling is required for the tzp-stimulated insulin secretion

# Does GIPR contribute to tzp activity in human islets?

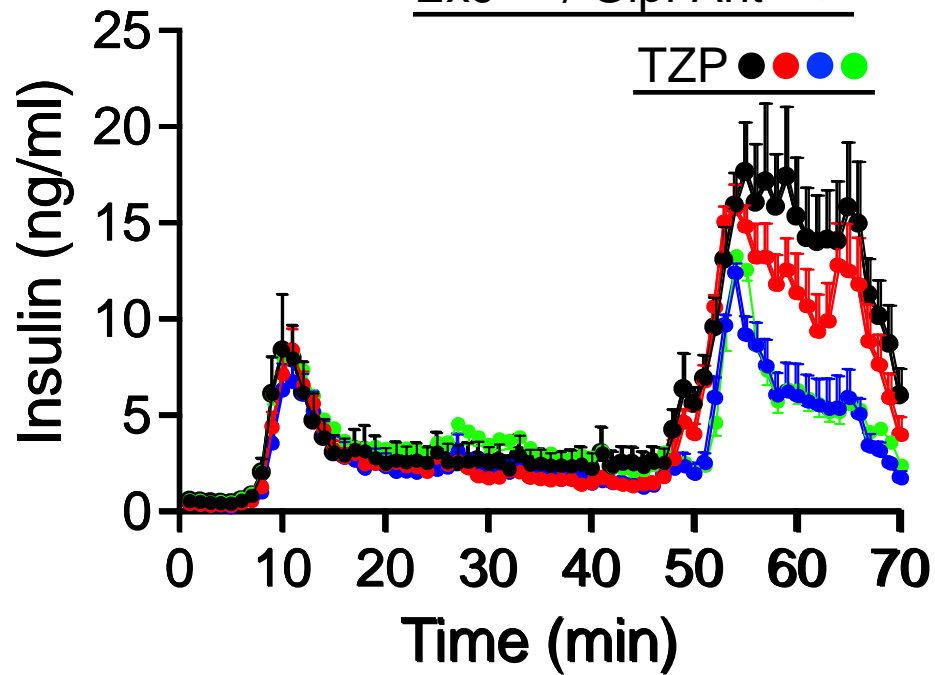
R434

● Control

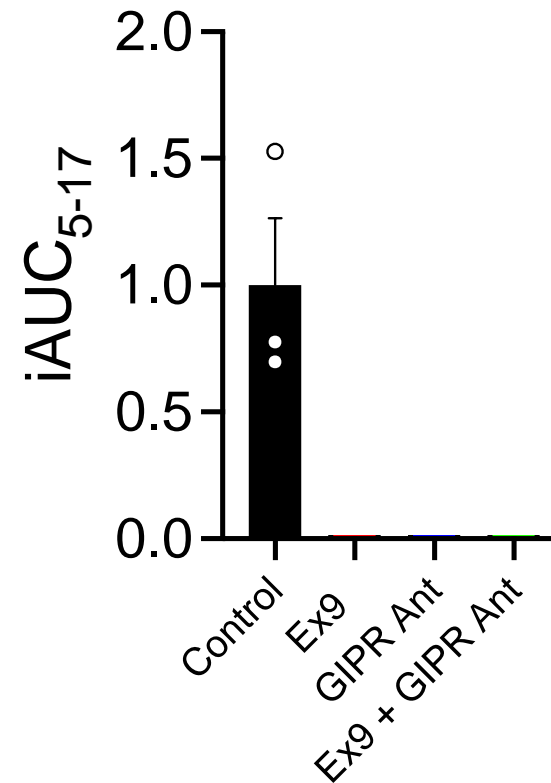
10G ● ● ● ●

Ex9 ● ● / Gipr Ant ● ●

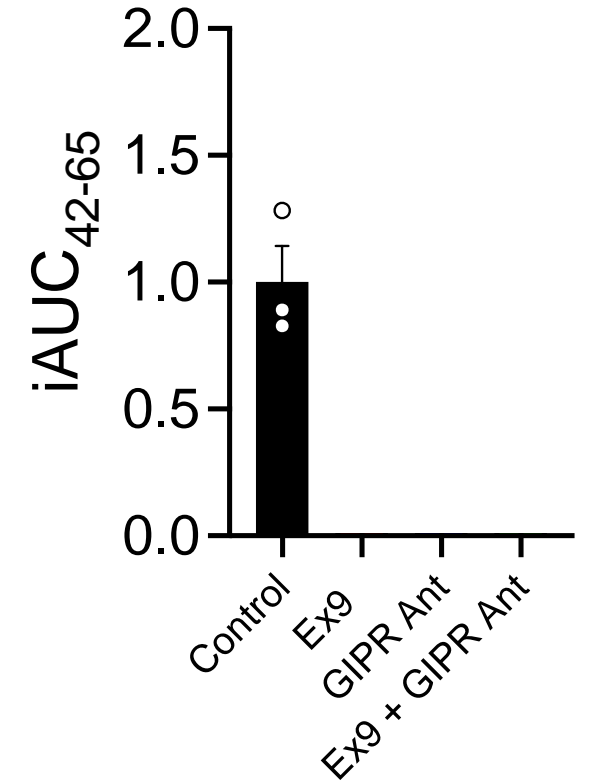
TZP ● ● ● ●



Glucose

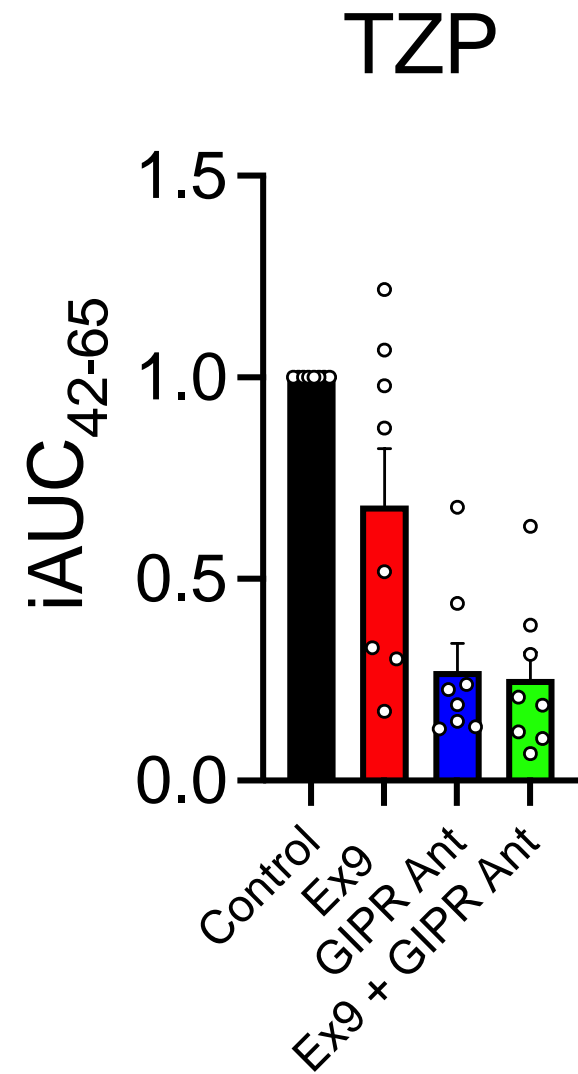
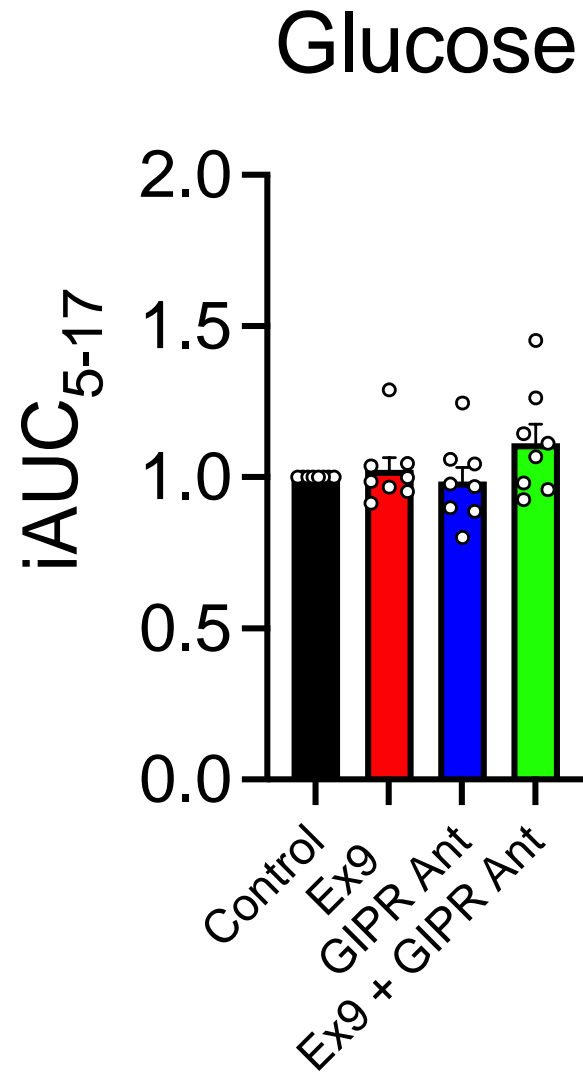
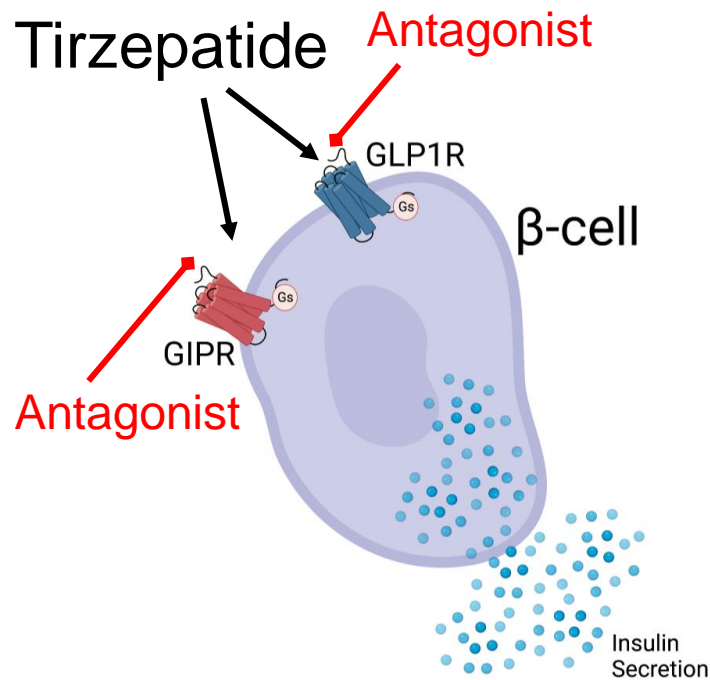


TZP



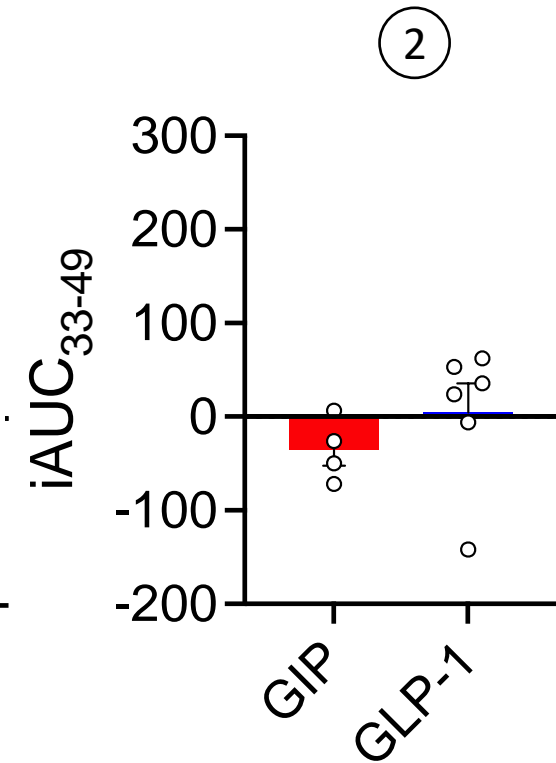
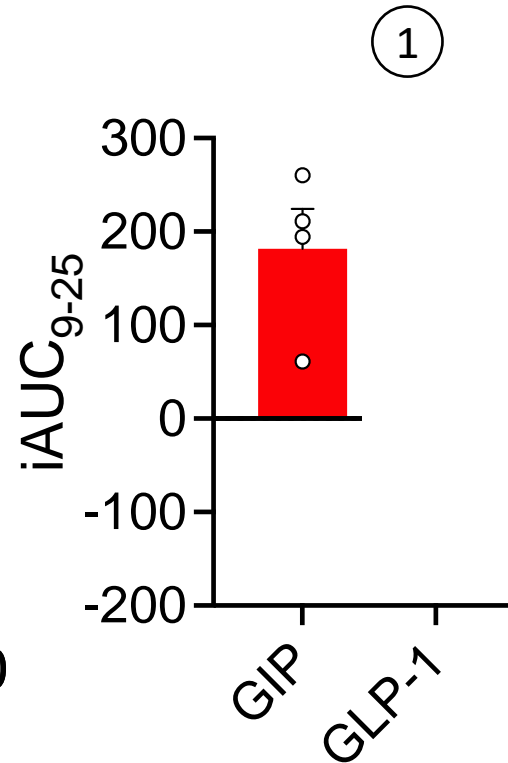
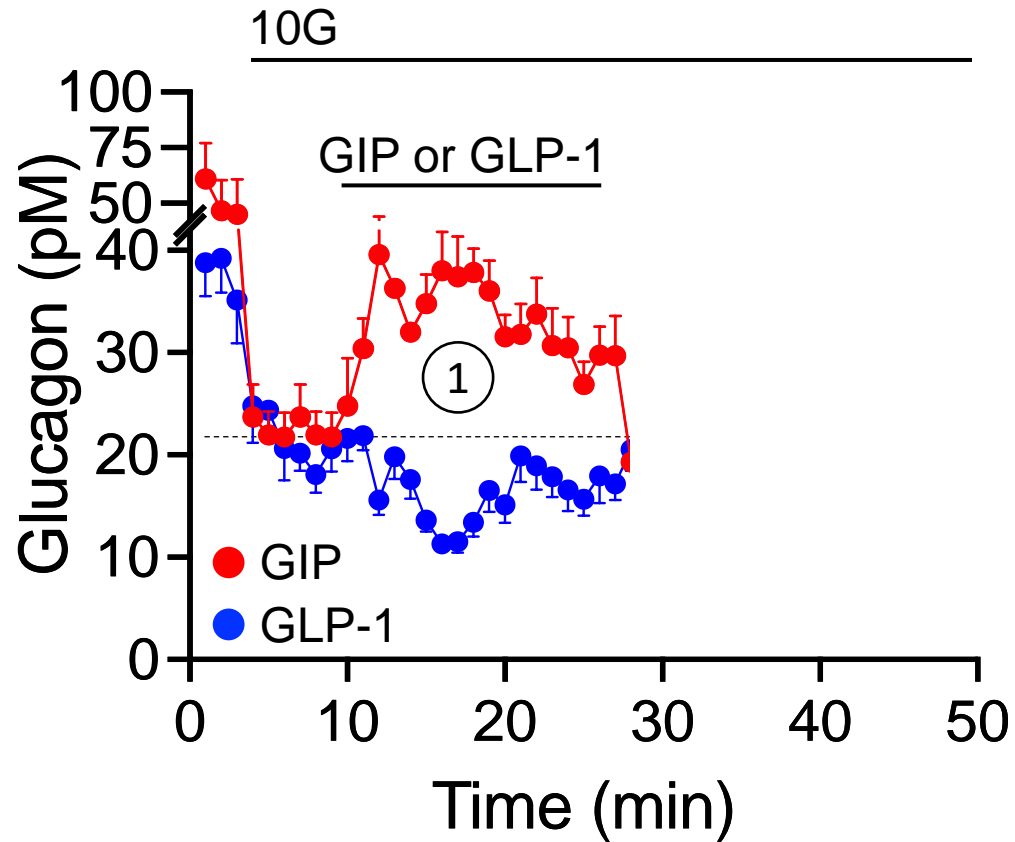


# Antagonizing GIPR consistently decreases TZP-stimulated insulin secretion



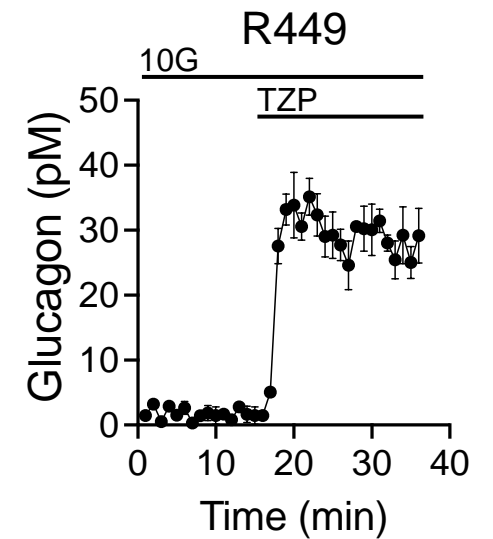
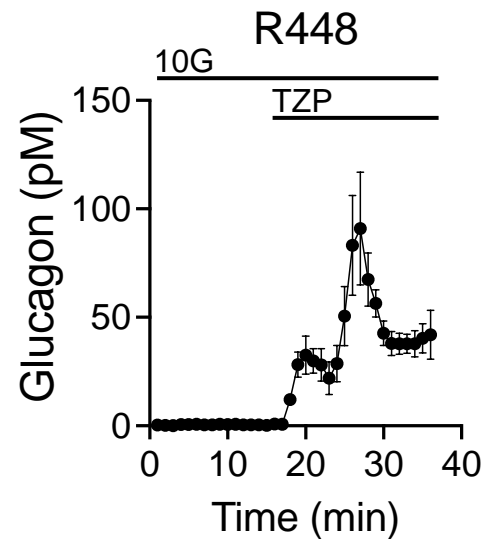
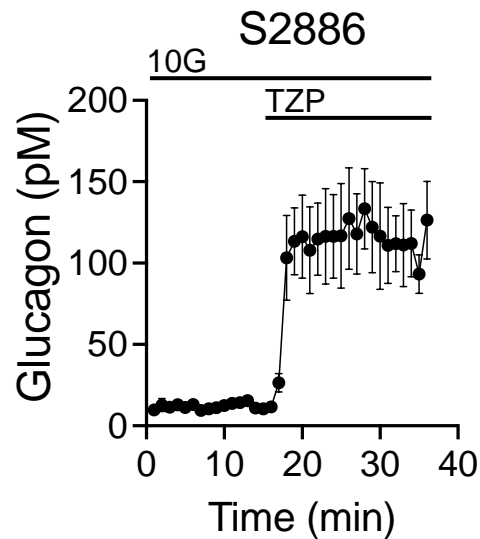
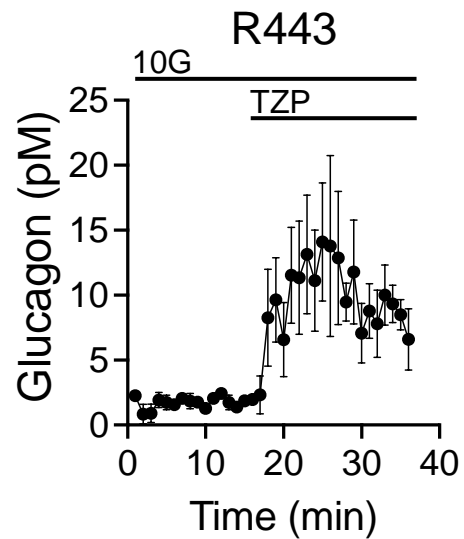
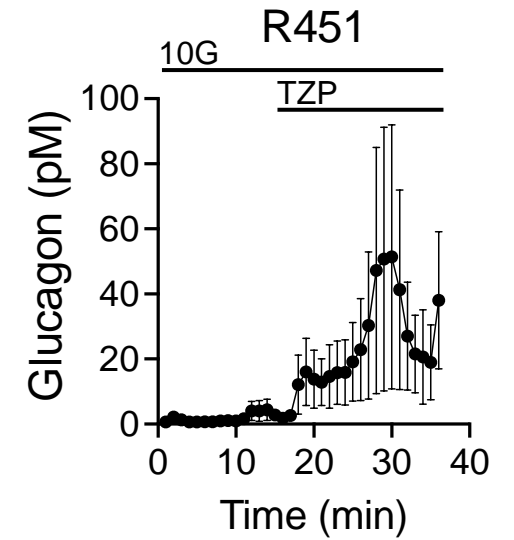
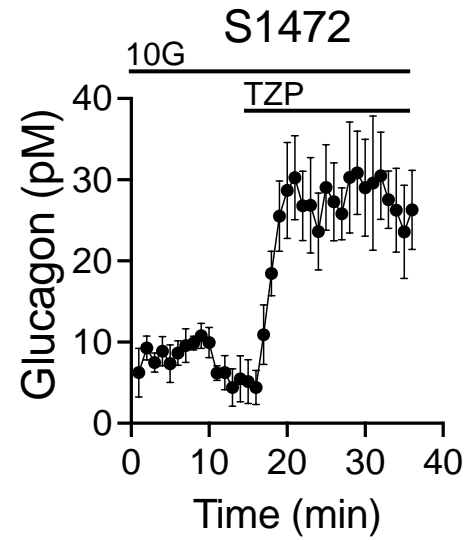
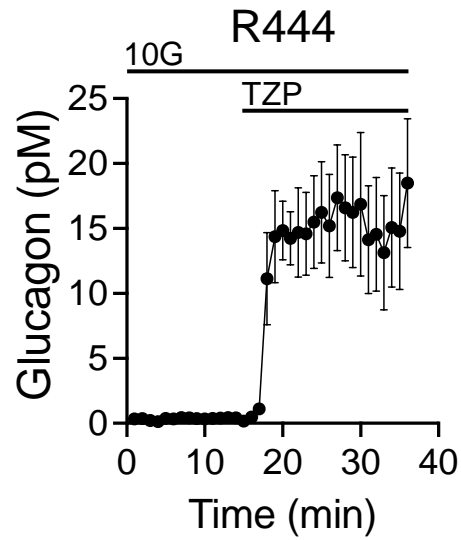
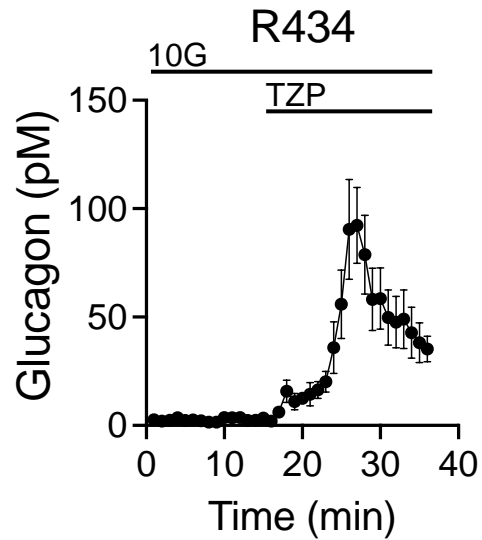
In human islets, blocking the GIPR consistently reduces TZP-stimulated insulin secretion

# Incretin action on glucagon secretion



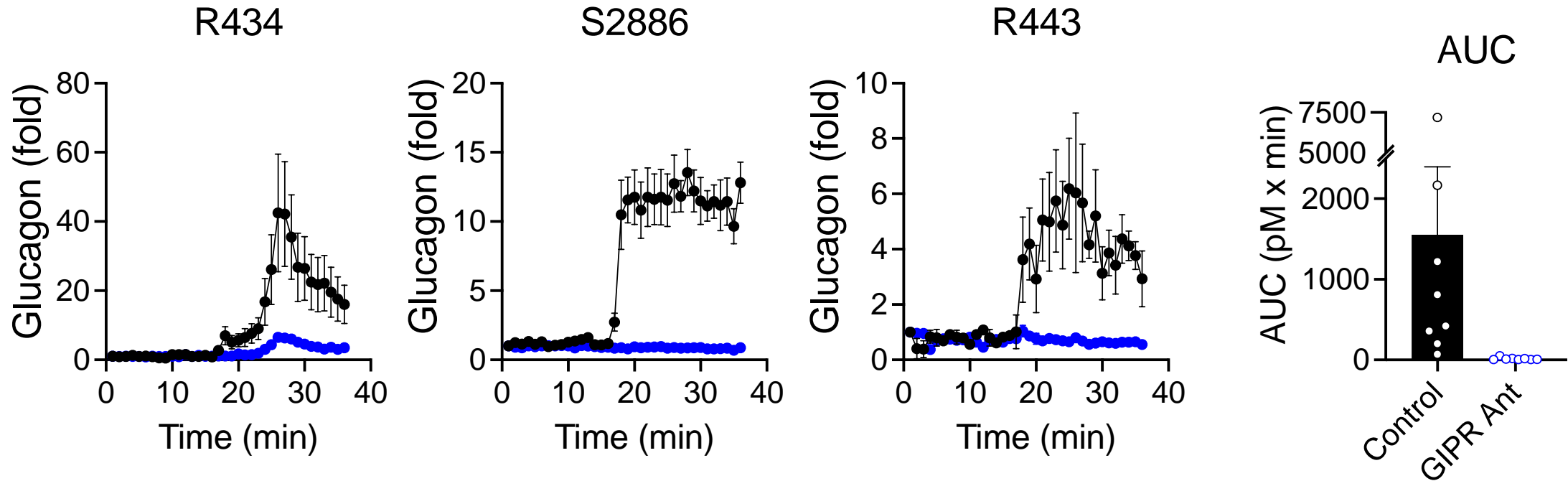
GIP stimulates, while GLP-1 inhibits, glucagon secretion

# Tirzepatide stimulates glucagon secretion



# Tirzepatide stimulates glucagon secretion

- Control
- GIPR Ant



Antagonizing the GIPR prevents tirzepatide-stimulated glucagon secretion

# Conclusions

1. Tirzepatide has reduced potency at the mouse GIPR compared to the human GIPR.

# Acknowledgements

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The logo for Eli Lilly, featuring the word "Lilly" in a red, cursive script font.

