Insights from neuroscience: Changing the set point

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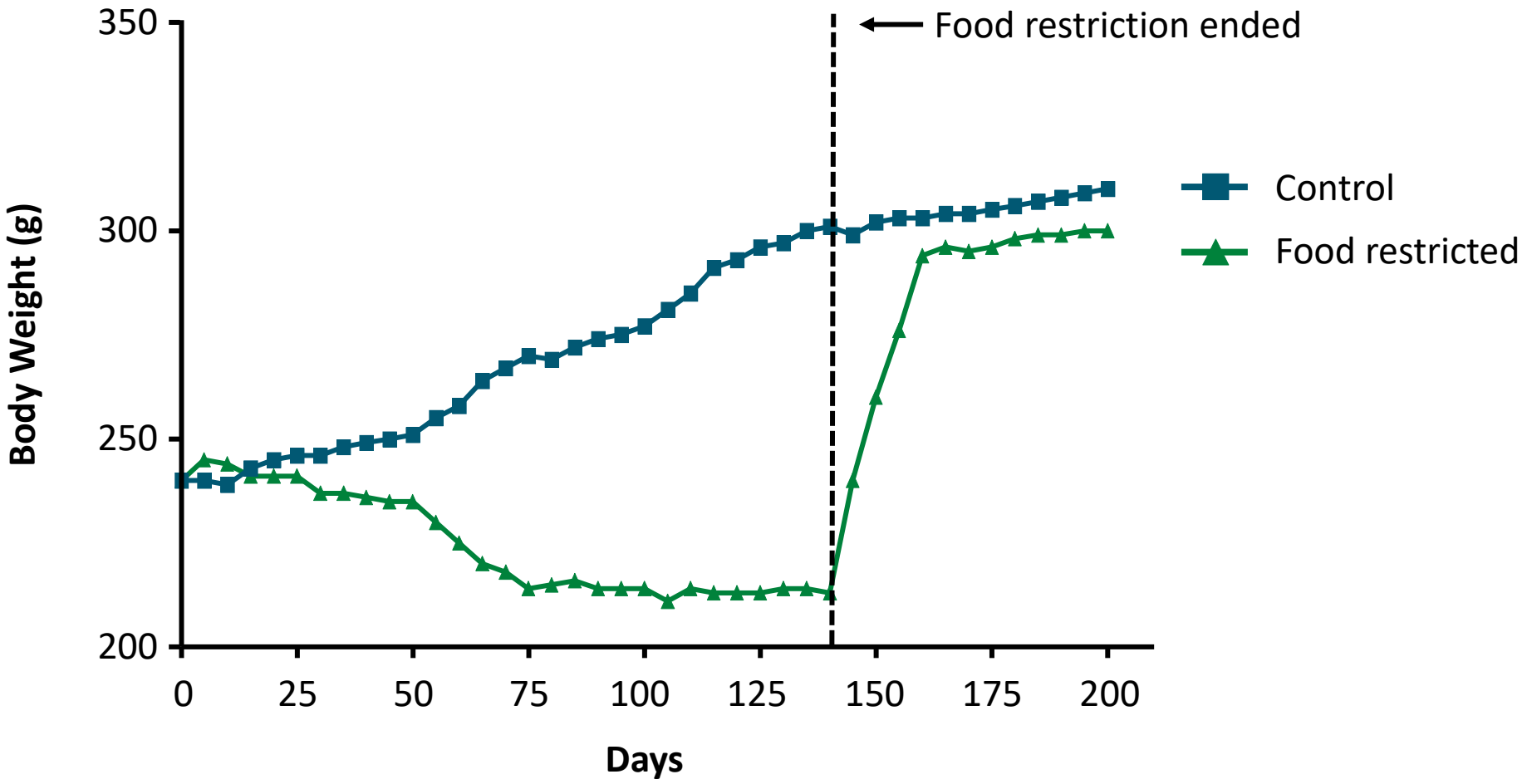
University of Michigan

@seeleyrj

Disclosures

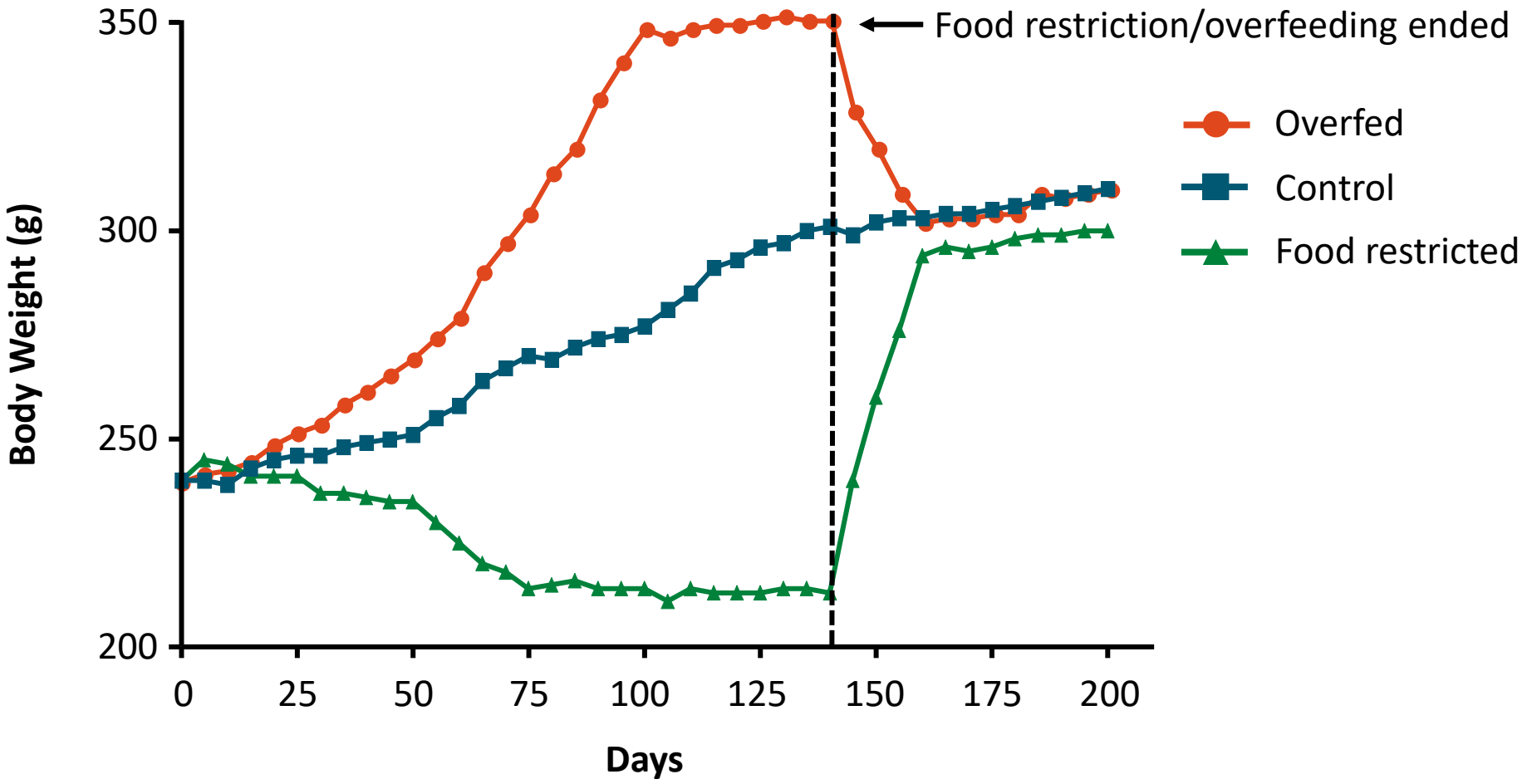
- Research Support: Novo Nordisk, Astra Zeneca, Eli Lilly, Amgen, Congruence, Fractyl, Bullfrog AI, Glyscend, Diasome
- SAB/Consultant: Novo Nordisk, Fractyl, Structure Therapeutics, CinRx, Eli Lilly, Congruence, Nuanced Health, Alveus
- Equity: Rewind Health, Nuanced Health, Fractyl, Congruence Bio, Eccogene

Negative Energy Balance in Rats



Bernstein. Proc Soc Exp Biol Med. 1975;150:546.

Positive Energy Balance in Rats



Bernstein. Proc Soc Exp Biol Med. 1975;150:546.

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Cell Metabolism
Review

Leveraging the Gut to Treat Metabolic Disease

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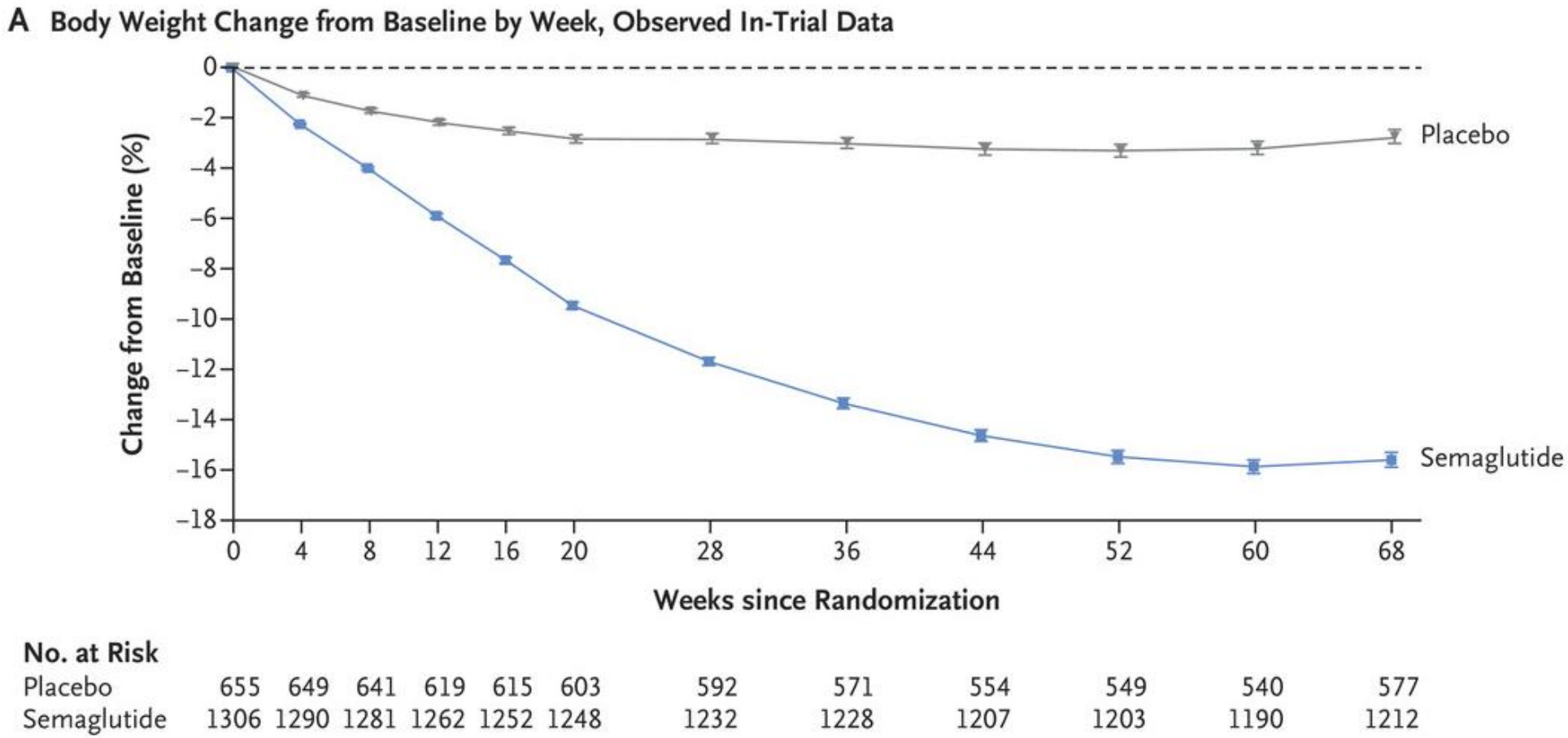
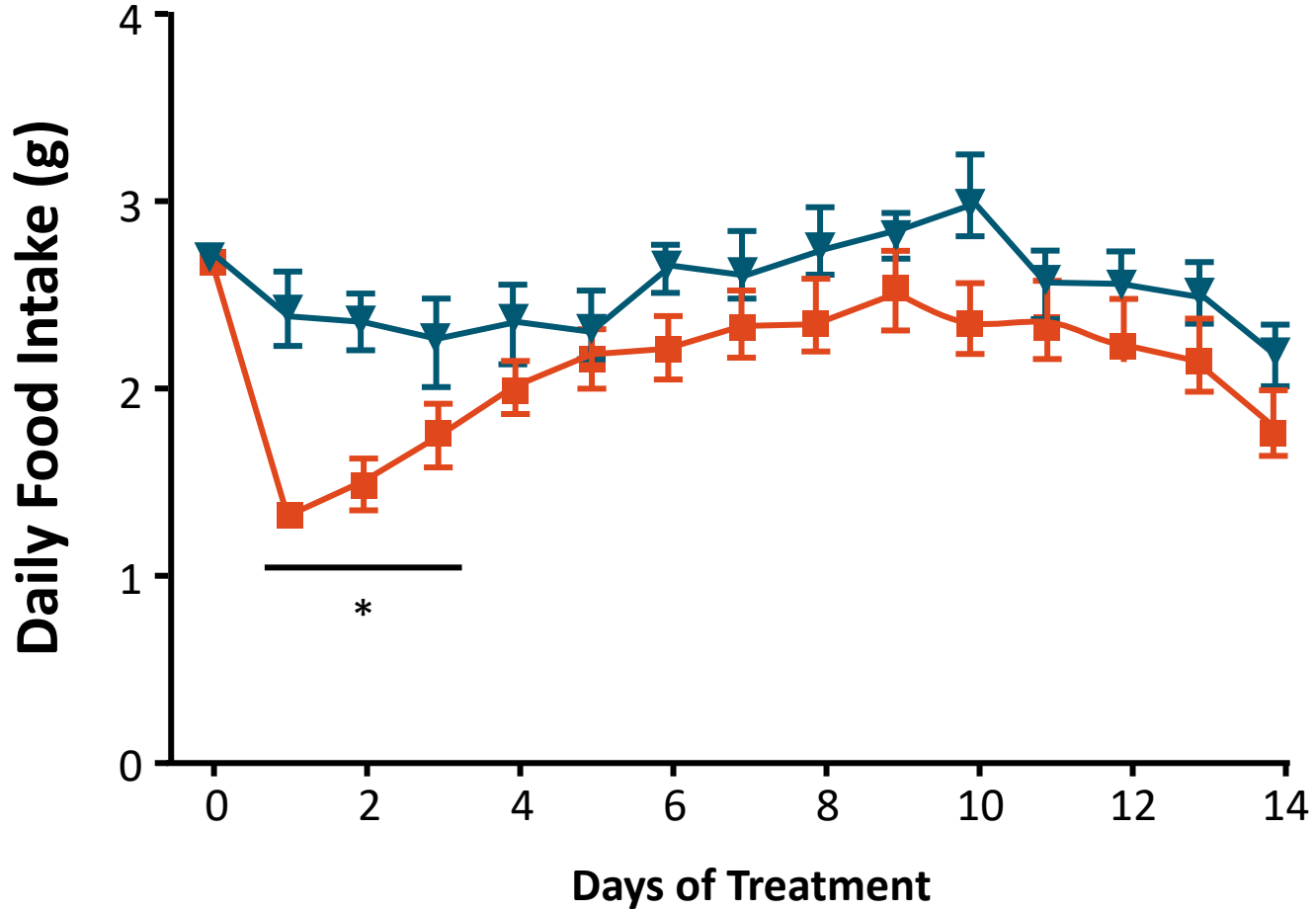
*Correspondence: seeleyrj@umich.edu
https://doi.org/10.1016/j.cmet.2020.02.014

Long-acting GLP-1R agonist



Wilding et al., NEJM, 2021

Short-term effect of lira on food intake



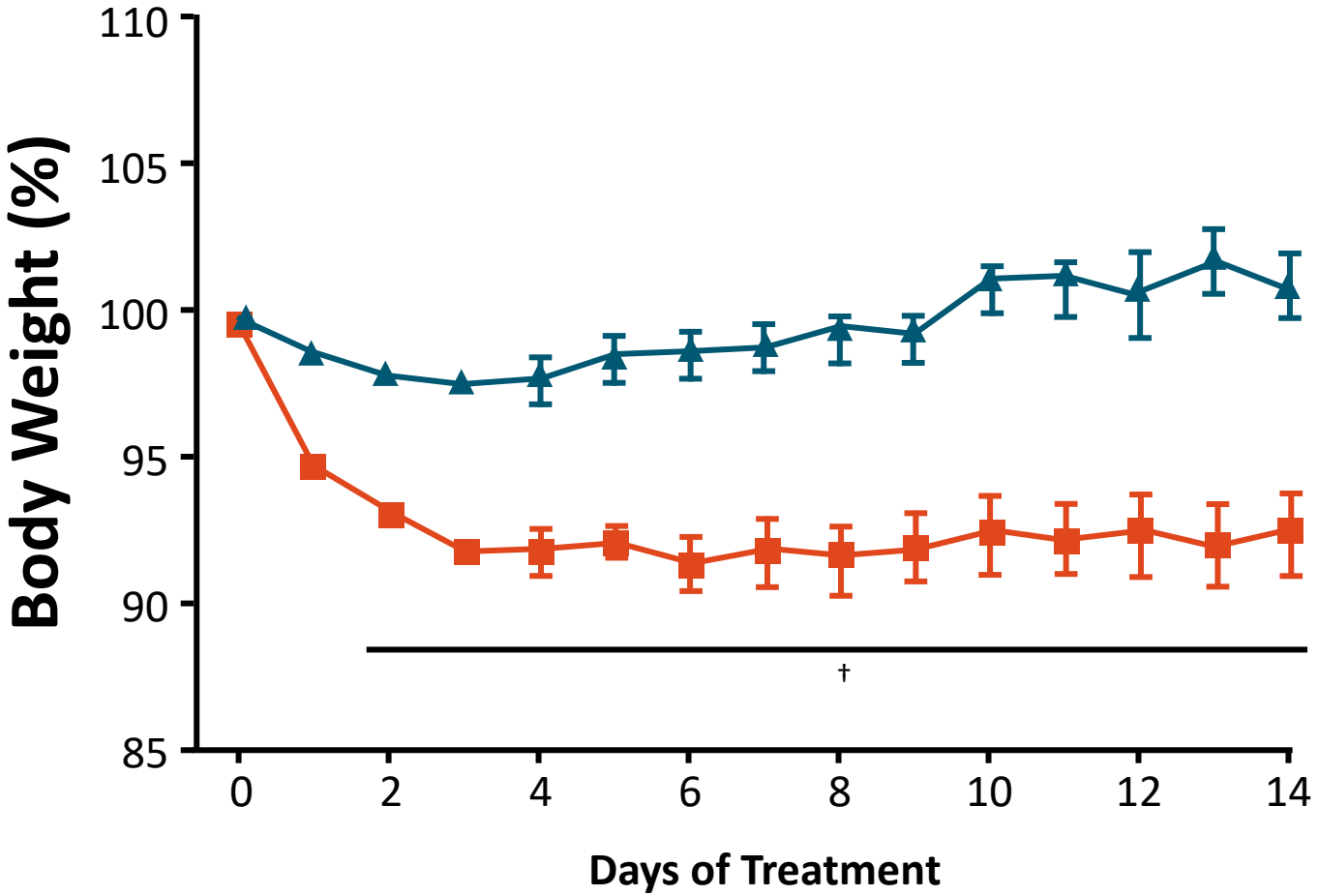
Vehicle

Liraglutide (Long-acting GLP-1R agonist)

*P <.001 vs saline.

Adams. Diabetes. 2018;67:1538.

Long-term effect on body weight



†*P* <.001 vs saline.

Adams. Diabetes. 2018;67:1538.

Weight regain after drug cessation

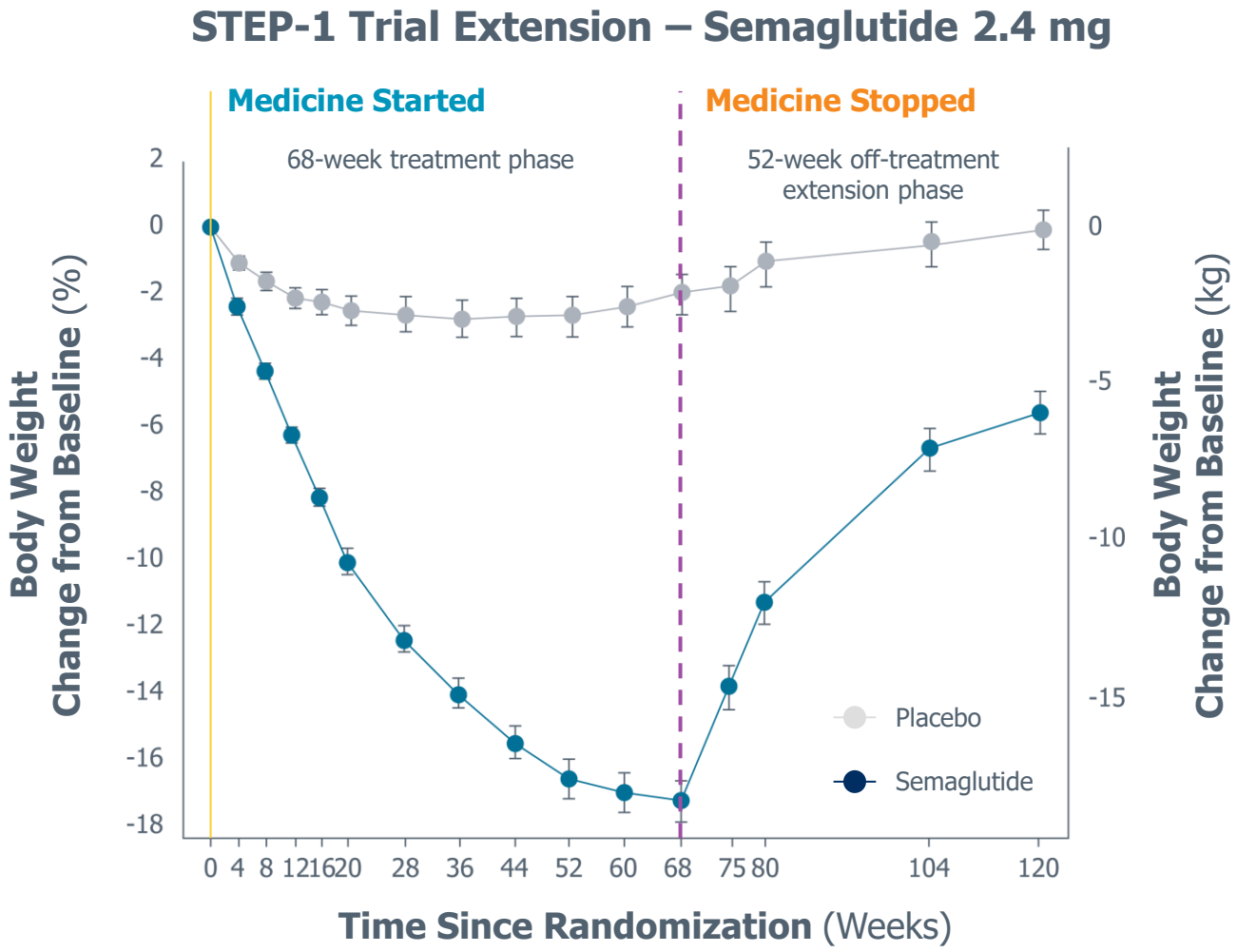
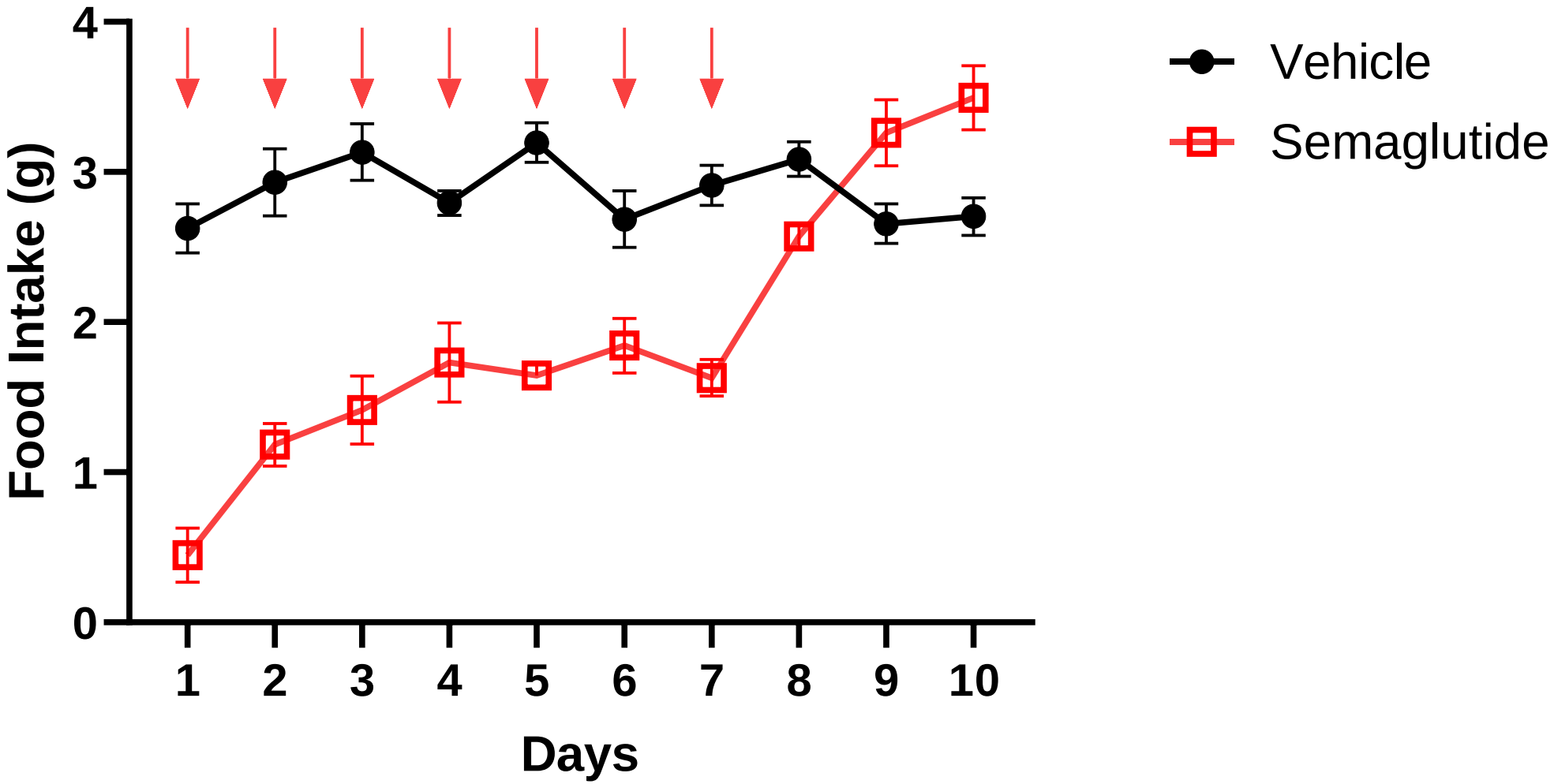


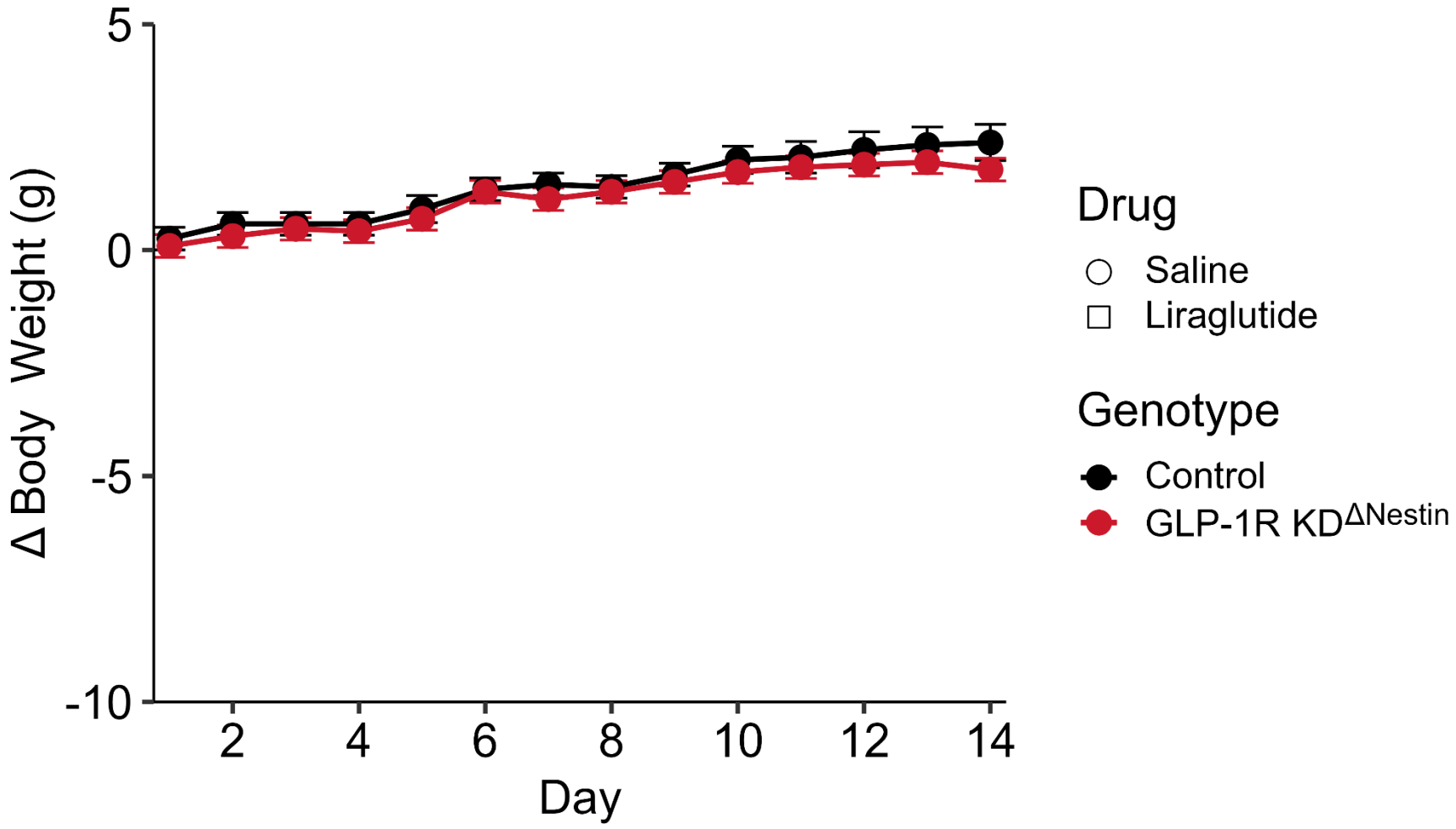
Figure adapted from Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564. 1. Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564. GLP-1=glucagon-like peptide 1

Overeating after drug is removed



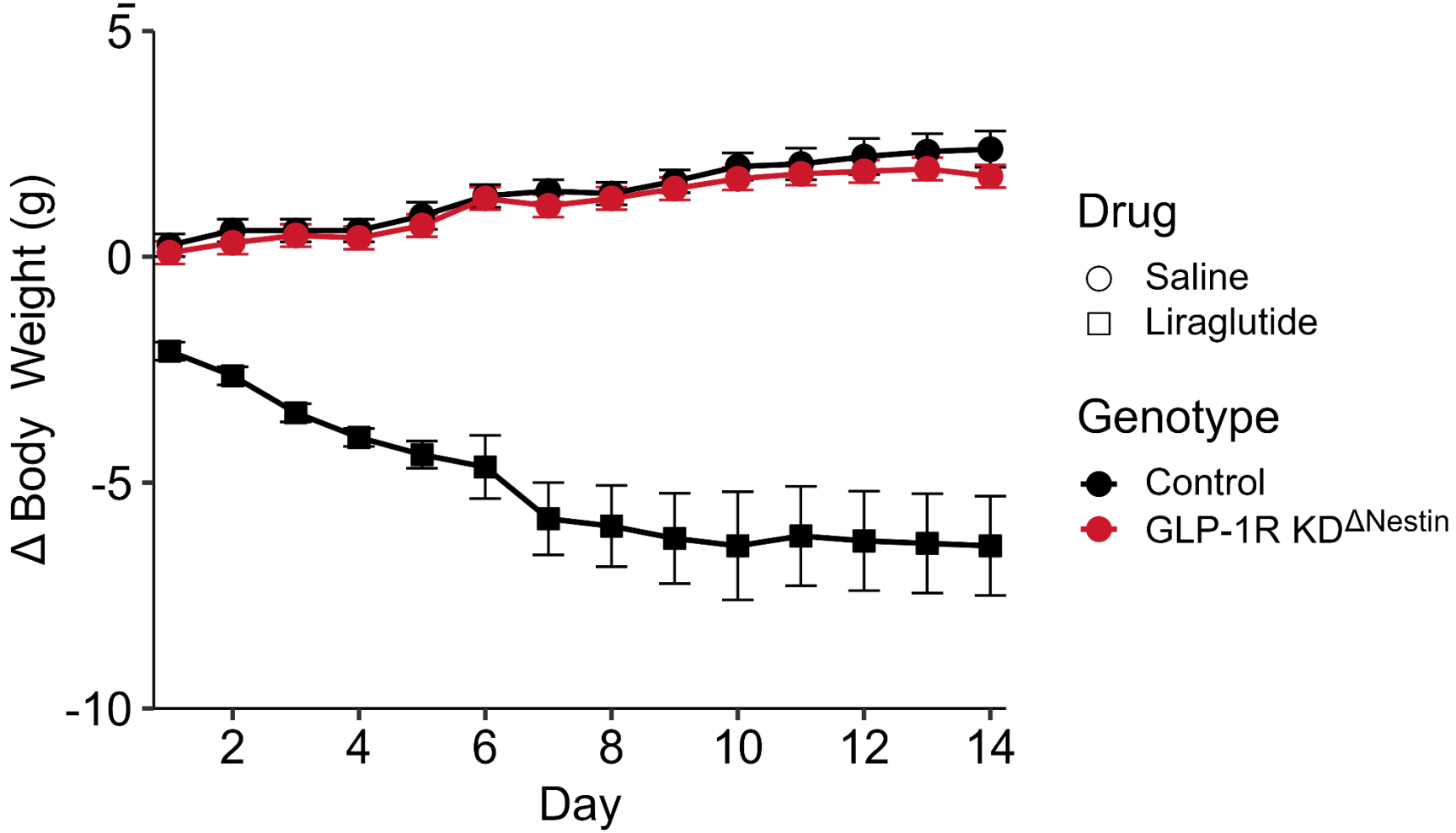
The brain, the brain, the brain

The Brain!



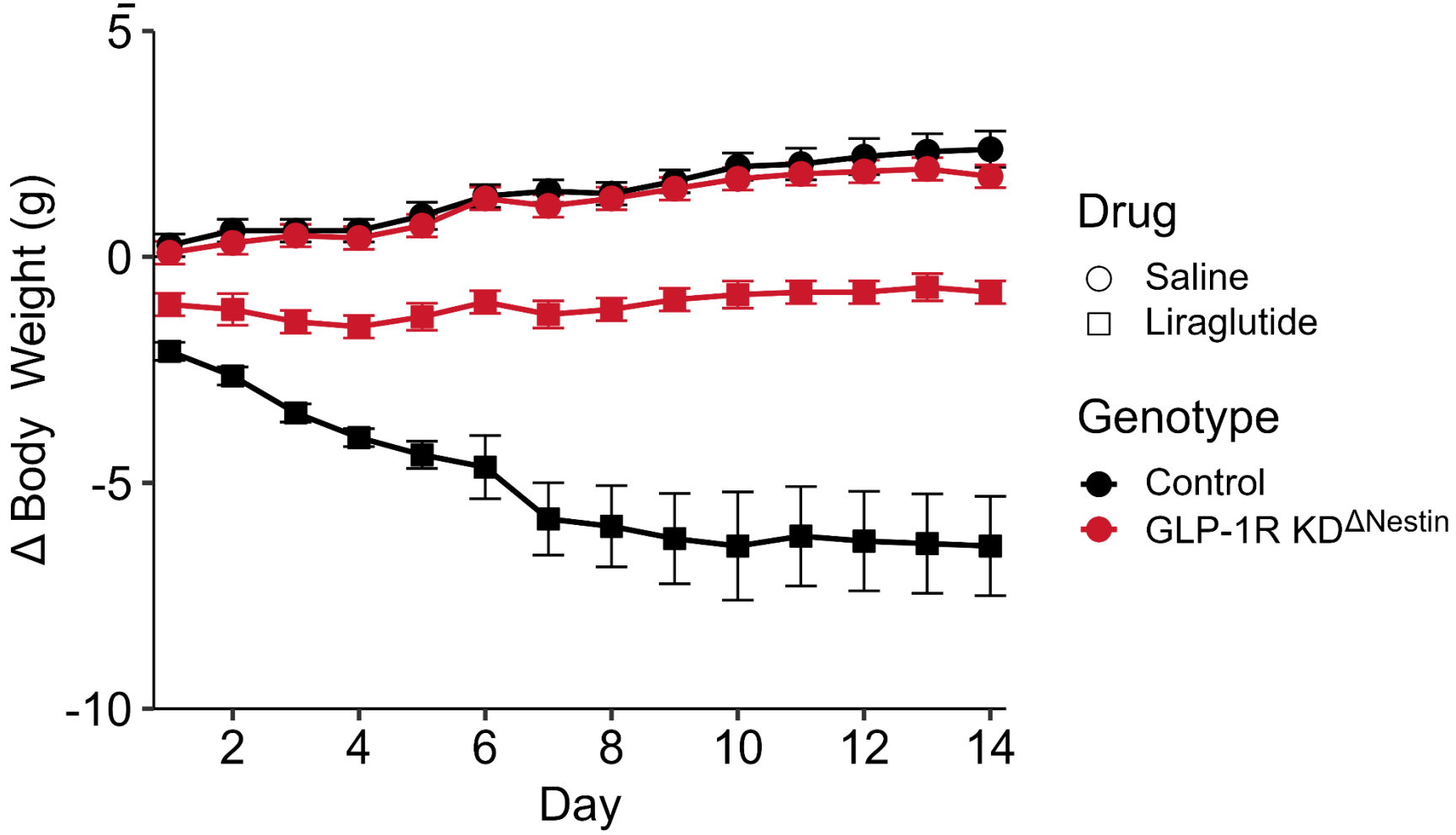
Sisley et al., *JCI* 2014

The Brain!



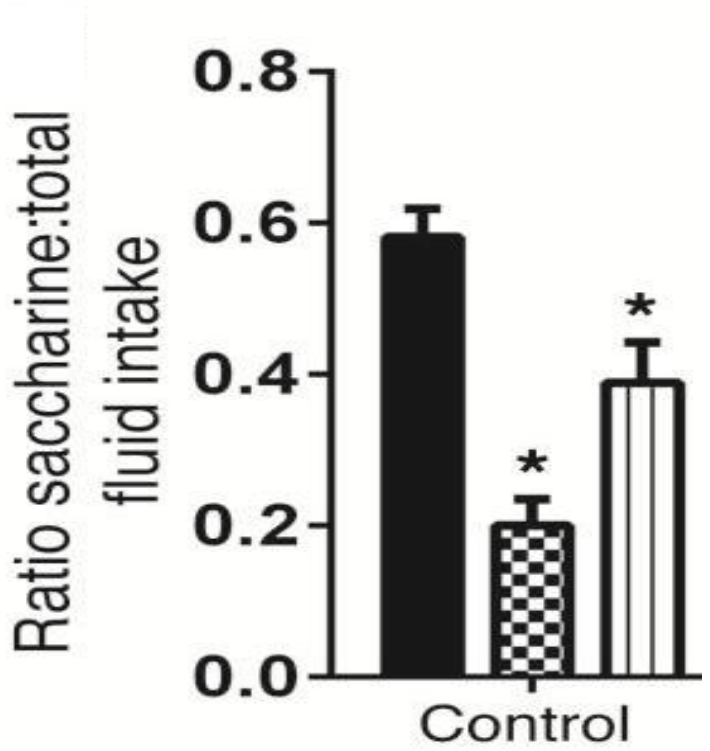
Sisley et al., *JCI* 2014

The Brain!



Sisley et al., *JCI* 2014

The Brain!


Ratio saccharine:total fluid intake
0.8
0.6
0.4
0.2
0.0
*
*
Control

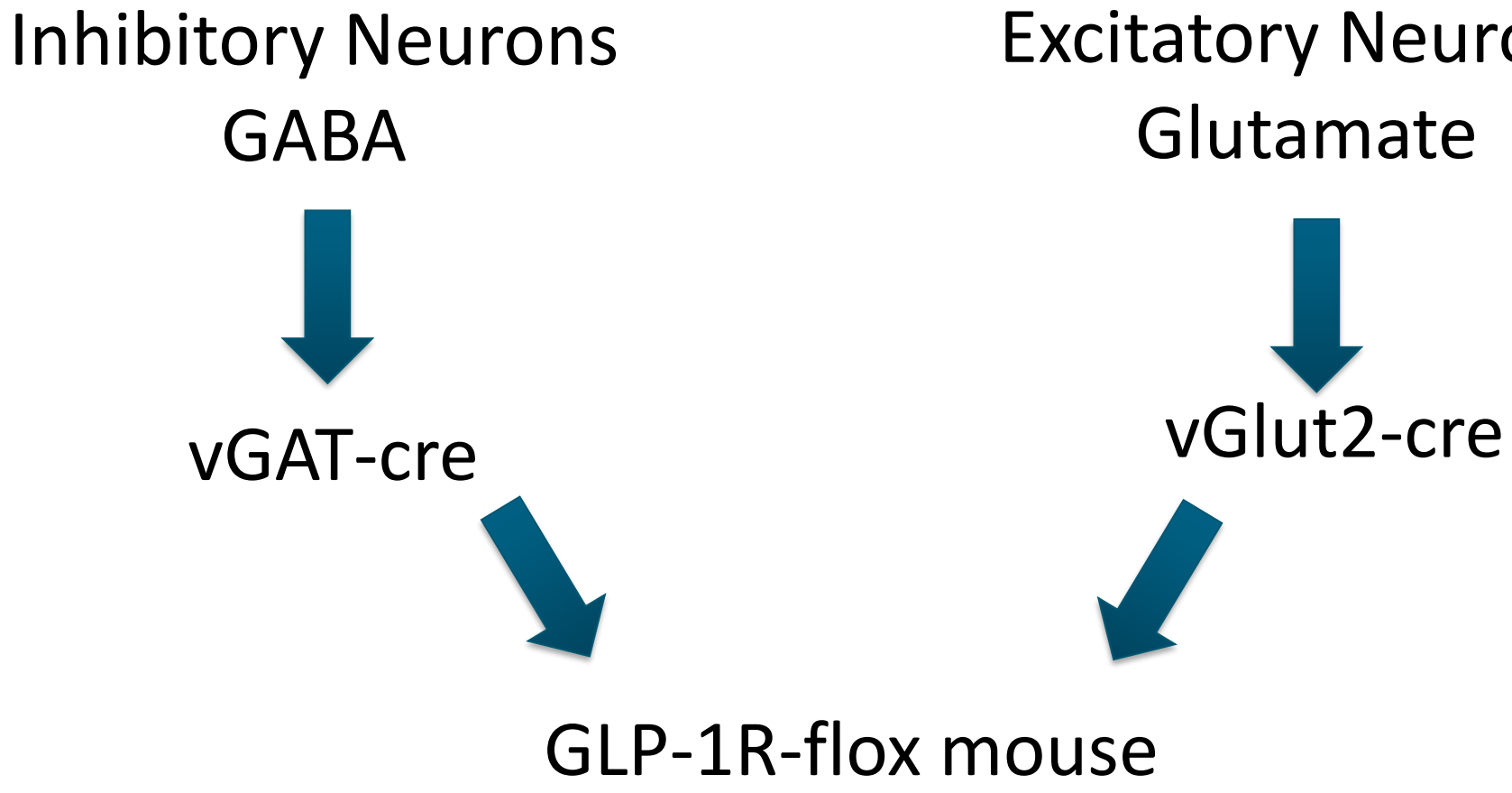

Saline
Liraglutide
LiCl

The brain, the brain, the brain

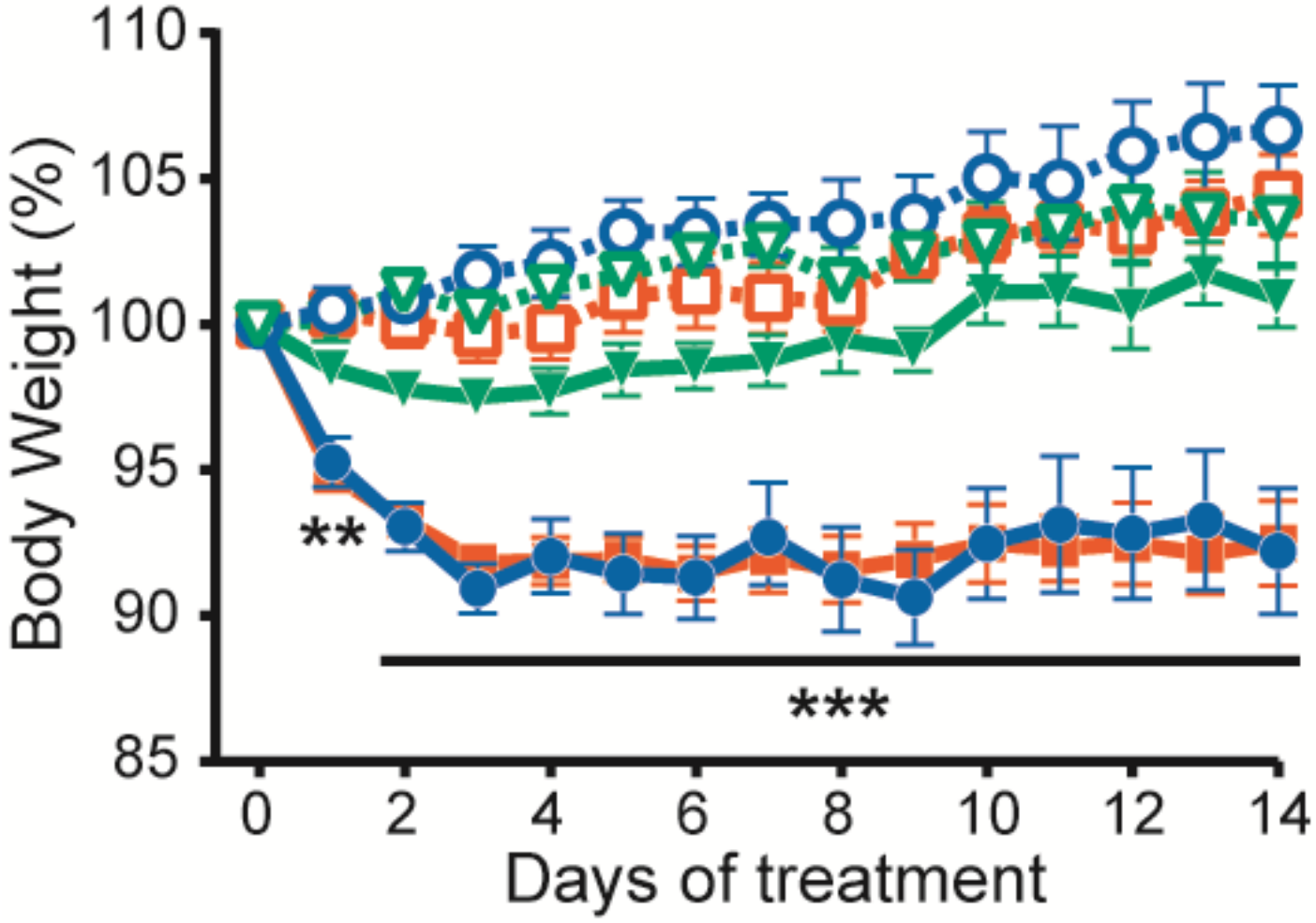
Where are these neurons?

1. Excitatory or inhibitory neurons

Excitatory Versus Inhibitory GLP-R Neurons

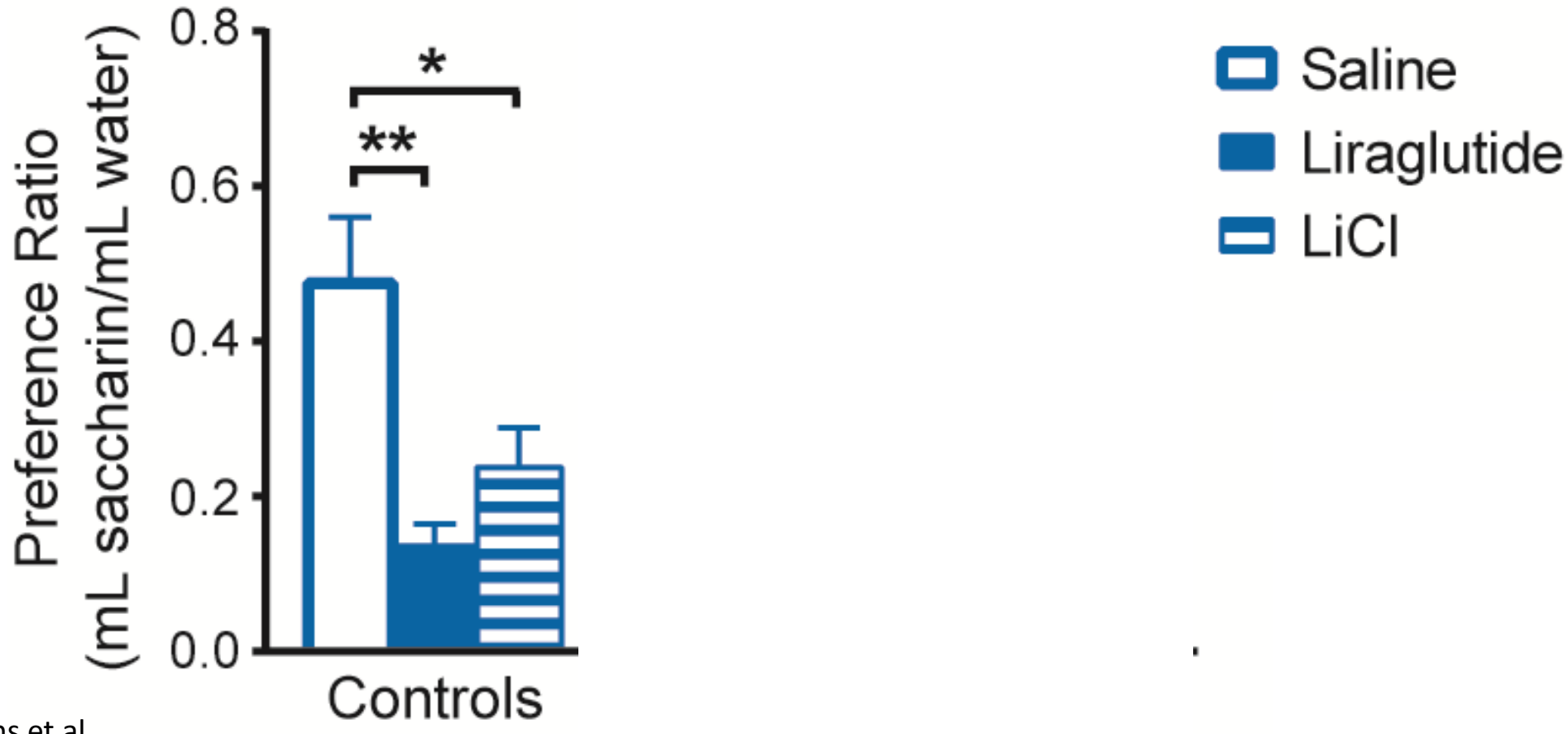


Excitatory Versus Inhibitory GLP-R Neurons



Adams et al.,
Diabetes 2018

Excitatory or inhibitory neurons?



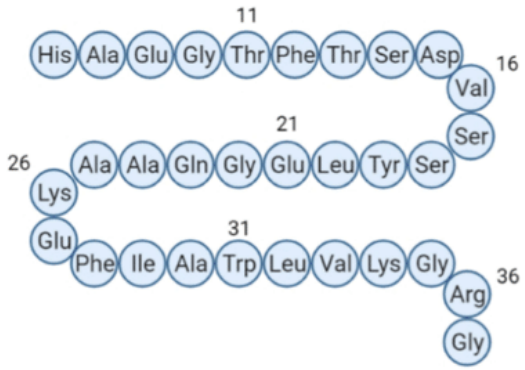
Adams et al.,
Diabetes 2018

Where are these neurons?

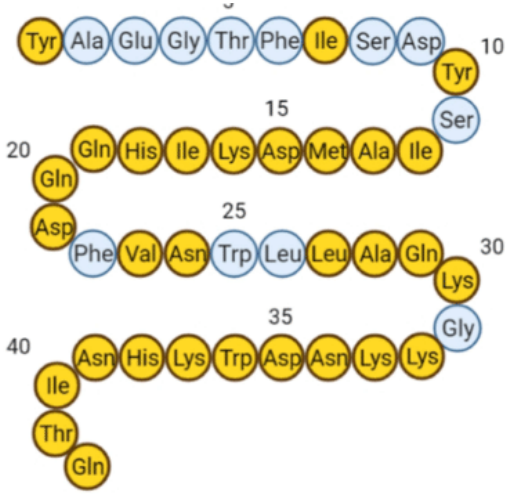
1. Excitatory neurons

The world of polypharmacy

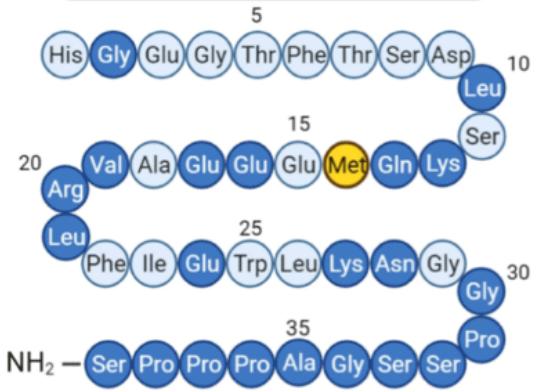
GLP-1



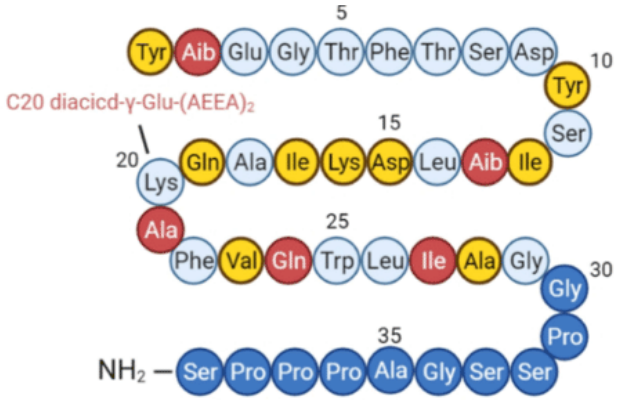
GIP



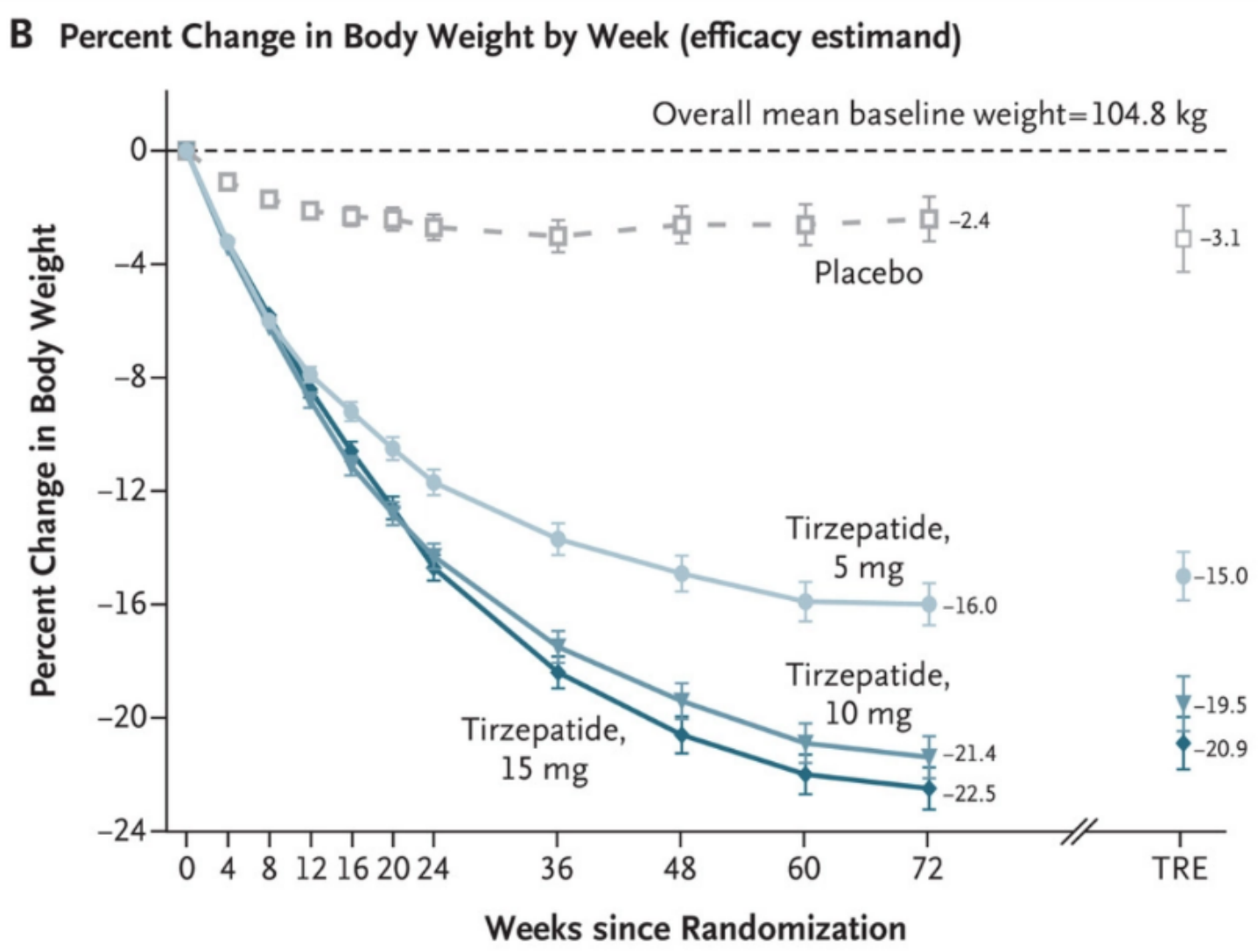
Exenatide



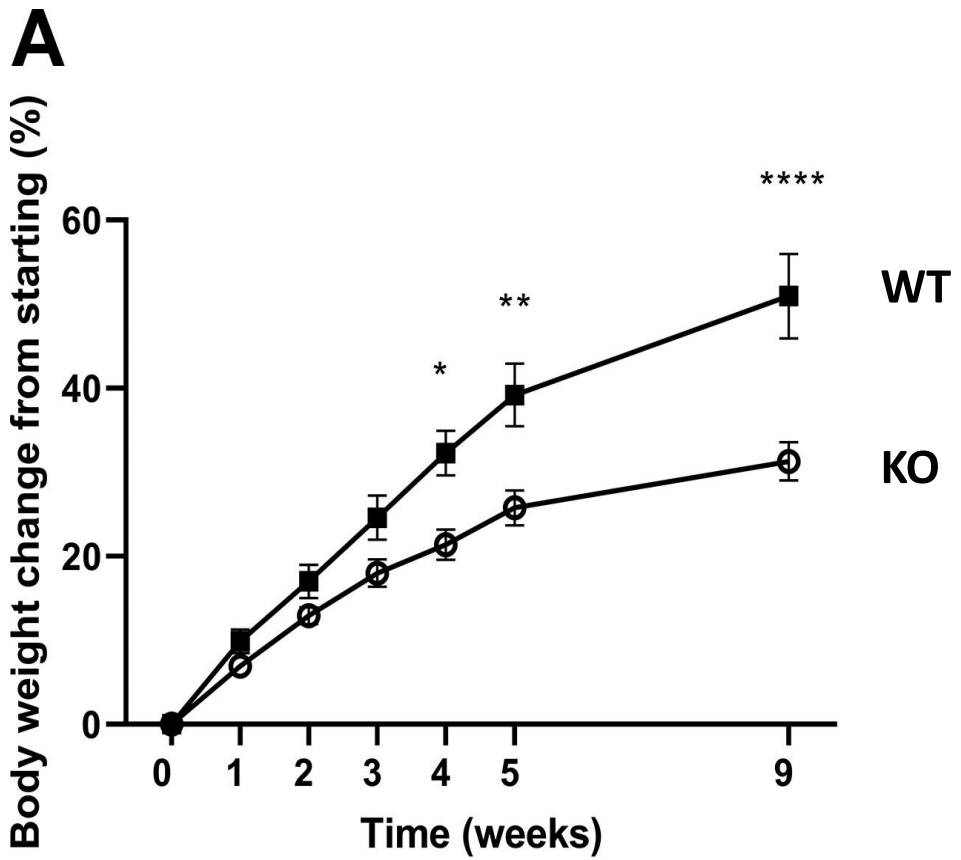
Tirzepatide



GLP-1-GIP Co-agonist



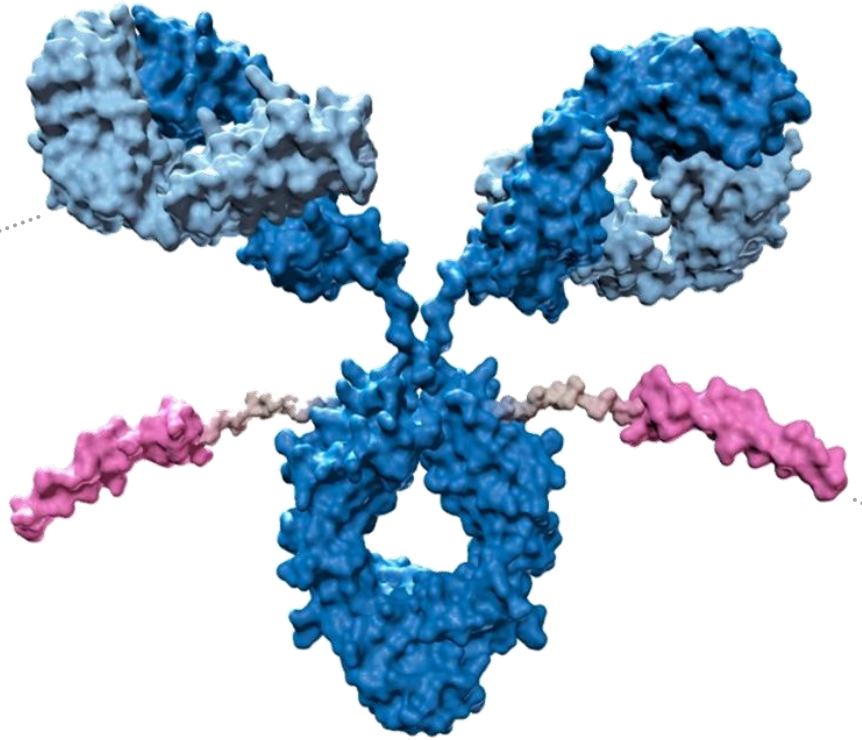
GIP Receptor KO Mice



DOI: (10.1152/ajpendo.00646.2020)

GIPR Antagonism?

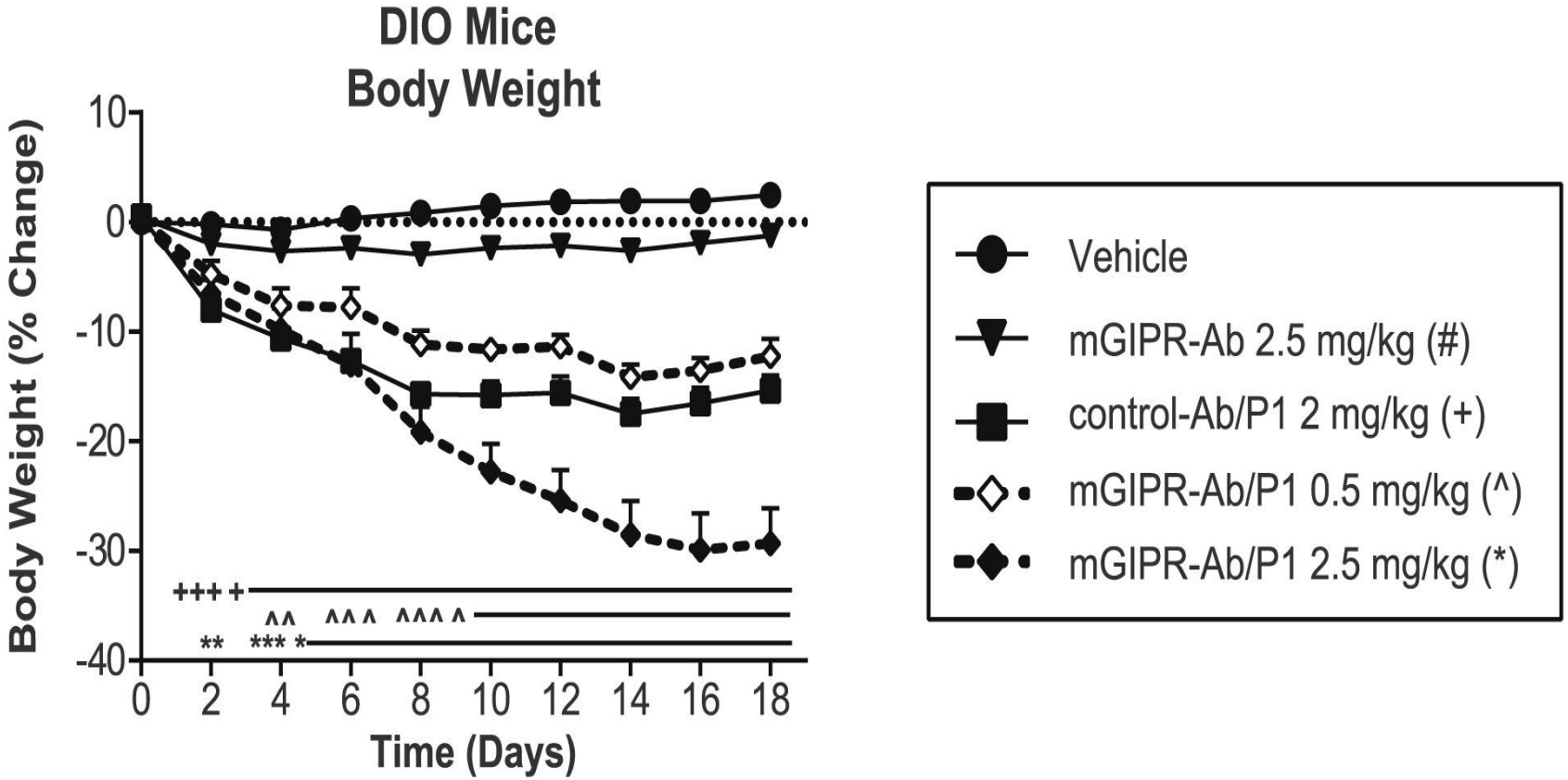
Anti-GIPR antibody
blocks GIPR



GLP-1 analog peptides
conjugated to antibody activate GLP-1Rs

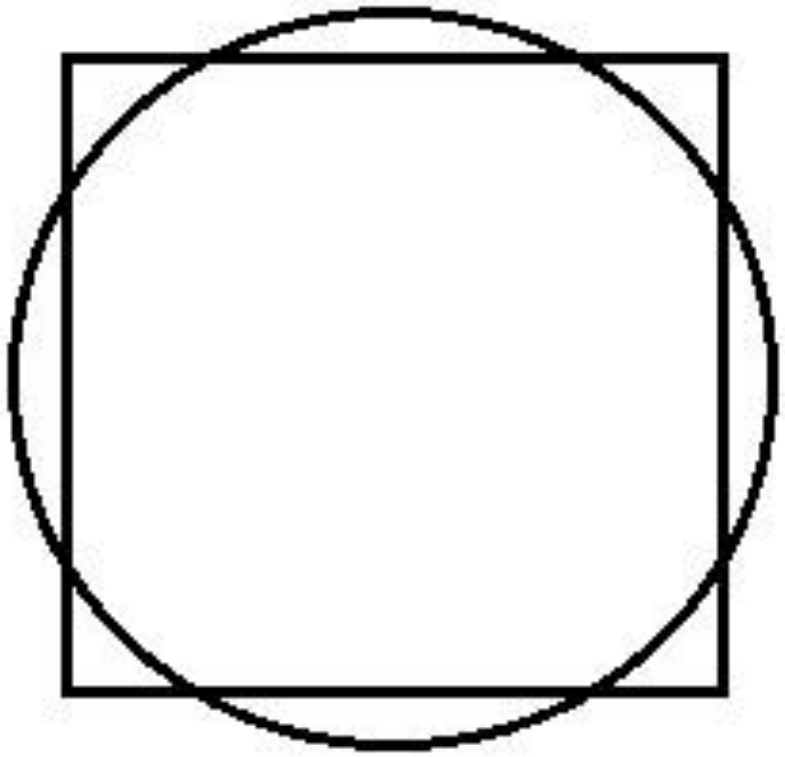
CR Med 2021 2DOI: (10.1016/j.xcrm.2021.100263)

GIPR Antagonism?

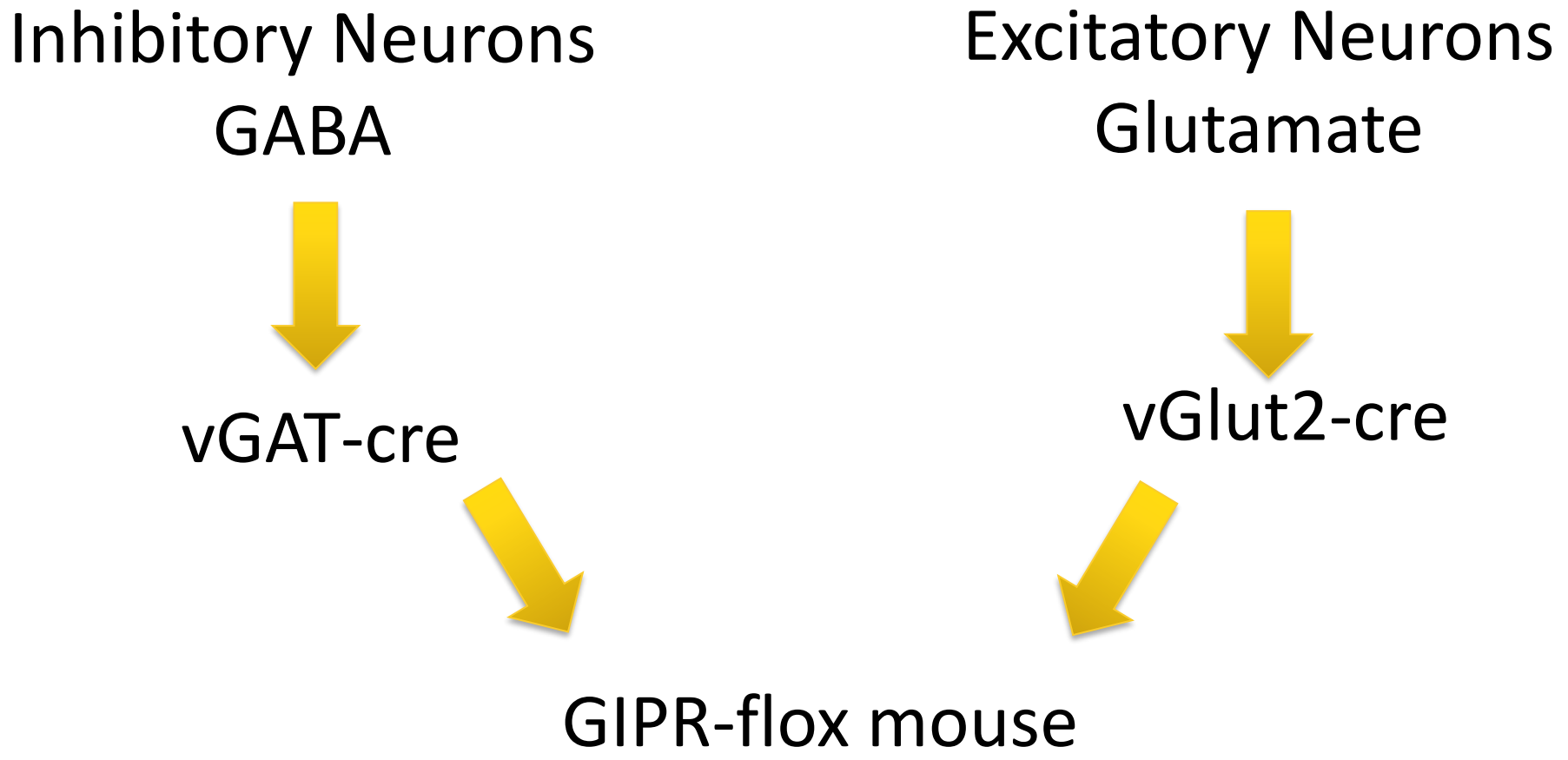


CR Med 2021 2DOI: (10.1016/j.xcrm.2021.100263)

GIP receptor agonism versus antagonism



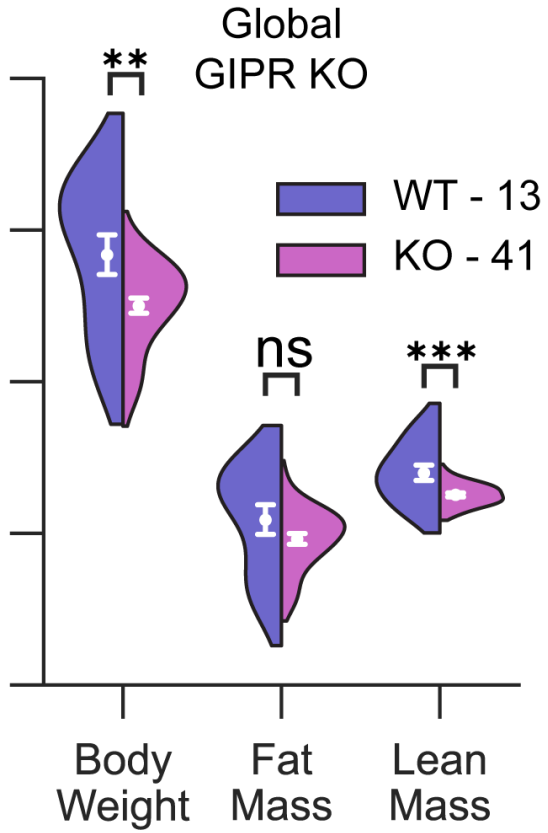
Role of GIPR in response to GLP-1 agonists



GIPR KO on Body Composition

After >8 weeks HFD

Jordan Wean, PhD



Wean et al, Mol Met 2025

nature metabolism

Letter

https://doi.org/10.1038/s42255-023-00931-7

Glucose-dependent insulinotropic polypeptide regulates body weight and food intake via GABAergic neurons in mice

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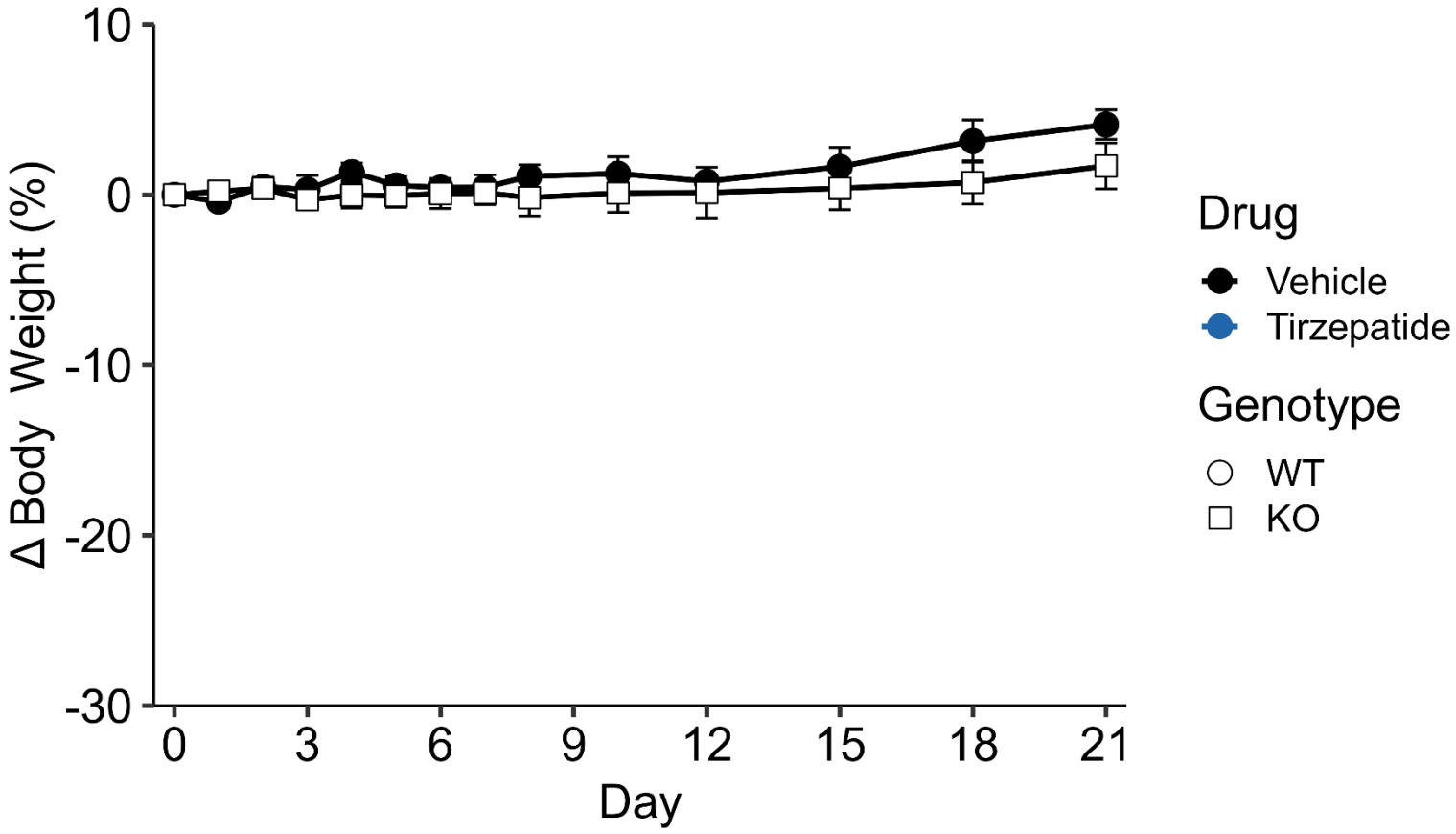
Check for updates

Arkadiusz Liskiewicz[1,2,3], Ahmed Khalil[1,2], Daniela Liskiewicz[1,2,4], Aaron Novikoff[1,2], Gerald Grandl[1,2], Gandhari Maity-Kumar[1,2], Robert M. Gutgesell[1,2], Mostafa Bakhti[2,5], Aimée Bastidas-Ponce[2,5], Oliver Czarnecki[2,5,6], Konstantinos Makris[1,2], Heiko Lickert[2,5,6], Annette Feuchtinger[7], Monica Tost[7], Callum Coupland[1,2], Lisa Ständer[1,2], Seun Akindehin[1,2], Sneha Prakash[1,2], Faiyaz Abrar[1,2], Russell L. Castelino[1,2], Yantao He[8], Patrick J. Knerr[8], Bin Yang[8], Wouter F. J. Hogendorf[8], Shiqi Zhang[5], Susanna M. Hofmann[5,9], Brian Finan[8], Richard D. DiMarchi[10], Matthias H. Tschöp[11,12], Jonathan D. Douros[8] & Timo D. Müller[1,2]

Jordan Wean, PhD

Global GIPR KO

After 21 Days of Daily Dosing



Wean et al, Mol Met 2025

Jordan Wean, PhD

Global GIPR KO

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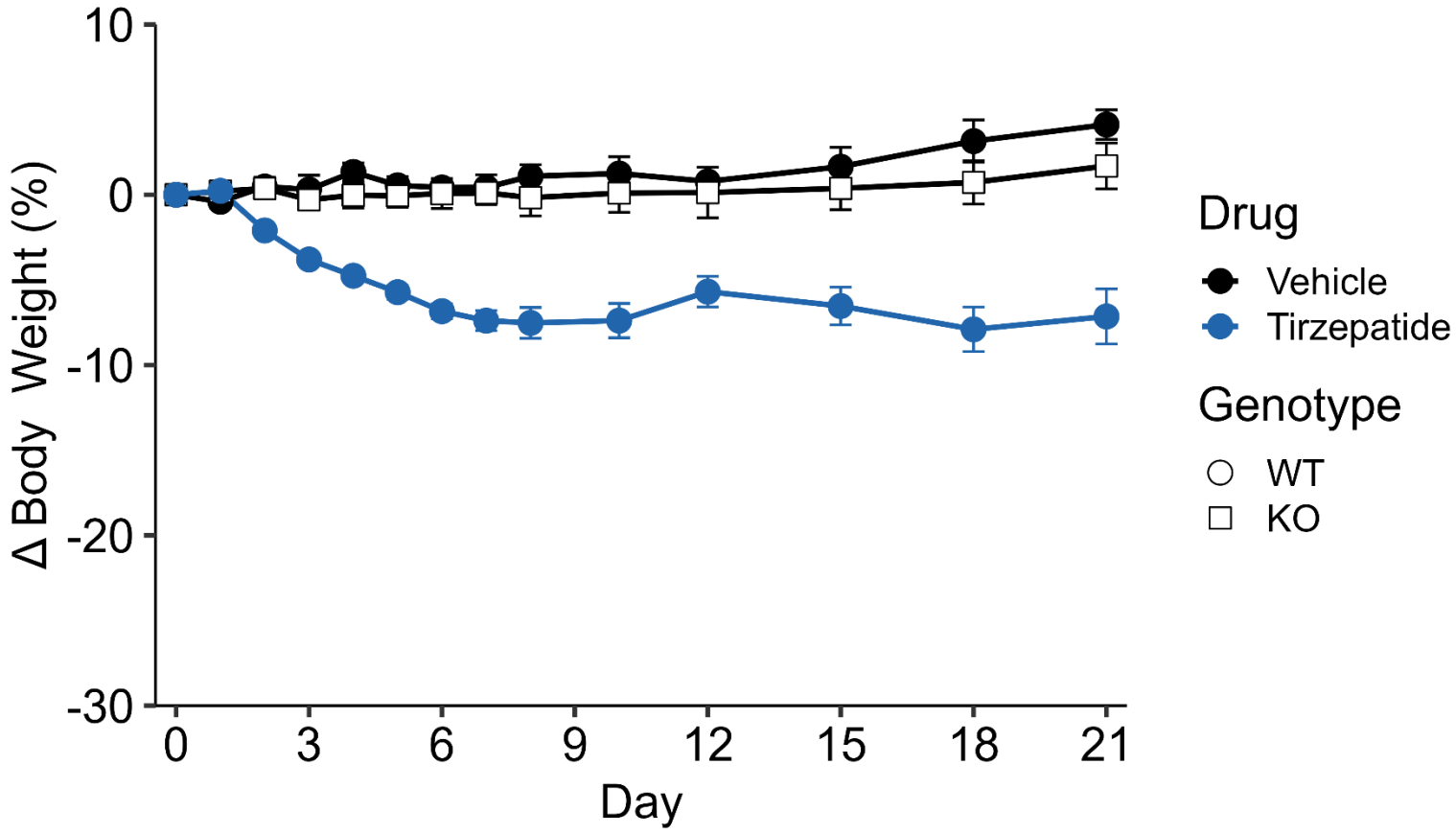

Wean et al, Mol Met 2025

Jordan Wean, PhD

Global GIPR KO

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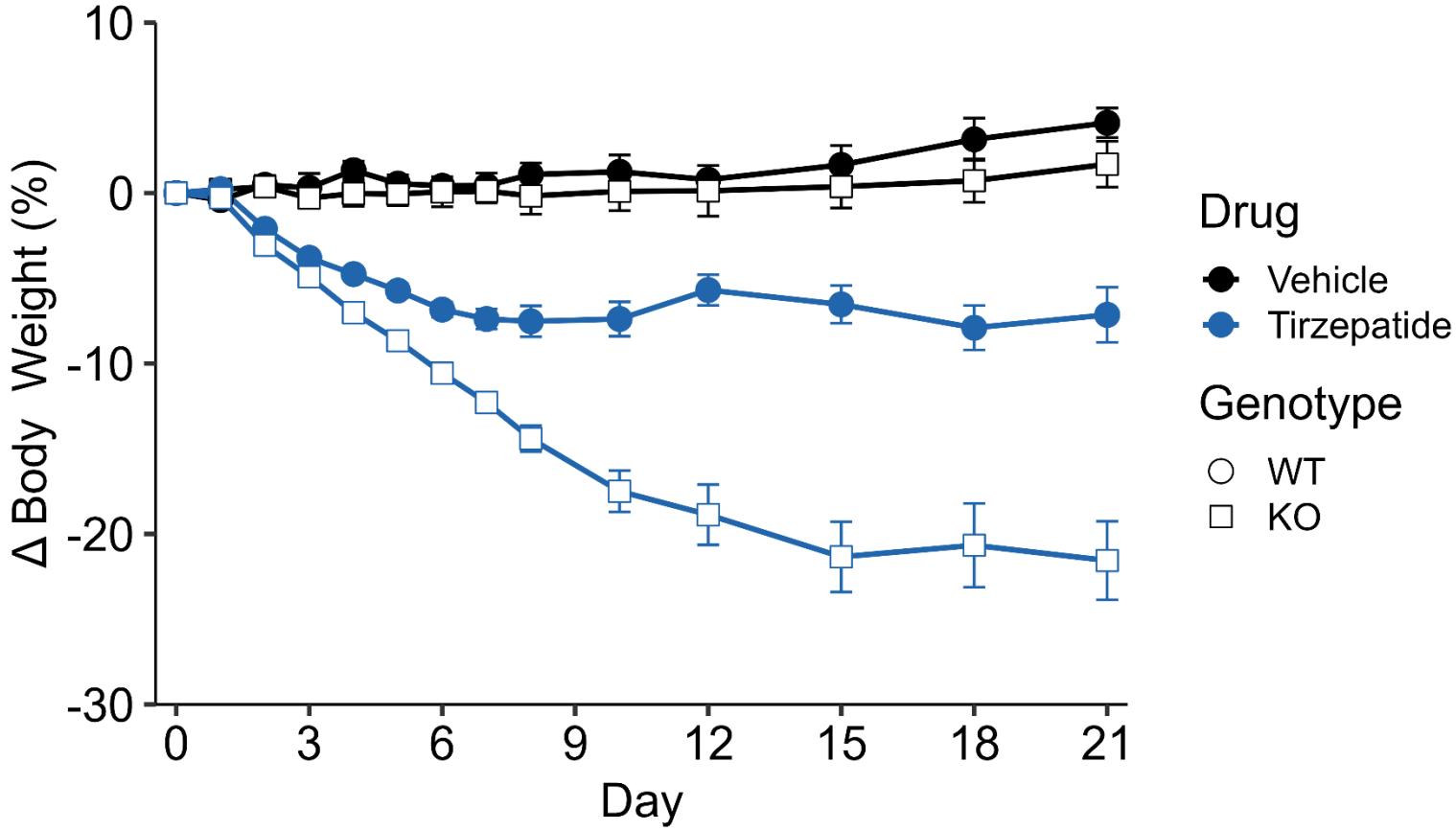
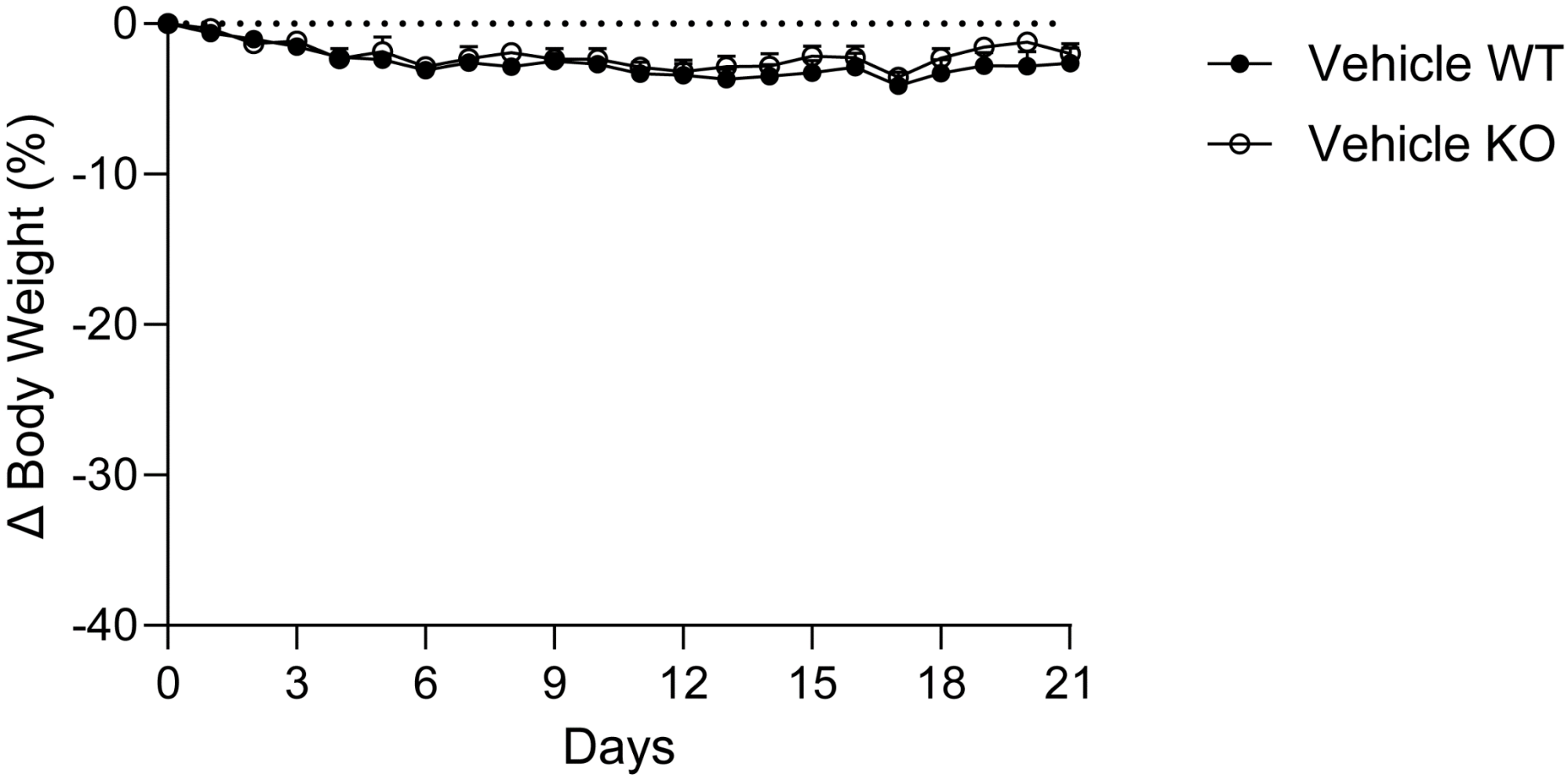


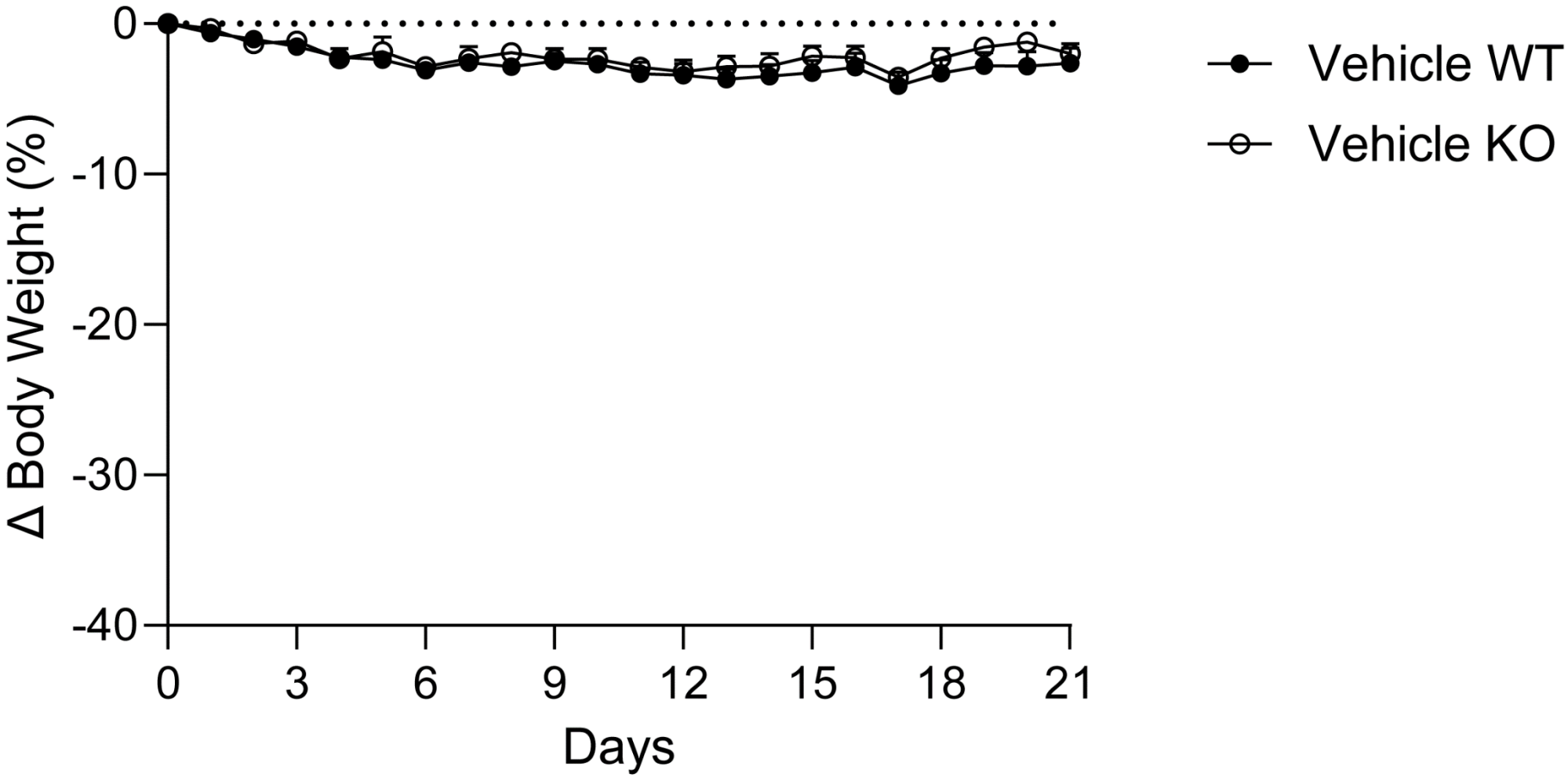
Wean et al, Mol Met 2025

GLP-1 plus GIP



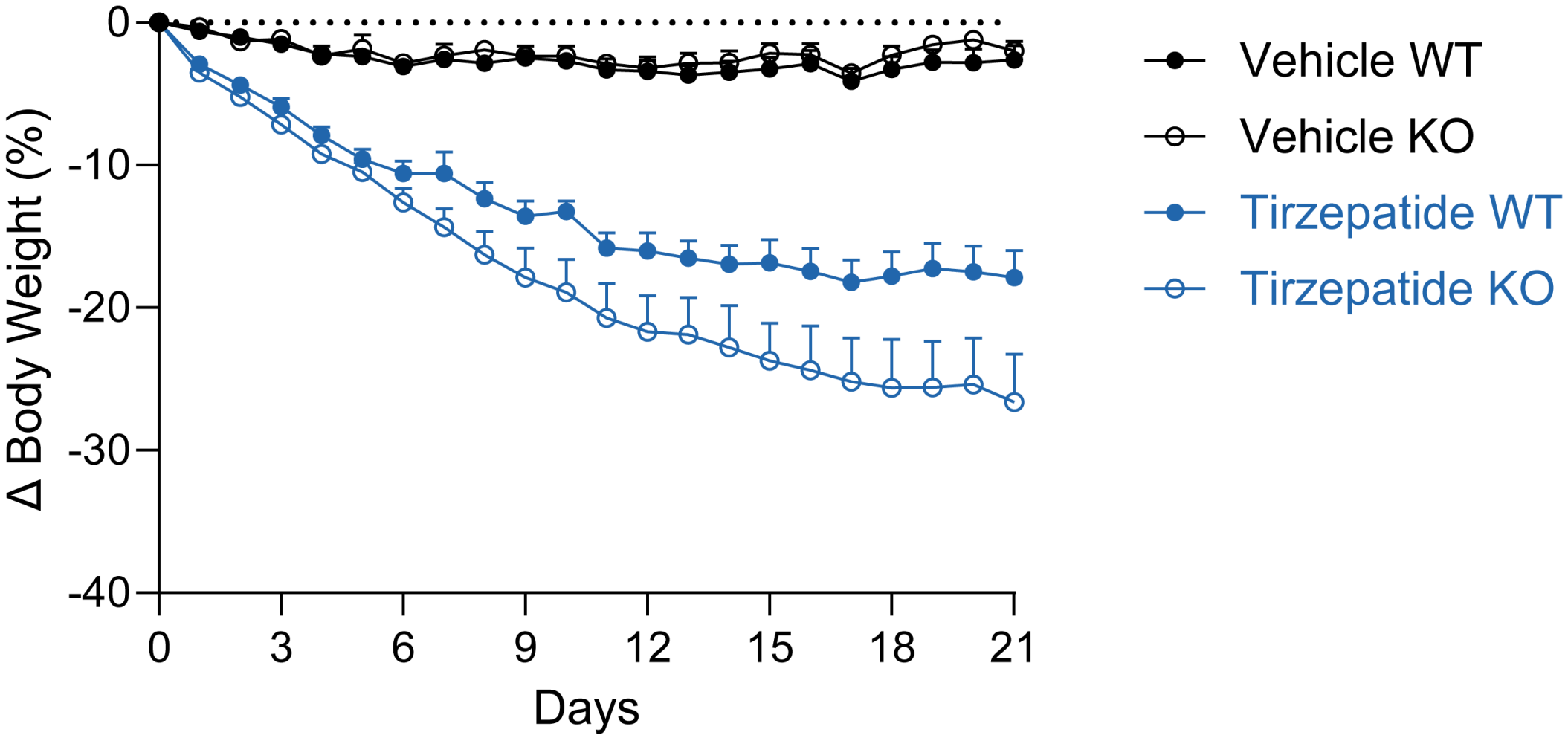
Wean et al, Mol Met 2025

GLP-1 plus GIP



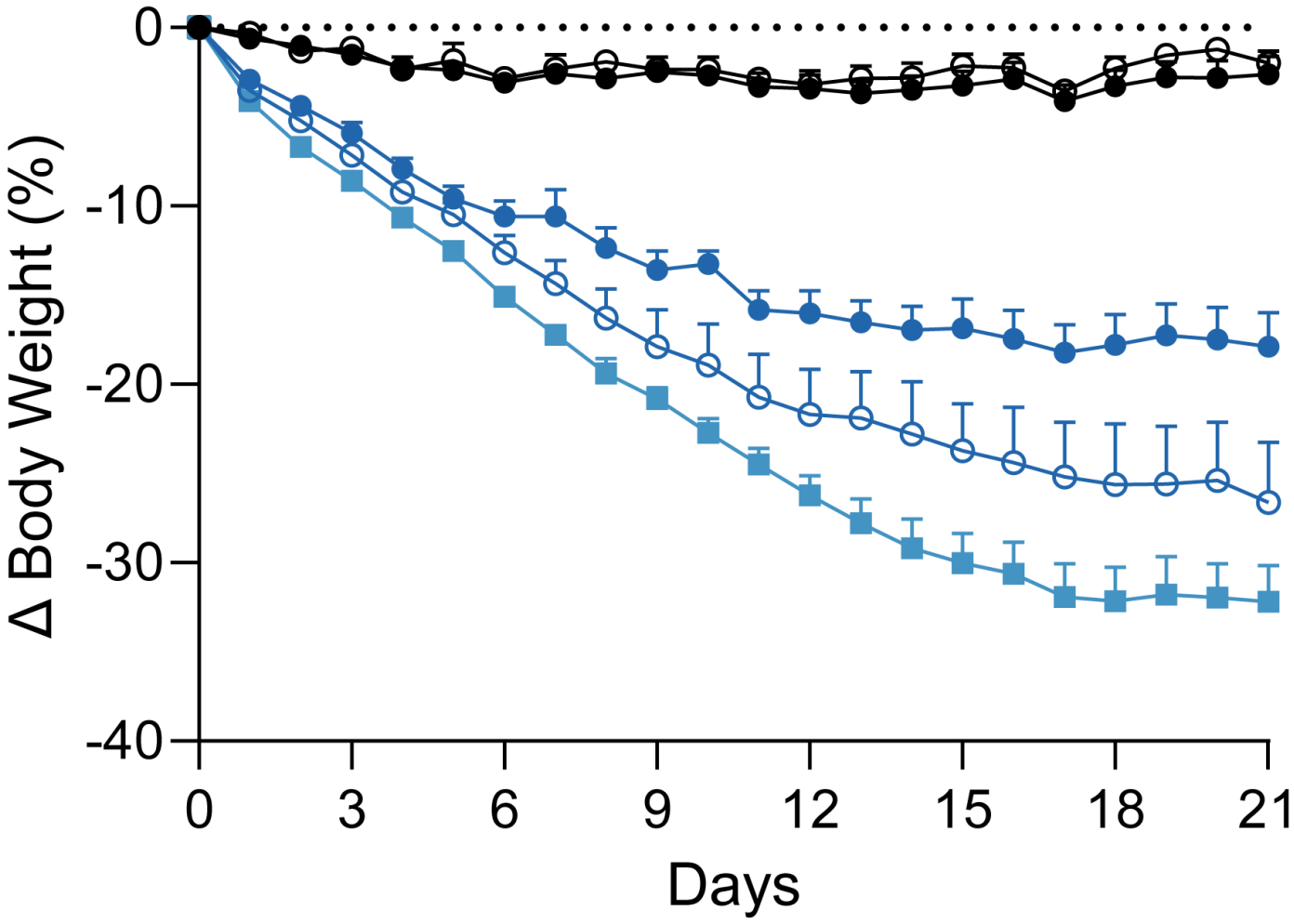
Wean et al, Mol Met 2025

GLP-1 plus GIP



Wean et al, Mol Met 2025

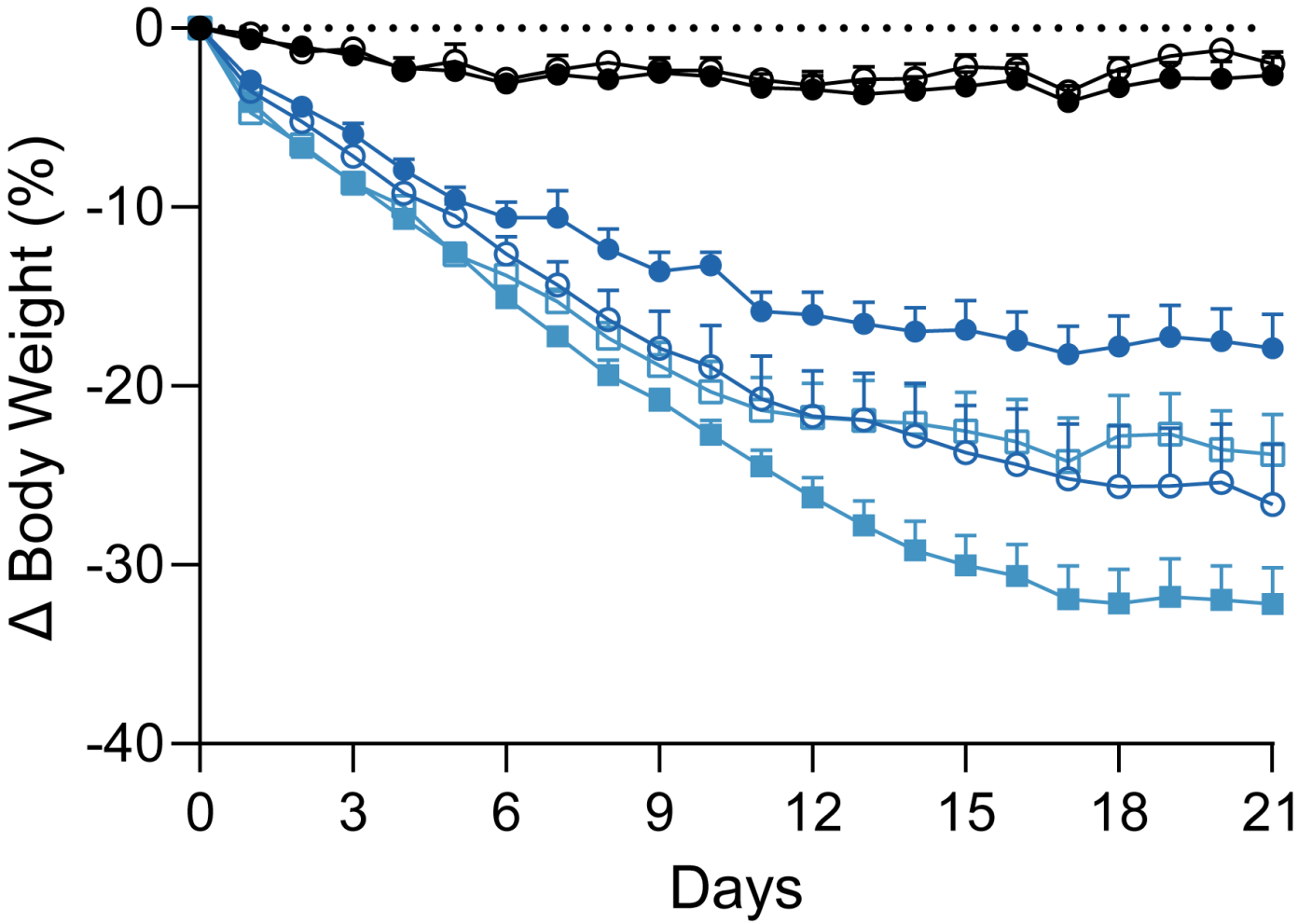
GLP-1 plus GIP



Vehicle WT
Vehicle KO
Tirzepatide WT
Tirzepatide KO
Tirzepatide + GIPR Agonist WT

Wean et al, Mol Met 2025

GLP-1 plus GIP

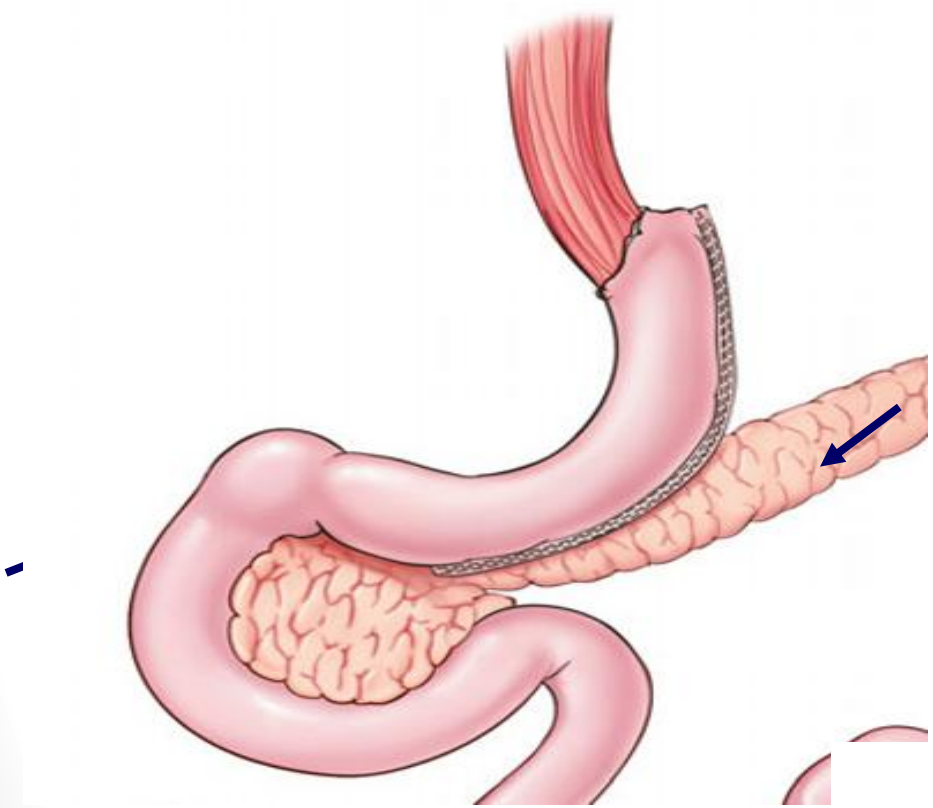


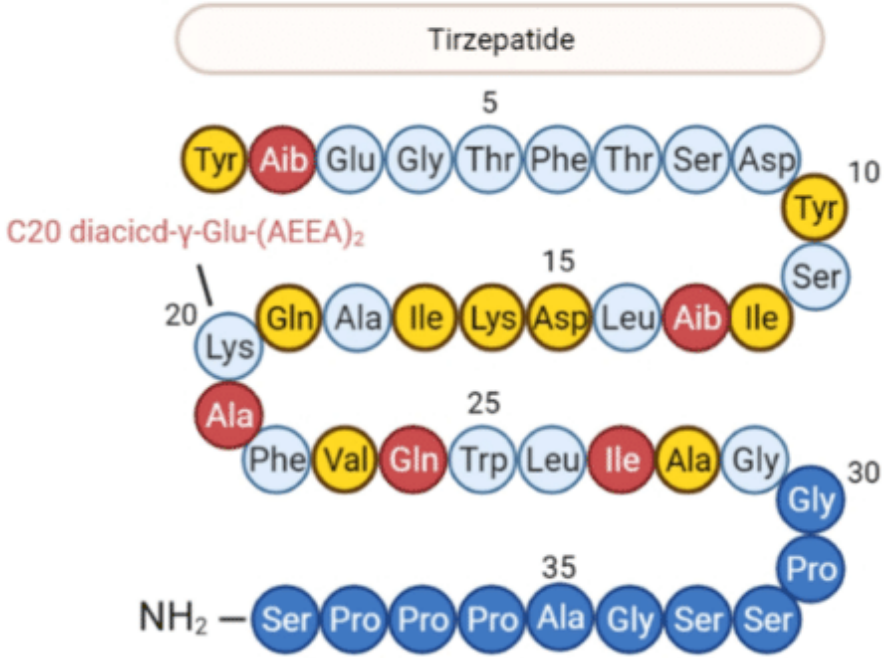
Vehicle WT
Vehicle KO
Tirzepatide WT
Tirzepatide KO
Tirzepatide + GIPR Agonist WT
Tirzepatide + GIPR Agonist KO

Wean et al, Mol Met 2025

Chronic disease treatment versus “one and done”

Surgery vs Pharmacology



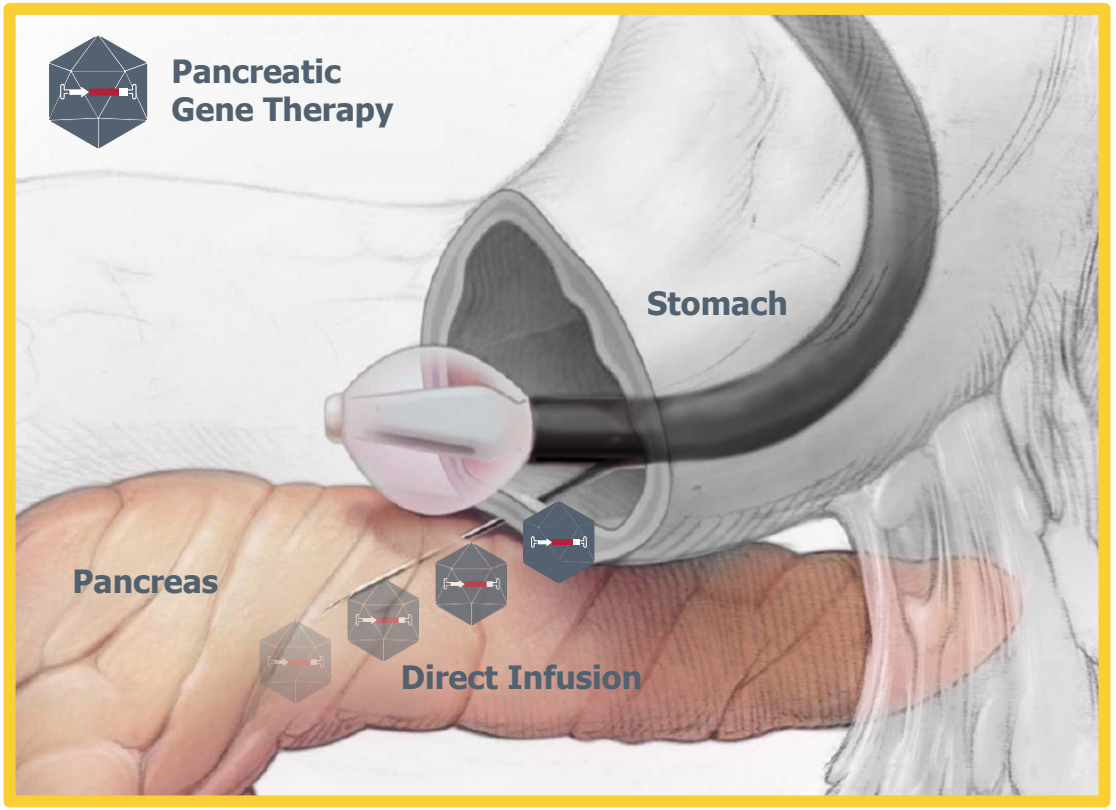


Gene Therapy Route of Administration to Pancreas

Local delivery enables low viral genome dosing with limited systemic virus exposure[1]

Islets are readily accessible[2,3] via already established, routine, upper endoscopic ultrasound procedures,[4] performed in ~300K patients per year in US[5]

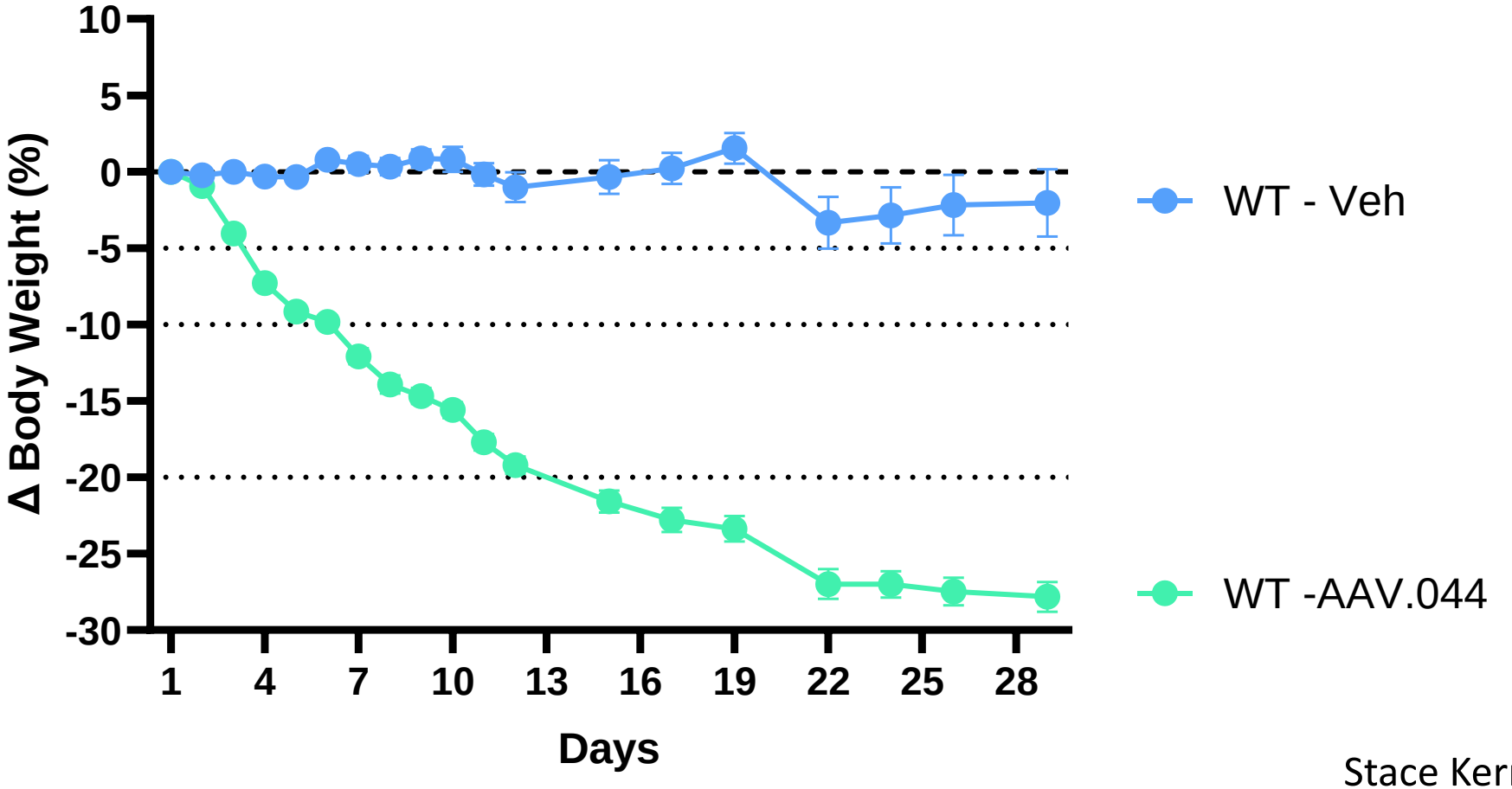
Procedural risk is further mitigated with device design (e.g., needle size, volume, controlled infusion rate)



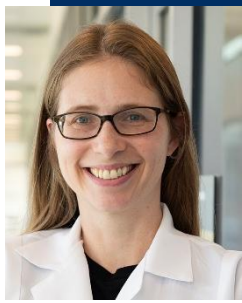
Endoscopic Procedure & PGTx Delivery

1. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191. 2. Docherty & Russ. Encyclopedia of Tissue Engineering and Regenerative Medicine 2019, pg. 367-374. 3. Ravi et al. Medicine (Baltimore). 2021 Apr 30;100(17):e25642. 4. Hasan & Hawes. Gastrointest Endosc Clin N Am. 2012 Apr;22(2):155-67. 5. Peery et al. Gastroenterology 2022 Feb: 162(2):621-644. PGTx=pancreatic gene therapy

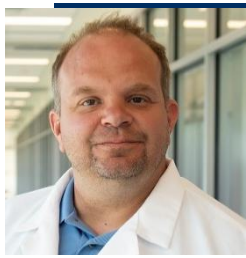
Gene Therapy



Seeley lab, unpublished



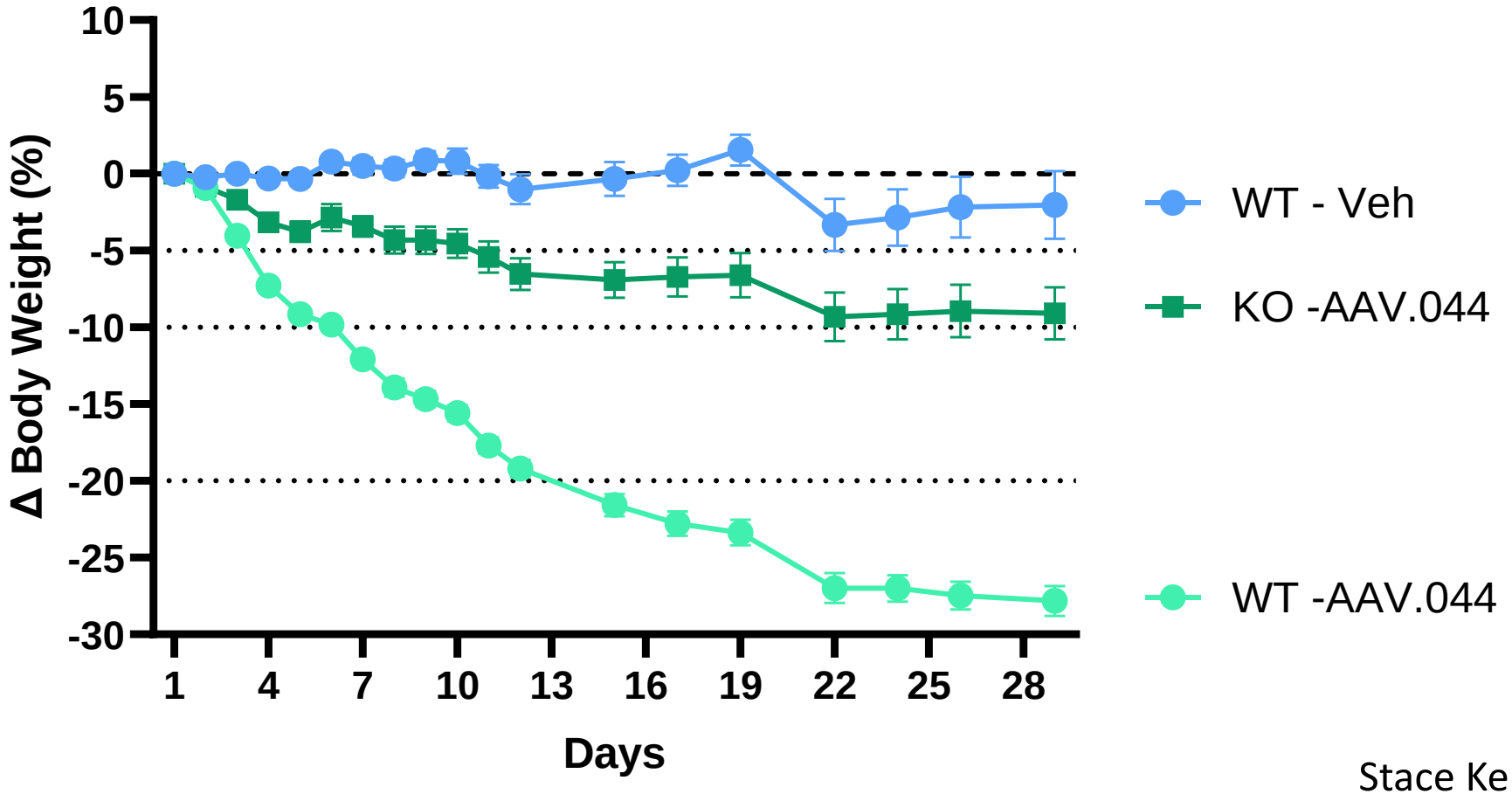
Chelsea Hutch, PhD



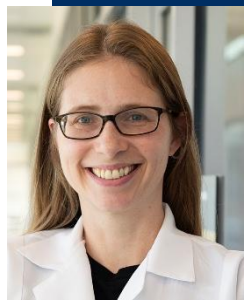
Stace Kernodle

Stace Kernodle
Chelsea Hutch

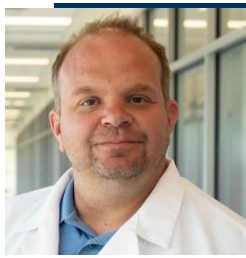
Gene Therapy



Seeley lab, unpublished



Chelsea Hutch, PhD



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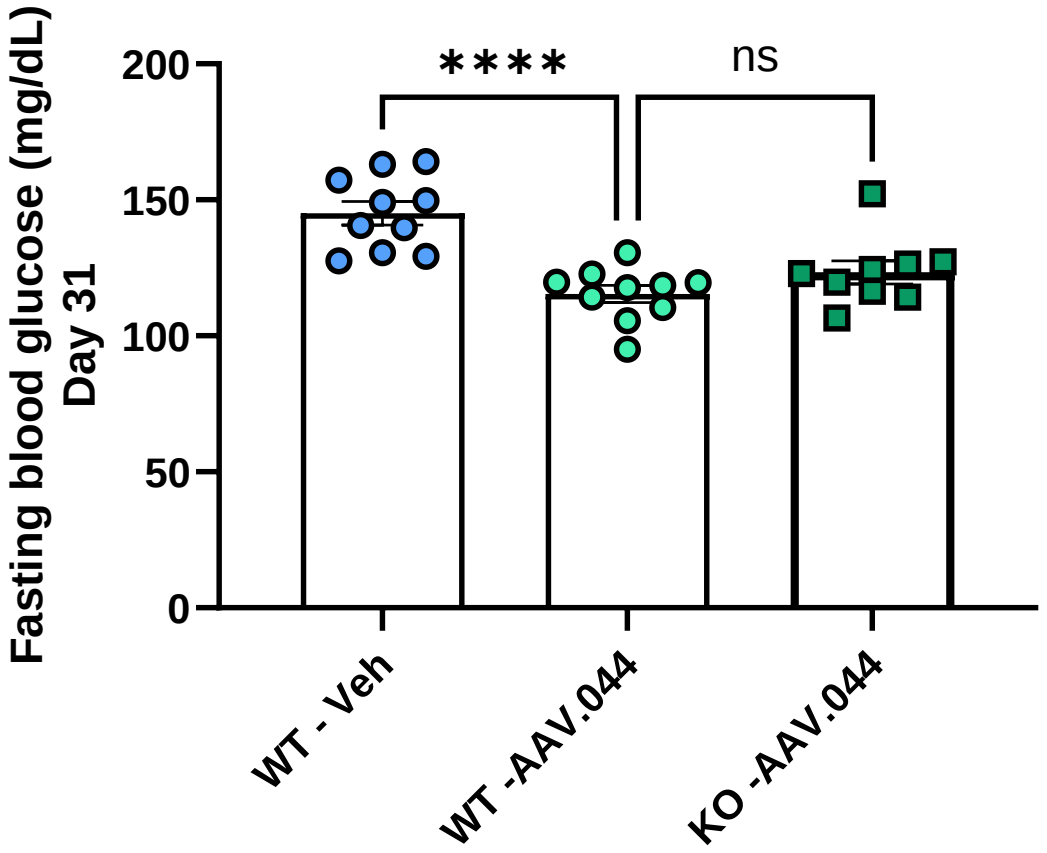
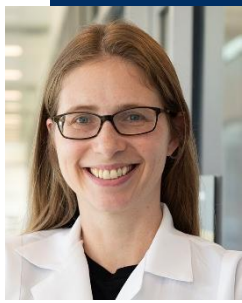
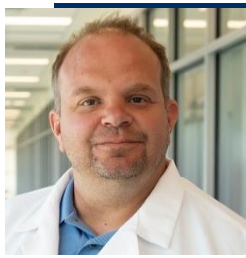




Chelsea Hutch, PhD



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Seeley lab, unpublished

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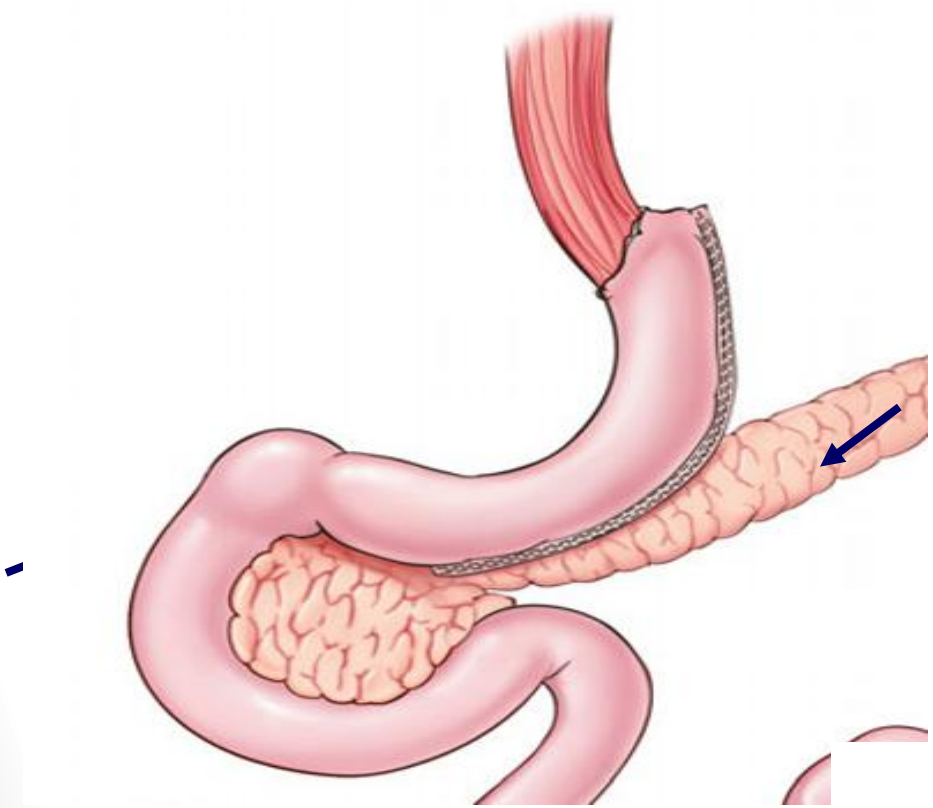
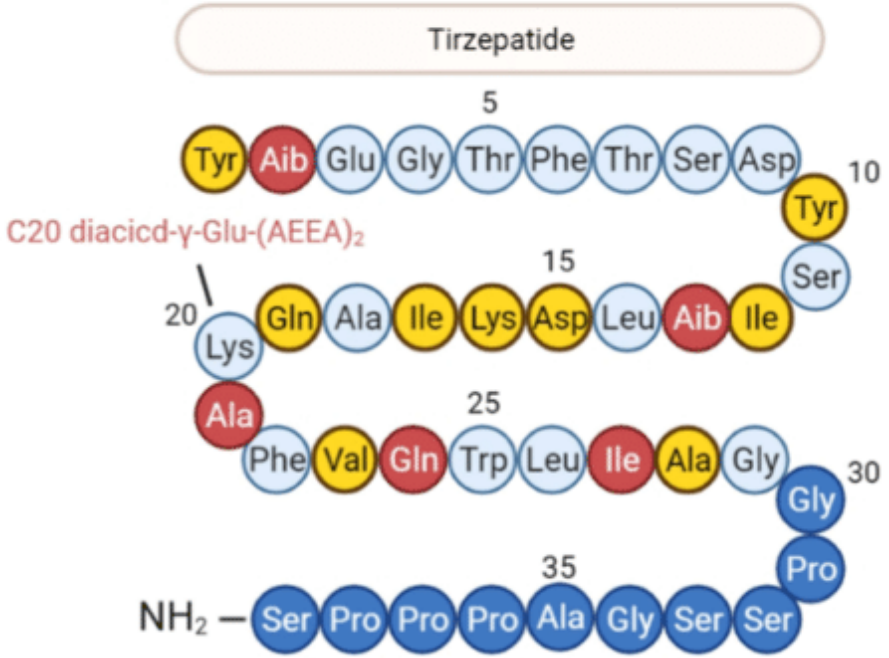
Chelsea Hutch

Surgery vs Pharmacology





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