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Understanding Amylin- and GLP-1R Agonist Combinations Mechanism of Action

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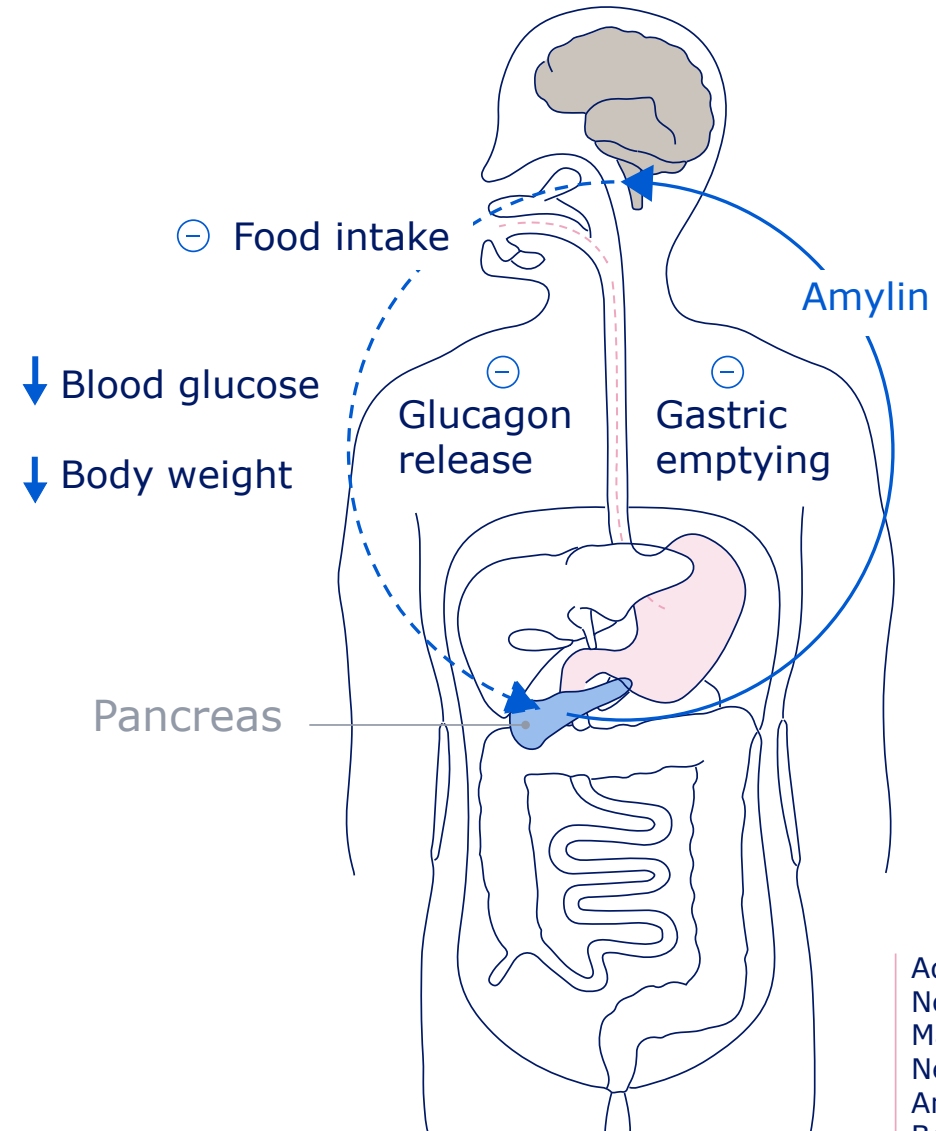
Disclosures

Thomas A. Lutz, Institute of Veterinary Physiology

- **Research collaboration:** Novo Nordisk
- **Consulting:** AbbVie, AstraZeneca, Novo Nordisk, ProLynx, Roche, Structure Tx, Verdiva, Zealand Pharma

Amylin affects multiple aspects of metabolism

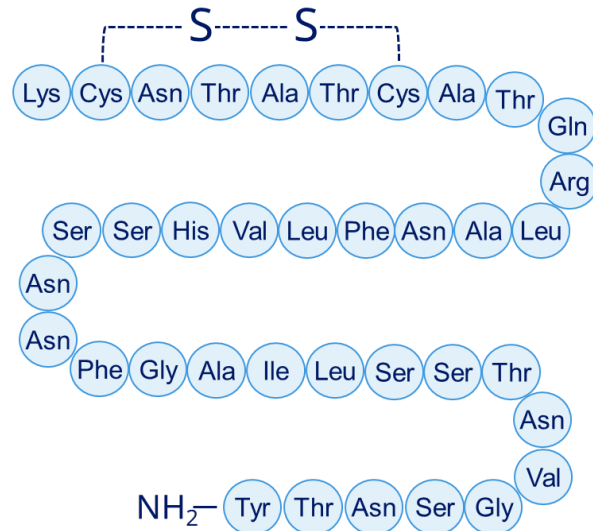
- Amylin is a **peptide hormone**, co-secreted with insulin from the pancreas
- Amylin mainly acts on the **area postrema** in the hindbrain to:
 - **Reduce eating**
 - **Slow gastric emptying**
 - **Inhibit glucagon secretion (rat)**
- Amylin **reduces eating in rodents** without any sign of visceral illness, taste avoidance or taste aversion



Amylin and GLP-1 affect similar aspects of metabolism

Amylin is a **peptide hormone**, co-secreted with insulin from the pancreas

- Amylin mainly acts on the **area postrema** in the hindbrain to:
 - **Reduce eating via increased satiation**
 - **Slow gastric emptying**
 - **Inhibit glucagon secretion (rat)**
- Amylin **reduces eating in rodents** without any sign of visceral illness, taste avoidance or taste aversion

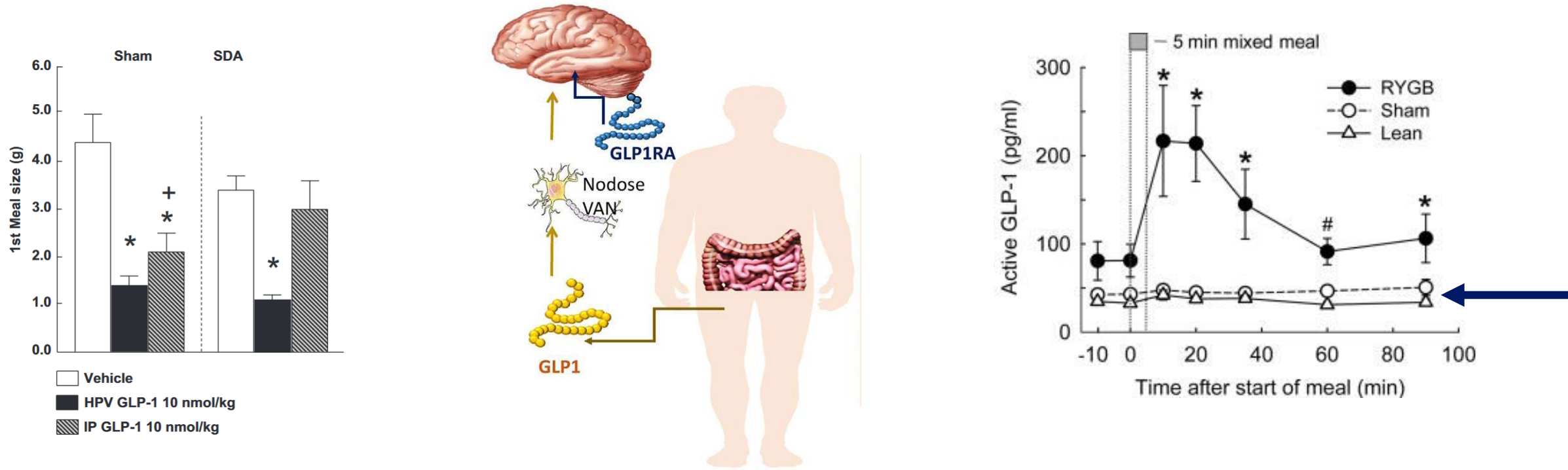


GLP-1 is an **incretin**, i.e. increases glucose-stimulated insulin secretion

- GLP-1 also:
 - **Reduces eating by inducing satiation**
 - **Slows gastric emptying**
 - **Inhibits glucagon secretion**
- GLP-1 and its agonists reduce eating but also induce signs of visceral illness, taste avoidance and taste aversion



Physiology versus pharmacology for GLP-1 action

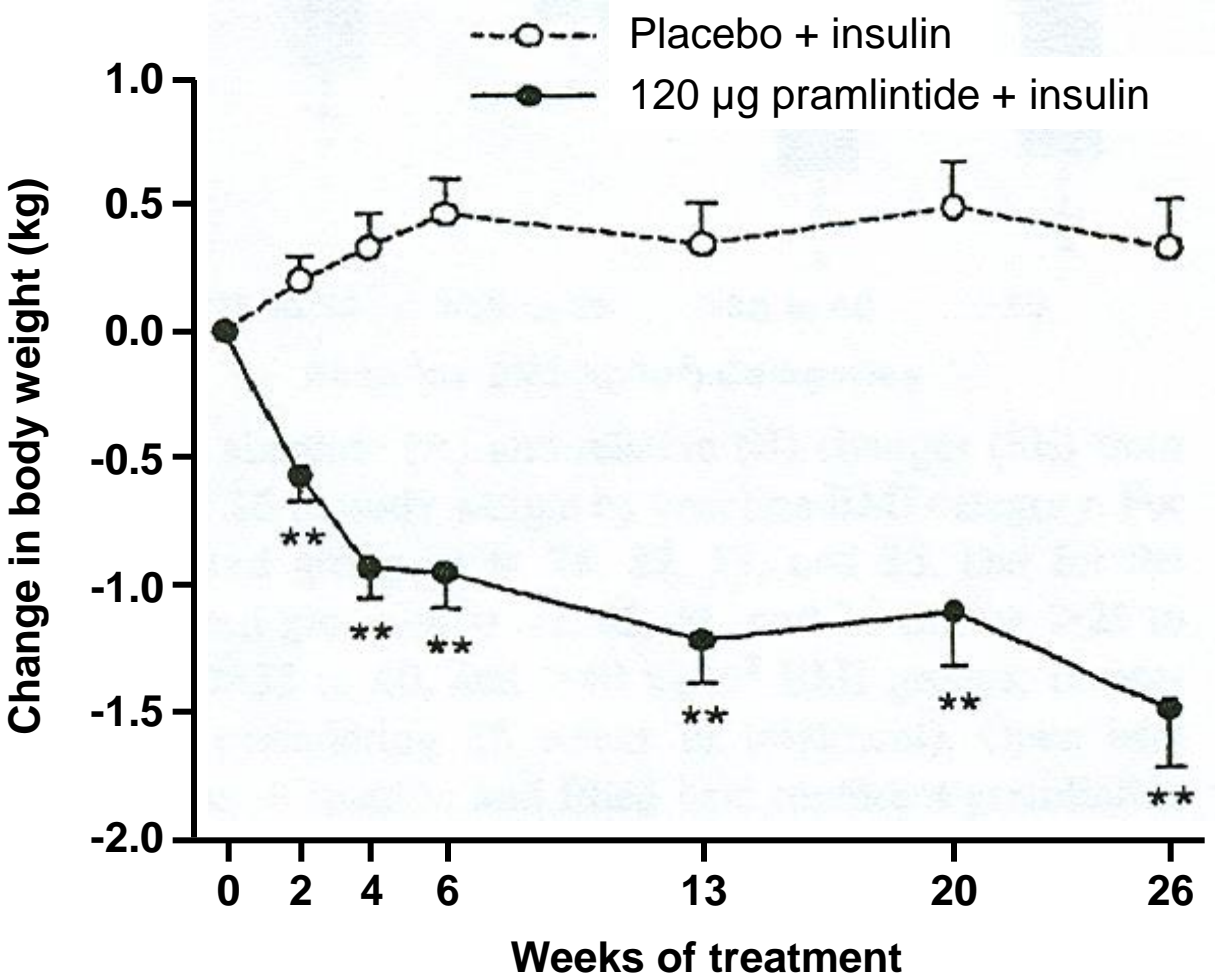


- Physiology: Paracrine action on vagal afferents mediates effect of endogenous GLP-1
- Pharmacology: Brain GLP-1 receptors mediate the effect of semaglutide

GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HPV, hepatic portal vein; IP, intraperitoneal; RYGB, Roux-en-Y gastric bypass surgery; SDA, subdiaphragmatic vagal deafferentations; VAN, vagal afferent neurons. Rüttimean et al., 2008; Drucker 2022; Shin et al., 2010.

Pramlintide, the first licensed amylin agonist, has been shown to reduce eating and body weight

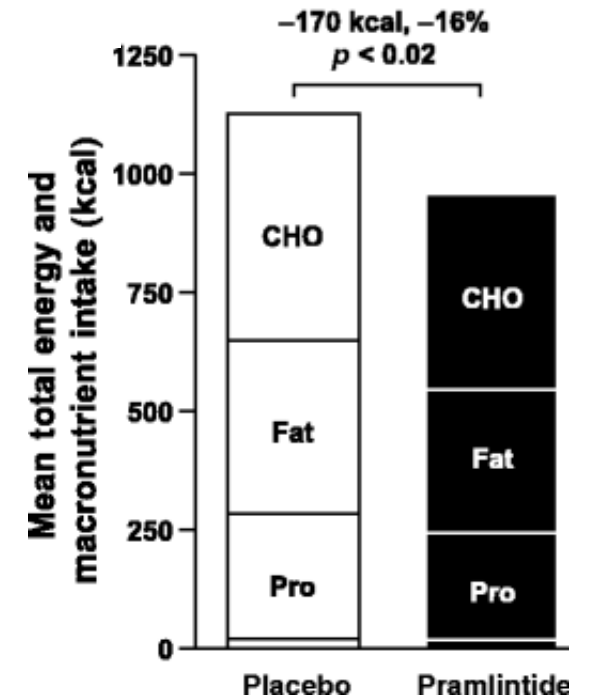
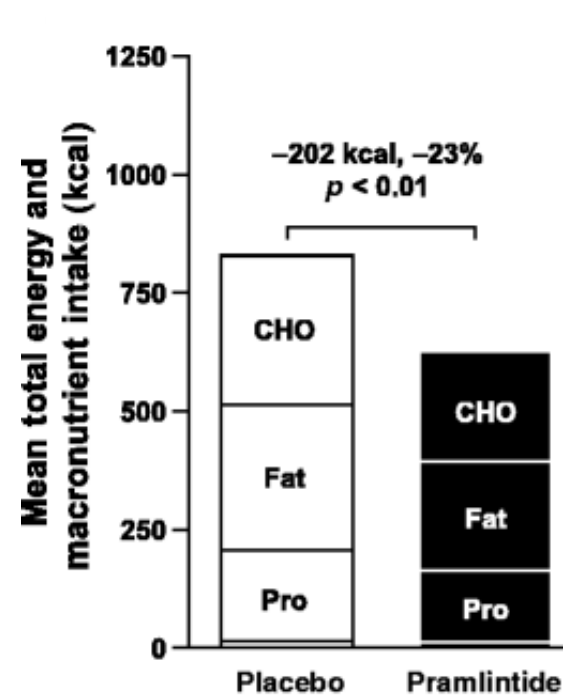
Pramlintide and insulin treated people with diabetes lose body weight compared to insulin only group



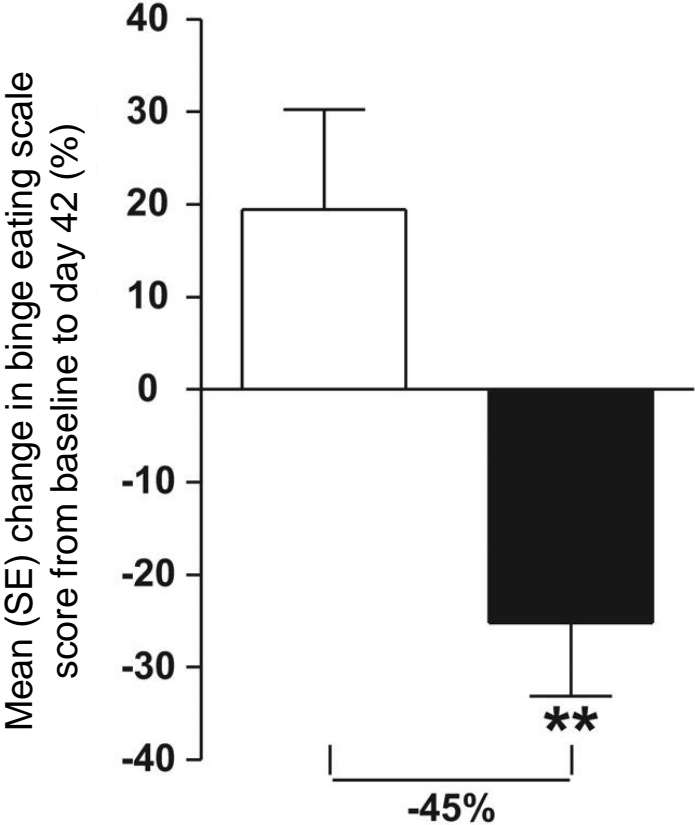
**P<0.0001
Hollander et al. 2004.

Pramlintide induces weight loss in people with obesity

- Pramlintide reduces energy intake by about 23% in insulin treated T2D
- Pramlintide reduces energy intake by about 16% in people with obesity, but without diabetes



Pramlintide reduces binge eating tendency

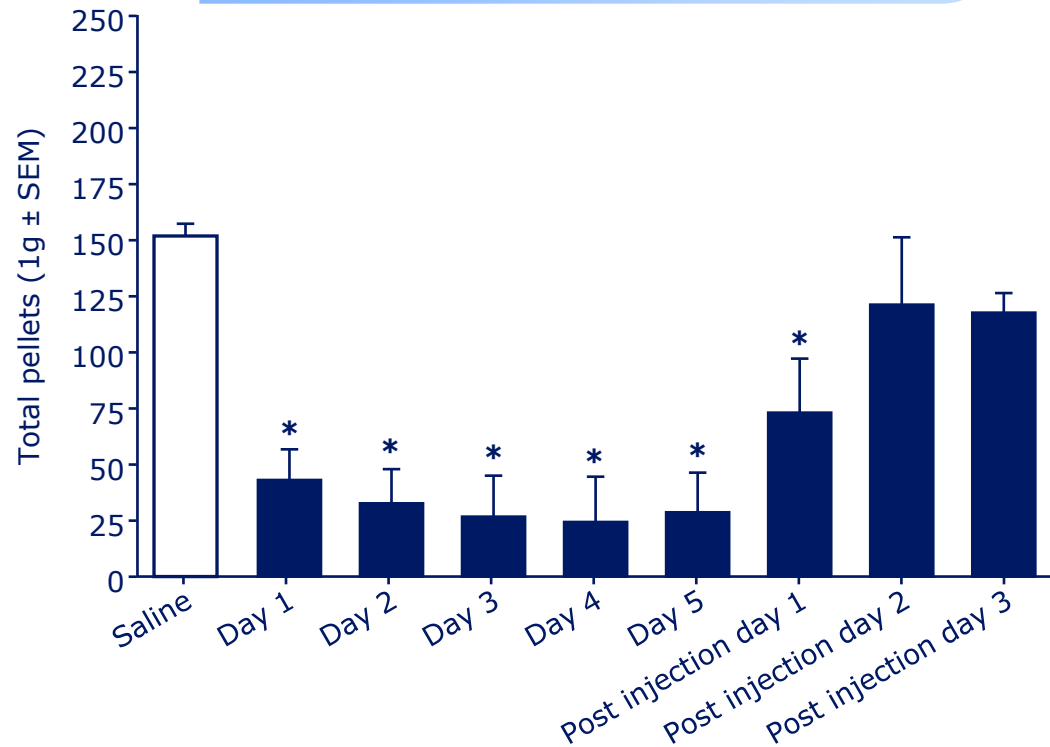


** $P < 0.01$.
Smith et al. 2007.

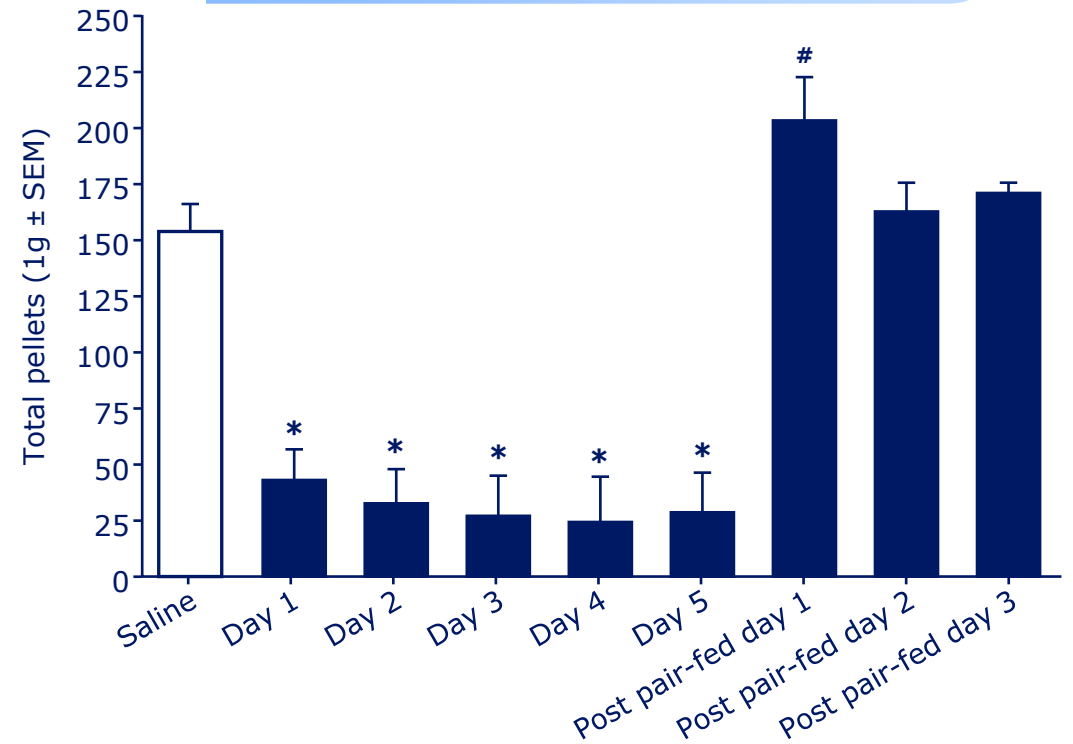
We have known
for a long time
that combining
amylin and
GLP-1 action
leads to
stronger effects
on eating and
body weight

Combination of amylin and GLP-1 analogues is more efficacious than single compounds in non-human primates

Drug administration



Pair feeding

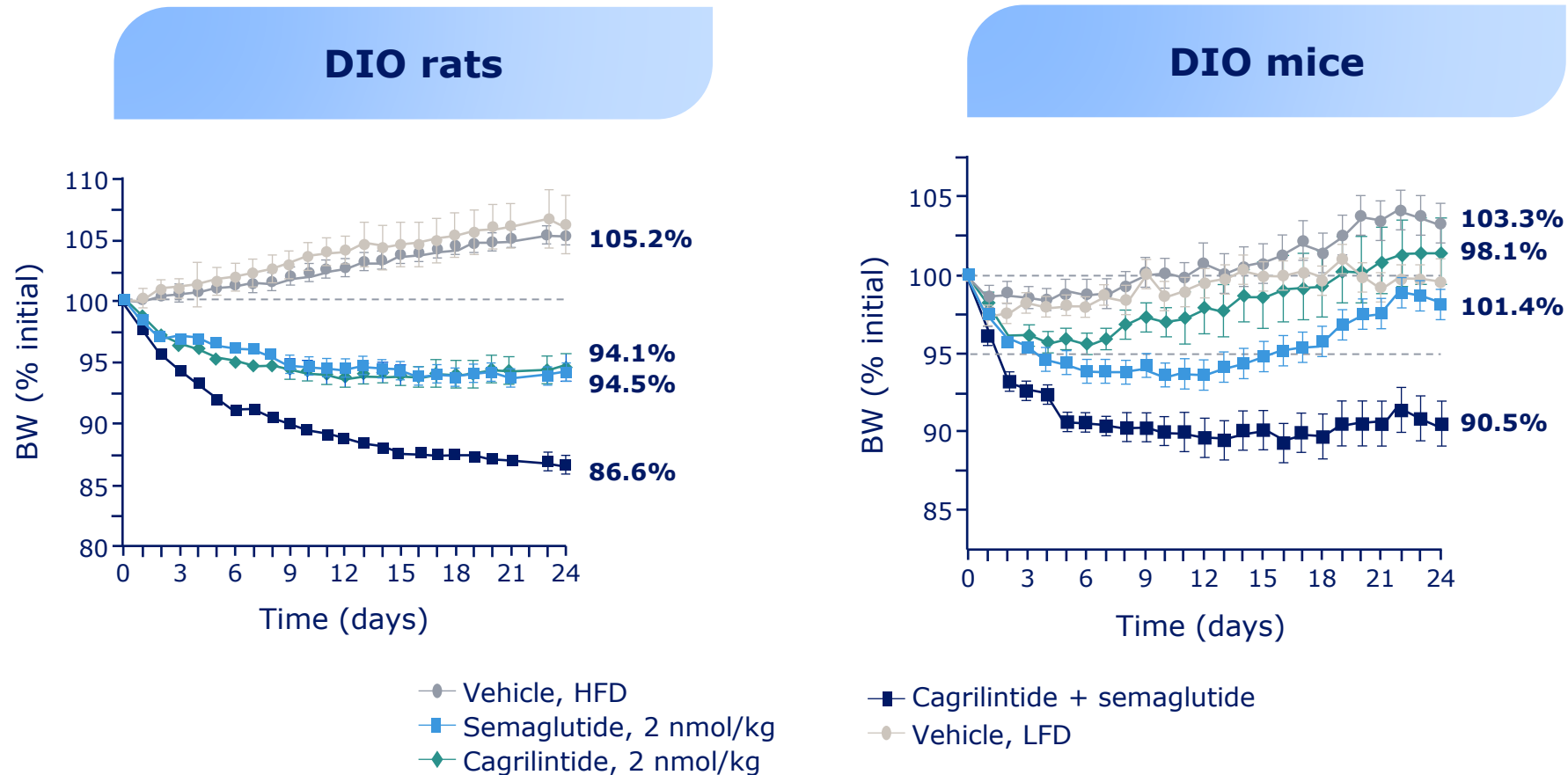


* $P < 0.001$; # $P < 0.05$.

GLP-1, glucagon-like peptide-1; SEM, standard error of the mean.

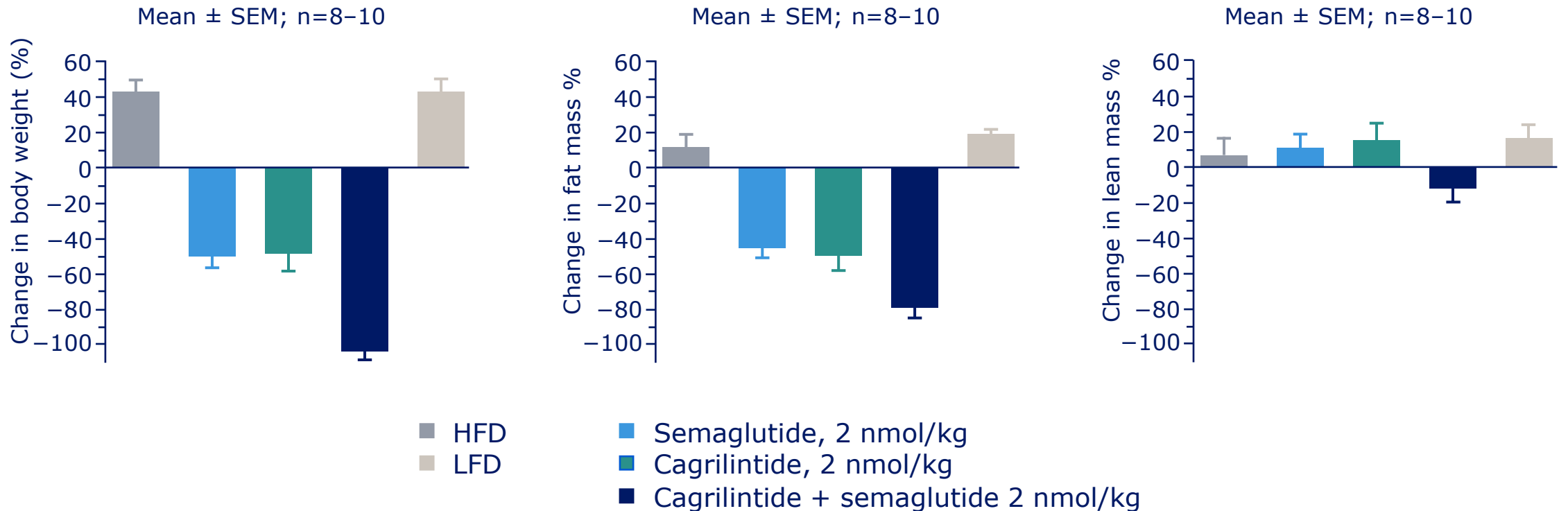
Bello et al. 2010

Cagrilintide and semaglutide in combination gives additive efficacy in rodent obesity models



BW, body weight; DIO, diet-induced obese; HFD, high fat diet; LFD, low fat diet.
John et al. 2021.

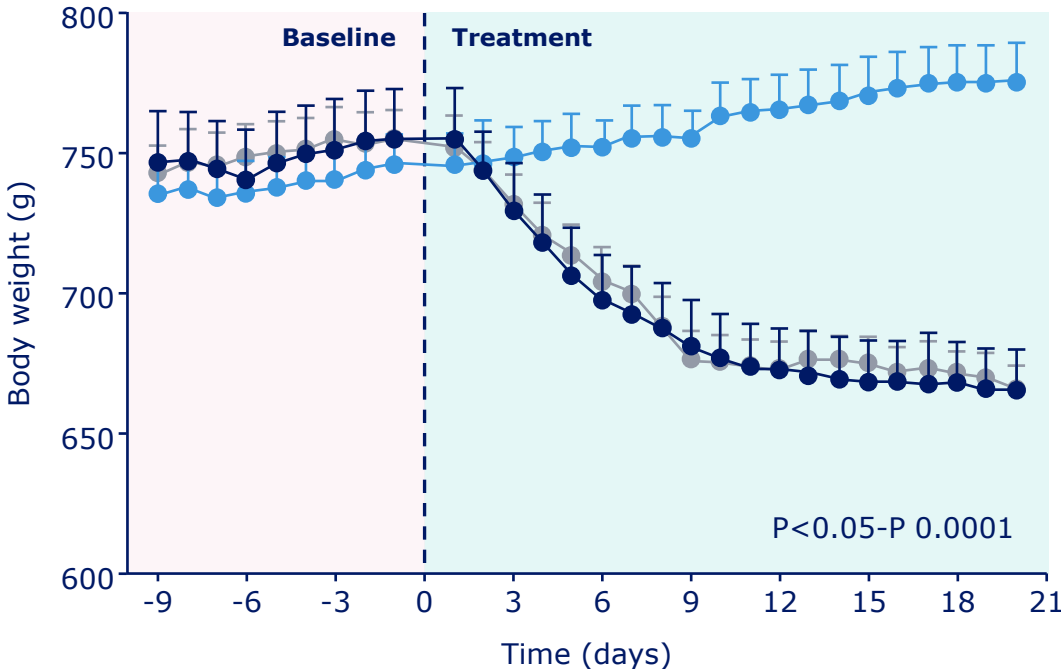
In DIO rats, weight loss with CagriSema is primarily due to loss of fat mass



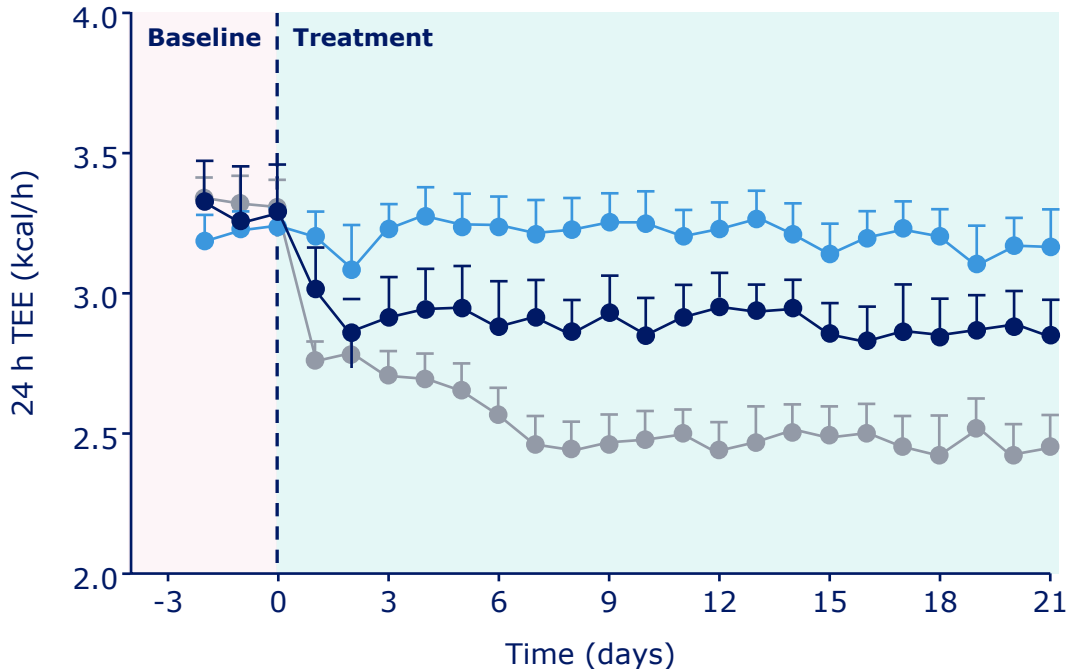
CagriSema attenuates metabolic adaptation

Normalised to body weight in male DIO rats

Change in body weight



Change in energy expenditure



● Vehicle ● CagriSema ● Weight matched

DIO, diet-induced obese; TEE, total energy expenditure.
Kuhre et al. 2023

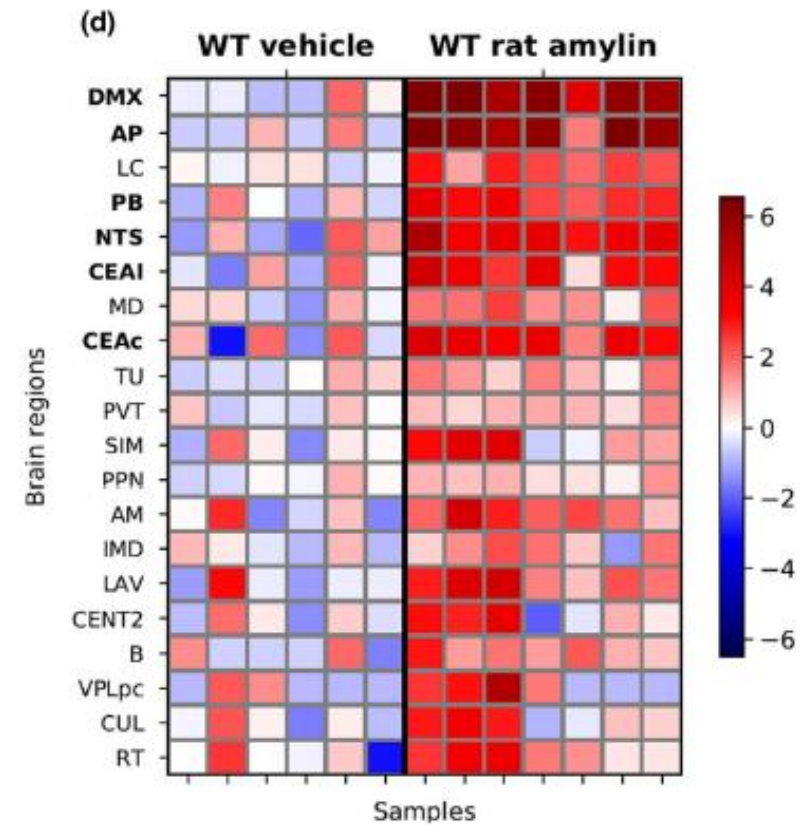
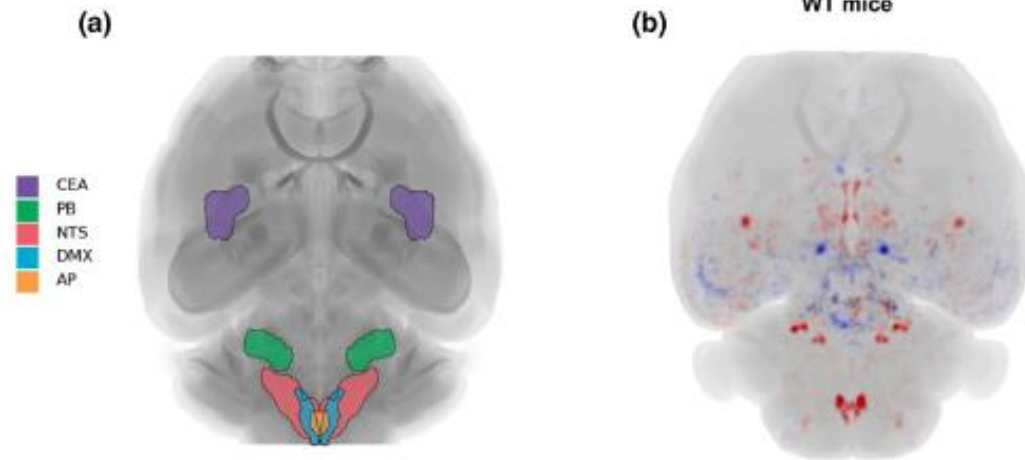
Which brain
areas are
activated by
amylin, GLP-1
and their
analogues?

RESEARCH REPORT | [Full Access](#)

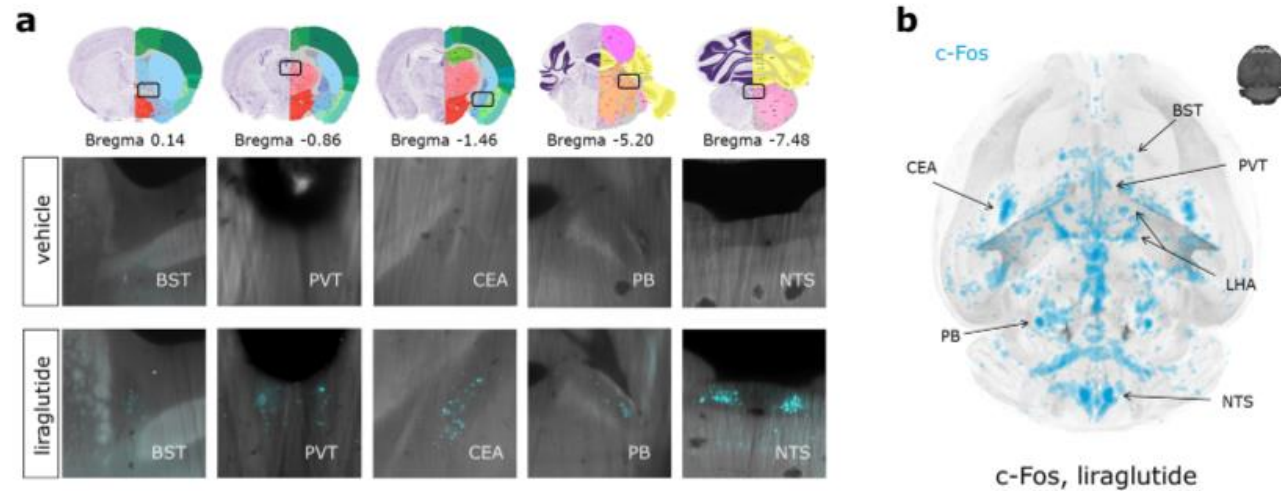
Whole-brain mapping of amylin-induced neuronal activity in receptor activity-modifying protein 1/3 knockout mice

Grethe Skovbjerg, Urmas Roostalu, Henrik H. Hansen, Thomas A. Lutz, Christelle Le Foll, Casper G. Salinas, Jacob L. Skytte, Jacob Jelsing, Niels Vrang, Jacob Hecksher-Sørensen ✉

First published: 27 April 2021 | <https://doi.org/10.1111/ejn.15254>



Globally, GLP-1 and its analogues activate similar brain areas as amylin

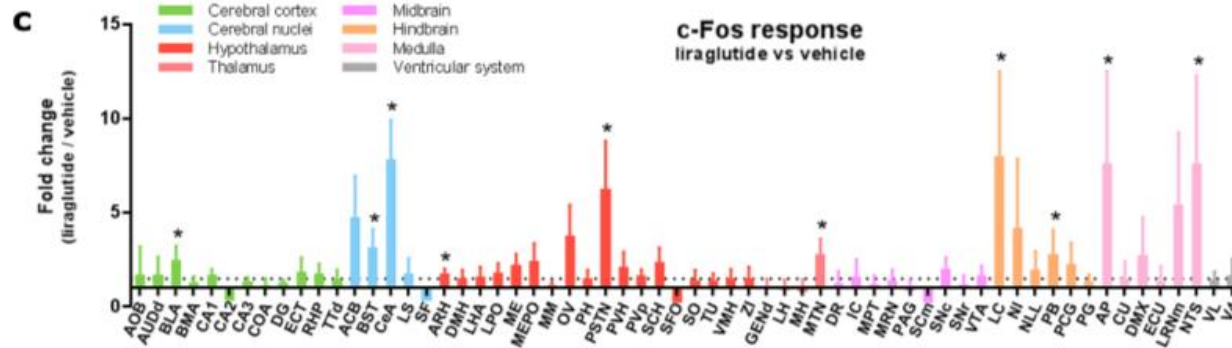


SCIENTIFIC REPORTS

OPEN Integrated Brain Atlas for Unbiased Mapping of Nervous System Effects Following Liraglutide Treatment

Received: 23 January 2018
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Published online: 09 July 2018

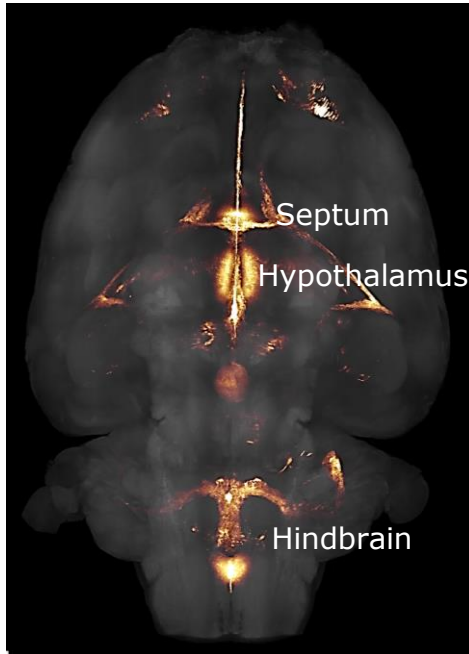
Casper Bo Gravesen Salinas^{1,2}, Tess Tsai-Hsiu Lu¹, Sanaz Gabery¹, Kasper Marstal^{2,4}, Tomas Alanentalo¹, Aaron Jeffrey Mercer³, Anda Cornea², Knut Conradsen², Jacob Hecksher-Sørensen¹, Anders Bjorholm Dah², Lotte Bjerre Knudsen¹ & Anna Secher¹



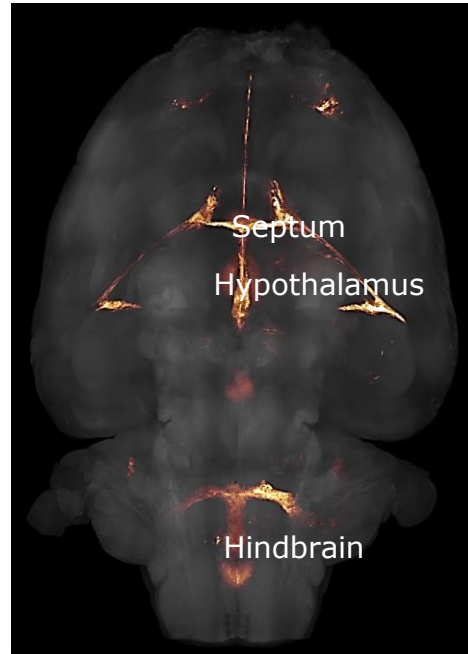
Fluorescently labelled amylin, GLP-1 and its analogues mainly reach circumventricular organs

Rat brains

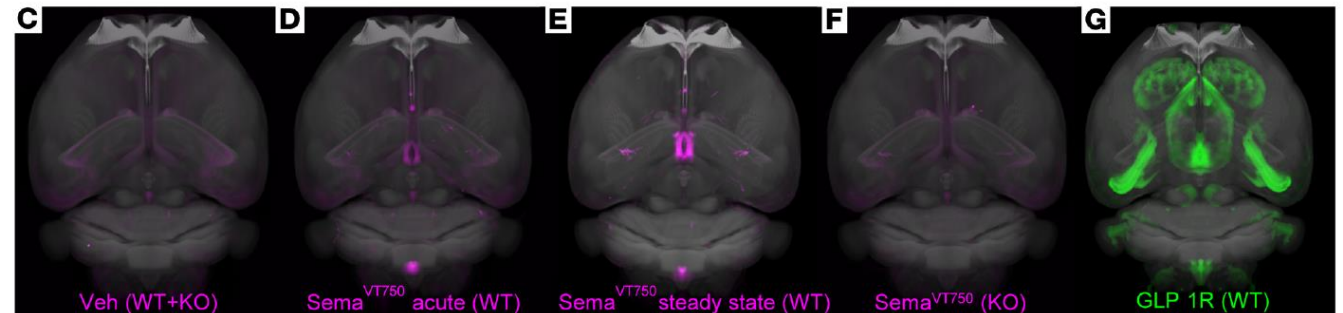
Fluorescently labelled cagrilintide or semaglutide



Cagrilintide^{VT750} 6h

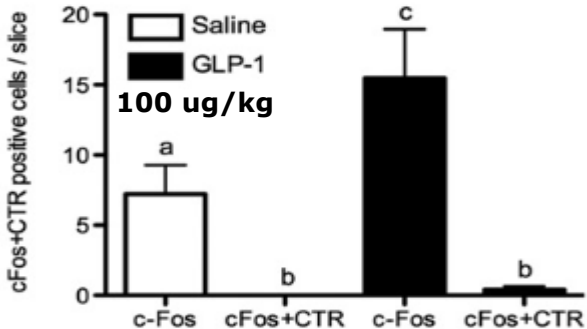
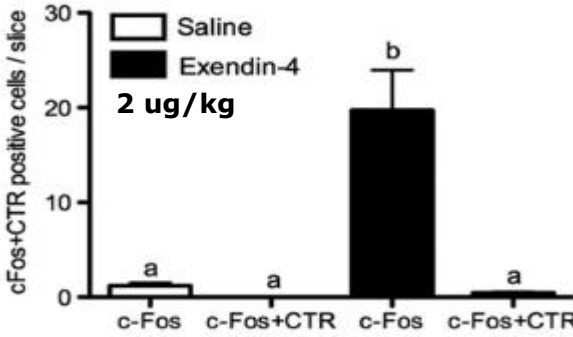
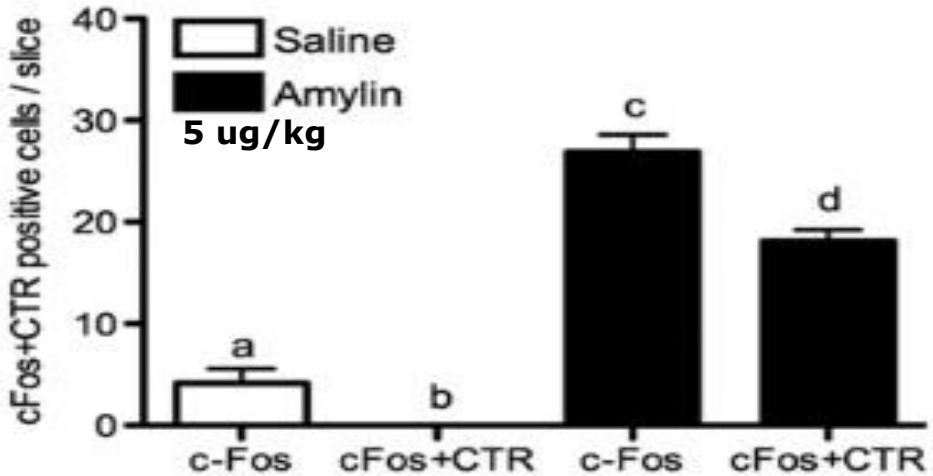
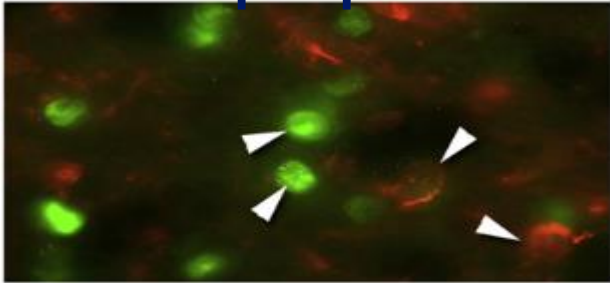
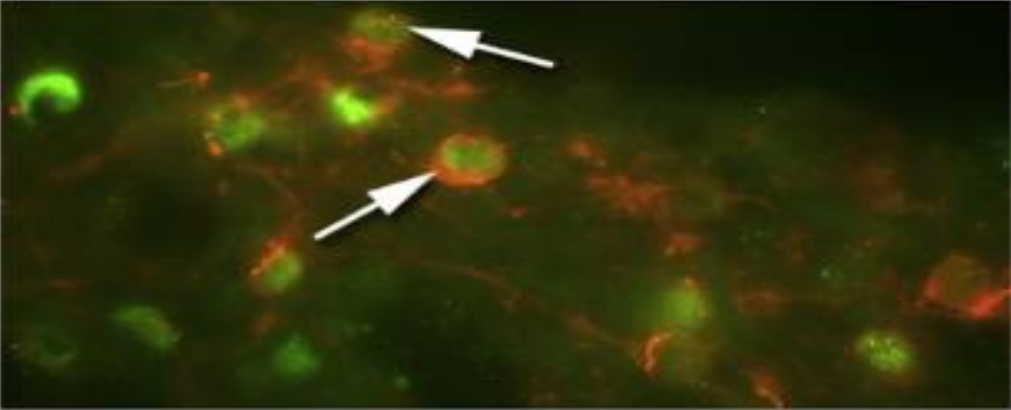


Semaglutide^{VT750} 6h



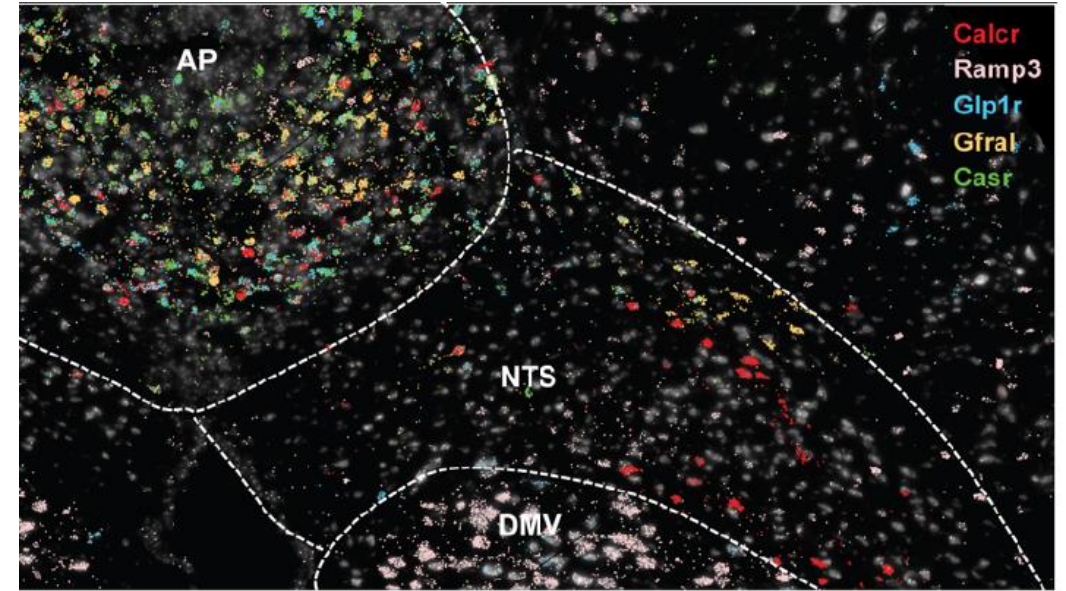
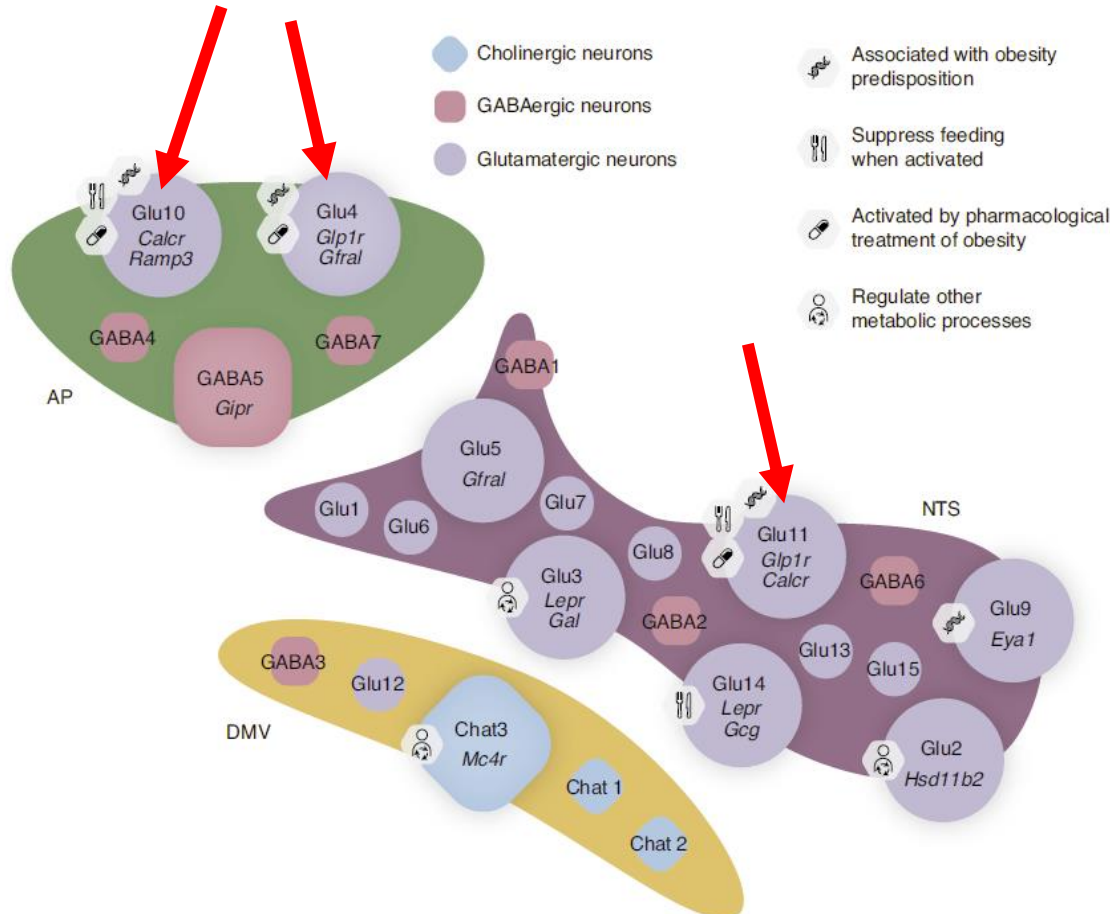
Do amylin and
GLP-1 act on
the same
neurones in
the caudal
hindbrain?

Glucagon-like peptide-1 receptor and calcitonin receptor activate separate neuronal population in AP



AP, area postrema; CTR, calcitonin receptor.
Zuger et al., 2013.

Single cell characterisation of amylin responsive neurones in the caudal hindbrain: Overlap between CTR and GLP-1R – case not resolved yet



Some CTR/RAMP3 cells seem to express GLP-1R

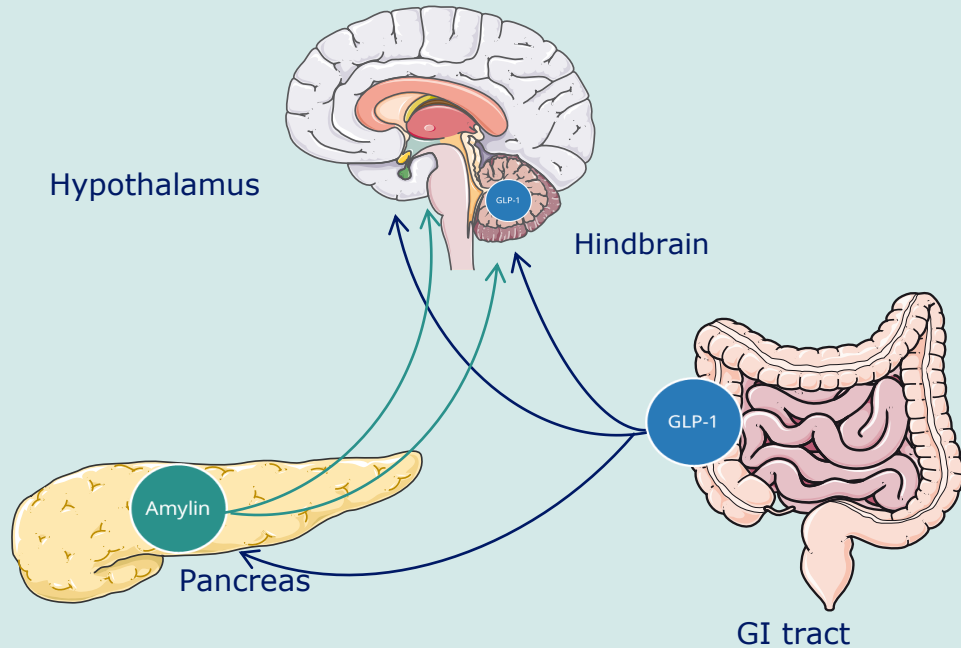
AP, area postrema; CTR, calcitonin receptor; DMV, dorsal motor nucleus of the vagus GLP-1R, glucagon-like peptide-1 receptor; NTS, nucleus of the solitary tract; RAMP3, receptor activity-modifying protein 3.
Ludwig et al., 2021; Zhang et al 2021, Dowsett et al., 2021; Ludwig et al., 2025 (pre-print).



Amylin and GLP-1 biology

GLP-1 and amylin biology

Interestingly, both the first amylin analogue (pramlintide) and the first GLP-1 analogue (exenatide) were licensed in 2005

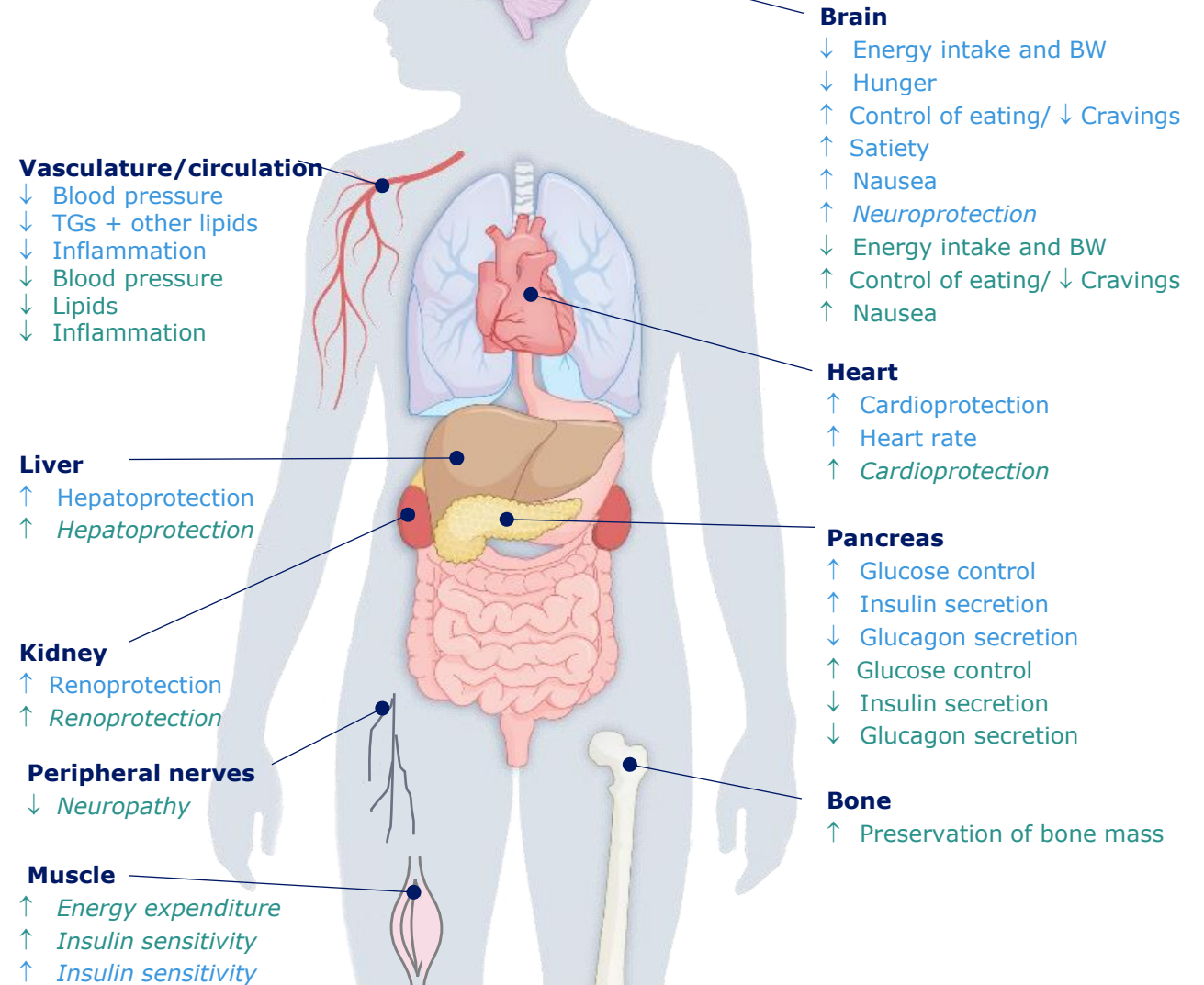


BW, body weight; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; TG, triglyceride.

Highlight of clinically proven effects and effects with preclinical/clinical-omics evidence with

GLP-1RA

Amylin



Not there yet but getting there!!





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