Do post-surgical changes in gut hormones help control food intake and regulate energy balance?

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IFSO
NAPOLI
2023

CONFLICT OF INTEREST DISCLOSURE

I have the following potential conflicts of interests to report:

Rachel Batterham is a full-time employee and share holder of Eli Lilly and Company Ltd.

This presentation represents my own opinions and not the opinions of Eli Lilly and Company

I have previously received funding from the following companies:

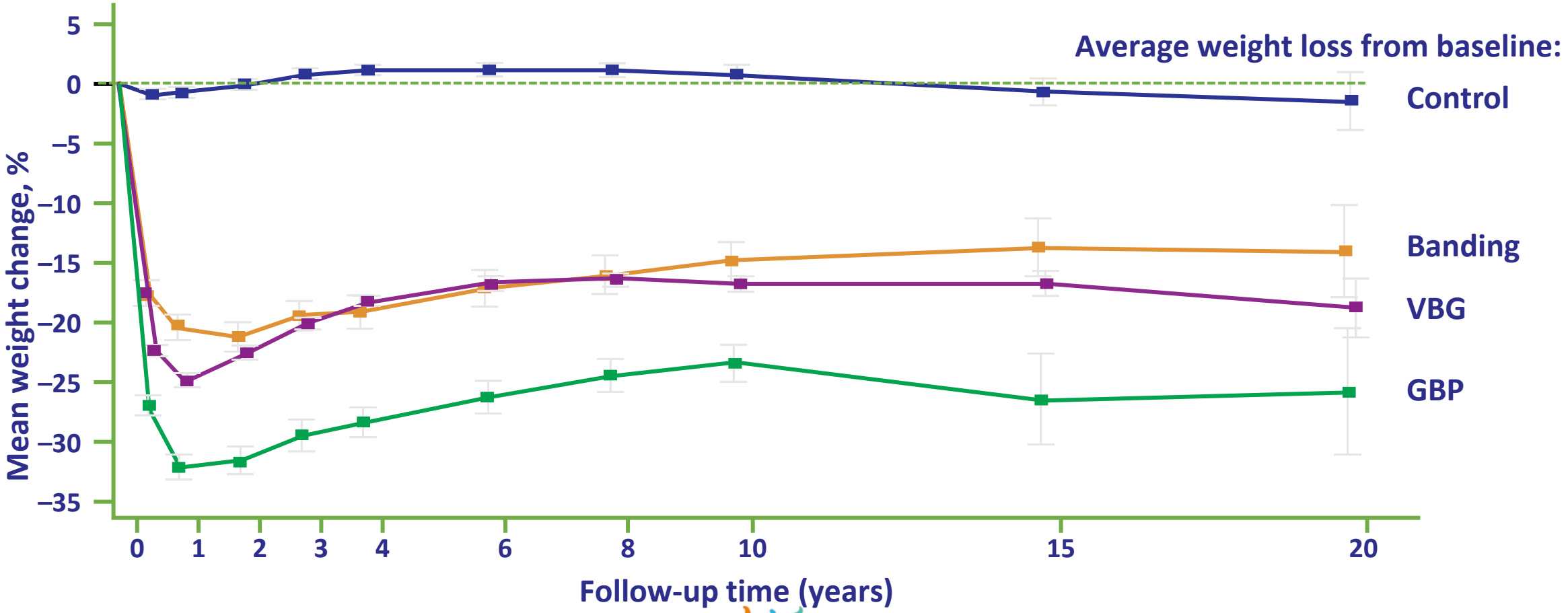
- For providing educational sessions or attending advisory boards (institutional and personal)

  Novo Nordisk, International Medical Press, ViiV, Pfizer, Gila Therapeutics Ltd, Eli-Lilly and Epitomee Medical Ltd.

- Institutional research grant support or funding for clinical trials

  Novo Nordisk and Rhythm Pharmaceuticals

Bariatric Metabolic Surgery (BMS) is associated with sustained weight loss



GBP, gastric bypass; VBG, vertical banded gastroplasty

Sjöström L et al. JAMA 2012;307:56–65

BMS reduces morbidity & mortality

Resolution/improvement in comorbidities

- T2D
- Hypertension
- Liver disease
- Pulmonary function (OSA and asthma)
- Musculoskeletal disorders

Reduced risk of certain types of cancer

Improved quality of life

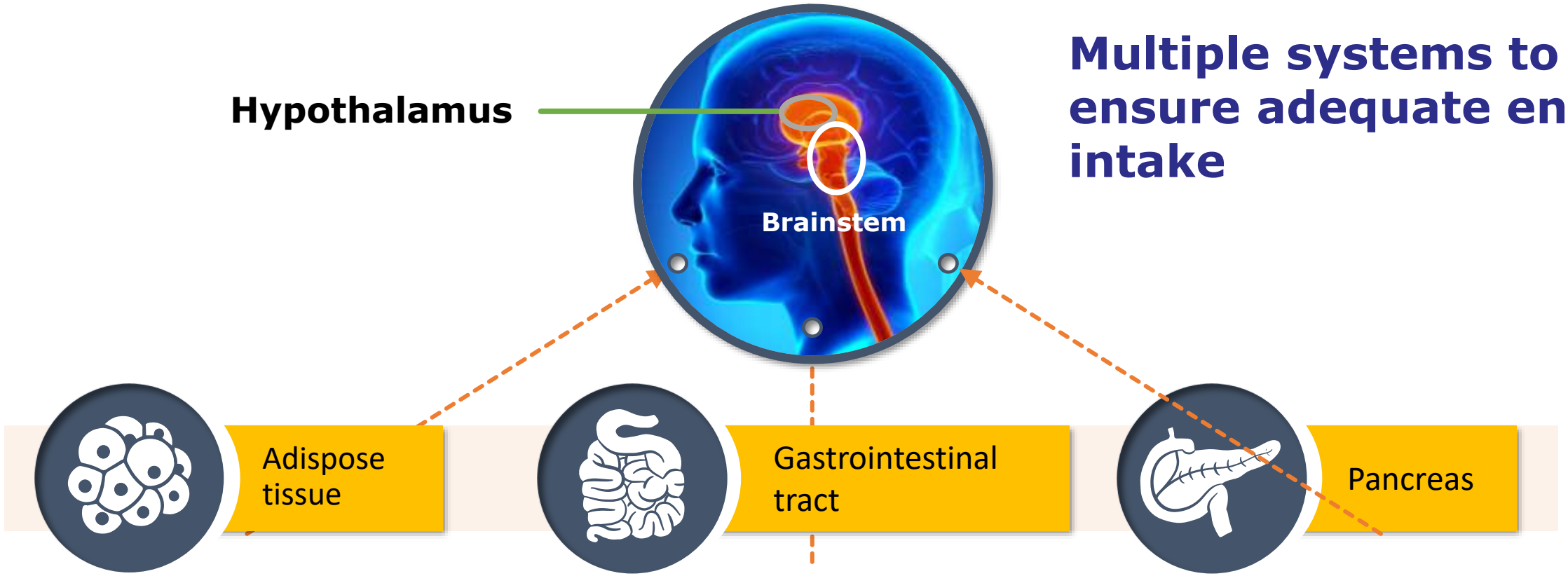
Prevention

- T2D, strokes and ischaemic heart disease

Mortality

BMS is the most effective treatment for people with severe obesity

Homeostatic regulation of body weight



Multiple systems to ensure adequate energy intake

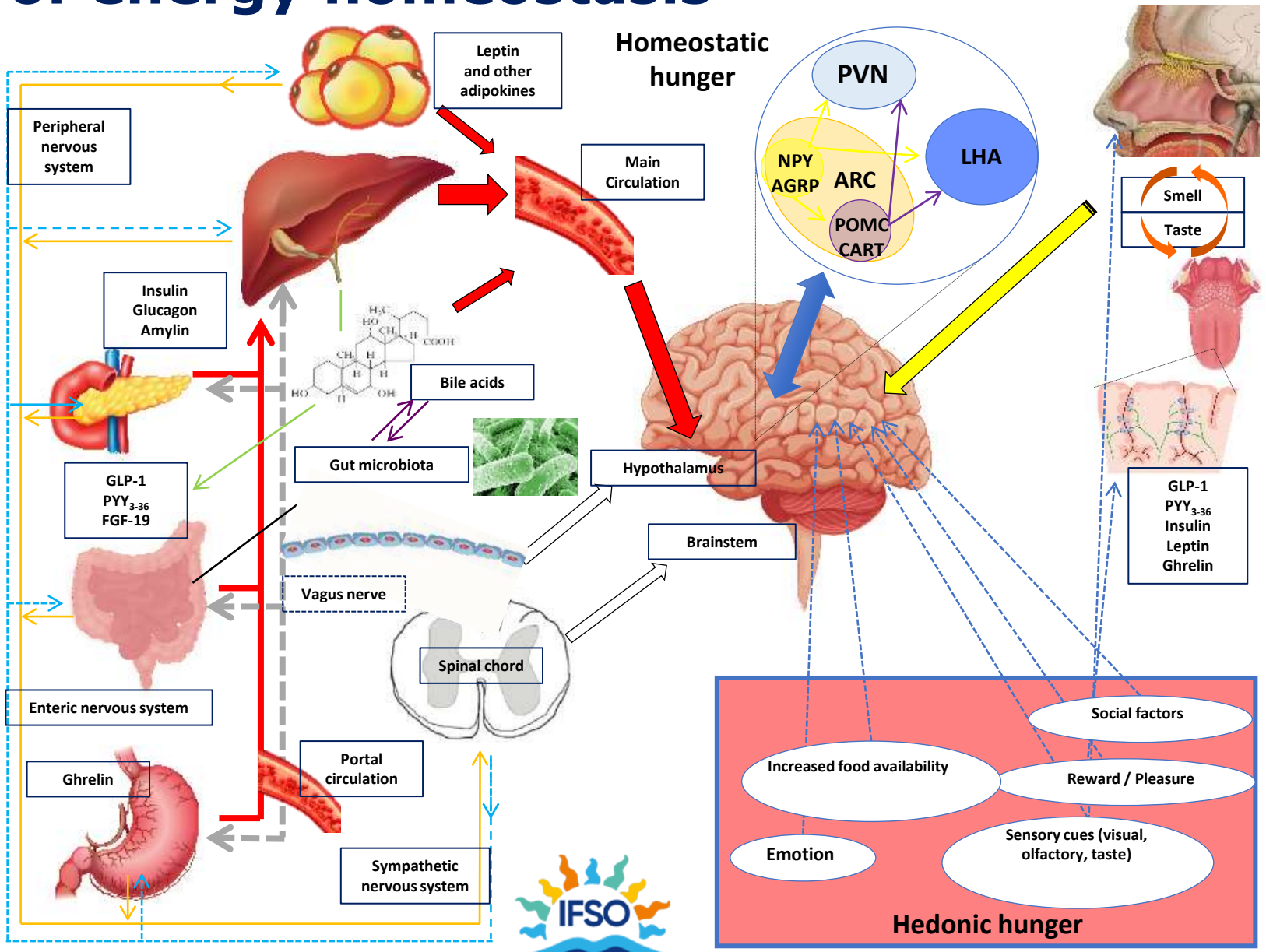
Badman MK & Flier JS. *Science* 2005;307:1909-1914
Woods SC & Seeley RJ. *Int J Obes Relat Metab Disord* 2002;26:S8-S10

Hedonic regulation of body weight

Sørenson LB, *et al. Int J Obes Relat Metab Disord* 2003;27:1152-1166;

Yu Y-H, *et al. Obes Rev* 2015;16:234-247

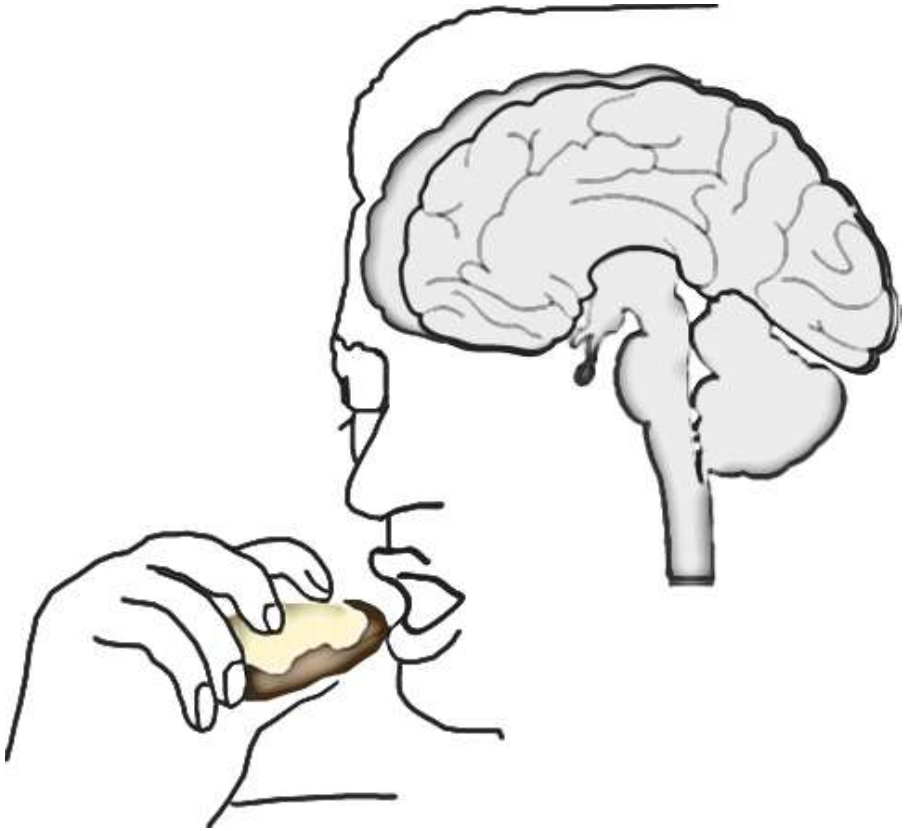
Regulation of energy homeostasis



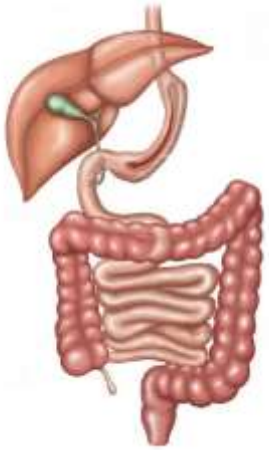
AGRP, agouti gene-related peptide; AOM, anti-obesity medication; CART, cocaine- and amphetamine-regulated transcript; GLP-1, glucagon-like peptide-1; LHA, lateral hypothalamic area; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY.
Source: Speaker's own image

Favourable post-surgery changes in eating behavior drive weight loss and weight loss maintenance

- Reduced hunger/ increased satiety
- Subjective/objective changes in taste and smell
- Altered food preference (away from high-energy dense foods)
- Reduced interest in food



Taste changes following bariatric surgery



- Changes in taste, food preference and food aversions common after bariatric surgery
- Taste and appetite changes → improved weight loss

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

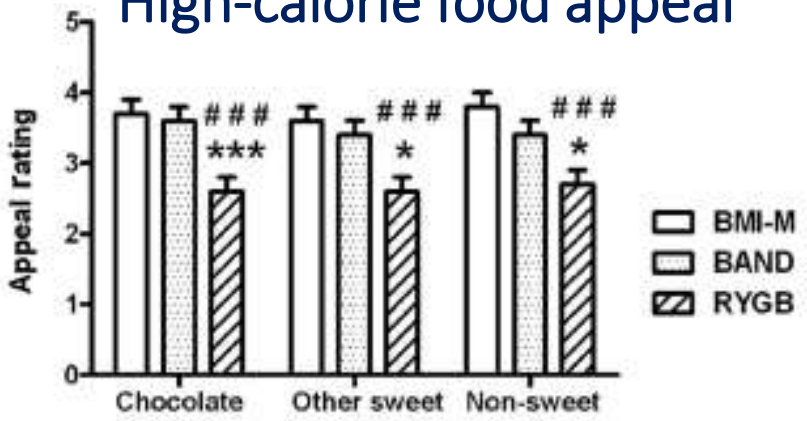
Reported appetite, taste and smell changes following Roux-en-Y gastric bypass and sleeve gastrectomy: Effect of gender, type 2 diabetes and relationship to post-operative weight loss

Makaronidis JM, Neilson S, Cheung WH, Tymoszuk U, Pucci A, Finer N, Doyle J, Hashemi M, Elkalaawy M, Adamo M, Jenkinson A, Batterham RL. Reported appetite, taste and smell changes following Roux-en-Y gastric bypass and sleeve gastrectomy: Effect of gender, type 2 diabetes and relationship to post-operative weight loss. Appetite. 2016;107:93-105.

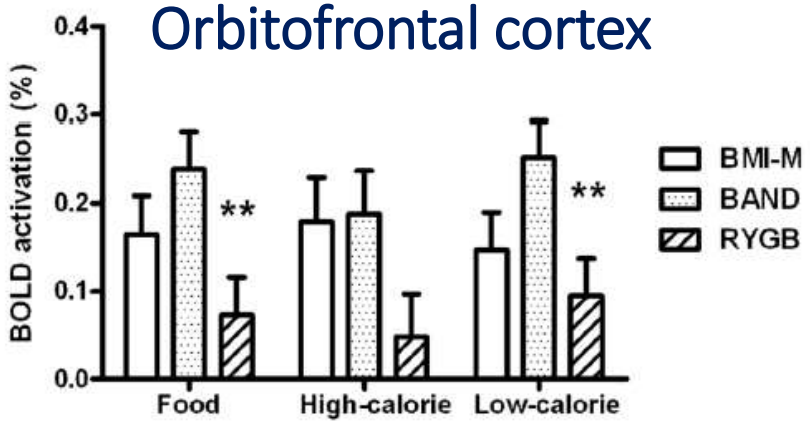
Bariatric surgery reduces hedonic responses

3 groups: RYGB, BAND and BMI-M, BMI approx. 35 kg/m^2

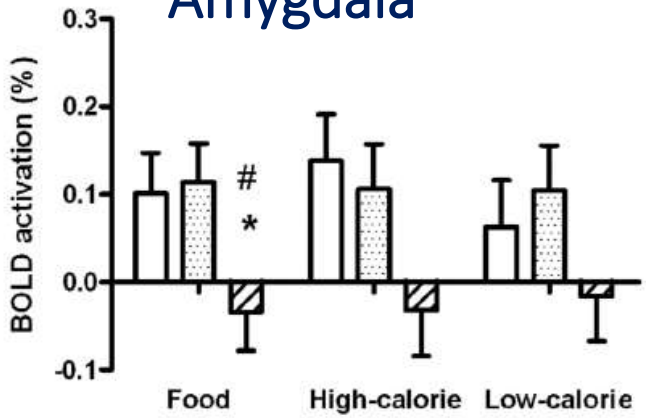
High-calorie food appeal



Orbitofrontal cortex



Amygdala



Scholtz S, *et al. Gut* 2014;**63**:891–902. doi:10.1136/gutjnl-2013-305008

Post-surgery CNS changes

Gastric-bypass surgery induced widespread neural plasticity of the obese human brain

Michael Rullmann Sven Preusser Sindy Poppitz Stefanie Heba Jana Hoyer
Tatjana Schütz Arne Dietrich Karsten Müller ,Burkhard Pleger **NeuroImage 172 (2018) 853-863**

ORIGINAL CONTRIBUTIONS

CrossMark

IFSO

Sleeve Gastrectomy Recovering Disordered Brain Function in Subjects with Obesity: a Longitudinal fMRI Study

Panlong Li[1,2,3] · Han Shan[4] · Shengxiang Liang[1,2,3] · Binbin Nie[2,3] · Hua Liu[2,3] · Shaofeng Duan[2,3] · Qi Huang[2,3] · Tianhao Zhang[2,3] · Guanglong Dong[5] · Yulin Guo[5] · Jin Du[6] · Hongkai Gao[7] · Lin Ma[4] · Demin Li[1] · Baoci Shan[2,3,8,9]

Resting-state brain connectivity changes in obese women after Roux-en-Y gastric bypass surgery: A longitudinal study

Gaia Olivo[1], Wei Zhou[1], Magnus Sundbom[2], Christina Zhukovsky[1], Pleunie Hogenkamp[1], Lamia Nikontovic[1], Julia Stark[1], Lyle Wiemerslage[1], Elna-Marie Larsson[3], Christian Benedict[1] & Helgi B. Schiöth[1]

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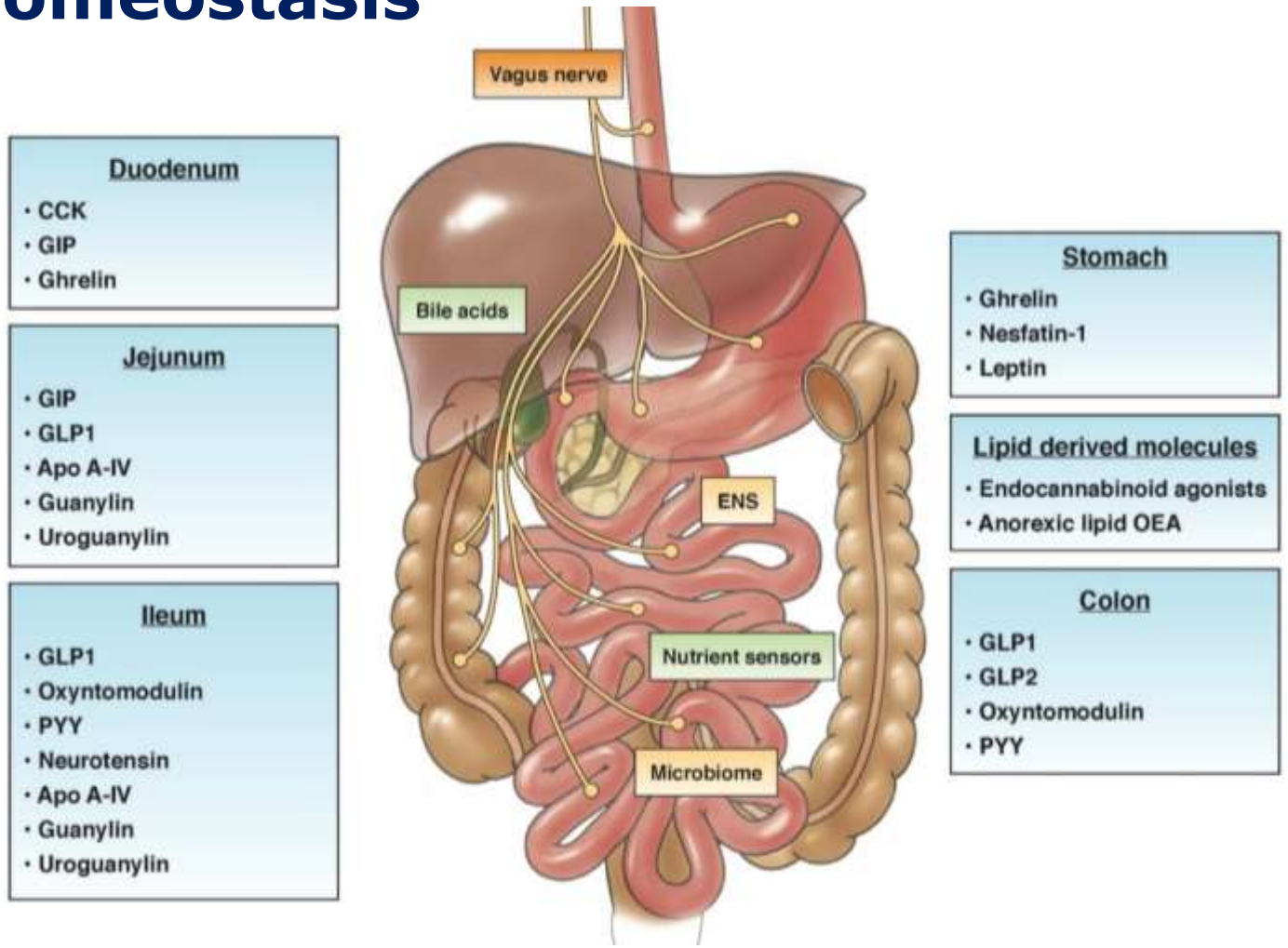
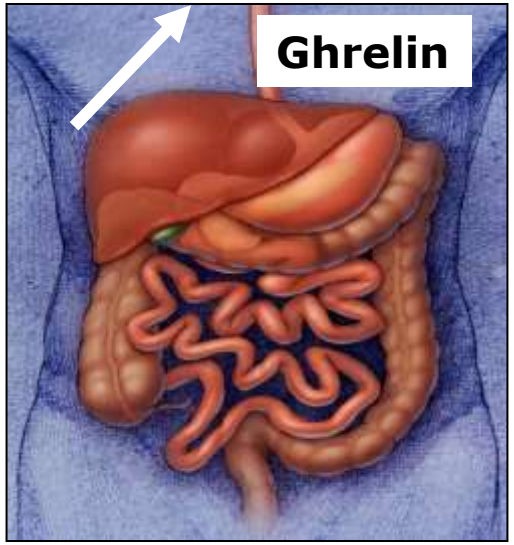
The gut plays a critical role in regulating energy and glucose homeostasis



Apo A-IV, apolipoprotein A-IV; CCK, cholecystokinin; ENS, enteric nervous system; GIP, gastric inhibitory polypeptide; GLP, glucagon-like peptide; OEA, oleoylethanolamide; PYY, polypeptide YY

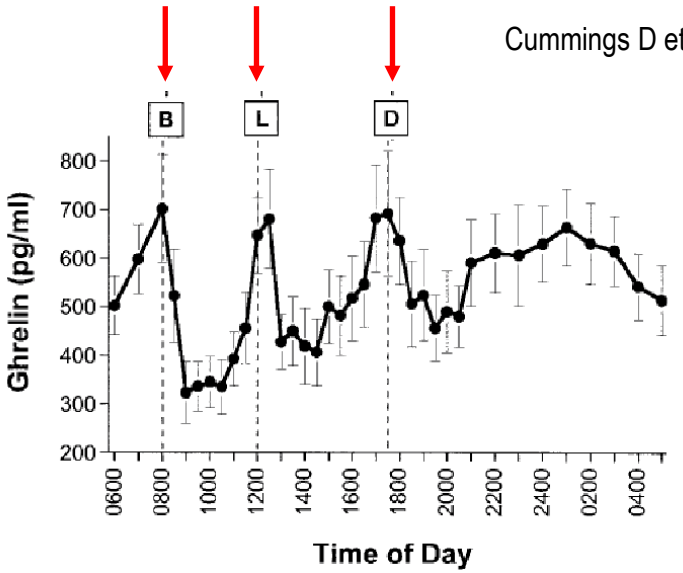
Monteiro MP, Batterham RL. *Gastroenterology* 2017;152:1707–17

Ghrelin – "Hunger hormone"

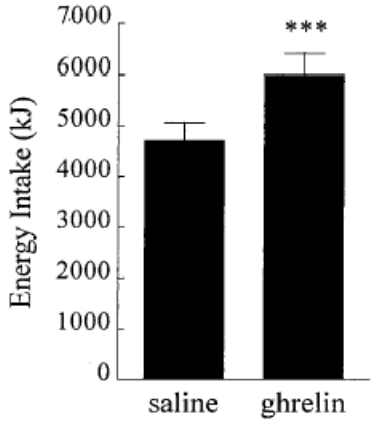


Pre-meal surges

Cummings D et al. Diabetes 2001

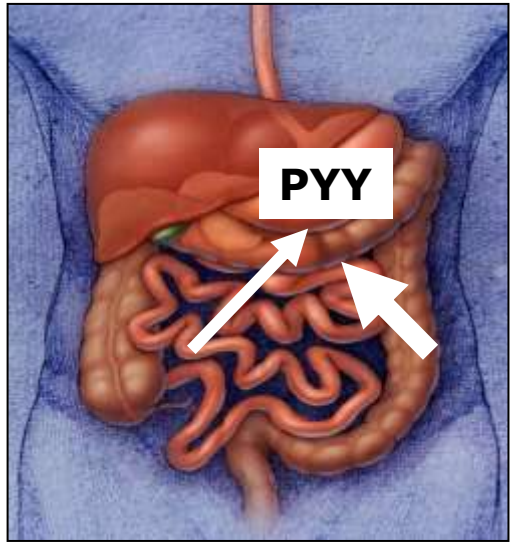


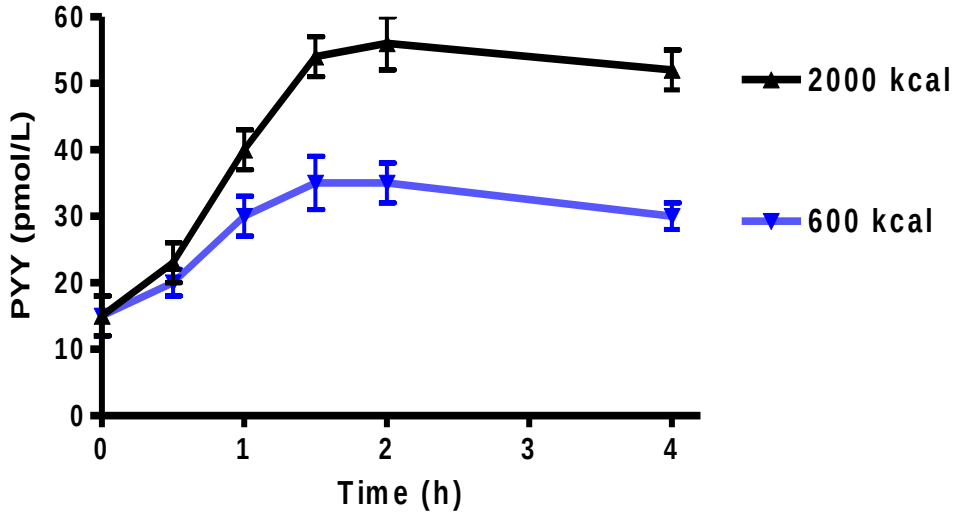
Increase hunger and caloric intake



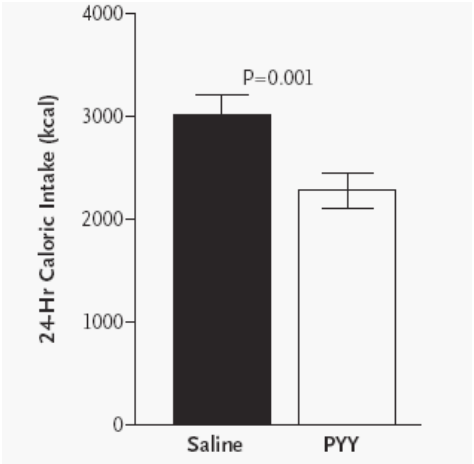
Wren et al. JCEM, Dec 2001

Peptide YY (PYY) reduces hunger & energy intake



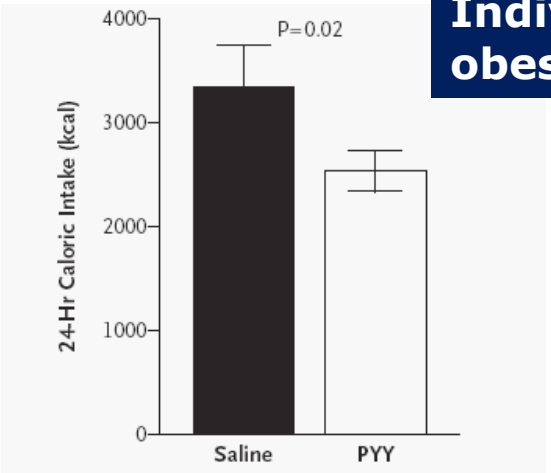


Individuals with normal weight



↓23.5 ± 6.5%

Individuals with obesity



↓16.5 ± 6.6%

Batterham *et al.* Nature 2002 and NEJM 2003

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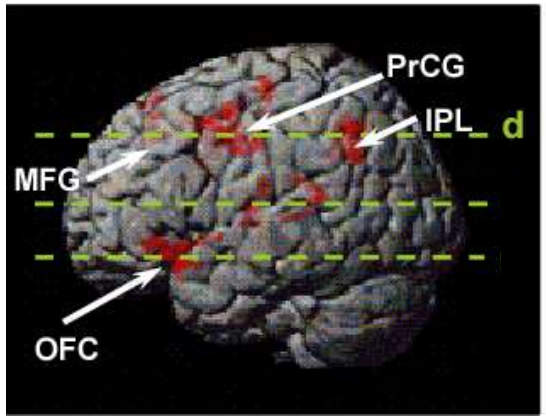
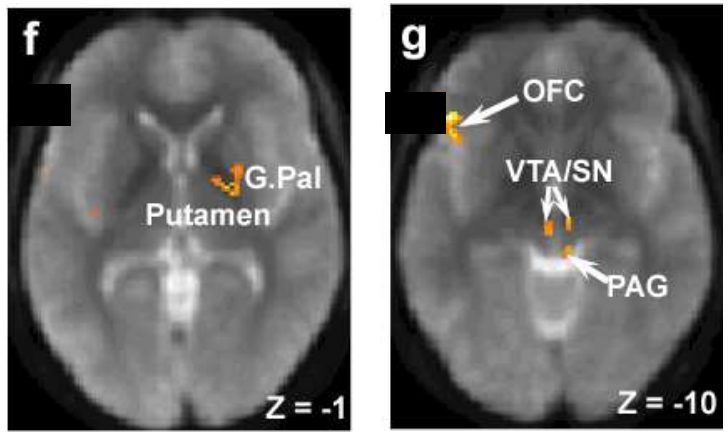
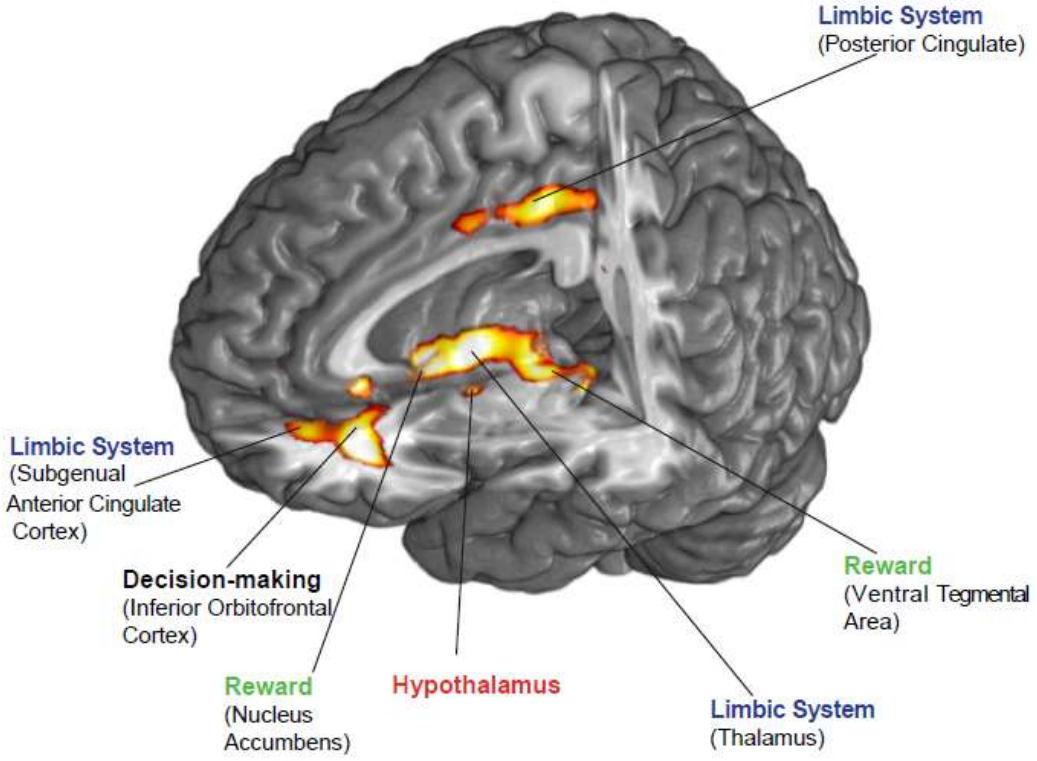
Gut hormones modulate neural activity in key brain areas that control eating and reward



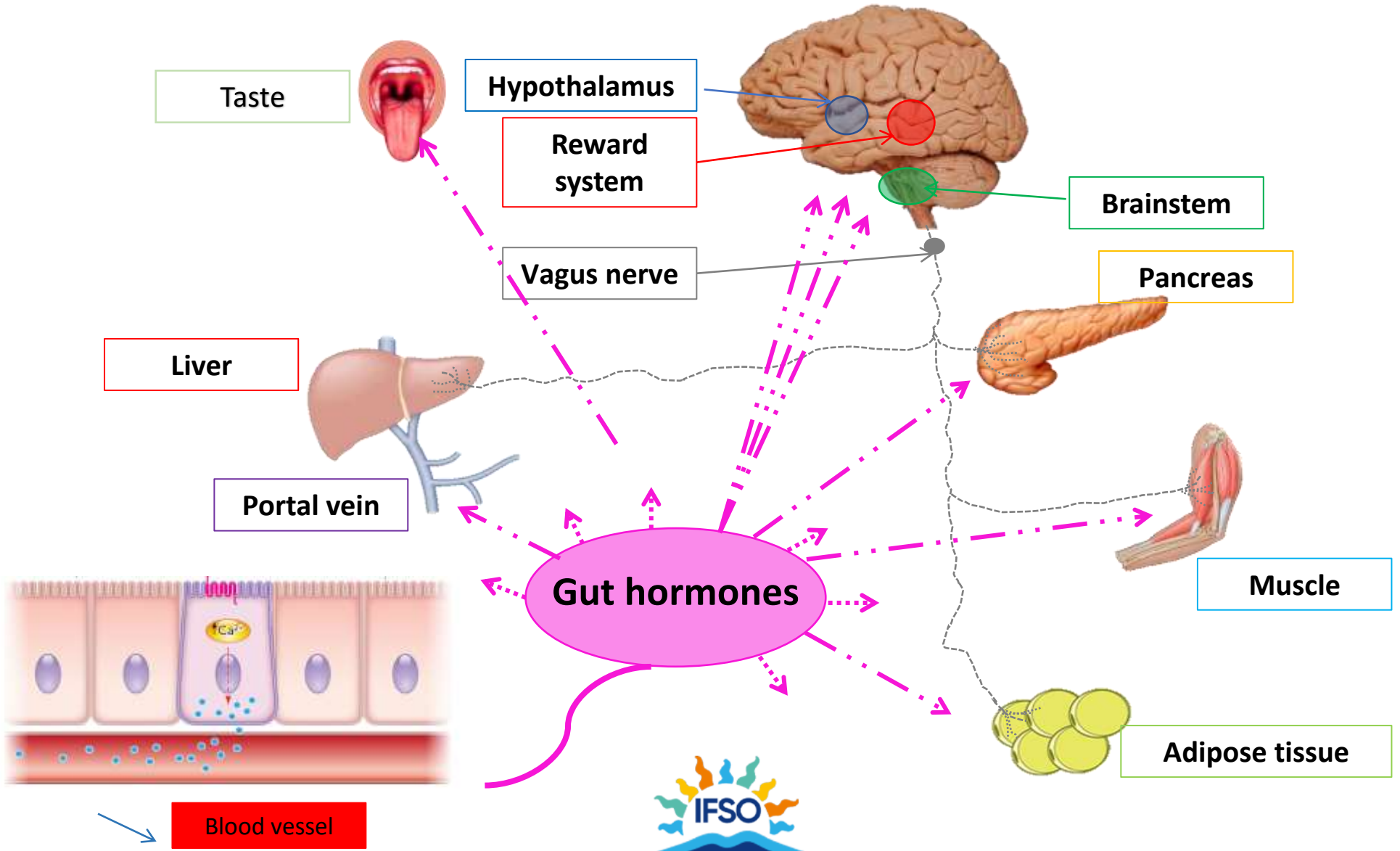




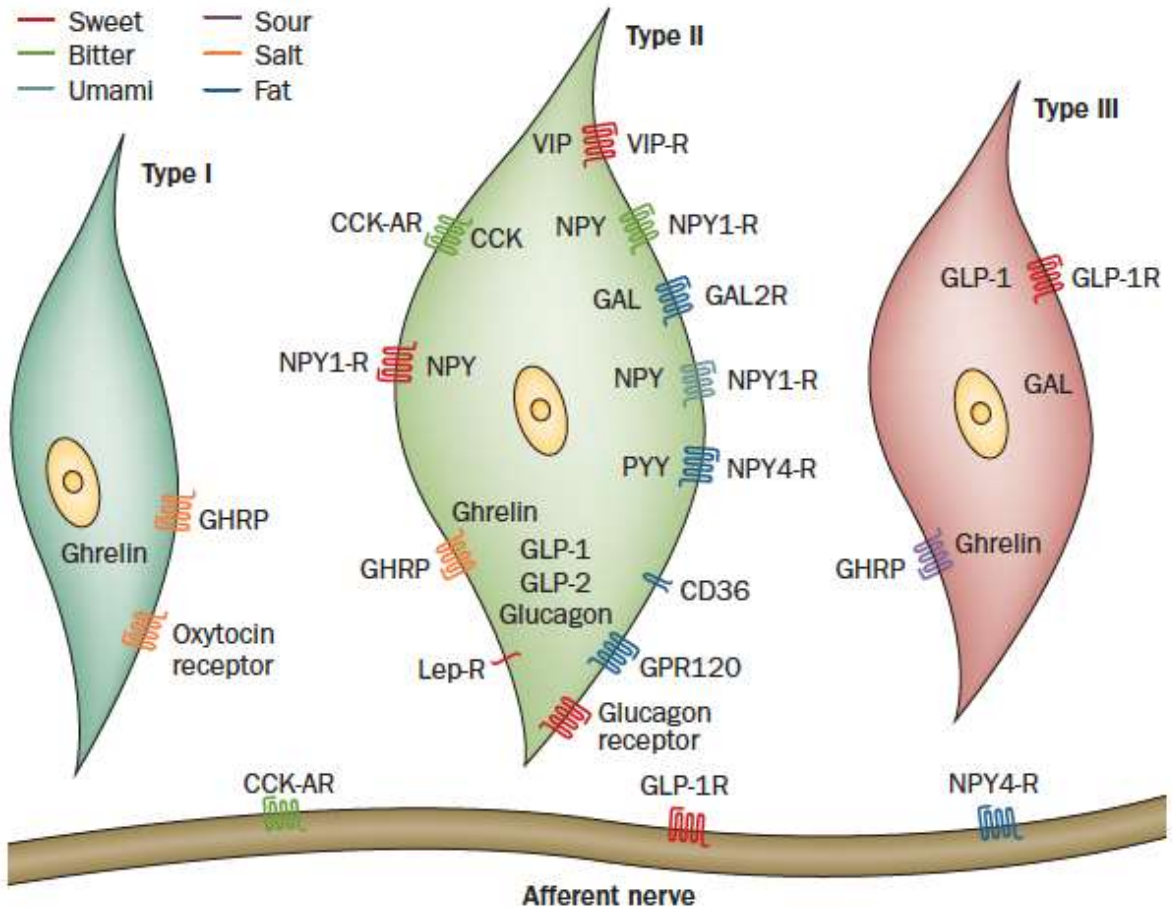
Batterham RL et al. *Nature* 2007;450:106–9; Karra E et al. *J Clin Invest* 2013;123:3539–51
Image from https://www.ucl.ac.uk/news/2013/jul/how-obesity-gene-triggers-weight-gain

Karra E et al., JCI 2013

Gut hormones acts peripherally & centrally



Interaction between taste & metabolic signals



Calvo SS, Egan JM. Nat Rev Endocrinol. 2015

Gut hormones & taste

- PYY, ghrelin and GLP-1 are present in saliva.
- Y2R, GHSR and GLP-1R are present on taste buds.

The FASEB Journal • Research Communication

Modulation of taste responsiveness by the satiation hormone peptide YY

Vol. 27 December 2013

The FASEB Journal • Research Communication

Glucagon-like peptide-1 is specifically involved in sweet taste transmission

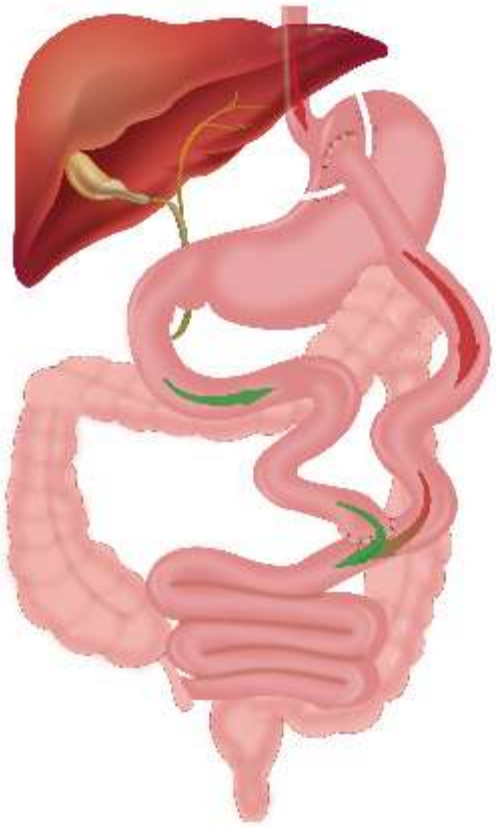
Published online February 12, 2015.

Altered Lipid and Salt Taste Responsivity in Ghrelin and GOAT Null Mice

PLOS | ONE

October 2013

How does bariatric surgery work?



Gastric Bypass

Sleeve Gastrectomy

Altered nutrient and/or biliary flow engenders changes in a multitude of gastro-intestinal signals.

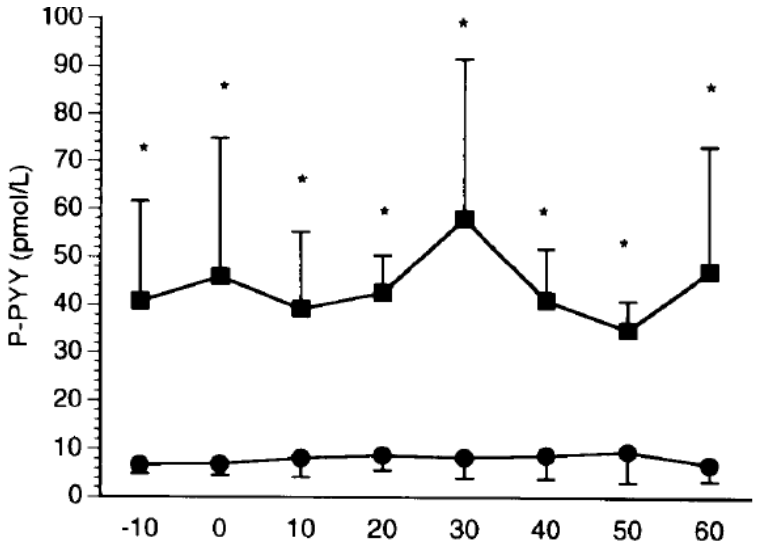
These altered GI signals lead to favourable change in eating behaviour and improvement in glucose homeostasis

Gut hormones proposed as mediators of weight loss post-surgery >25 years ago

Gastrointestinal hormones and gastric emptying 20 years after jejunoileal bypass for massive obesity

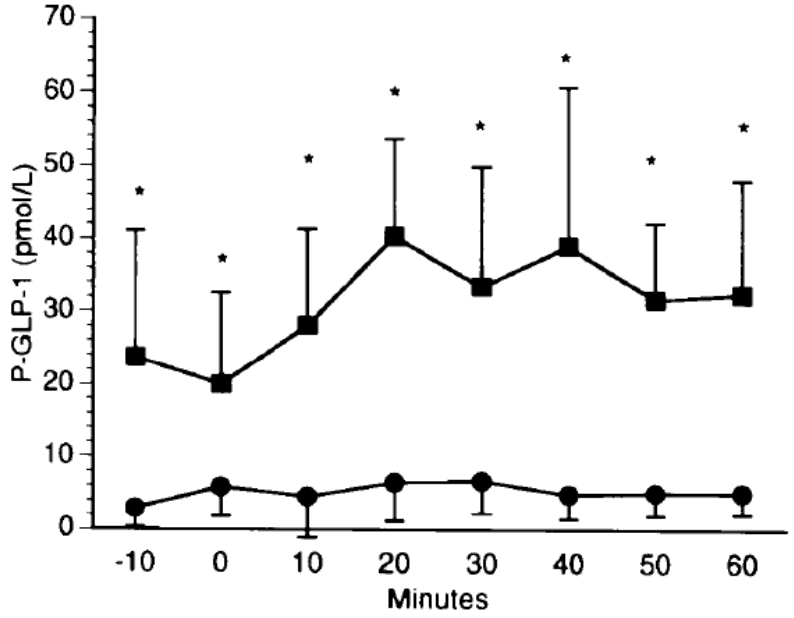
E Näslund[1], P Grybäck[2], PM Hellström[2], H Jacobsson[2,4], JJ Holst[5], E Theodorsson[6] and L Backman[1]

International Journal of Obesity (1997) 21, 387–392

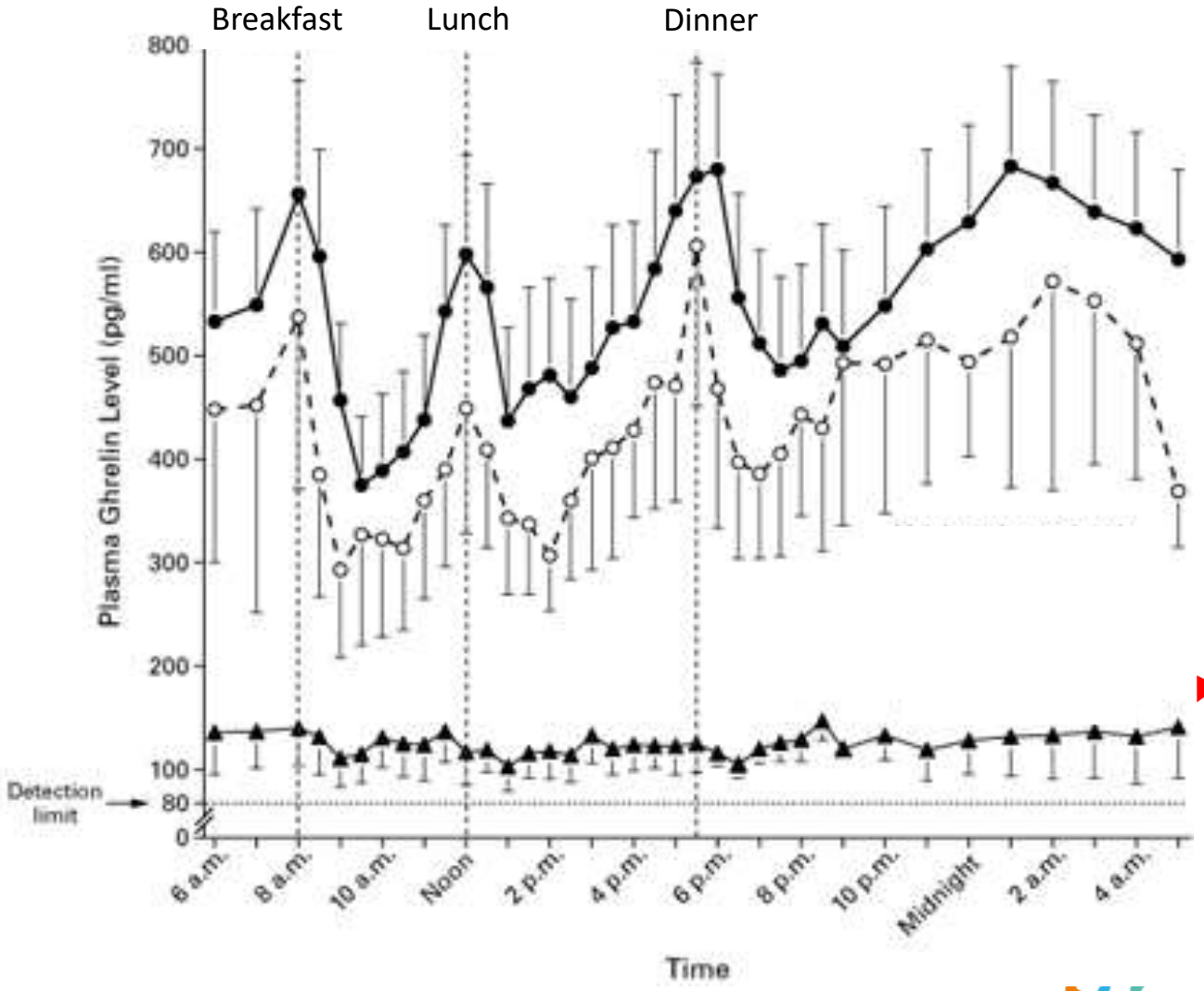


Subjects 20 years after JIB

Control subjects with obesity



Renewed interest : Ghrelin & RYGB



Normal weight controls

Match controls with obesity

Gastric bypass group

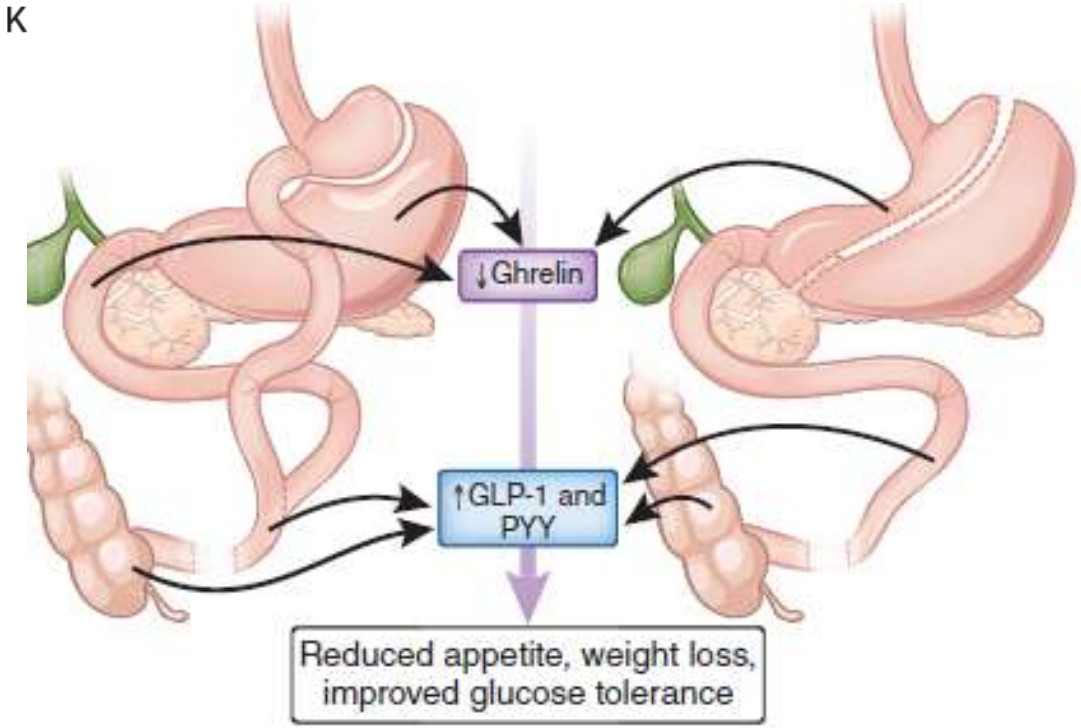
Cummings et al. N Engl. J. Med. May 2002

Reduced blood levels of the hunger hormone ghrelin, increased blood levels of PYY & GLP-1

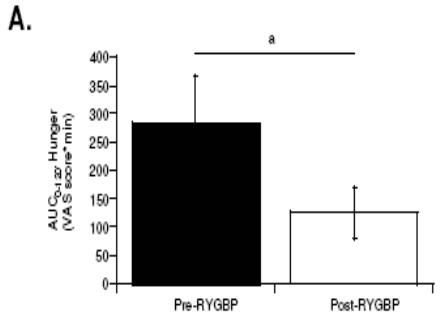
BETWEEN BEDSIDE AND BENCH

■ BENCH TO BEDSIDE

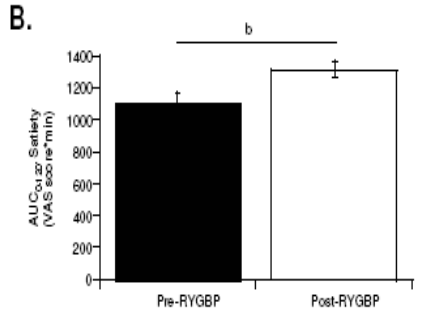
Metabolic insights from cutting the gut



↓ hunger



↑satiety



Nat Med. 2012

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Literature regarding gut hormones controversial

Standardisation is important

- Circulating gut hormone levels are altered by:
  a. Stress
  b. Physical activity
  c. Food consumed the previous day

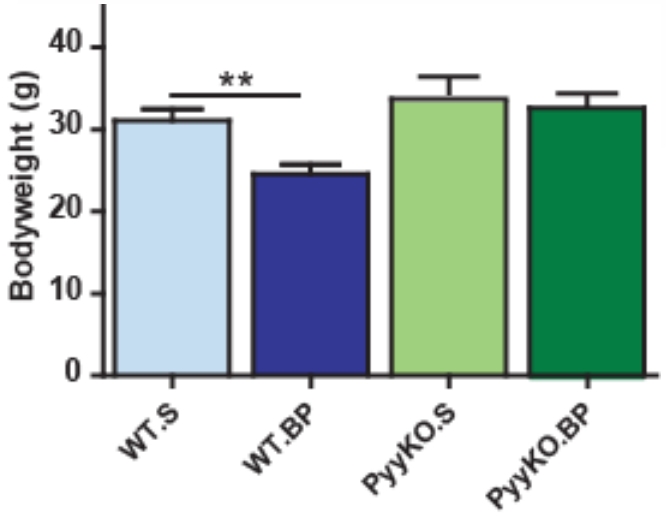
Comparing apples with pears

- Different isoforms e.g. acyl and desacyl ghrelin, active and total GLP-1, total PYY and PYY3-36

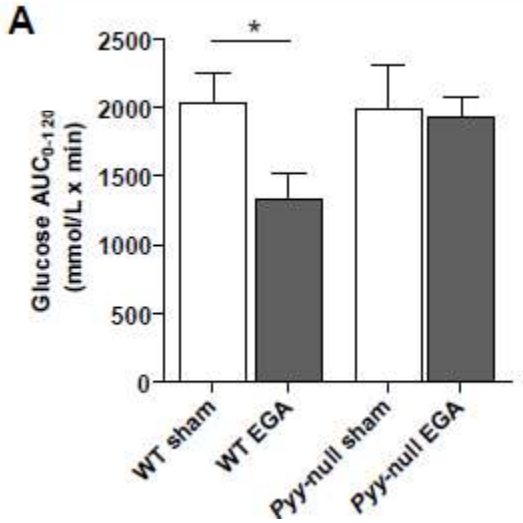
Rapidly degraded in blood/plasma

- Appropriate inhibitors and rapid processing

PYY plays a key role in mediating early weight loss and glycaemic improvement

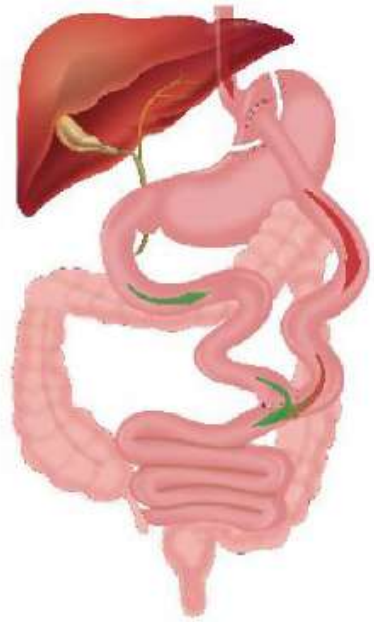


Chandarana *et al.*,
Diabetes 2011



Chandarana K. et al, Mol Metabolism 2013

RYGB and SG differentially affects gut-derived signals



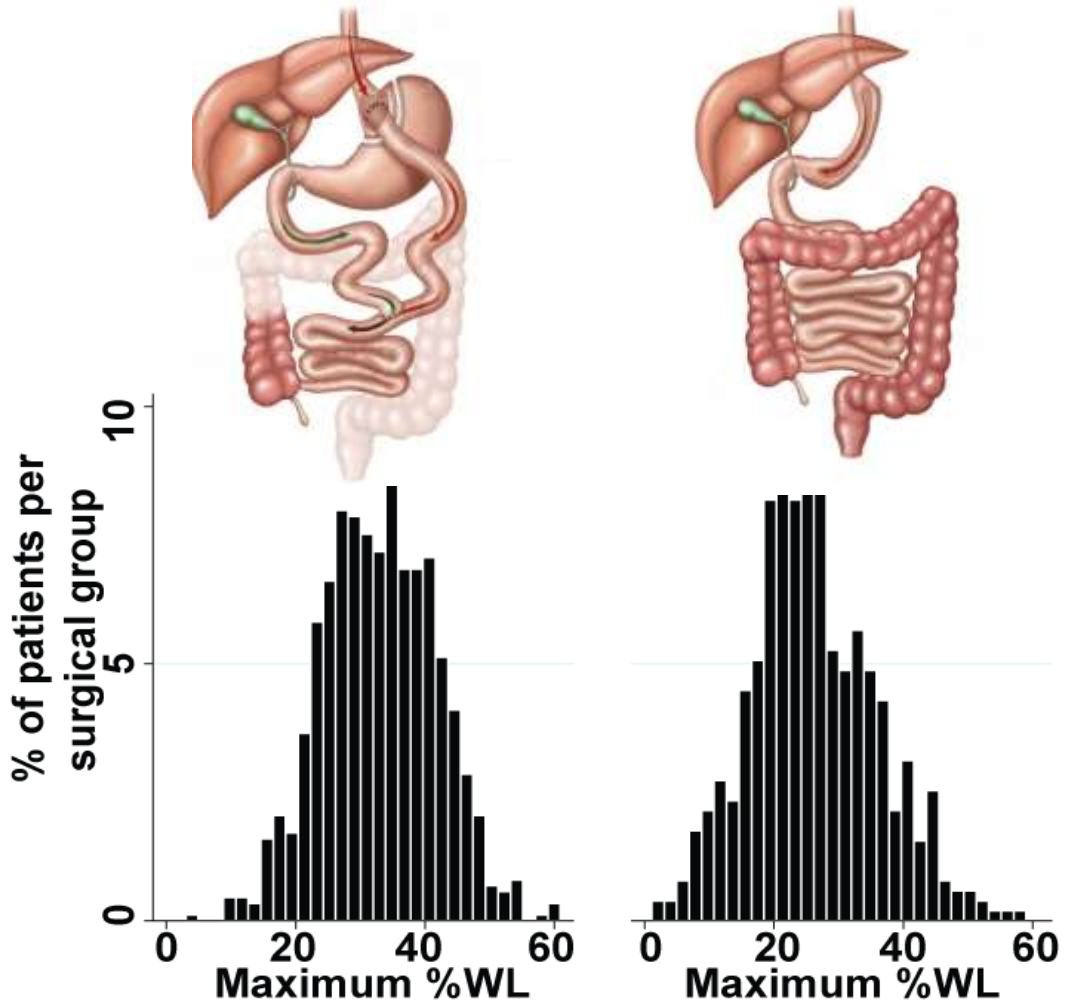
RYGB

RYGB		SG
+	Calorie restriction	+
↑	Vagal nerve signaling	↑
+	Taste and smell changes	+
+	Food aversions	+
↓	Ghrelin	↓↓
↑	Bile acid secretion	↑
↑	Intestinal glucose uptake	
+	Fat malabsorption	
↑↑	GLP-1	↑
↑↑	PYY3-36	↑
↓	GIP	
↑	Oxyntomodulin	
↑↑	FGF-19	↑
↑	CCK	↑
↓	Gastrin	↑
↑	Neurotensin	

SG

A Pucci and RL Batterham
Journal of Endocrinological Investigation
May 2018

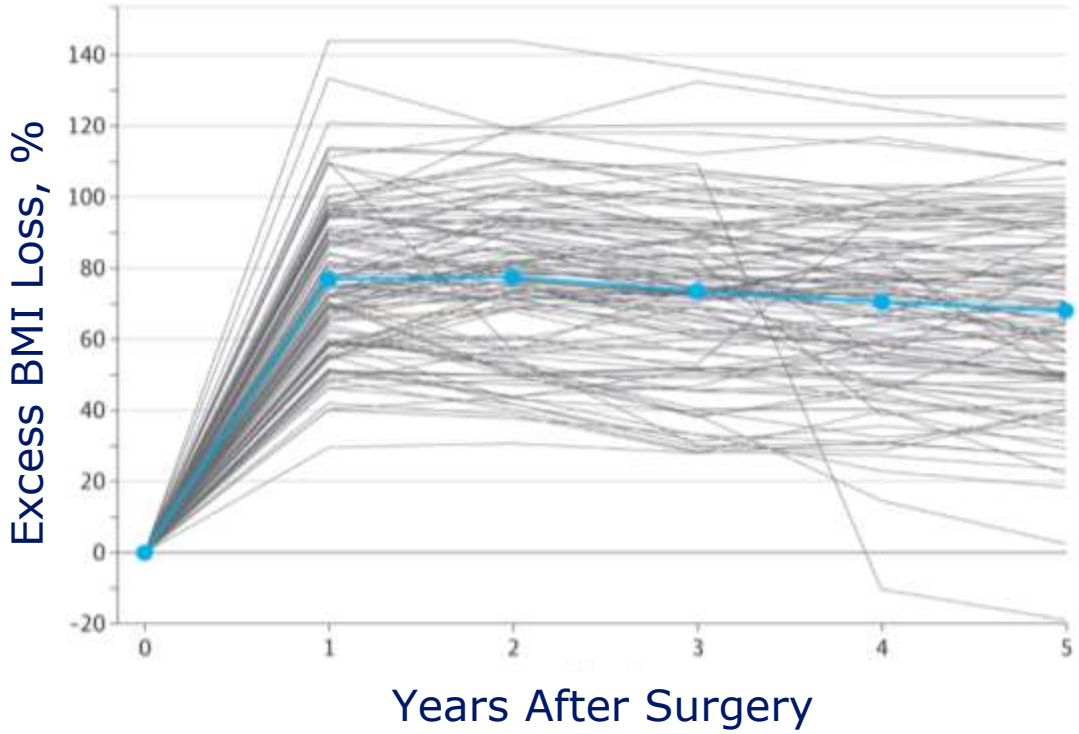
Variation in post-surgery weight loss & metabolic response



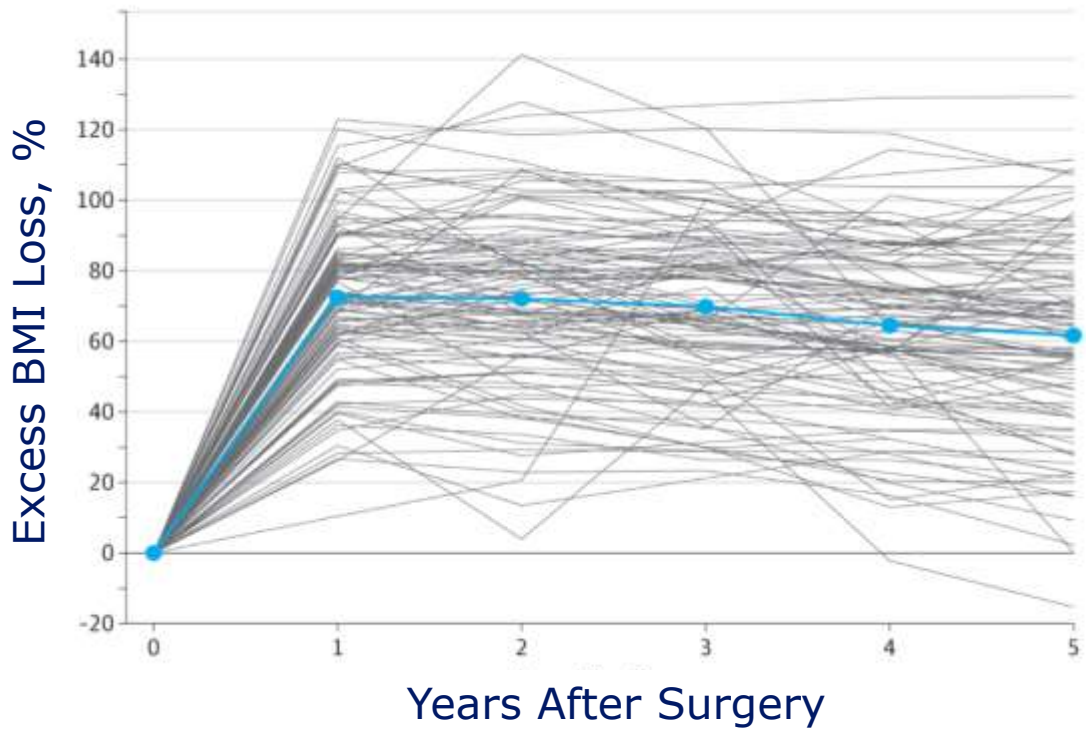
Manning, *et al. Surg Endosc*. 2015;29:1484–91

Variable individual weight loss

RYGB



SG



Greater weight loss linked to prolonged improvement/remission of co-morbidities

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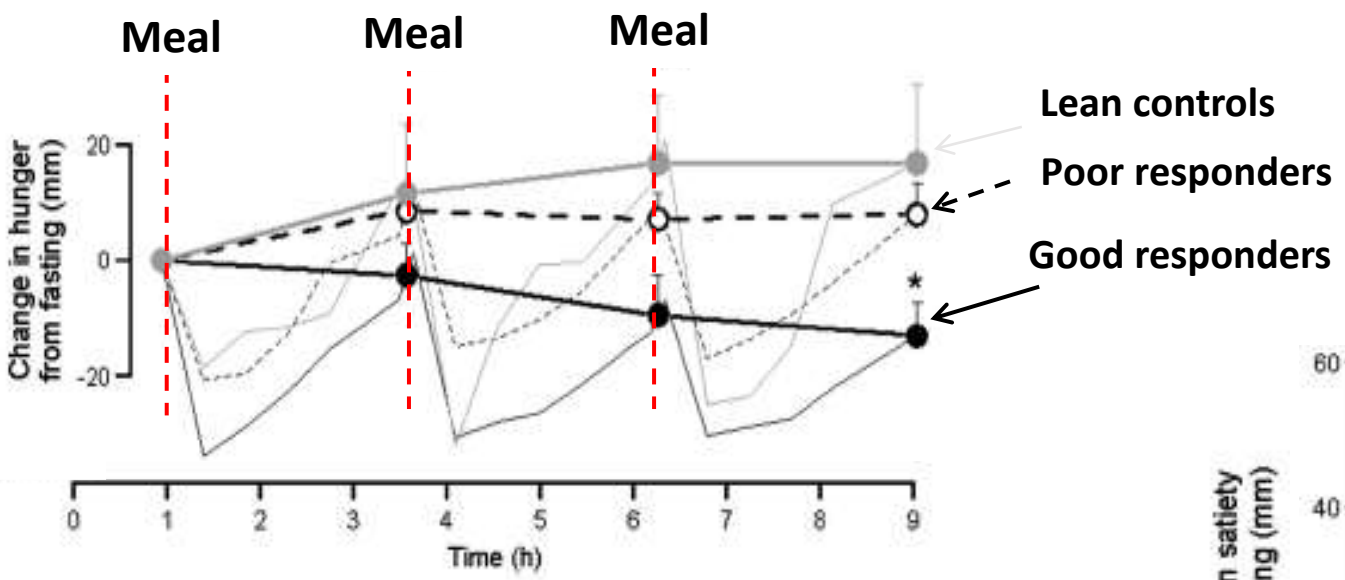
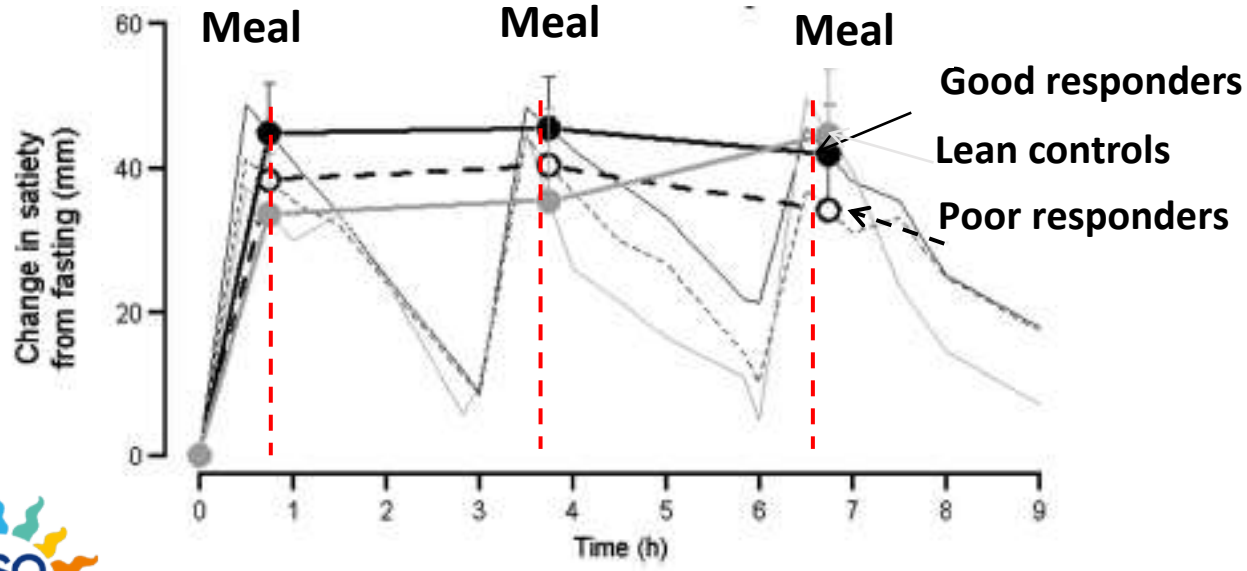
Peterli. *et al JAMA* 2018;319:255-265.

Differential subjective hunger and satiety in good *vs*. poor weight loss responders

Hunger

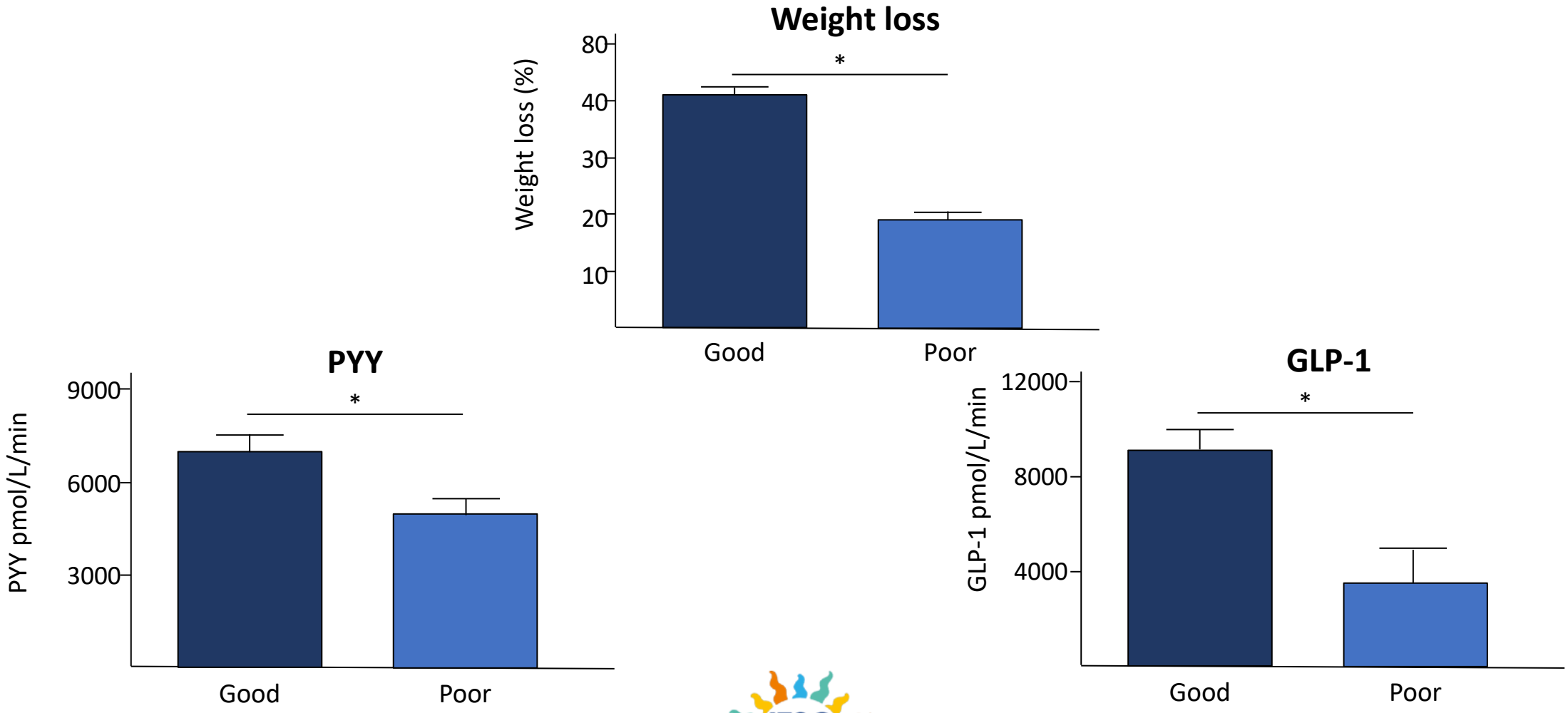


Satiety



Dirksen et al; Int J Obes (Lond) 2013

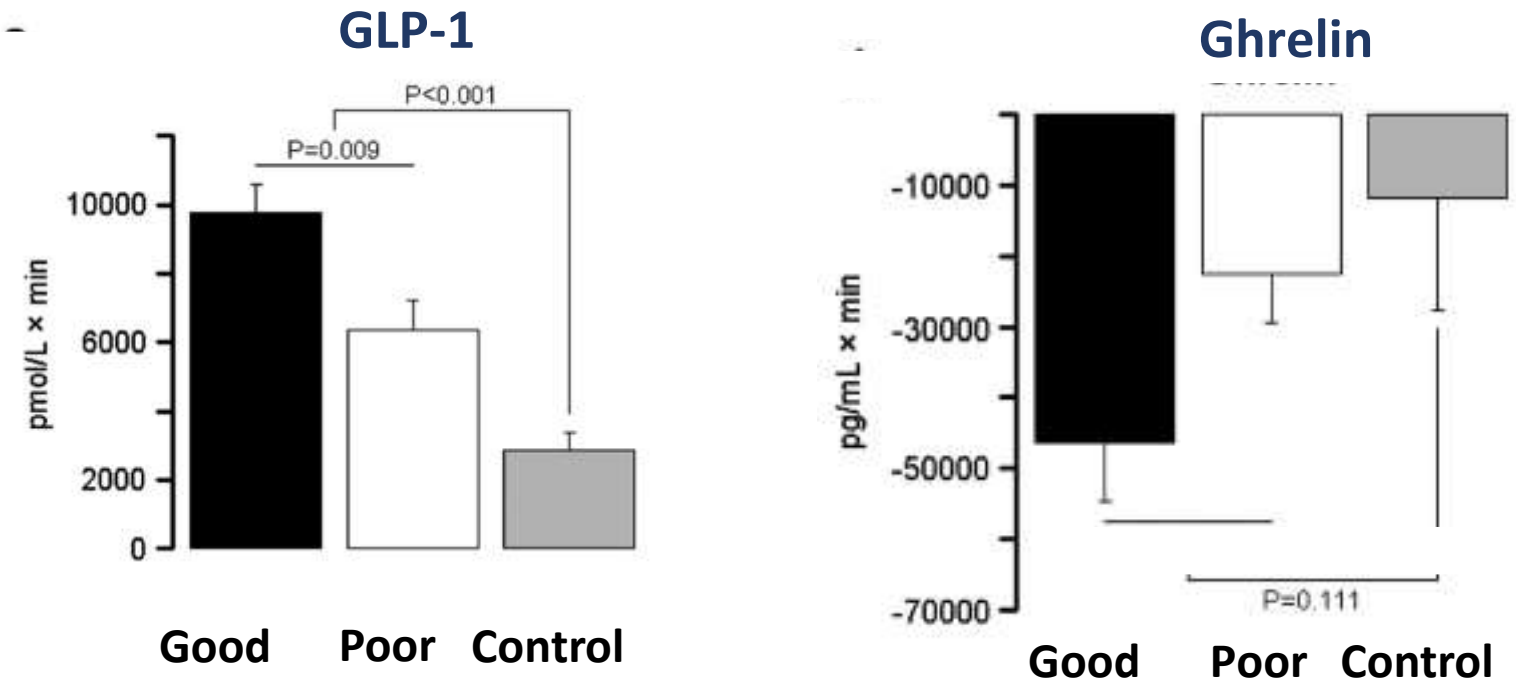
Differential gut hormone response in good *vs*. poor weight loss responders (1)



*P<0.05. GLP-1, glucagon-like peptide 1; PYY, peptide YY

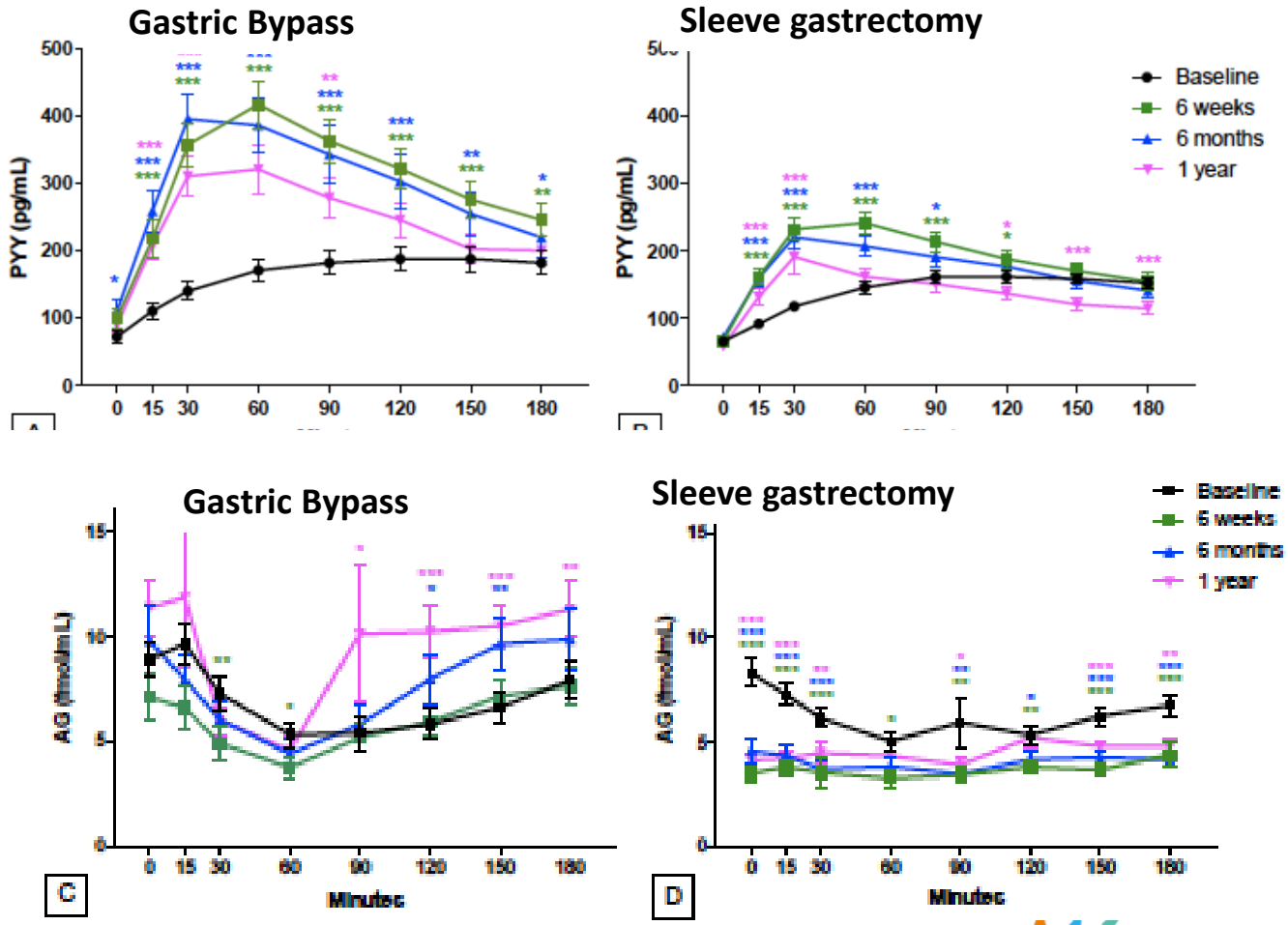
le Roux et al. *Ann Surg* 2007;246:780–5

Differential gut hormone response in good *vs*. poor weight loss responders (2)



Dirksen et al; Int J Obes (Lond) 2013

Do longitudinal changes in gut hormones associate with weight loss?



85 patients (27 GB and 54 SG) longitudinal fasted and meal-stimulated gut hormone assessments Pre-surgery, 6 weeks, 12 weeks, 26 weeks and 52 weeks

No pre-op predictors of 1-year %weight loss

6-week post-surgery PYY associated with %weight loss

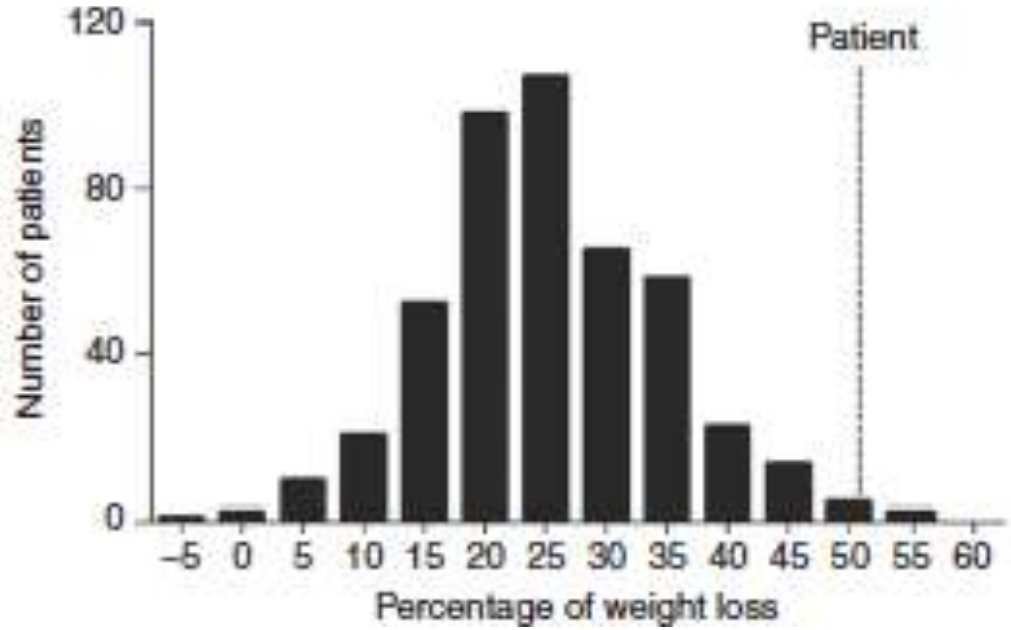
Chaiyasoot K unpublished

“Super” post-SG PYY response associated with severe anorexia and weight loss

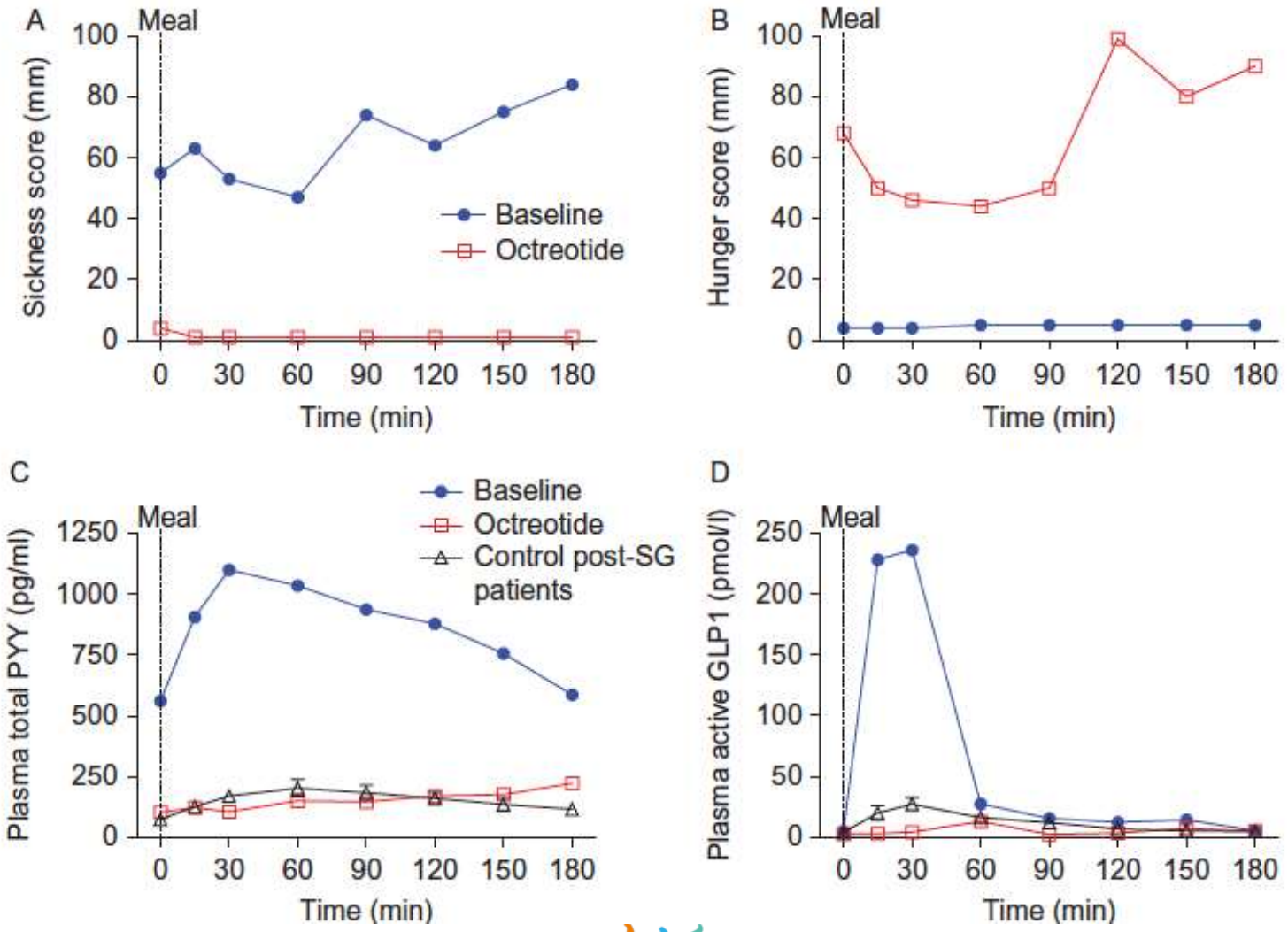
A case of severe anorexia, excessive weight loss and high peptide YY levels after sleeve gastrectomy

Andrea Pucci[1,2], Wui Hang Cheung[1,2], Jenny Jones[1], Sean Manning[1,2,3], Helen Kingett[2], Marco Adamo[2], Mohamed Elkalaawy[2,4], Andrew Jenkinson[2], Nicholas Finer[1,2], Jacqueline Doyle[2], Majid Hashemi[2] and Rachel L Batterham[1,2,3]

Endocrinology, Diabetes & Metabolism CASE REPORTS

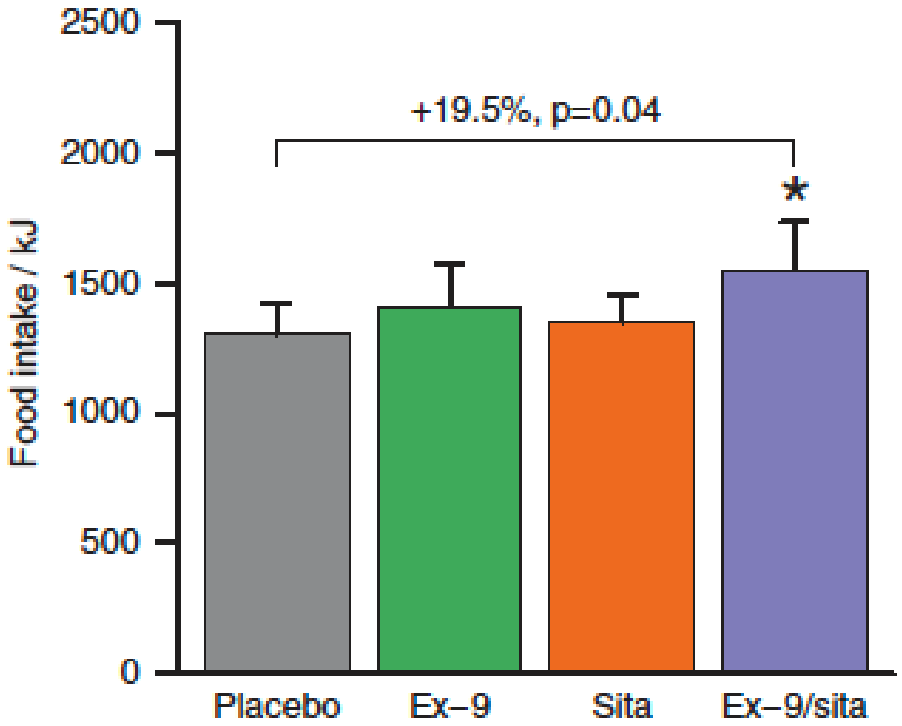


Insights from extremes



A Pucci and others

GLP-1 and PYY contribute to reduced energy intake post-RYGB



- Placebo
- Ex-9 (GLP-1R antagonist)
- Sitagliptin (DPP4 inhibitor)
- Ex-9 + DPP4i

GLP-1 blockage with Ex-9 + reduced PYY3-36 lead to 20% increase in energy intake

Svane et al., International Journal of Obesity 2016

Summary

- RYGB and SG alter eating behavior and this underlies the long-term weight loss
- RYGB and SG engender multiple changes which act in concert to reduce energy intake and improve glucose homeostasis
- Genetics and biology of a person impact upon weight loss
- Multiple mechanisms contribute
- We are still learning!

Acknowledgements

UCL Centre for Obesity Research Team

UCLH Bariatric Centre for Weight Management and Bariatric Surgery Team

The Sir Jules Thorn Charitable Trust

Rosetrees Trust
Supporting the best in medical research

Obesity Empowerment Network UK www.oen.uk

FUNDED BY
NIHR | National Institute for Health and Care Research

Robert Luff Foundation

The STONEYGATE Trust

Thank you for your attention

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