Imperial College London

Ghrelin, PYY, PP & appetite

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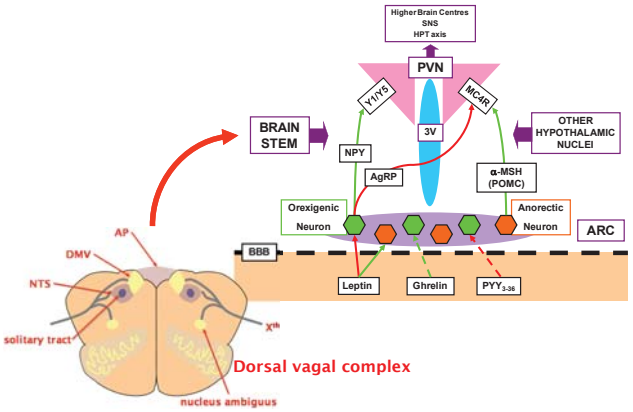
Learning objectives

1. Describe the structure, release pattern and biological actions of the gut hormones PYY, PP and ghrelin
2. Discuss the physiological relevance of the biological actions of these hormones
3. Critically discuss the evidence regarding the targeting of central circuits by these hormones
4. Discuss the potential for therapeutic use of these hormone signalling systems

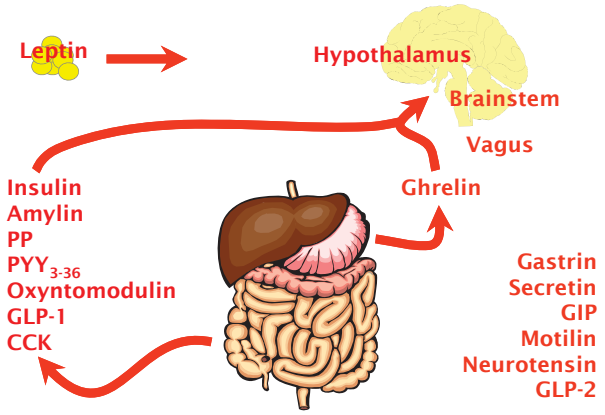
Plan

- Revision – CNS control of appetite
- Gut hormones overview
  - Peptide YY (PYY)
  - Pancreatic Polypeptide (PP)
  - Ghrelin

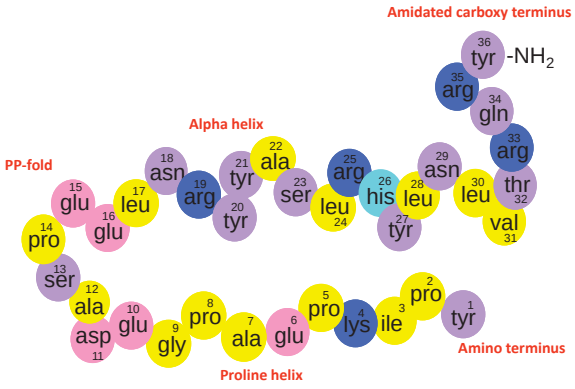
CNS control of appetite



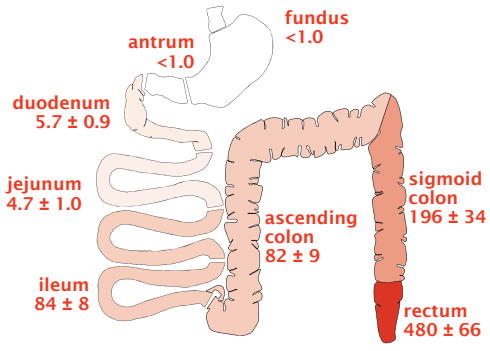
Gut hormones & appetite



Peptide YY



Intestinal distribution of PYY (pmol/g)

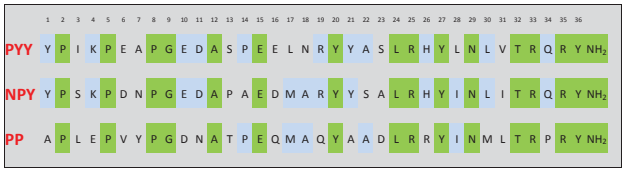


Adrian et al, Gastroenterology 1985; 89:1070-7

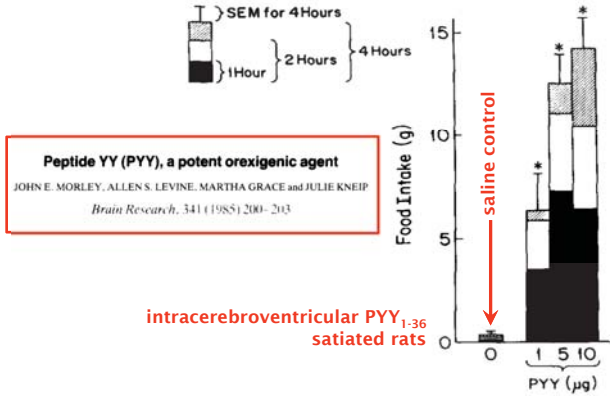
PYY_{1-36} effects

- ↑
- ↓
- ↓
- ↓
-
- ↓
- ↓

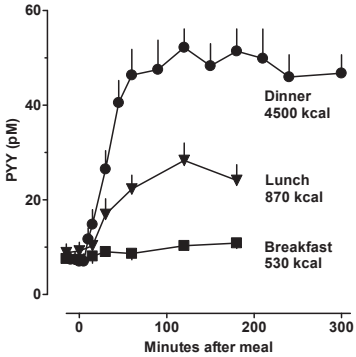
PYY is a member of the PP-fold family



PYY_{1-36} acts like NPY centrally…

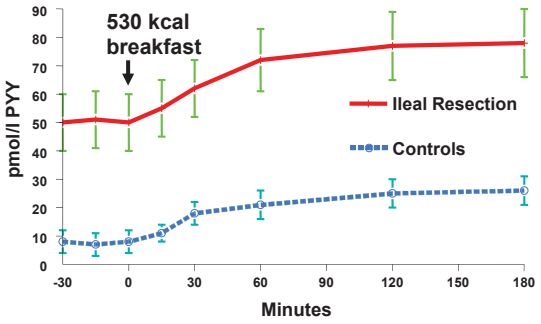


… but PYY is secreted after meals…



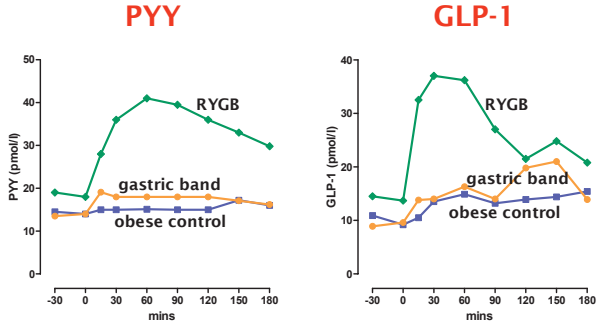
Adrian et al, Gastroenterology 1985; 89:1070-7

… and elevated after ileal resection…



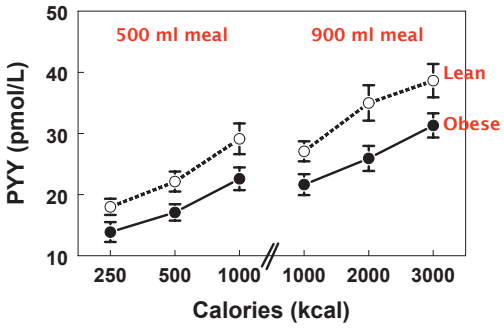
Adrian & Bloom, Surgery 1987; 101:715-719

… and elevated after RYGB…



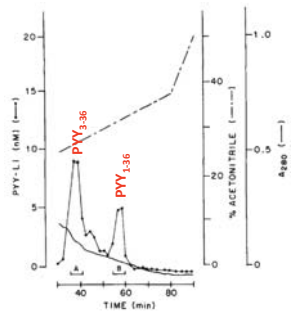
adapted from: le Roux et al, Ann Surg 2006; 243: 108-14

… and is low in obesity…

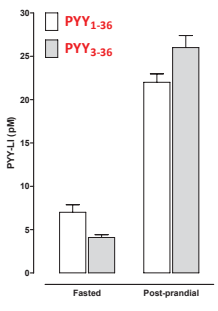


Le Roux et al, Endocrinology 2006; 147:3-8

PYY exists in two forms: 1-36 & 3-36

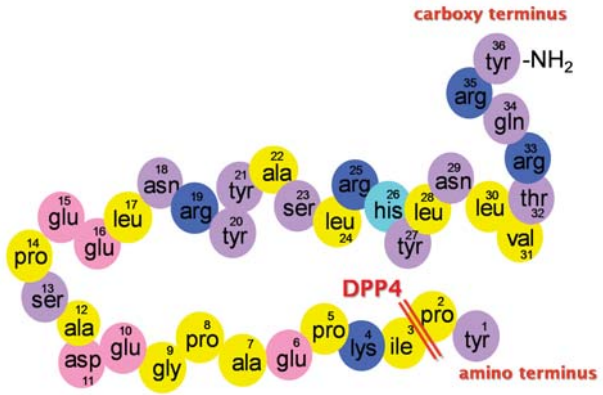


Eberlein et al, Peptides 1989; 10: 797

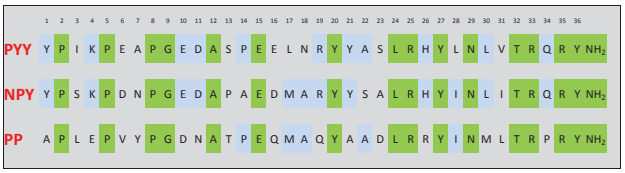


Grandt et al, Regul Pept 1994; 51: 151

PYY length confers receptor selectivity



PYY structure / function



PYY_{1-36}:

PYY_{3-36}:

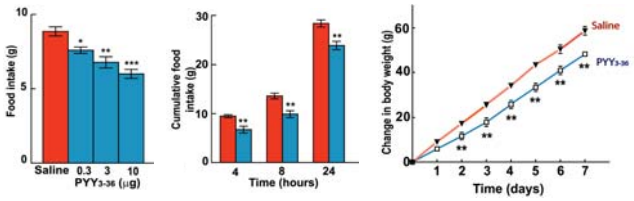
NPY:

PP:

PYY_{3-36} and satiety

intraperitoneal PYY_{3-36} in fasted rats

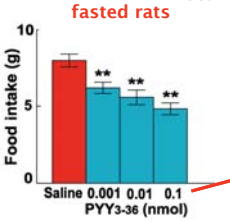
repeated i.p. PYY_{3-36} in rats

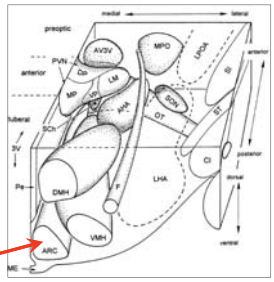


Batterham *et al.* Nature 2002; 418:650-4

PYY_{3-36} sites of action

intra-arcuate PYY_{3-36} fasted rats

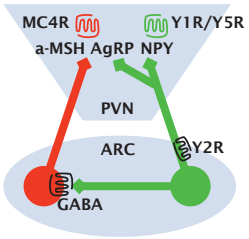




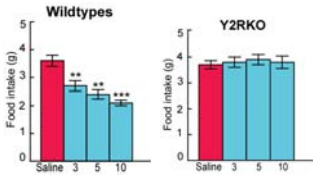
intra-arcuate Y2R antagonist blocks peripheral PYY_{3-36}

Batterham *et al.* Nature 2002; 418:650-4

PYY_{3-36} sites of action

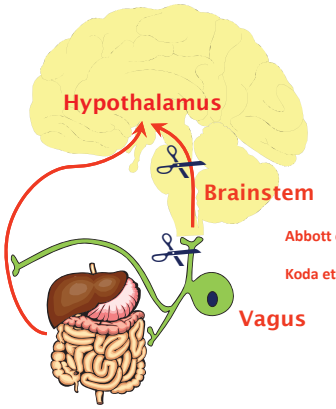


Y2R knockout mice resistant to PYY_{3-36}



Batterham *et al.* Nature 2002; 418:650-4

PYY_{3-36} sites of action

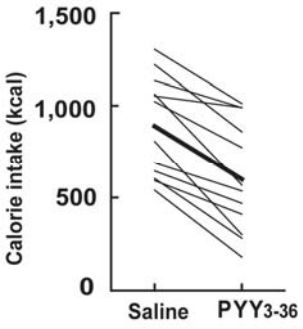


Abbott et al, Brain Research 2005; 1044: 127

Koda et al, Endocrinology 2005; 146: 2369

PYY_{3-36} human infusion

obese volunteers
90 min i.v. infusion
free choice buffet



Batterham et al, N Engl J Med 2003; 349:941-8

PYY + OXM have additive satiety effect

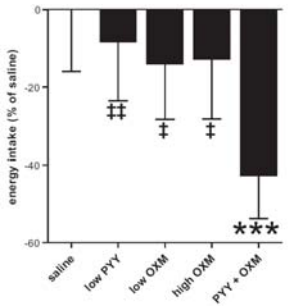
PYY_{3-36} and Oxyntomodulin Can Be Additive in Their Effect on Food Intake in Overweight and Obese Humans

Diabetes 59:1635–1639, 2010

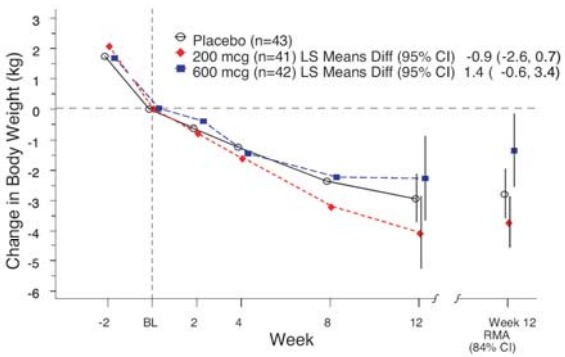
Benjamin C.T. Field,[1] Alison M. Wren,[1,2] Veronique Peters,[1] Kevin C.R. Baynes,[1,3] Niamh M. Martin,[1] Michael Patterson,[1] Sara Alsarraf,[1] Vian Amber,[1] Katie Wynne,[1] Mohammad A. Ghatei,[1] and Stephen R. Bloom[1]

Simultaneous IV infusions in obese human volunteers

PYY_{3-36} 0.25 pmol/kg/min
Oxyntomodulin 1.5 pmol/kg/min



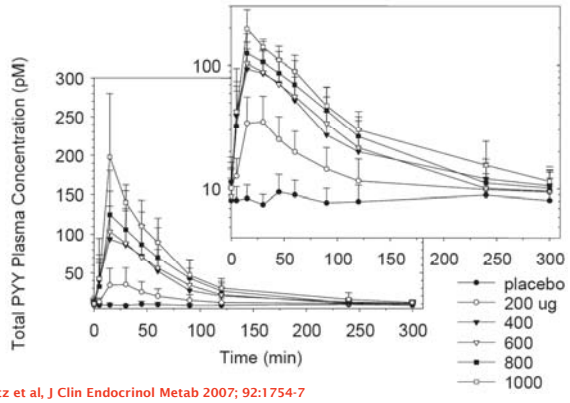
PYY_{3-36} as a drug target?



Gantz et al, J Clin Endocrinol Metab 2007; 92:1754-7

Is nausea the opposite of hunger?

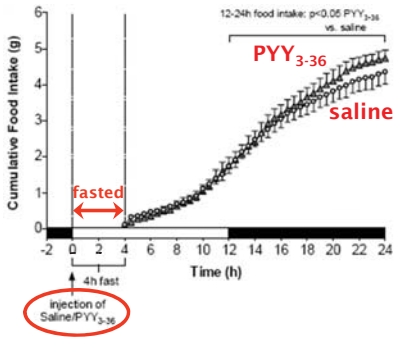
PYY_{3-36} as a drug target?



Gantz et al, J Clin Endocrinol Metab 2007; 92:1754-7

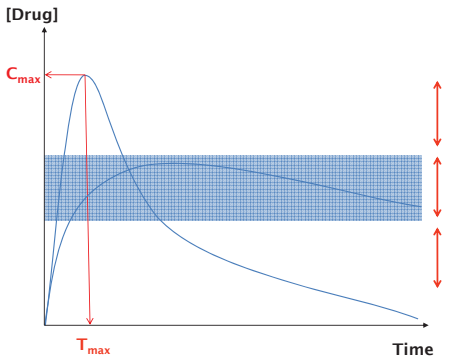
PYY_{3-36} delayed orexigenic effect

previously *ad libitum* fed C57BL/6 mice



Parkinson *et al*, Am J Physiol Endocrinol Metab 2008; 294:E698-708

PYY_{3-36} as a drug target?



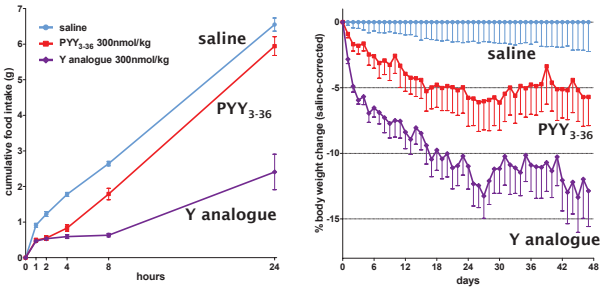
Long-acting analogue of PYY_{3-36}

acute food intake

fasted lean C57BL/6 mice
n = 8 per group

chronic weight loss

diet-induced obese C57BL/6 mice
n = 8 – 11 per group

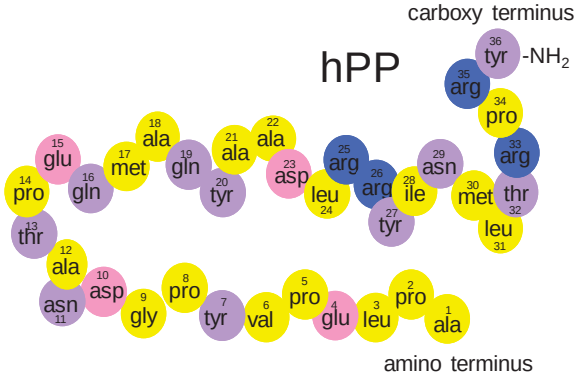


unpublished data

PYY_{3-36} summary

- Reduces appetite
- Rapidly cleared from circulation
- Rapid peak causes nausea & vomiting
- Appetite overswing occurs

Pancreatic polypeptide



Released from PP islet cells after meals

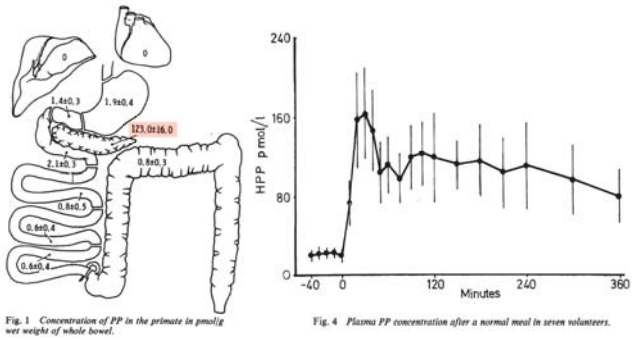
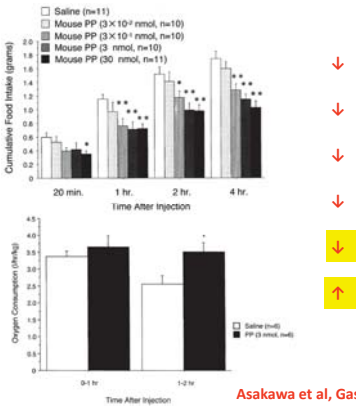


Fig. 1 Concentration of PP in the primate in pmol/g wet weight of whole bowel.

Fig. 4 Plasma PP concentration after a normal meal in seven volunteers.

Adrian et al, Gut 1976; 17:940-4

PP actions



↓
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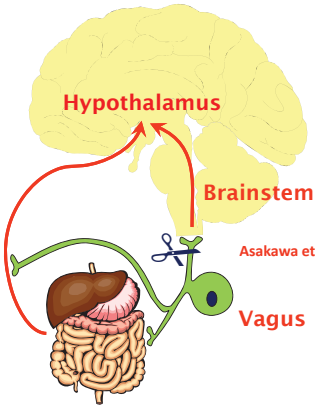
↑

Asakawa et al, Gastroenterology 2003; 124: 1325

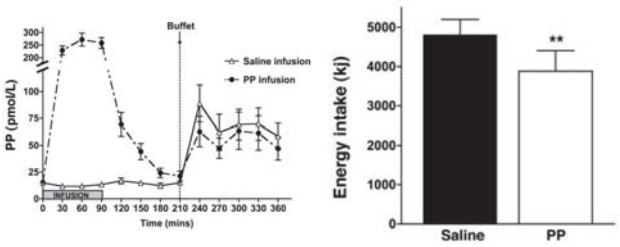
PP sites of action



Asakawa et al, Gastroenterology 2003; 124: 1325

PP and human energy intake

PP IV infusion 10 pmol/kg/min for 90 mins
to lean human volunteers



Batterham et al, J Clin Endocrinol Metab 2003; 88:3989-92

PP as a drug target?

7TM / Prosidion / Imperial

Ghrelin

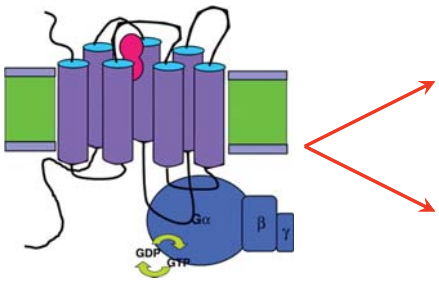
28aa gastric hormone

Ghrelin O-acyltransferase
'GOAT'

Yang *et al.* Cell 2008
Gutierrez *et al.* Proc. Natl. Acad. Sci 2008

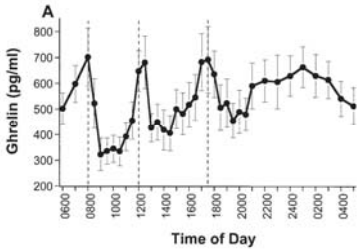
Human ghrelin

Ghrelin: agonist at the GHS-R1a



Ghrelin: agonist at the GHS-R1a

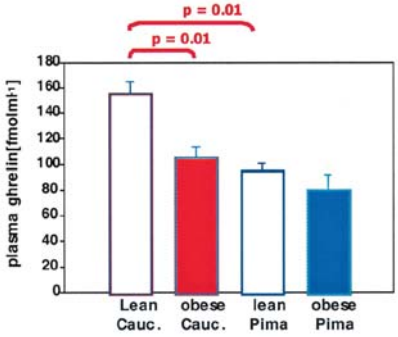
plasma level highest pre-meal



meal cue
GH secretagogue
↑ after weight loss

Cummings et al, Diabetes 2001; 50:1714-9

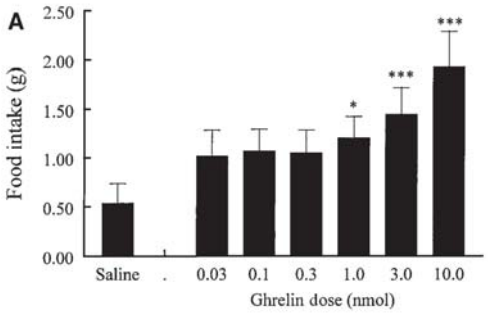
Fasting plasma ghrelin concentration



Tschöp et al, Diabetes 2001 50:707-9

Ghrelin: site of orexigenic action

intraperitoneal injection in fasted rats



Wren et al, Diabetes 2001; 50:2540-7

Ghrelin: site of orexigenic action

intra-nuclear cannulated rats

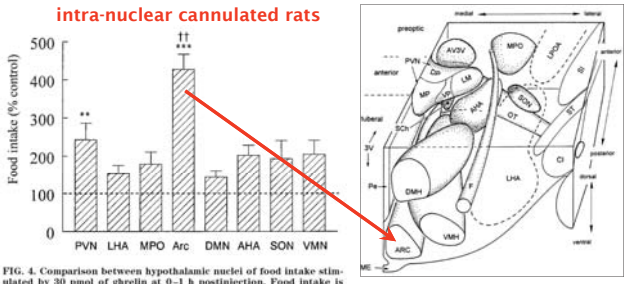
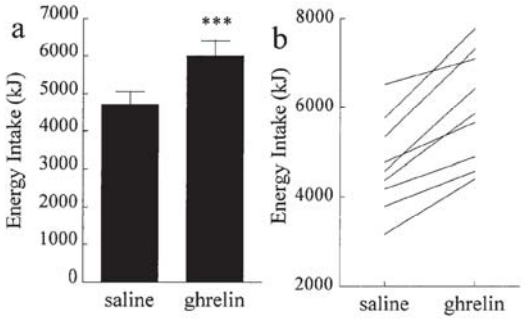


FIG. 4. Comparison between hypothalamic nuclei of food intake stimulated by 30 pmol of ghrelin at 0–1 h postinjection. Food intake is expressed as a percentage of control. Control food intake is indicated by dotted line. $^{\dagger\dagger}P < 0.01$ versus PVN, $P < 0.001$ versus all other nuclei; $^{***}P < 0.001$ versus saline, $^{**}P < 0.01$ versus saline.

Wren et al, Diabetes 2001; 50:2540-7

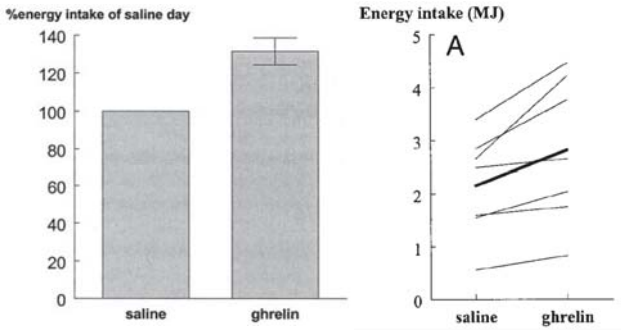
Ghrelin and human appetite

Ghrelin IV infusion 5.0 pmol/kg/min



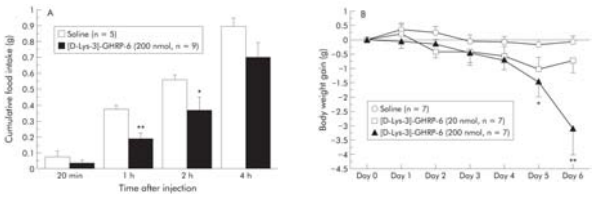
Wren et al, J Clin Endocrinol Metab 2001 86:5992-5

Energy intake after ghrelin infusion in cancer patients with cachexia



Neary et al, J Clin Endocrinol Metab 2004 89:2832-6

Effect of GHS-R1a peptide antagonist



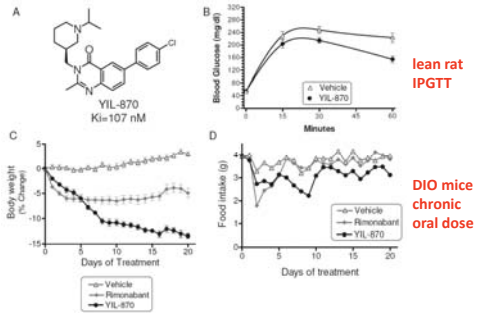
Fasted *ob/ob* mice, acute IP injection

Repeated IP injection, *ob/ob* mice

Asakawa et al, Gut 2003; 52: 947

GHS-R1a orally available antagonist

Bayer Research Center small molecule



lean rat IPGTT

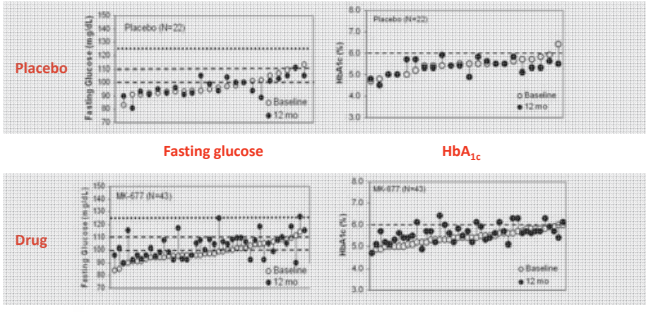
DIO mice chronic oral dose 10 mg/kg

DIO mice chronic oral dose

Esler et al, Endocrinology 2007 148:5175-85

Ghrelin: the elixir of eternal youth?

Oral ghrelin mimetic phase 2 study



Fasting glucose

HbA_{1c}

Nass et al, Ann Intern Med 2008 149:601-11

Ghrelin summary

- GHS-R1a antagonists synthesised
- Cause weight loss
- Off-target effects on GH axis
- Future unclear

Summary

1. Describe the structure, release pattern and biological actions of the gut hormones PYY, PP and ghrelin
2. Discuss the physiological relevance of the biological actions of these hormones
3. Critically discuss the evidence regarding the targeting of central circuits by these hormones
4. Discuss the potential for therapeutic use of these hormone signalling systems