Appetite regulation
the role of peptides and neurotransmitters in obesity

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Conflict of interest

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Our prehistorical progenitors clearly did not have the opportunity to suffer from obesity.

Thrifty genes theory – genes predisposing to effective energy storage enabled to survive during times of starvation, however they predispose to obesity nowadays.
The Foresight Obesity Project: Obesity System Map

>300 solid or dashed lines to indicate positive and negative influences
Obesity systems map – core engine
Complex systems approach to understanding obesity
The relationship between fat mass (FM), fat-free mass (FFM) and BMI and objectively measured total daily energy intake at baseline (week 0, before exercise) and after 12 weeks of imposed exercise. (a–c) Week 0 and (d–f) week 12.
FFM and not FM influenced within day profile of hunger and fullness sensations
Body composition and Energy Balance

- Fat Mass and Fat-Free Mass contribute to Resting Metabolic Rate
Resting metabolic rate is associated with huger, self determined meal size and daily energy intake and may represent a marker for appetite

Interpretation: Resting Metabolic rate is a driver of Meal Size and daily Energy Intake

Caudwell et al AJCN 2013
DRIVE AND INHIBITION IN APPETITE CONTROL

Drive from FFM and RMR

Adipose tissue

Signals from GI tract

Eating pattern
Meaning and frequency

Energy intake

How does physical activity influence this system?

Modified by Blundell after Badman and Flier, Science 2005
Multiple endocrine signals influence food intake

These signals are processed by the brain and translated into feelings of satiety or hunger.

Hormonal signals:
- Leptin
- Adiponectin
- Resistin
- GLP-1
- OXM
- PYY
- CCK
- Ghrelin
- Amylin
- Insulin
- PP

Organs:
- Adipose tissue
- Gut
- Pancreas

CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide-YY

Components of appetite

**Hunger**
Drive to consume

**Wanting**
Motivation to consume a specific food (craving)

**Satiety**
End state of satisfaction (between-meal inhibition)

**Fullness**
Physical feeling experienced in the gut

**Satiation**
Negative feedback, leading to meal termination (within-meal inhibition)

**Liking (hedonic)**
Sensory pleasure elicited by contact with food

**Prospective food consumption**
How much an individual feels they would like to eat

Homeostatic vs. hedonic appetite regulation
Two systems simultaneously influence appetite

**Homeostatic regulation**
- Biological systems act to maintain body weight by:
  - Regulation via peptide hormones that can induce hunger/satiety
  - Changes in EE:
    - EE decreases (resting + total EE) → Weight loss
    - EE increases (metabolic + energy cost of activity) → Weight gain

**EE feedback loop**

**Hedonic regulation**
- Reward of survival behaviours (e.g. sex or eating) through pleasure
  - Operates even in the presence of satiety signals
  - Can lead to food consumption beyond homeostatic need
  - Link between hedonic attraction to high calorie foods and obesity

EE, energy expenditure; WG, weight gain; WL, weight loss

Hall et al. Am J Public Health 2014;104:1169–75
Central regulation of appetite

Hypothalamic regulation
- The hypothalamus integrates signals from several different systems
- Multiple hypothalamic nuclei are involved such as the ARC and PVN
- Two main opposing neuronal types:
  - AgRP/NPY neurons (hunger)
  - CART/POMC neurons (satiety)

Hedonic control systems
- Appetite is influenced by homeostatic (metabolic) and hedonic (pleasure, emotional) factors
- Hedonic appetite systems comprise external sensory information processing, reward processing, and cognition and executive functions
- Multiple different areas are involved including the amygdala and the cortex

Gut hormone system
- The gut and adipose tissue produces several hormones that promote satiety (e.g. GLP-1, CCK) or hunger (i.e. ghrelin)
- These may influence central appetite control centres either directly or relayed indirectly via vagal afferents and the brainstem

ARC, arcuate nucleus; AgRP, agouti-related peptide; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; DMN, dorsomedial hypothalamic nucleus; GLP-1, glucagon-like peptide-1; NPY, neuropeptide Y; OXM, oxyntomodulin; LHA, lateral hypothalamic area; PP, pancreatic polypeptide; PYY, peptide-YY; POMC, pro-opiomelanocortin; PVN, paraventricular hypothalamic nucleus; NTS, nucleus tractus solitarius; VMN, ventromedial hypothalamic nucleus

Hypothalamic regulation of appetite
Peripheral signals modulate appetite and energy expenditure via hypothalamic neurons

Effectors

Hypothalamus

Second order neurons

Arcuate nucleus

Satiety

MC3/4R
αMSH

AgRP

Hunger

Y1/Y5R

Apex of the pro-opiomelanocortin neurons (POMC/CART)

Leptin
Insulin

Adiposity signals

PYY
PP

GLP-1
OXM

Satiety peptides

Ghrelin

Hunger signals

Hindbrain

Nucleus tractus solitarius

Feeding
Gastric emptying
Metabolic rate

Vagal afferents


α-MSH, α-melanocyte stimulating hormone; AgRP, Agouti-related protein; CART, cocaine and amphetamine regulated transcript; GLP-1, glucagon-like peptide-1; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY
Science of regulation: Traditional fundamental drivers

- Glucostatic - Mayer (1954)
- Thermostatic - Brobeck (1954)
- Aminostatic - Mellinkoff (1956)
- Lipostatic - Kennedy (1953)
1994 – adipose tissue can produce hormones – discovery of leptin

Mutation of *ob* gene encoding protein hormone *leptin* produced by adipocytes results in morbid obesity in mice

Leptin treatment of leptin-deficient *ob/ob* mice normalized their body weight and recovered their fertility

The size and endocrine profile of adipocytes reflects obesity or leanness
The number of adipocytes remains widely stable during the life

Malnutrition
(Anorexia nervosa)

Normal
(slightly overweight)

Obese
Gut Peptides

- Ghrelin
- Peptide YY (PYY)
- Cholecystokinin (CCK)
- Pancreatic polypeptide (PP)
- Amylin
- Glucose-dependent insulinotropic polypeptide (GIP)
- Glucagon-like peptide-1 (GLP-1)
- Oxyntomodulin
Ghrelin

- A peptide hormone released into circulation from the stomach
- First discovered as an endogenous ligand for the growth-hormone-secretagogue receptor (GHS-R).
- Composed of 28 amino acids
- Acylation is necessary for ghrelin to bind to the GHS-R and to cross the blood–brain barrier.
- The only known factor to increase appetite through the circulation.
Stimulation of feeding by ghrelin

![Bar chart showing the effect of ghrelin and GHRP-6 on two-hour food intake.](chart.png)
Interactions of ghrelin with NPY
Ghrelin serves as a physiological meal initiator in human

Cummings et al. 2001

wide range of circulating ghrelin values between two individuals and the heterogeneity of the surge before breakfast

Ghrelin levels are increasing during the day before each meal

Cummings et al. 2001
Food fails to suppress ghrelin in obese

Postprandial ghrelin response in obese is (in contrast to healthy subjects) independent of caloric content and macronutrient composition of a meal.

Contribute to resistance to weight loss in some of obese patients?

Figure 1. Mean (± SEM) ln(ghrelin) response in lean and obese subjects following a test meal. There is a significant fall in ln(ghrelin) at 30 minutes following the meal in lean subjects (p=0.003, ANOVA for multiple comparisons with baseline), but no fall in obese subjects.

English et al. 2002
What is GLP-1?

- GLP-1 is a peptide comprised of 31 amino acids
- Member of incretin family
- Secreted predominantly from L-cells in the gut, but also the brain (nucleus tractus solitarius)

Enzymatic degradation by DPP-4

$t_{1/2} = 1.5–2$ min

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{1/2}$, half-life

GLP-1 is released in response to food intake

adapted from: Orskov et al. Scand J Gastroenterol 1996;31:665–70
GLP-1 secretion and receptor expression

GLP-1 is secreted by:
- Neurons in hindbrain
- L-cells of the gut

GLP-1R is expressed in:
- Brain
- Lung
- Heart
- Pancreas
- Kidney
- Gastrointestinal tract

GLP-1R, glucagon-like peptide-1 receptor

GLP-1 increases satiety and reduces hunger
In normal weight subjects

- Infusion increased plasma GLP-1 from 10 pmol/L to 60–90 pmol/L

Data are mean ± SEM. GLP-1, glucagon-like peptide-1; SEM, standard error of mean

GLP-1 reduces energy intake in humans

- Flint et al. 1998 (n=19)
- Näslund et al. 1998 (n=6)
- Näslund et al. 1999 (n=8)
- Long et al. 1999 (n=10)
- Gutzwiller et al. 1999a (n=16); 0.38 pmol/L
- Gutzwiller et al. 1999a (n=16); 0.75 pmol/L
- Gutzwiller et al. 1999a (n=16); 1.50 pmol/L
- Gutzwiller et al. 1999b (n=12)
- Flint et al. 2001 (n=17)
- Beglinger et al. (unpublished b) (n=12)
- Beglinger et al. (unpublished a) (n=15)

Data are mean and 95% CI. CI, confidence interval; GLP-1, glucagon-like peptide-1

Adapted from: Verdich et al. J Clin Endocrinol Metab 2001;86:4382–9
Liraglutide is a once-daily, human GLP-1 analogue

Human endogenous GLP-1

T½ = ~2 mins

Liraglutide

97% amino acid homology to human GLP-1; improved PK: albumin binding through acylation; heptamer formation

Slow absorption from subcutis
Resistant to DPP-4
Long plasma half-life (T½ = 13 h)

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PK, pharmacokinetics; T½, plasma half-life

- GLP-1R is necessary for liraglutide uptake in the brain

- Liraglutide binds neurons within the arcuate nucleus (ARC)

- Liraglutide-dependent body weight reduction in rats is independent of GLP-1Rs in the vagus nerve, area postrema, and paraventricular nucleus
Liraglutide\textsuperscript{594} was localised in CART/POMC neurons in rat brain

Liraglutide\textsuperscript{594}, Alexa Fluor\textsuperscript{594} C5-maleimide-liraglutide; CART, cocaine- and amphetamine-regulated transcript; POMC, pro-opiomelanocortin

GLP-1 activates areas of brain involved in appetite regulation

- The postprandial GLP-1 response is associated with activation of areas of the human implicated in regulation of appetite and food intake.

- Peak postprandial increases in plasma GLP-1 concentrations are correlated with increases in regional cerebral blood flow in the left dorsolateral prefrontal cortex and the hypothalamus.

GLP-1, glucagon-like peptide-1; PET, positron emission tomography

Liraglutide$^{750}$ was detectable in the mouse brain following peripheral administration.

Peripheral (sc) injection of 120 nmol/kg $^{18}$F-liraglutide in mice for 4 days

Liraglutide$^{750}$

Liraglutide\textsuperscript{750} was detectable in the mouse hypothalamus.

Peripherally administered GLP-1R agonists reduce food intake and body weight through signaling mechanisms requiring functional GLP-1Rs in the ARC of the hypothalamus

GLP-1 directly activates POMC/CART neurons and indirectly inhibits, via GABAergic transmission, the neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, which collectively results in signals that reduce food intake. Although GLP-1 generates signals that are transmitted through the vagus nerve or converge on the NTS or PVN of the hypothalamus (Hyp), these regions are not required to transduce an anorectic GLP-1R-dependent signal.

Proposed regulation of neuronal activation by liraglutide

- GLP-1 stimulates POMC neurons directly through the GLP-1R
- GLP-1 indirectly inhibit ARC-NPY neurons through an local inhibitory GABA neuron

Liraglutide increases satiety and reduces hunger
Via neurons in the arcuate nucleus

Liraglutide

Satiety

Hunger

Arcuate nucleus

POMC/CART

NPY/AgRP

AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin
Central GLP-1Rs mediate the body weight lowering effect of liraglutide

- Central GLP-1Rs
  - Not required for glucose-lowering effect of liraglutide
  - Glucose lowering is mediated by pancreatic β-cells

*P<0.05 compared with saline treatment, same genotype unless otherwise indicated
GLP-1Rs, glucagon-like peptide-1 receptors

Adapted from: Baggio, Drucker J Clin Invest 2014;124:4223–6
Female Sprague-Dawley rats made obese through supplementary candy feeding could select candy (5 different kinds) or chow.

**Liraglutide affects food preference in rats**

**Food choices switch away from candy**

**Total 12-week consumption**
- Liraglutide: ~4,500 Kcal
- Control: ~5,100 Kcal

**Compared with control, liraglutide was associated with**
- Significant reductions in total calorie intake and candy consumption
- A relative increase in chow consumption

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**Candy**

<table>
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<tr>
<th></th>
<th>Liraglutide</th>
<th>Control</th>
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<tbody>
<tr>
<td><strong>Mean consumption over 12 weeks (kcal)</strong></td>
<td>2100</td>
<td>3700</td>
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- *p<0.001*

**Chow**

<table>
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<th>Liraglutide</th>
<th>Control</th>
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<tbody>
<tr>
<td><strong>Mean consumption over 12 weeks (kcal)</strong></td>
<td>1400</td>
<td>1000</td>
</tr>
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- *p<0.01*

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Female Sprague-Dawley rats made obese through supplementary candy feeding could select candy (5 different kinds) or chow.

Adapted from Raun K, et al *Diabetes* 2007;56:8–15
Liraglutide 3.0 mg influences all dimensions of appetite

Appetite ratings were assessed by visual analog scale. Data are presented as mean ± standard error. PFC, prospective food consumption

Liraglutide 3.0 mg influences all dimensions of appetite

5 weeks treatment including 0.6 mg weekly dose escalation. Ratings are AUC_{15-300 min/285 min} reported as FAS LS-means. *Statistical significance $p \leq 0.01$ vs. placebo. Data for overall includes 100 minus scores for hunger and PFC. AUC, area-under-the-curve; FAS, full analysis set; LS, least squares; PFC, prospective food consumption

Liraglutide 3.0 mg reduces energy intake but does not increase energy expenditure

Data are estimated means. In the post hoc analysis for total energy expenditure, body weight after 5 weeks of treatment was added to the original linear mixed-effect model.

5-hour gastric emptying with liraglutide 3.0 mg is comparable to placebo

Data are estimated means after 5 weeks of treatment. Full analysis set. AUC, area-under-the-curve

Liraglutide reduces brain activity related to highly desirable food cues

- Liraglutide 1.8 mg decreased activation of the:
  - parietal cortex in response to highly desirable food images
  - insula and putamen, areas involved in the reward system

The y-axis represents effect size of the activation (z scores). Blood oxygen level-dependent contrasts are superimposed on a T1 structural image in neurological orientation. The colour bar represents voxel T value.

Farr et al. Diabetologia 2016;59:954–65

Liraglutide 1.8 mg is not approved for weight management
Oxyntomodulin: dual GLP-1/glucagon agonist concept

- Secreted by L-cells along with GLP-1
- It has shown that OXM potentiates glucose stimulated insulin secretion via the GLP-1 receptor and is an incretin in its own right

GLP-1 and Glucagon Receptor Dual Agonist

- In response to meals, oxyntomodulin:
  - Activates both **GLP-1** and **glucagon receptors**
  - Reduces appetite and increases energy expenditure, leading to substantial weight loss in overweight and obese individuals

Lount et al. *Obesity (Silver Spring).* 2013;21:1093-1103
Laferrere et al. *J Clin Endocrinol Metab* 2010;95:4072-4076
Wynne et al. *Int J Obesity* 2006 9;30:1729-1736
Peripheral Oxyntomodulin Reduces Food Intake

MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study

Philip Ambery, Victoria E Parker, Michael Stumvoll, Maximilian C Posch, Tim Heise, Leona Plum-Moerschel, Lan-Feng Tsai, Darren Robertson, Meena Jain, Marcella Petrone, Cristina Rondinone, Boaz Hirshberg, Lutz Jermutus
Complex systems are involved in pathophysiology of obesity

FFM determines BMR, energy intake, and hunger

FM has important role on tonic inhibition of appetite

Central regulation of appetite: Gut hormone system, Hedonic control systems, Adipose hormone system

Multiple hormonal signals influence appetite: Leptin, Ghrelin, Oxyntomodulin, PYY, Insulin, CCK

Liraglutide 3.0 mg is a GLP-1 receptor agonist which:

- Increases satiety and reduces hunger sensation centrally in the brain
- Influences all dimensions of appetite
- Reduces energy intake but does not increase energy expenditure

OXM is a dual GLP1, glucagon agonist that decreases food intake and body weight