The (un)natural history of endocrine weight-regulation

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Significance of weight-regulation

- In nature hunger prevails; temporarily relieved by food intake
- Great variations in food intake between days - yet body mass (BM) relatively stable
- Humans: obesity currently the greatest challenge in industrial countries
- Nature and some developing countries: scarcity of nutrition

Cues for weight-regulation

- Photoperiod
- Temperature
- Food availability
- How do these phenomena regulate the annual cycles of mammalian species in nature?
- How are these cues transmitted via the CNS to influence foraging behaviour?

Short-term weight-regulation

- Fast signals from the digestive tract:
- Stretching of the ventricle
- Ingested glucose, amino acids and lipids

-> *Satiety signals*

Short-term endocrine weight-regulation

Cholecystokinin:

- Secreted from the intestine and the CNS during food intake
- Secretion increased due to ingested fat, amino acids and protein degradation products
- Receptors in the ventricle and the liver
- Reseptorit vatsalaukussa ja maksassa

->Signals to CNS
-> Food intake reduced e.g. by slowing the emptying of the ventricle

Peptide 1:

- Related to glucagon
- Secreted from the intestine after a meal rich in lipids or carbohydrates
- Gastric emptying delayed -> satiety

Gastrin releasing polypeptide GIP

- Produced in the ventricular mucosa
- Reduces appetite
- “Novel hormone”, requires further research

Long-term regulation of the energy balance

- Has more significance when considering the whole life history of an individual or a species
- Required to ensure adequate energy reserves for growth, wintering, reproduction, lactation, migration etc.

Classic endocrine transmitters of weight-regulation

- Insulin (energy storage)
- Glucagon (energy mobilisation)
- Cortisol (energy mobilisation)
- Lipids (storage as triacylglycerols, mobilised as free fatty acids = FFA)
- Nitrogen balance
- Growth hormone (GH, mobilisation of white adipose tissue = WAT)
- Sex steroids (distribution of WAT etc.)

Insulin

- Increases and decreases food intake
- Blood glucose levels fall acutely -> decrease in food intake
- CNS: decrease in food intake
- Fasting concentrations correlate with the percentage of fat in the body (BMI)
- Food intake-> Increased insulin secretion from islets -> Insulin enters the hypothalamus

Insulin and neuropeptide Y

- Neuropeptide Y: neurotransmitter in the hypothalamus
- Neuropeptide Y ↑ -> Food intake ↓ Neuropeptide Y ↓ ->response to fasting, energy sparing, food intake ↑
- Insulin -> neuropeptide Y ↑, food intake ↓

New theory of weight regulation

- Kennedy 1953 : fat the most important form of energy storage in mammals
- Does fat participate in weight-regulation?
- Is there a feedback signal produced by the fat tissue (WAT) informing the CNS about the energy reserves and influencing food intake?

- Human obesity an increasing problem with associated diseases (blood pressure, coronary, diabetes, arthrosis)
- Nature: nonpathologic obesity during some parts of seasonal cycles, especially during late summer and autumn
- How to study?
- Early 70's:
- Mutations in mice causing excessive food intake, obesity and diabetes

Fat tissue self-regulation

- More fat: enough energy reserves, less food intake
- Less food available, fat mass diminishes, more foraging
- No reproduction, sexual maturation or seasonal rest unless energy reserves are sufficient
- Novel peptides
- Leptin and ghrelin

***Ob*-mouse**

- Excessive food intake
- Pathological obesity
- Sterility
- Lacks a satiety signal
- This signal substance can be found in the blood of a healthy mouse and its wild-type blood restores satiety (Coleman 1972)

***Db*-mouse**

- Phenotype the same as with ob-mouse but the blood of a healthy mouse does not restore satiety (Coleman 1972)
- No deficiency of satiety signal but lack of receptors

Zhang *et al*. 1994

- Cloning of the *ob* gene
- Product of the *ob* gene: *ob* protein or *leptin* (Greek: *leptos*, "thin")
- Secreted from WAT, concentrations increase with WAT mass
- Satiety signal
- Decreases rapidly by fasting in humans and rodents

Plasma leptin concentrations

- Positive correlation with WAT mass in humans and conventional laboratory rodents

- Obese subjects > normal weight subjects
- Women > men
- Leptin levels fall rapidly due to fasting and increase again after food intake has been resumed

Effects of leptin

- **Where fat is needed, leptin takes part in the regulatory processes!**
- Sexual maturation
- Satiety
- Food intake
- Nutritional scarcity -> leptin levels fall -> response to fasting initiated
- *Ob*-mice: reduced food intake
- *Ob*-mice: burn fat more compared to carbohydrates
- *Ob*-mice: increased heat production
- *Ob*-mice: fertility restored
- *Ob*-mice: glucose levels normalise
- Wild-type mice: similar but less pronounced effects

Leptin as an anorectic agent?

- Congenital leptin deficiency (< 10 globally?): cured by leptin therapy
- Conventional obesity: weight loss 7 % with sc. leptin therapy
- No statistical difference compared to other therapies
- No longer considered a promising cure for obesity

Leptin paradox

- Leptin can cure the *ob*-mouse. Why do the high leptin levels of an overweight human subject not cause weight loss?!
- Leptin resistance??
- Leptin an indicator of WAT mass and obesity, not an anorectic agent??

Solution? Obesity in nature

- In nature the intake of food virtually always of benefit
- Pathological obesity and concurrent diseases virtually inexistent (Coronary disease, elevated blood pressure, diabetes etc.)
- Seasonal obesity a natural phenomenon in the boreal climate: autumnal accumulation of WAT followed by wintertime scarcity

Ensuring adequate energy reserves for the winter?

- If leptin reduced food intake in nature animals could withdraw from eating “too early”

->Uptake of leptin through the blood-brain barrier sturable at relatively low levels
->The amount of leptin entering the CNS virtually the same in obese and normal-weight subjects, food intake can continue
->Ecologial signinificance of leptin: survival of animals in the scarcity of the natural environment?

Ghrelin

- 90's: synthetical growth hormone secretagogues
- Secretagogue receptor: natural ligand?
- Hosoda *et al*. 1999: ghrelin
- "Ghre" Indo-European stem "grow"

Kojima *et al*. 1999

- Ghrelin (Indo-European "ghre" = grow)
- Antagonistic to leptin
- Decreases with increased WAT mass
- Increases rapidly in fasting in humans and rodents
- Exogenous ghrelin increases feeding
- Secreted in e.g. stomach, kidney, placenta ja hypothalamus
- Exogenous ghrelin increases the BM and food intake of rodents
- Decreases fat utilisation
- Increases HCl secretion in the stomach
- Increases GH secretion in humans
- Act antagonistic to leptin in the hypothalamus: ghrelin activates NPY release, leptin inhibits NPY release

Plasma ghrelin concentrations

- Obese individuals have lower ghrelin levels (opposite to leptin!)
- Fasting triggers an increase in ghrelin concentrations
- Exogenous leptin causes an increase in ghrelin concentrations
- Ghrelin levels increase before food intake and return to basal levels an hour postprandially

Adiponectin

- Aka arcp30 (adipocyte complement-related protein)
- Very abundant, 0.01-0.05 % of all plasma proteins
- Secreted almost exclusively in adipose tissue
- Some mRNA expression also ion hepatocytes under special conditions (e.g. interleukin-6 treatment)

Regulation of adiponectin

- Insulin stimulates
- PPAR receptors importat and PPAR agonist reduce adiponectin expression
- Adsrenergic stimulation reduces
- No adiponectin receptors idenfied up to date, probably acts through cell surface receptors and adenylate cyclase

Plasma adiponectin levels

- Opposite to leptin:
- Plasma concentration low in obesity, higher in normal-weight subjects
- *Ob*-mice, *db*-mice have lower plasma adiponectin
- Weight reduction increases plasma adiponectin levels

Effects of adiponectin

- Reduces plasma concentrations of triglycerides and fatty acids
- Fat oxidation in muscle increases
- Plasma glucose reduces
- Reduces weight gain and ameliorates increase in adipose tissue mass
- No inhibition of food intake
- Body temperature increases
- Stimulates energy expenditure
- Inhibits inflammatory processes and possibly atherogenesis

Peptide YY (PYY)

- Discovered in 1980
- Belong to the same peptide family as NPY and pacreatic polypeptide
- Present in the ileum and large intestine
- Also found at low levels in the hypothalamus

PYY secretion

- Released from the GI-tract in response to fatty acid containing meals
- Suggests functions in the short-time regulation of food intake
- Inhibits gastric motility, gastric acid secretion and insulin secretion

PYY and food intake

- Confusing and mutually contradictory results
- Batterham et al 2003 N Engl J Med: Inhibition of food intake in obese subjects due to PYY
- Morley et al. 1985 and many others: unparalleled orexigenic effects

Weight-regulation in nature: examples

- Decoupling of plasma leptin levels and adiposity
- Raccoon dog: two months of total food deprivation - leptin levels unaffected
- Blue fox: three-week fasting periods - minor effects on leptin
- Arctic fox: no effect of fasting but increases during re-feeding
- Antarctic fur seals: increasing leptin during early food deprivation

Raccoon dog weight regulation

- Leptin high in winter - can mediate satiety
- No physiological need for food intake during winter sleep
- High leptin - no foraging
- Leptin cannot act as the adiposity signal in the raccoon dog in winter
- Low ghrelin levels and high leptin levels in winter can have a similar effect:
- Both enhance the use of fat as metabolic fuel

Weight-regulation and natural history

- Weight-regulatory hormones have not evolved to enhance human survival in the abundant western way of life; thir functions should also be considered in the natural environment
- Animal species must have evolved to cope with periodic scarcity and starvation
- In nature obesity a possible threat but starvation much more likely
- Evolutionary the emphasis could be more on surviving food deprivation
- Weight-regulation allows the intake of excessive amounts of food when available and succeeds in this task magnificently
- -> Obesity, diabetes and related pathological conditions
- Principal function of weight-regulatory hormones to signal about the oncoming scarcity and trigger the response to fasting? Saturable transport of leptin via the blood-brain barrier etc.