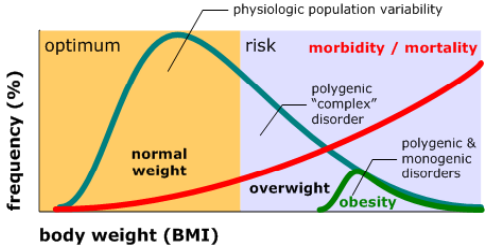
# Metabolic syndrome and obesity



# Body weight

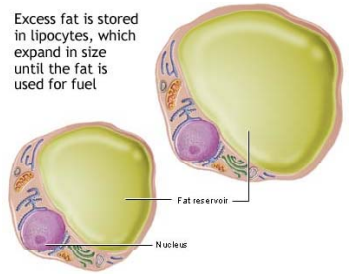
- adipose tissue
  - males ~10–20% of body weight
  - females 20–30% of body weight
- body weight **increases with age** in both genders
- it is a **continuous trait**, establishing normal range is arbitrary to certain extent
  - ideal weight is associated with the longest life- expectancy
- body weight is viewed also in the cultural, geographical and historical context
- obesity is a one of many symptoms in some diseases – especially endocrinopathies
  - hypothyreosis
  - Cushing syndrome
  - hypogonadism
- however, majority of obese subjects are affected by "common" obesity of multifactorial origin






# Overweight / obesity

- defined as an excessive deposition of fat in the body with concurrent **hyperplasia** and **hypertrophy** of adipose tissue
  - ↑ differentiation of pre-adipocytes
  - ↑ deposition of lipids in adipocytes
- obesity is, first of all, consequence of **abnormal long-term regulation of energy homeostasis**
- criteria
  - **BMI** (body mass index)
    - malnutrition BMI <18.5
    - normal weight 20 – 24.9
    - overweight 25 29.9
    - obesity BMI >30 (mild 30 – 34.9, moderate 35 - 40, morbid >40)
      - BMI unfortunately doesn't indicate the distribution of fat = android (male pattern, apple) and gynoid (female pattern, pear)
      - male pattern has more health risks
  - fat distribution is more precisely reflected in **WHR index** (waist-hip ratio)
  - nowadays it's common to measure just **waist circumference**
    - females: mild risk > 80 cm, high risk > 88 cm
    - males >94 and >102 cm, respectively
  - thickness of **skin fold**
  - exact measurement of body fat content
    - underwater weighing
    - conductance (bioimpedance)
    - computer tomography and magnetic resonance
    - DEXA

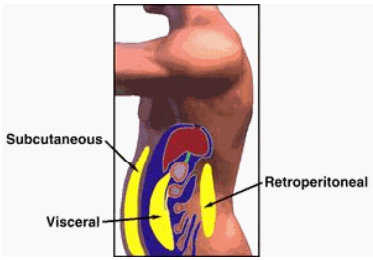


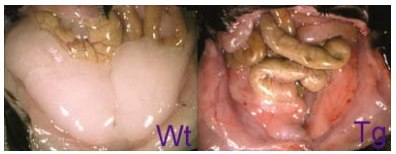


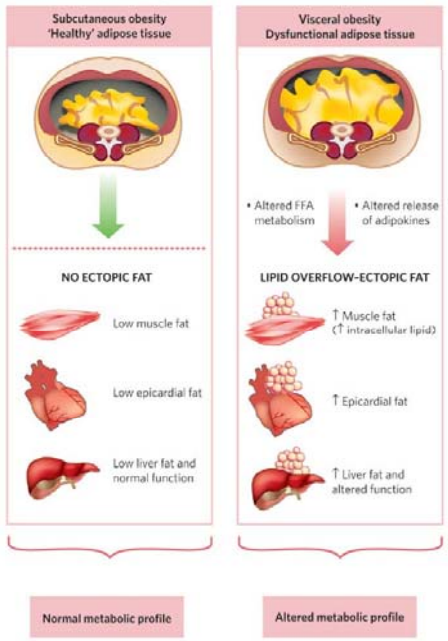


# Fat distribution

- "**brown**" adipose tissue (BAT) – newborns
  - neck, back, around large vessels = thermoregulation
    - mitochondiral "uncoupling" of oxidation of FFA and ATP synthesis
- "**white**" (WAT) stored at
  - in **subcutaneous** adipose tissue
    - aesthetic but not metabolic catastrophe
  - in obese subjects also in **visceral** region
    - intra-abdominally – e.g. omentum, mesenterium
    - retroperitoneally
    - epicardium
      - local source of FFA?
      - possible paracrine effect of secreted factors on the heart
    - others (orbital, joints, synovia)
  - and also intra-organ in **muscles** and **liver**
    - two important organs influencing insulin sensitivity
      - ↑ NEFA
      - ↑ adipokines

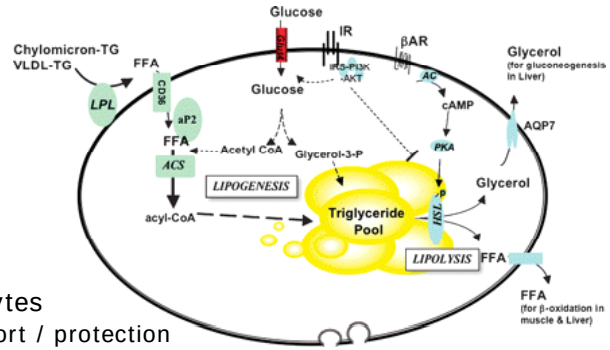







# Metabolism of adipocyte

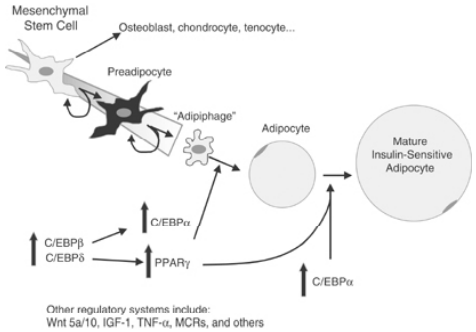



- function of adipocytes
  - mechanical support / protection
  - thermoisolation
  - energy store
  - endocrine organ (~$1 \times 10^9$ of cells = by far the largest!!!)
    - insulin-sensitising factors (negatively correlating with number of adipocytes)
    - insulin-desensitising factors (positively correlating with number of adipocytes)
    - pro-inflammatory factors (cytokines)



# Adipocyte differentiation

- pluripotent mesenchymal cell (MSC) → adipoblast → pre-adipocyte → adipocyte
- control (transcription factors)
  - peroxisome proliferator-activated receptor γ (PPARγ)
    - ☛ expressed mainly in fat tissue
    - ☛ stimulates adipocyte differentiation, lipogenesis and fat storage
  - CCAAT regulatory enhancer binding protein α (CREBPα)
  - sterol-regulatory element binding protein 1c (SREBP1c)
  - others (Wnt signalling pathway)



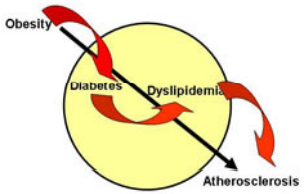



# Evolution of obesity

- **unlimited storage of fat is not metabolically „safe“!!!**
  - as to why is not clear?
- critically limited energy resources in adverse living conditions were likely evolutionary much more important factor than eventual consequences of affluence
  - selection of **“thrifty genotype”** in the hunter-gather period enabled its carriers to make the most from minimal resources and represented **selective advantage**
  - the very same metabolic regulatory tools preventing us from life-threatening energy depletion form basis of metabolic diseases nowadays
    - esp. insulin and leptin resistance
- humoral products of adipose tissue actively participate in multiple regulations negatively affecting
  - carbohydrate and lipid metabolism
  - vascular homeostasis and circulation
    - ↑ ICAM, ↓ NO
  - immunity
    - ↑some cytokines and RAF
  - fibrinolysis
    - ↑ PAI-1
  - reproduction

# Consequences of obesity

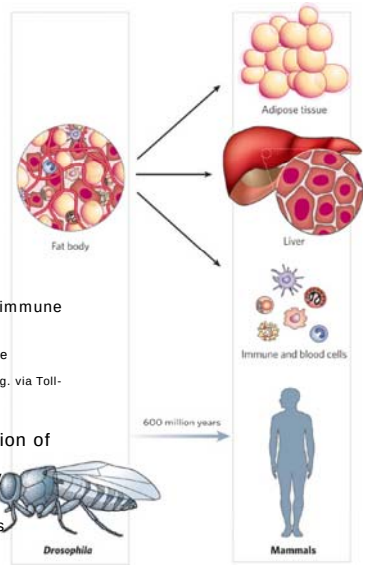
- risks associated with obesity
  - cardiovascular
    - metabolic syndrome (diabetes, hypertension, dyslipidemia) → atherosclerosis
  - tumours
    - ovary, endometrial, breast, colorectal, kidney cancers
  - musculoskeletal system
    - arthrosis of lower limb joints
  - infertility
  - polycystic ovary syndrome
  - biliary calculosis
  - respiratory insufficiency (morbid obesity – Pickwick syndrome)
  - sleep apnoea



The Metabolic "Axis of Evil"



# Evolution of obesity and inflammation




- ability to store energy for periodical fasting was equally important as an ability to fight infection
  - biologically interconnected systems for energy storage and immune reaction developed
    - single system in lower organisms (e.g. fat body in insects)
    - separate systems in higher organisms (liver, adipose tissue, bone marrow), but dynamic cooperation
      - hormones of adipose tissue and nutrients regulate immunity (e.g. via Toll-like receptors)
    - interaction exist even within organs
      - e.g. liver: hepatocytes/adipocytes/Kuppfer cells
- two periodically changing situations required redistribution of energy
  - fasting (or danger) → stress reaction → decline of immunity
    - ↑ glucocorticoids / ↓ lymphocytes
  - storage of energy→ production of humoral factors in fat tissue with pro-inflammatory effect → removal of pathogens



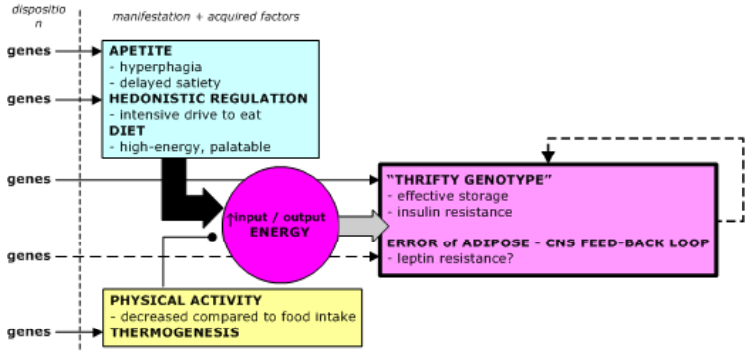
# Ethiopathogenesis of obesity

- obesity develops as a consequence long-term imbalance between
  - energy intake
    - food
  - energy expenditure
    - basal metabolic rate (~60% of daily expenditure)
    - thermic effect of food (~10-15%, different for various macronutrients)
    - activity energy expenditure
      - exercise energy expenditure
      - non-exercise activity thermogenesis (daily chores, posture, fidgeting)

- favouring higher intake (= **positive balance**) due to
  - relatively higher intake
  - lower expenditure
  - combination of both
- but why?
  - is there any feed-back loop between **adipose tissue and** central and peripheral organs influencing metabolism and food intake in order to prevent increase of body weight over the threshold necessary for optimal functioning of organism?



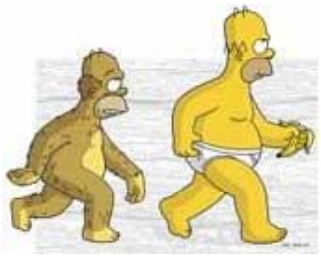
# Pathogenesis of obesity




- **endogenous and exogenous factors likely contribute equally**:
  - endogenous - genetic
  - exogenous – diet (amount, frequency, quality), physical activity, education, social class, psychological factors (personality), stress
- **recent change of behavioural and environmental** (not genetic!) **factors** is responsible for the current epidemic of obesity in developed countries (and its growing prevalence in developing ones)
  - although generic predisposition plays probably and important role it isn't genes that would change rapidly recently!

# Genetics of obesity

- candidate genes = genetic polymorphism in genes encoding products involved in
  - regulation appetite/satiety
    - peripheral and central orexigenic / anorexigenic mediators and their receptors
    - endocannabinoid system
  - adipose tissue differentiation and metabolism
    - PPARs, enzymes, adipokines and their receptors
  - carbohydrate metabolism
    - inzulin receptor signal cascade
    - post-receptor sensitivity
  - thermogenesis
    - uncoupling proteins
- genome-wide search for obesity genes





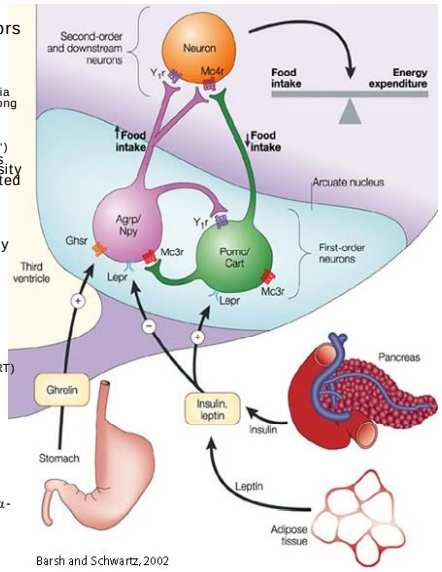
# Regulation of food intake

- food intake is a periodical event
- main stimuli regulating timing of meals are
  - **appetite** respectively **hunger**
    - appetite = natural desire to eat which changes behaviour in order to get access to food
    - hunger = feeling of imperative need of food associated with various objective symptoms, esp. negatively perceived stomach contractions
  - **satiety**
    - satiety = opposite of hunger, follows after adequate meal
- frequency of meals, portion size, quality, type of processing is influenced by various exogenous and endogenous factors
  - social, psychogenic, emotional, habitual, daily regimen, cost, season etc.
- regardless these short-term physiological fluctuations **energy balance should be balanced in healthy man in long-term** so that energy intake equals expenditure
- however, the regulation of food intake (and body weight) is not purely homeostatic but quite a complex process involving neural and hormonal regulation
  - **homeostatic regulation**
    - afferent signals are so far much better understood than efferent signals
  - **hedonistic regulation**
    - satisfaction after meal



# Homeostatic regulation

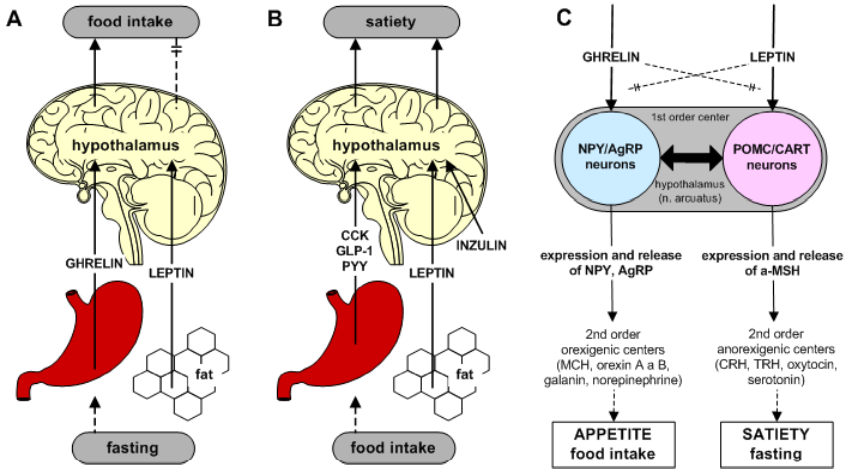
- afferent signals (= appetite vs. satiety):
  - **peripheral signals** via systemic humoral factors and sensitive information from GIT informing about gastric distension and motility (via n. vagus and n. tractus solitarii)
    - the most important humoral factors are:
      - **insulin** – postprandial release paralleling the glycemia
      - **leptin** – adipose tissue hormone, likely involved in long term modulation of sensitivity to peripheral "satiety signals from GIT (cholecystokinine (**CCK**), glucagon-like peptide 1 (**GLP-1**) and **peptide YY)**
      - **ghrelin** - hormone released from stomach whose concentration rises during fasting („hunger mediator")
    - concentration of leptin (and indirectly of insulin) is proportional to the adipose tissue mass and intensity of their signals in CNS (via their receptors) is related to their plasma levels
    - meal composition (amount of carbohydrates, proteins and lipids) is reflected in afferent signalisation – changes of insulinemia after meal containing sugar (glycemic index) and proteins, dietary lipids influence insulinemia and thus satiety minimally
  - **central** integration of signals takes place in **hypothalamus** (hypothalamic nuclei – nucleus arcuatus) by local neurotransmitters:
    - orexigenic mediators (neurotransmitters)
      - **neuropeptide Y** (NPY)
      - **agouti-related peptide** (AgRP)
    - anorexigenic mediators (neurotransmitters)
      - **proopiomelanocortine** (POMC)
      - **cocaine-amphetamine-regulated transcript** (CART)
- efferent signals
  - events initiated by primary centres in hypothalamus are not entirely known yet by they evidently involve complex cooperation network aming various CNS regions which influence behaviour in order to seek food
  - secondary mediators
    - orexigens - orexin A and B, galanin and norepinephrine
    - anorexigens – melanocyte-stimulating hormone (α-MSH), corticoliberin (CRH), thyreotropin-releasing hormone (TRH) and serotonin




Barsh and Schwartz, 2002

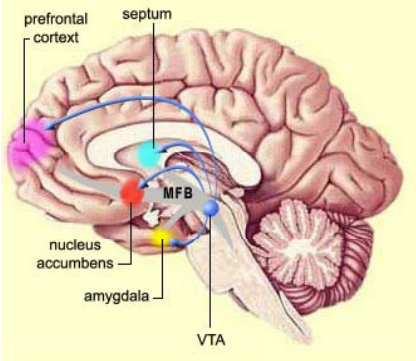


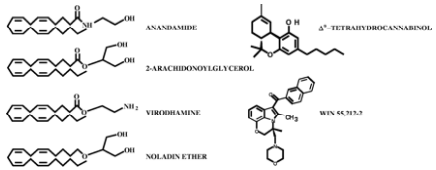
# Peripheral and central signalisation in regulation of food intake



# Hedonistic regulation

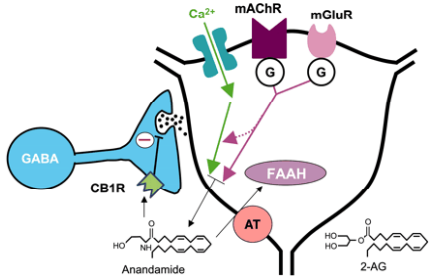
- = sensations connected with meal (e.g. palatability, vision, reward, ...)
- afferent signals
  - gustatory and olfactory pathways into particular centres
  - cortical regions (prim. and associated centers)
    - ventral tegmental area (VTA) – dopaminergic stimulation
  - sub-cortical regions - limbic system (amygdala)
    - they mediate the "good" feeling
    - neuro-modulators are **endocanabinoids** binding to CB1 and 2 receptors
      - anandemid (arachidonoylethanolamid, AEA)
      - 2-arachidonoylglycerol (2-AG)
  - basal ganglia (n. accumbens and pallidum)
  - prefrontal cortex
- homeostatic and hedonistic regulation are largely independent
  - therefore, unfortunately, the type and amount of meal very often doesn't corresponds with metabolic needs






# Retrograde signaling by EC

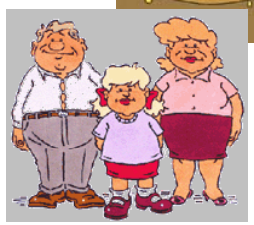



- The endocannabinoids (EC) anandamide and 2-AG are synthesized in postsynaptic target cells such as hippocampal pyramidal cells (right). Synthesis is initiated by calcium influx through voltage-gated calcium channels, or by the activation of G protein-coupled neurotransmitter receptors, including type I metabotropic glutamate receptors (mGluR) or muscarinic acetylcholine receptors (mAChR)
- The EC gain access to the extracellular space and activate CB1 cannabinoid receptors found concentrated on certain nerve terminals, e.g., of cholecystokinin-containing GABAergic interneurons in hippocampus
- CB1 activation causes presynaptic inhibition of GABA or glutamate release by inhibiting calcium channels, interfering with vesicle release, and activating potassium channels
- The EC are taken up into postsynaptic or presynaptic cells by the anandamide transporter (AT). The degradative enzyme FAAH is present in postsynaptic cells, and monoglyceride lipase (not shown), which degrades 2-AG, is found in presynaptic terminals.



# Environmental factors

- lack of physical activity
- change of diet
  - lipid-rich diet brings twice as muc energy in the same amount compared to carbohydrates and proteins
  - lipids mediate the satiety much later than sacharides (→ insulin)
- national cuisine traditions
- family habits
- educational and social status
- consumption of alcohol can play a role too
  - non-negligible energy content

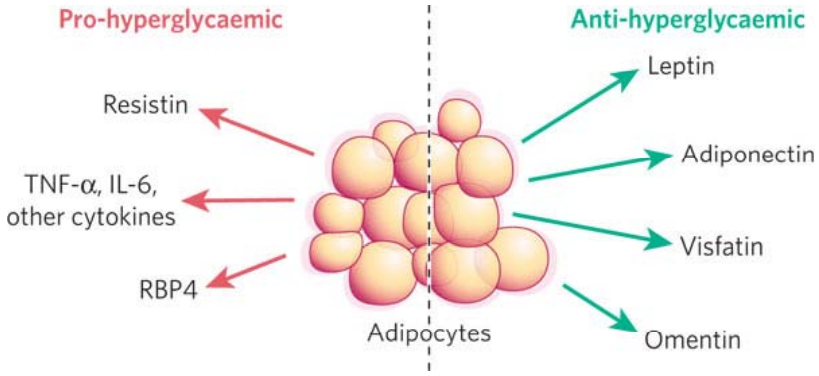




# Endocrine activity of adipose tissue

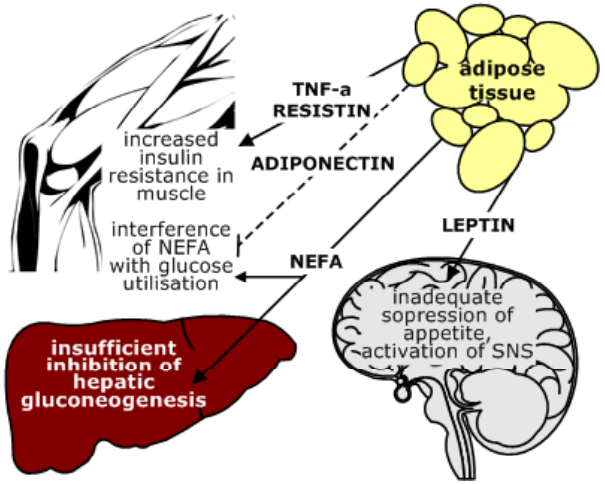
| HORMONE | TARGET TISSUE / ORGAN | PLASMA LEVELS | METABOLIC EFFECT |
|---|---|---|---|
| Leptin | CNS (hypothalamus), muscle, ovary) | pozitive correlation with BMI | central – long-term ↓ of appetite and ↑ of sympathetic activity; peripheral - ↑ insulin sensitivity and lipid metabolism |
| Adiponectin | insulin-dependent tissues (muscle!) | negative correlation with BMI | ↑ of insulin sensitivity, ↑ NEFA oxidation, antiinflammatory |
| Resistin | insulin-dependent tissues (muscle!) | pozitive correlation with BMI in rodents | ↑ insulin resistance, pro-inflammatory |
| TNF-α | insulin-dependent tissues (muscle!) | pozitive correlation with BMI | interferes with insulin receptor signalling (phosphorylation of serin residues) – ↑ insulin resistance |
| IL-6 | ? | pozitive correlation with BMI | ? (pro-inflammatory?) |
| Angiotensinogen | adipose tissue (para- and autocrine action), endocrine as a part of systemic RAAS? | expression in adipose tissue positively correlates with BMI | influence adipocyte differentiation, ↑ lipogenesis, circulatory effect of obesity ij systemic circulation? |

# Adipokines vs. insulin sensitivity



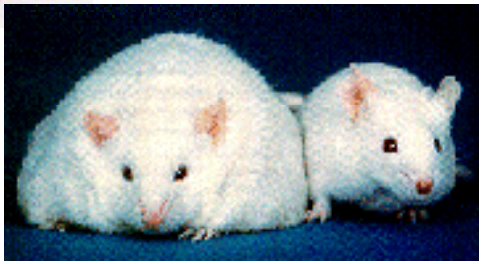



# Hormones of adipose tissue



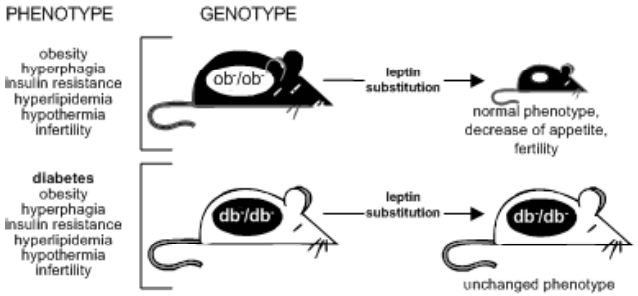



# Spontaneously obese strains of mouse - mutations in Ob or Db genes



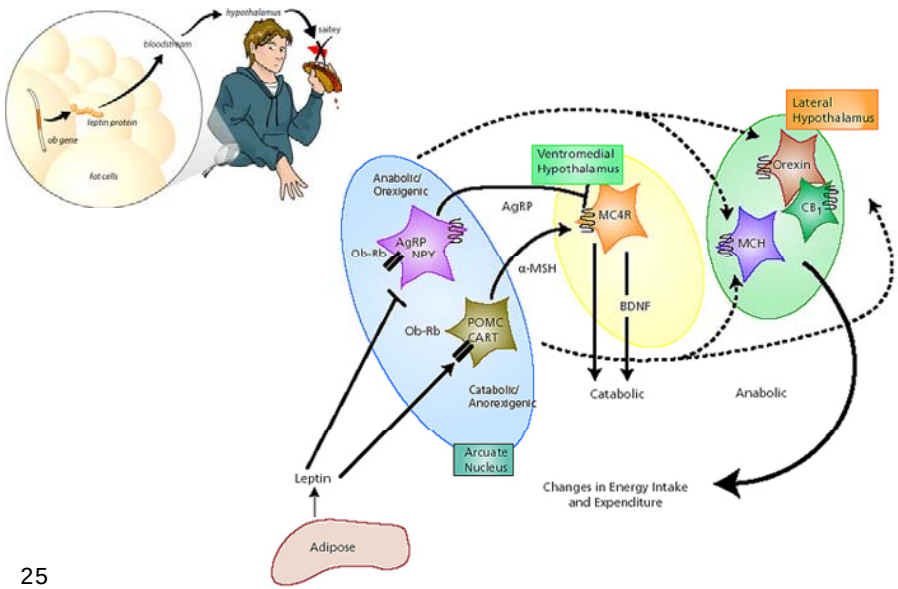


# Leptin [“*leptos*” = lean]




- central hormone in regulation of energy homeostasis and food intake (thermogenesis?)
- central and peripheral action
- obesity is associated with hyperleptinemia
  - **leptin resistance???** (parallel to insulin resistance) is hypothesised to play a role in the pathogenesis of obesity
  - endogenous highly set “adipostate” might be also a problem of relapses in obese subjects after loosing weight

## Regulation of hypothal. centers by leptin






## Other less common causes of obesity / hyperphagia

- tumors and lesions of ventromedial hypothalamus
  - mostly craniopharyngeoma
- monogenic genetic syndromes
  - Prader-Willi syndrome
    - deletion or alteration of expression of group of genes on the proximal part of long arm of paternal chromosome 15
    - abnormally increased appetite (hyperphagia) and subsequent morbid obesity, muscular hypotonia, mental retardation, low height, hypogonadism and acromicria (small hands and feet)
      - high levels of ghrelin are common in PW patients - consequence of primary genetic defect?