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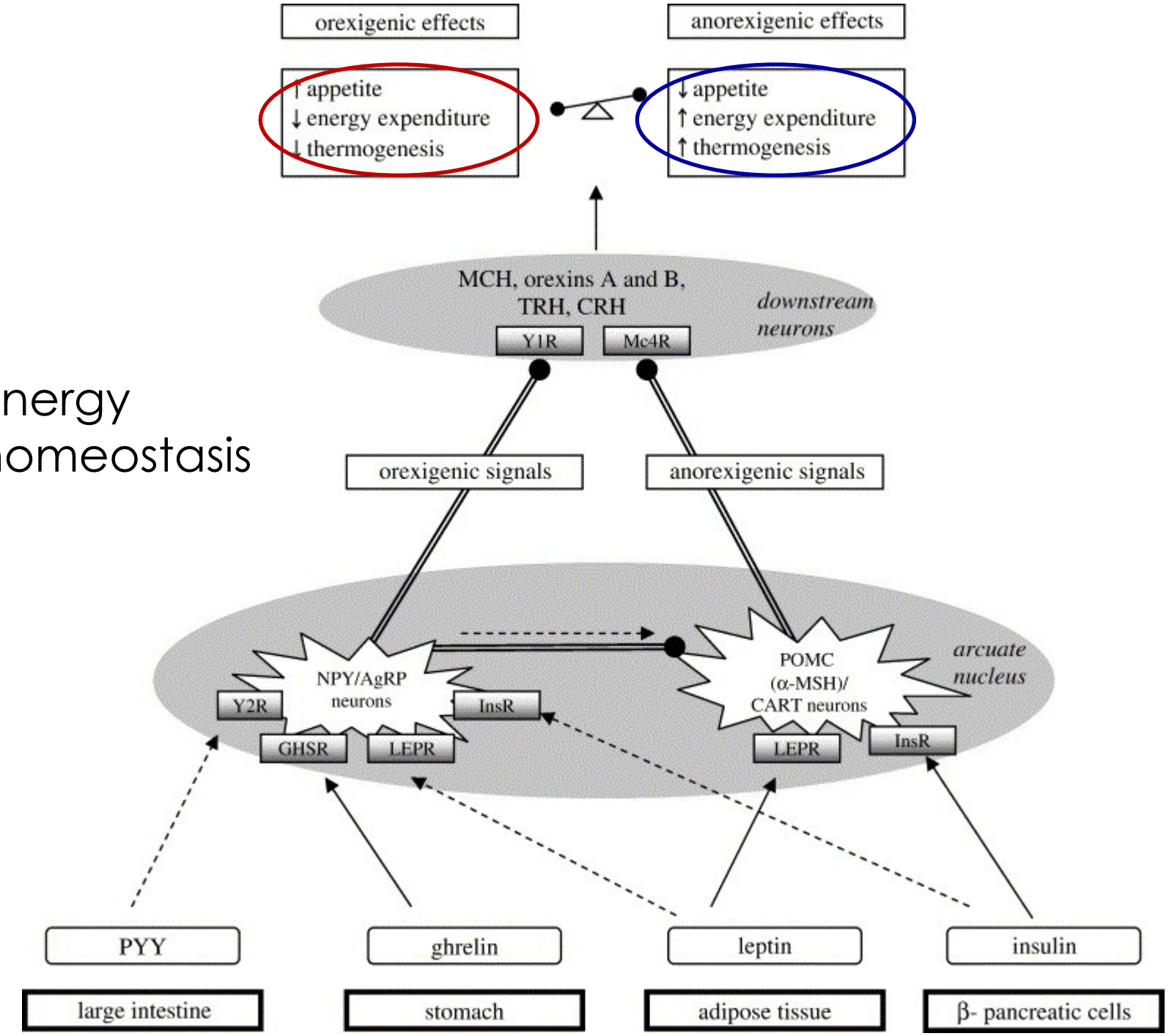
Eating disorders

ZLA - spring 2020

Energy homeostasis

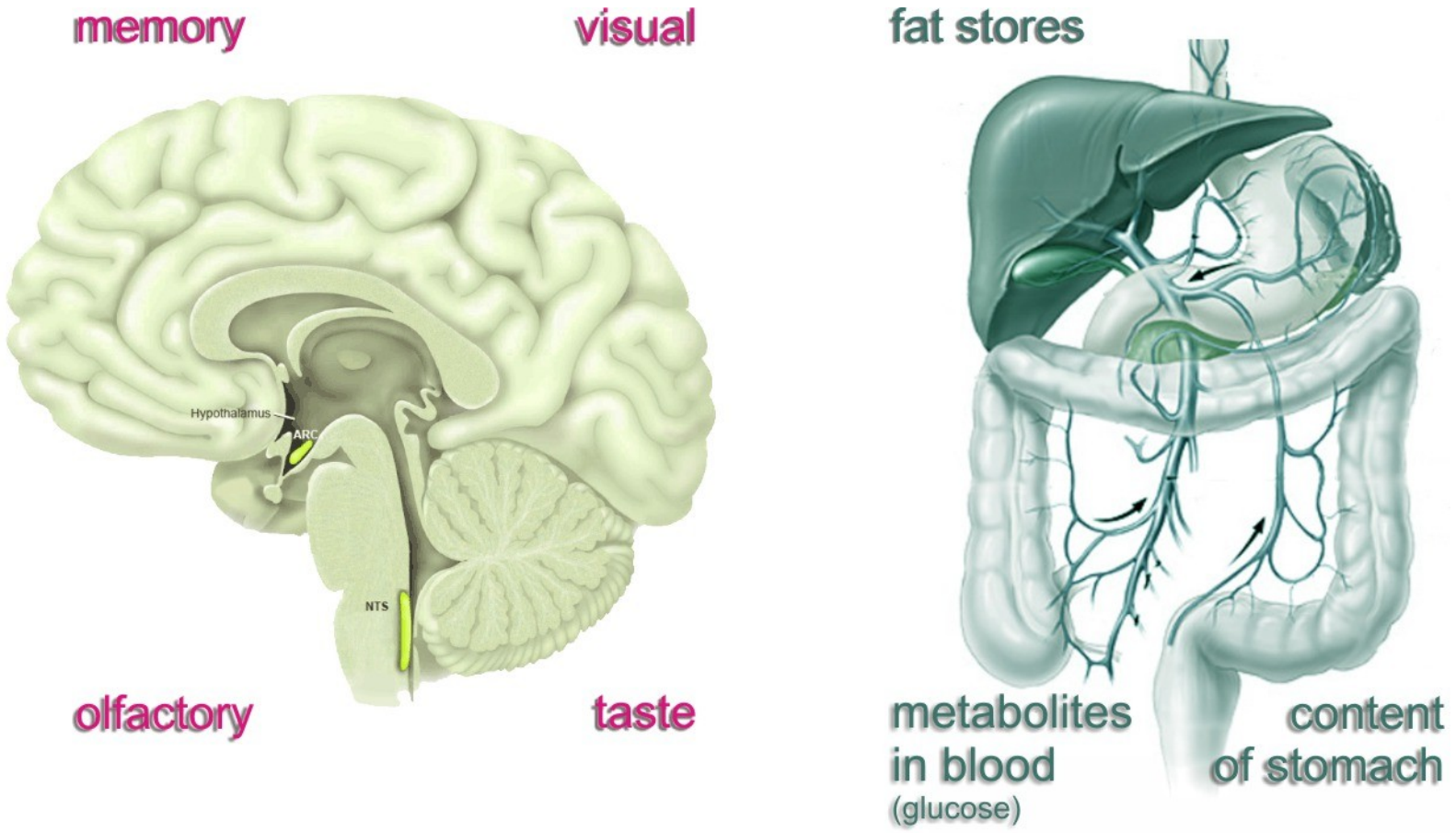


History

- Lipostatic hypothesis (Kennedy 1953) – adipose tissue products specific „lipostatic“ factor

- Glukostatic hypothesis (Mayer and Thomas 1967) – changes in glycemia lead to stimulation /inhibition of food intake (brain and liver)
- Combination of both hypotheses???

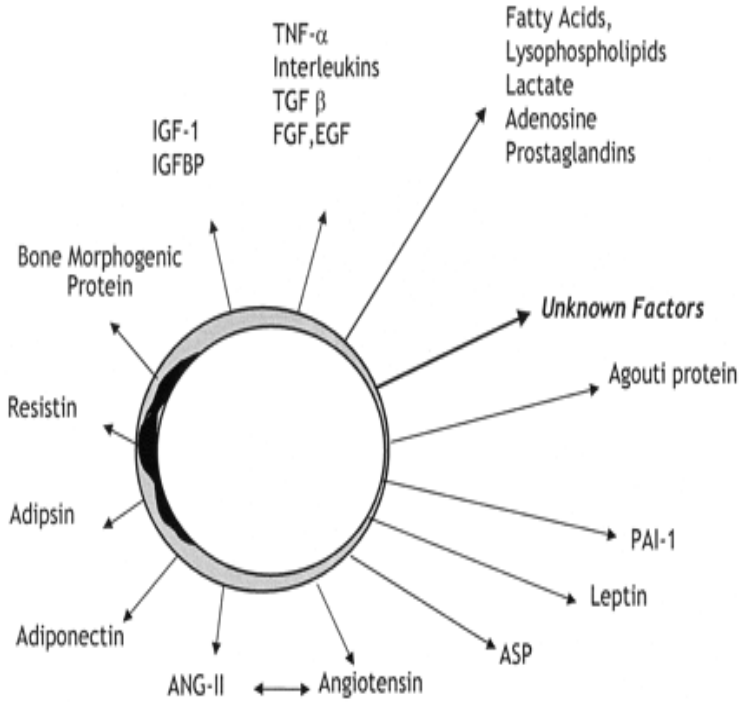
It is necessary to distinguish common homeostatic regulations of food intake and hedonic regulations



WAT produces adipokines

These factors are produced by adipocytes, but also by macrophages, fibroblasts, endothelial cells and other cells in adipose tissue

To date, a lot of adipose tissue-derived factors has been described. These factors with pleiotropic functions in many processes including regulation of energy metabolism, inflammation, food intake, insulin sensitivity etc. Markedly contribute to metabolic regulations and its pathologies.



They are usually:

1. Proinflammatory (TNF-α, IL-6, resistin)
2. Anti-inflammatory (adiponektin)

They are very important in metabolic regulations

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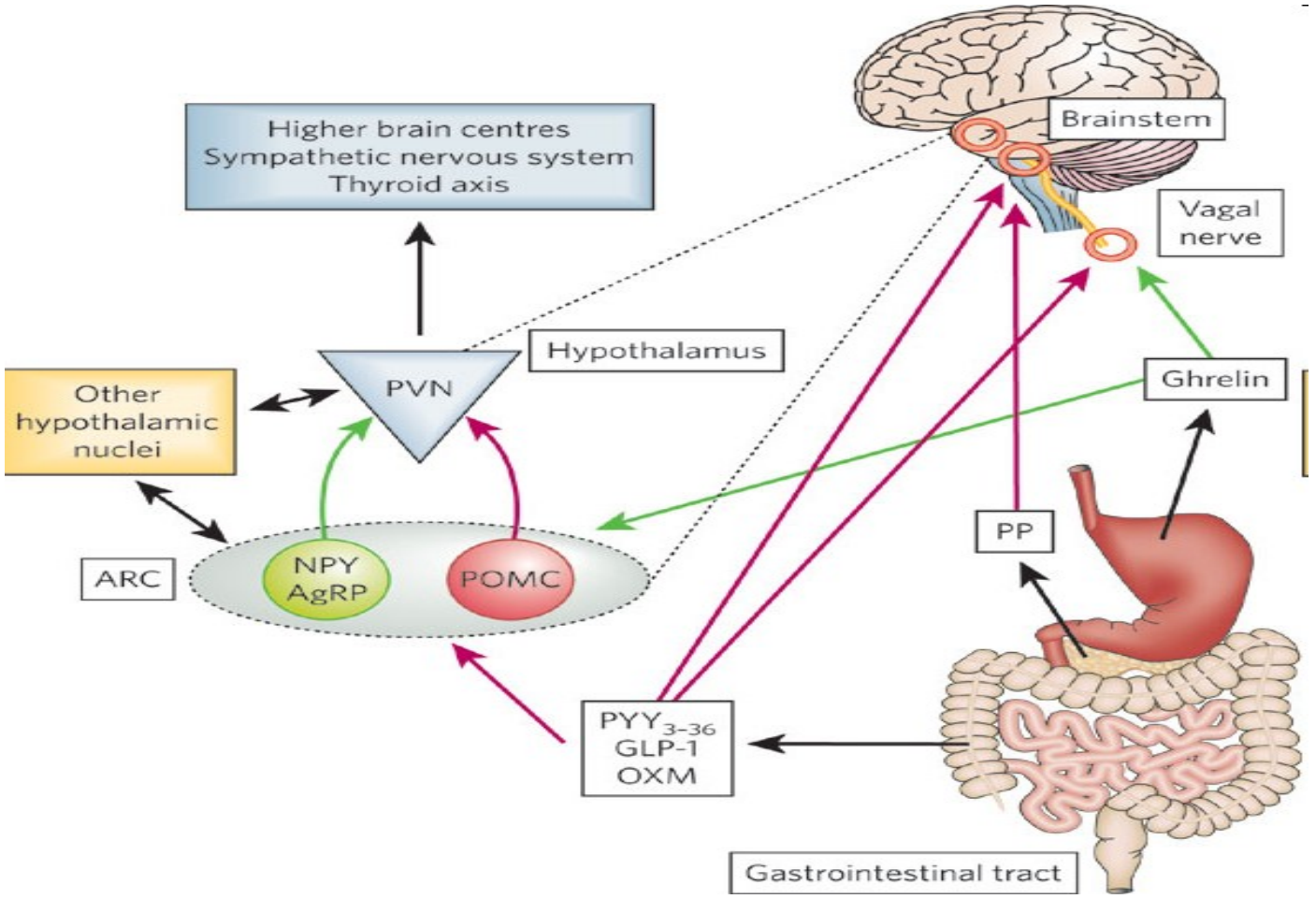
CENTRAL AND PERIPHERAL CIRCUITS IN REGULATION OF FOOD INTAKE



Gut hormones and the regulation of energy homeostasis
Kevin G. Murphy and Stephen R. Bloom
Nature 444, 854-859(14 December 2006)

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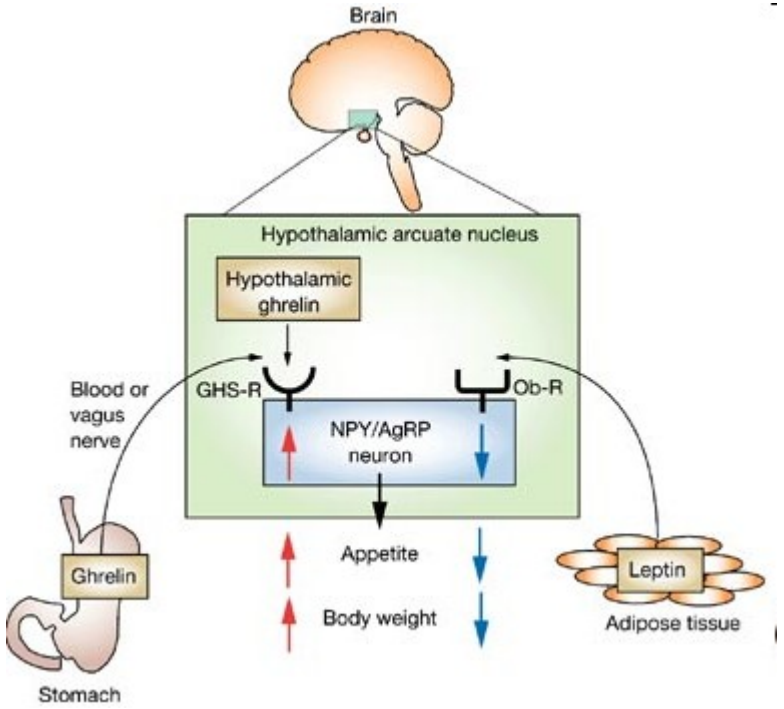
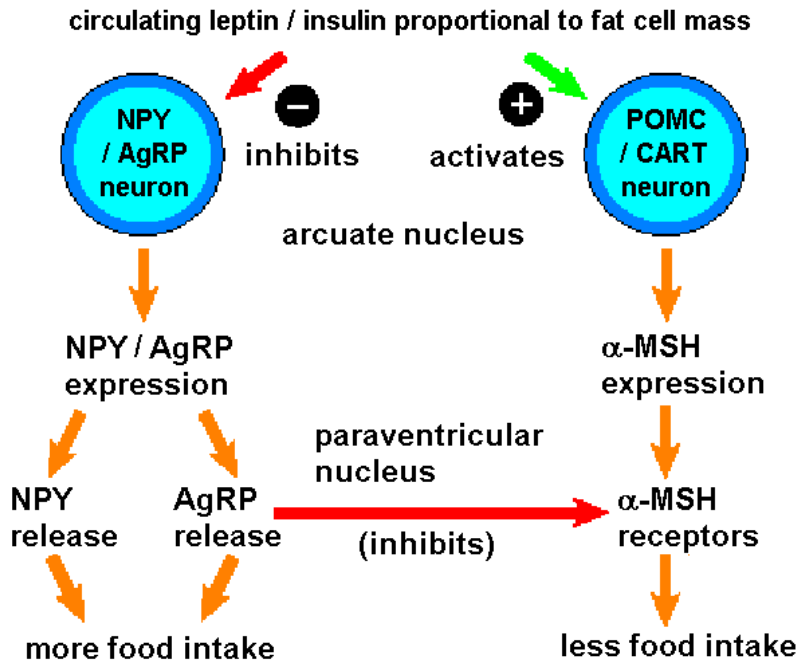
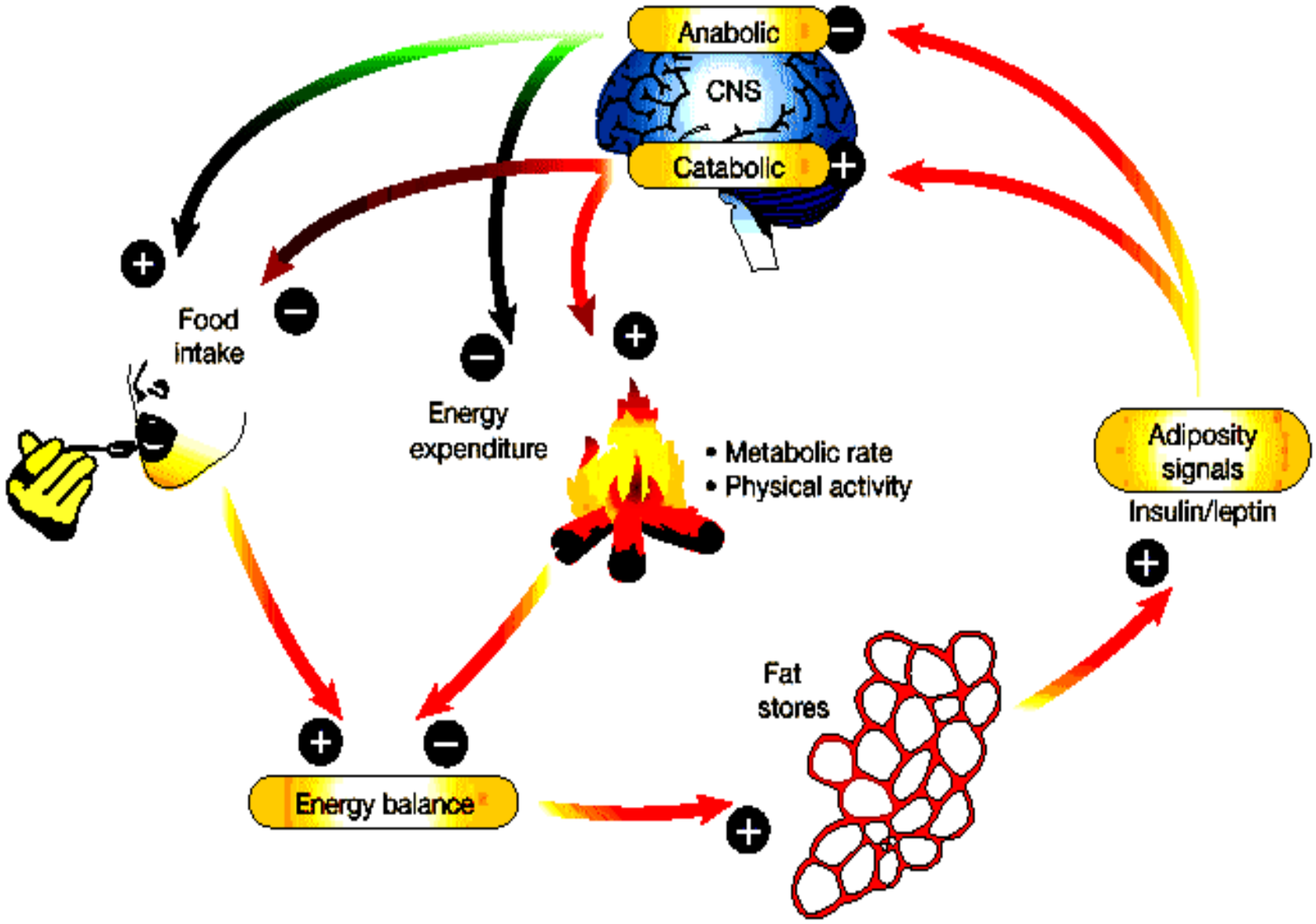
REGULATION OF FOOD INTAKE





Drug Insight: the functions of ghrelin and its potential as a multitherapeutic hormone
Masayasu Kojima and Kenji Kangawa
Nature Clinical Practice Endocrinology & Metabolism (2006) **2**, 80-88


Anabolic
CNS
Catabolic
Food intake
Energy expenditure
• Metabolic rate
• Physical activity
Adiposity signals
Insulin/leptin
Fat stores
Energy balance

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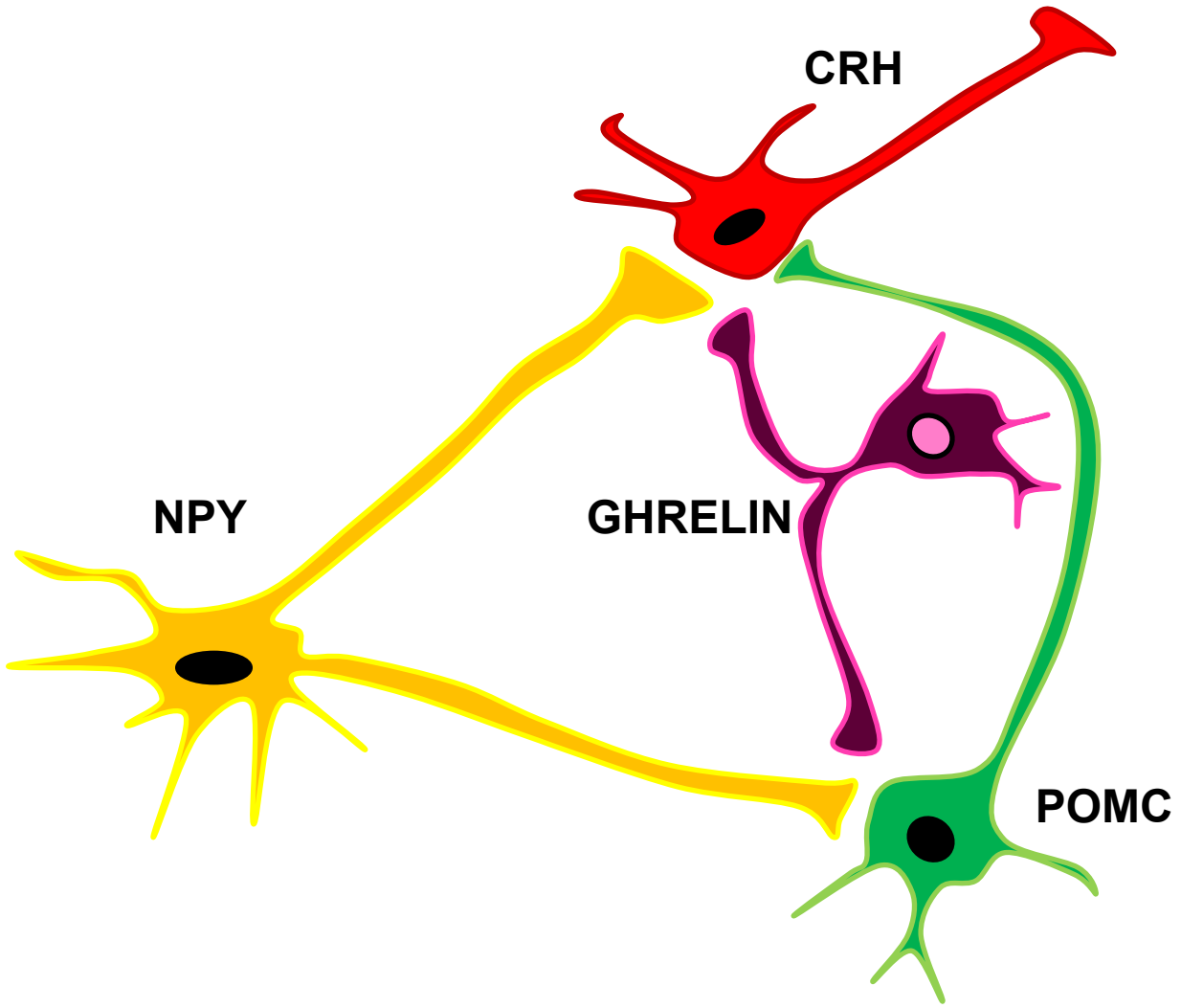
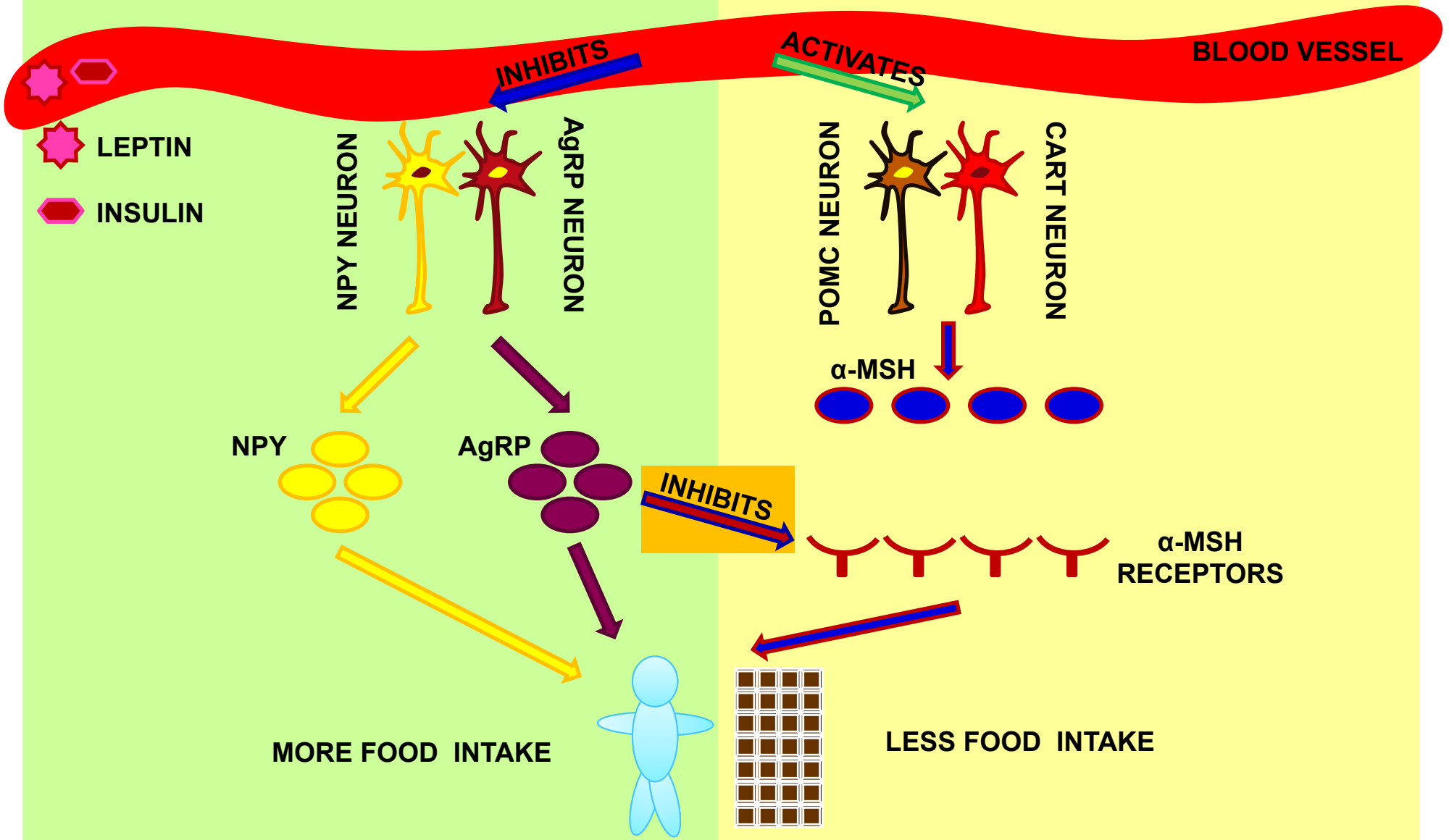
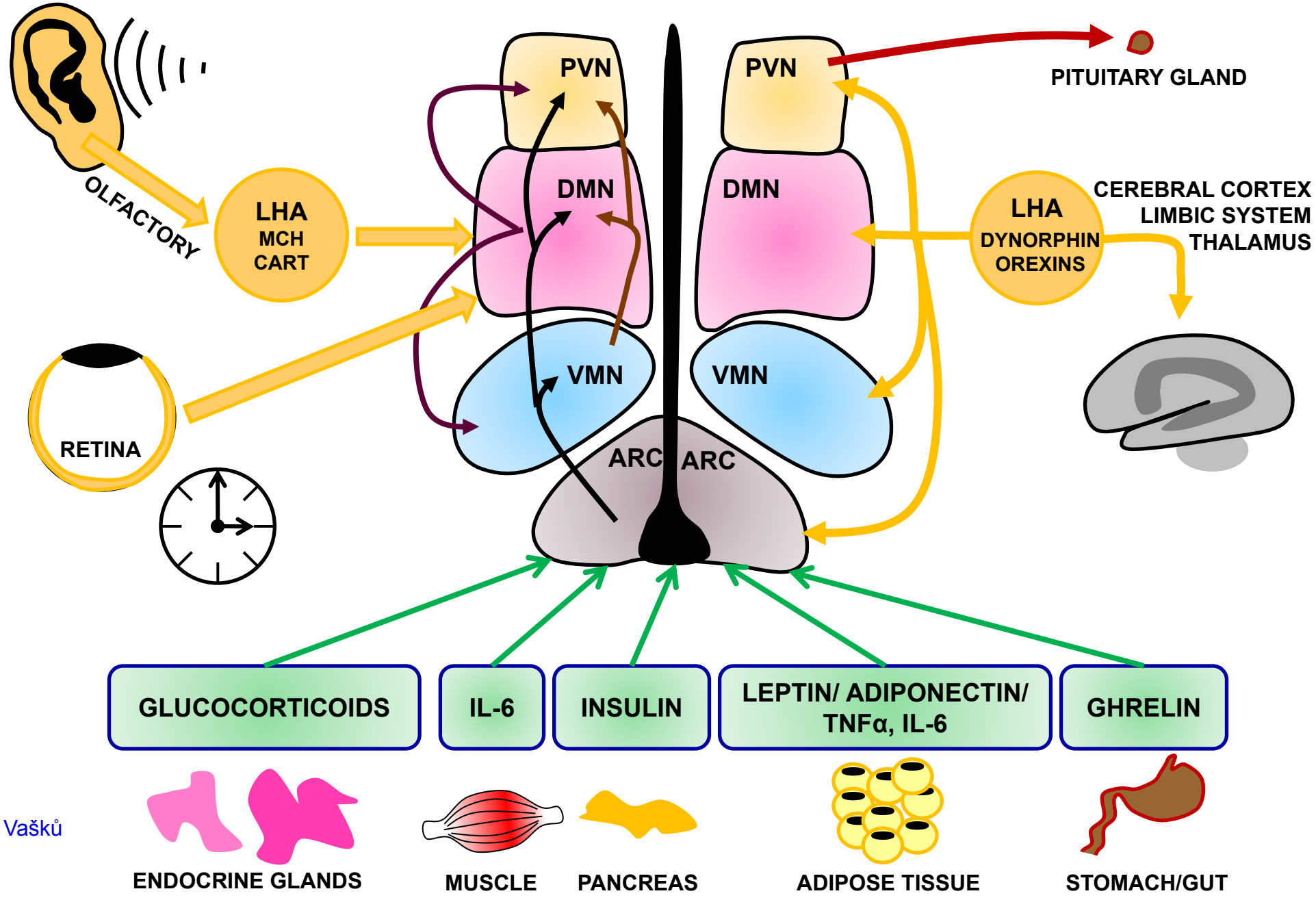
BASIC COMMUNICATION AMONG NEURONS



OREXIGENIC- ANOREXIGENIX PATHWAYS

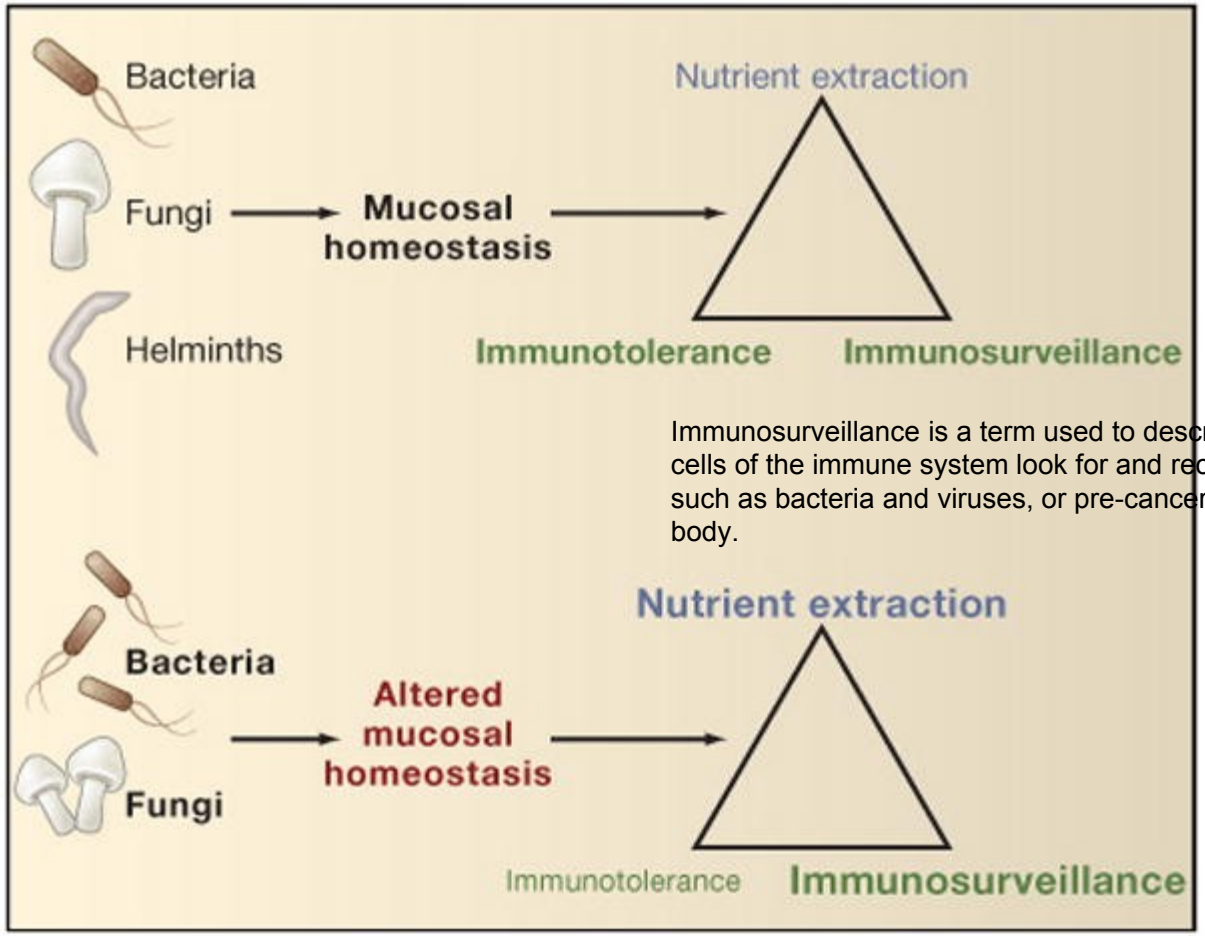


HYPOTHALAMUS



PATHWAYS OF TRANSCRIPTION FACTORS PARTICIPATING IN NUTRITION BASED INTERACTIONS

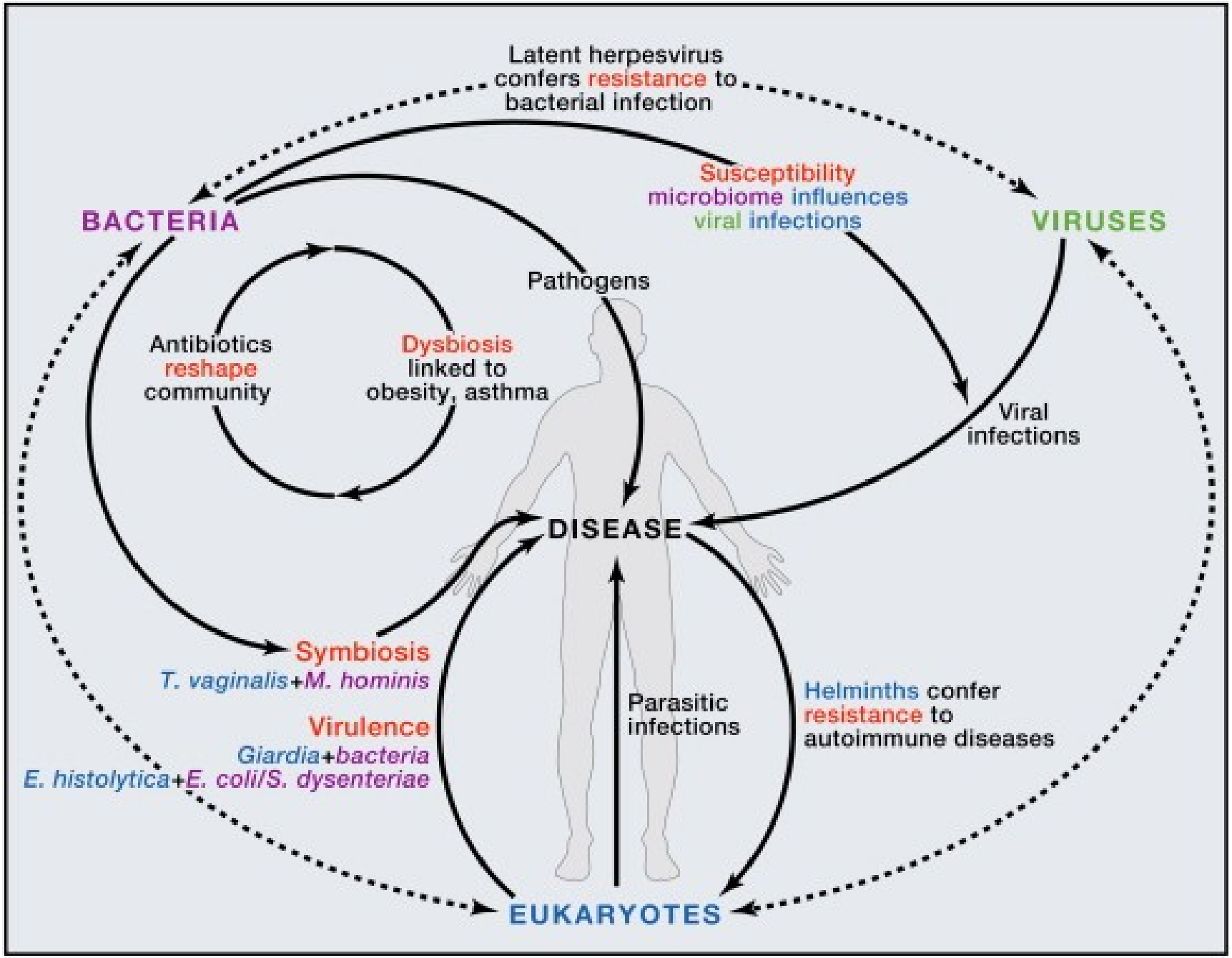
Nutrient	Compound	Transcription factor
Macronutrients		
Fats	Fatty acids Cholesterol	PPARs, SREBPs, LXR, HNF4, ChREBP SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
Micronutrients		
Vitamins	Vitamin A Vitamin D Vitamin E	RAR, RXR VDR PXR
Minerals	Calcium Iron Zinc	Calcineurin/NF-ATs IRP1, IRP2 MTF1
Other food components		
	Flavonoids Xenobiotics	ER, NFκB, AP1 CAR, PXR



Immunosurveillance is a term used to describe the processes by which cells of the immune system look for and recognise foreign pathogens, such as bacteria and viruses, or pre-cancerous and cancerous cells in the body.

The loss of universal helminth infection as occurred in earlier human evolution may alter the numbers or types of bacterial and fungal commensals and thus affect normal mucosal tissue homeostasis. In susceptible or highly exposed individuals, such alterations might alter the balance between immunotolerance, immunosurveillance and nutrient extraction. This imbalance may contribute to the appearance of inflammatory systemic dysregulation at mucosal surfaces, resulting in increases in asthma and allergic diseases, particularly in the setting of environmental changes that have increased exposure to indoor allergens and pollutants, and even to increases in obesity, which can be a risk factor for severe asthma.

Cell 2012; 148: 1258–1270



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Stages of Metabolism

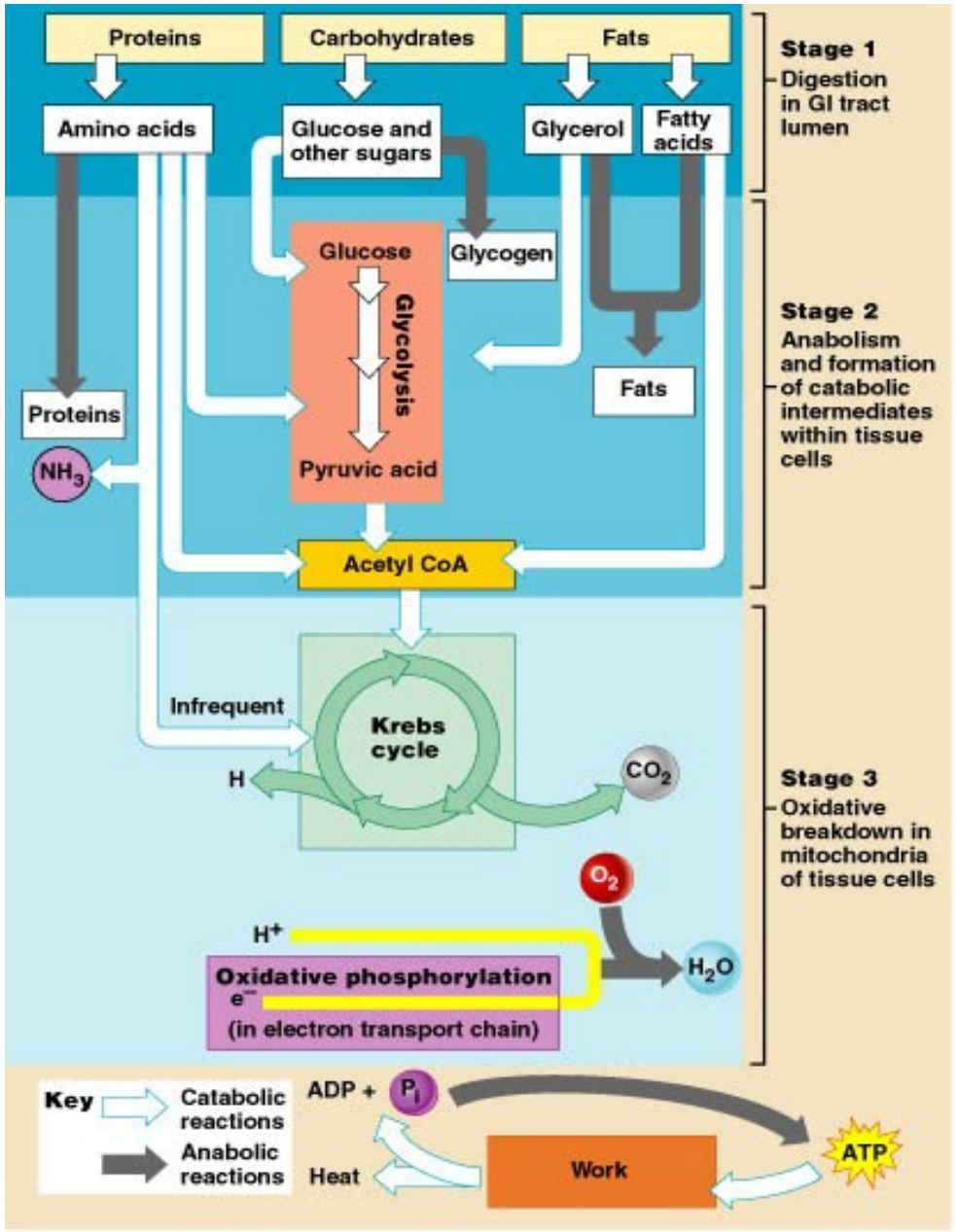

Figure 24.3

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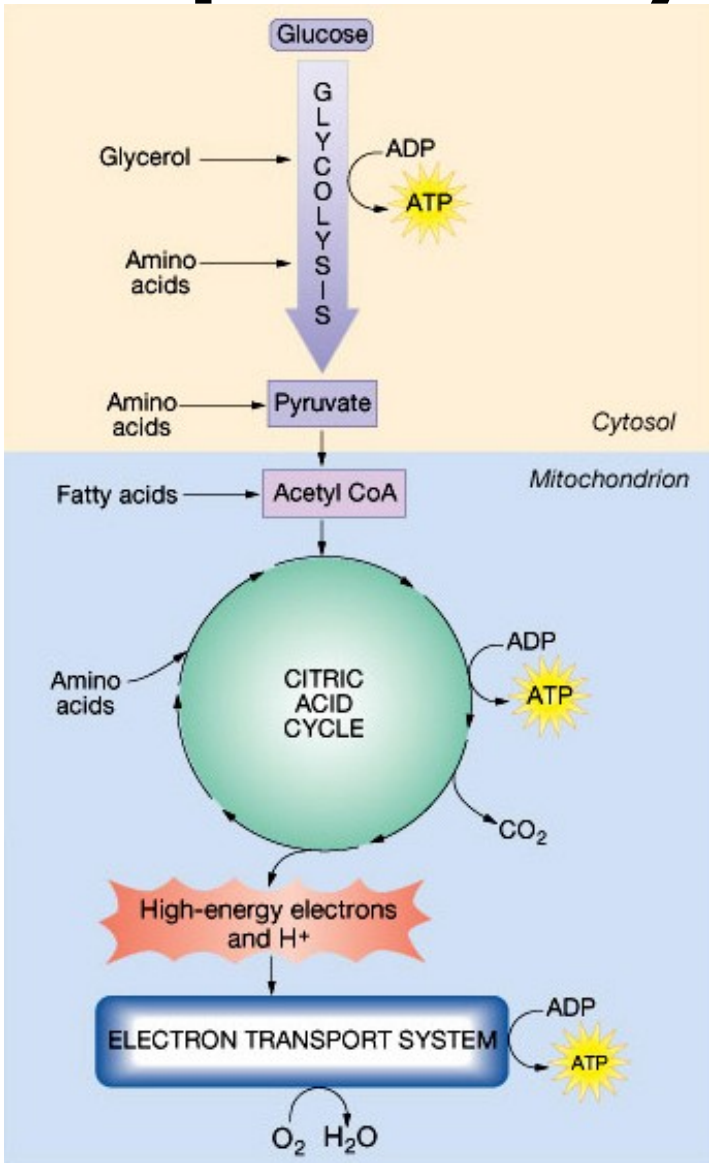
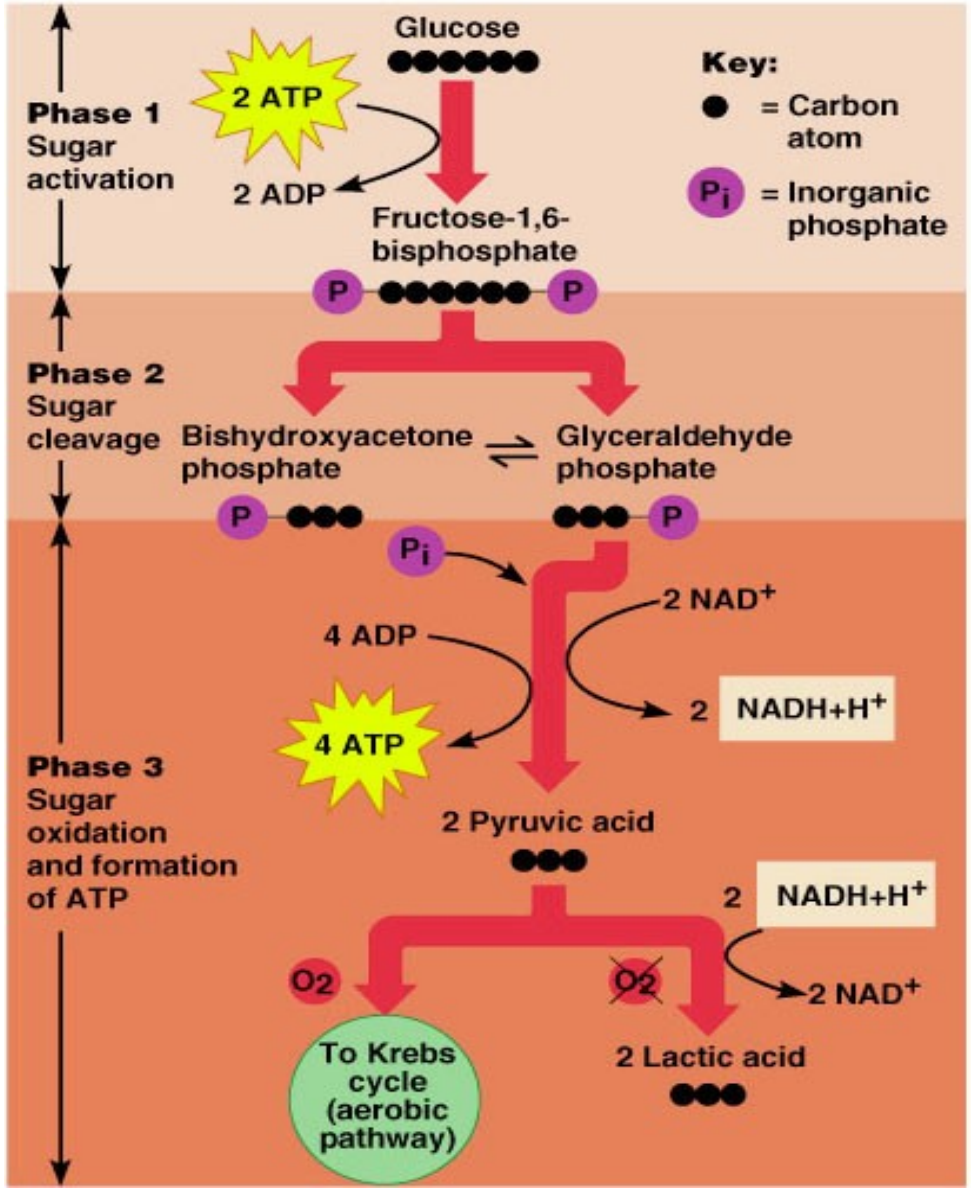
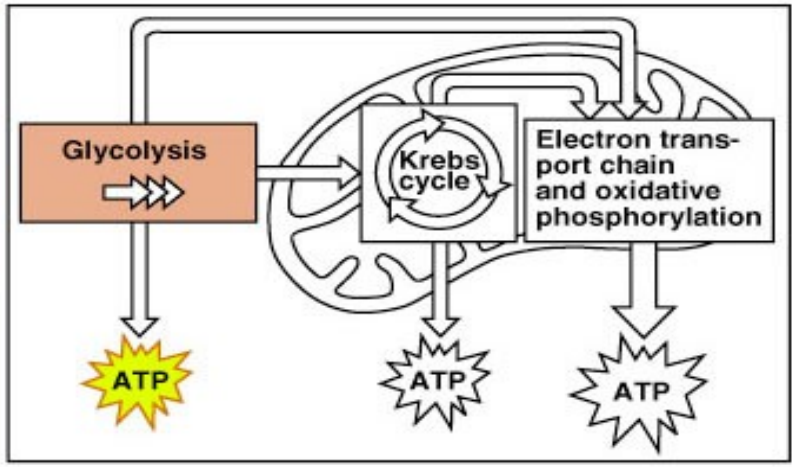
Metabolic pathways



Glycolysis





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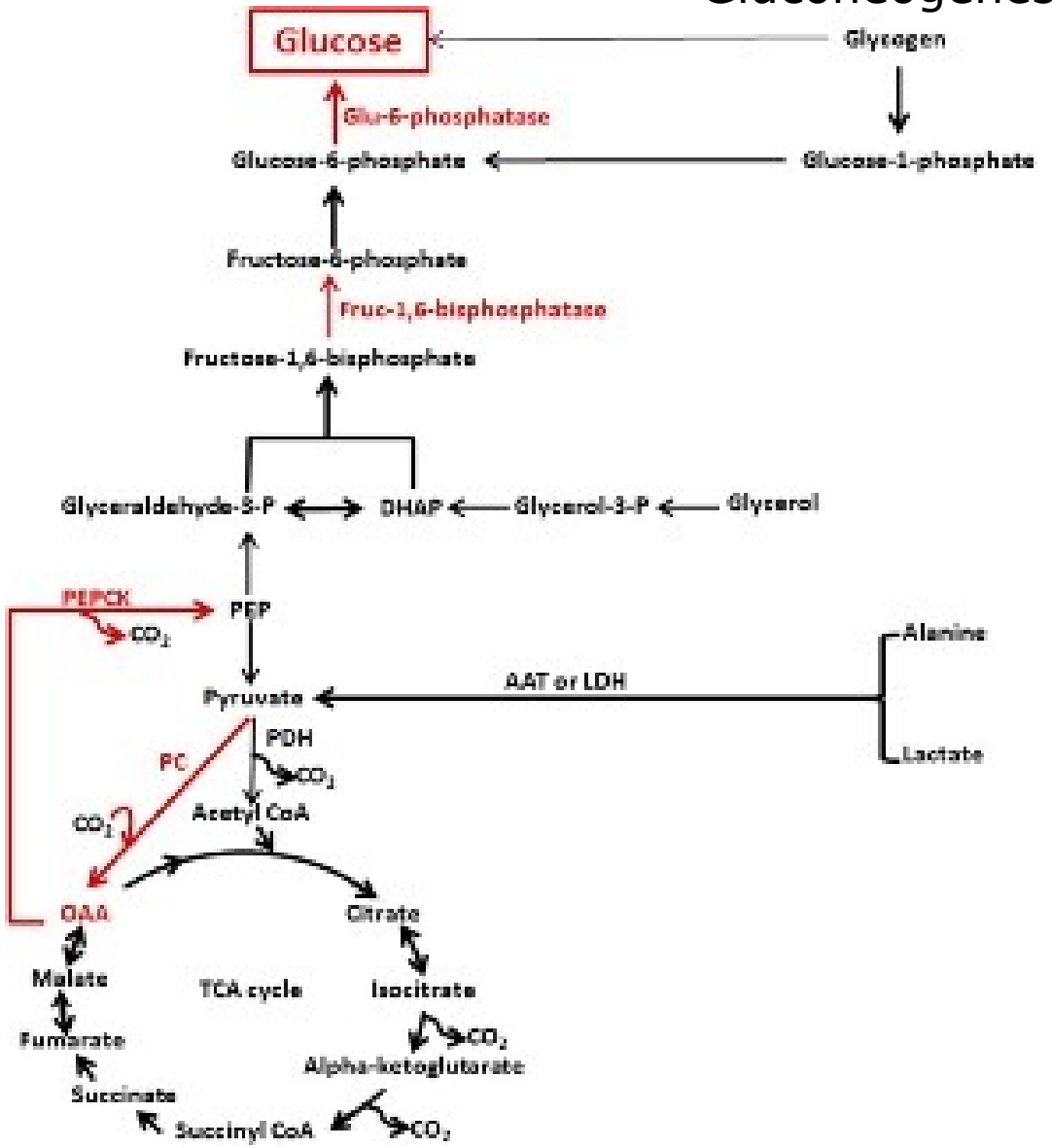
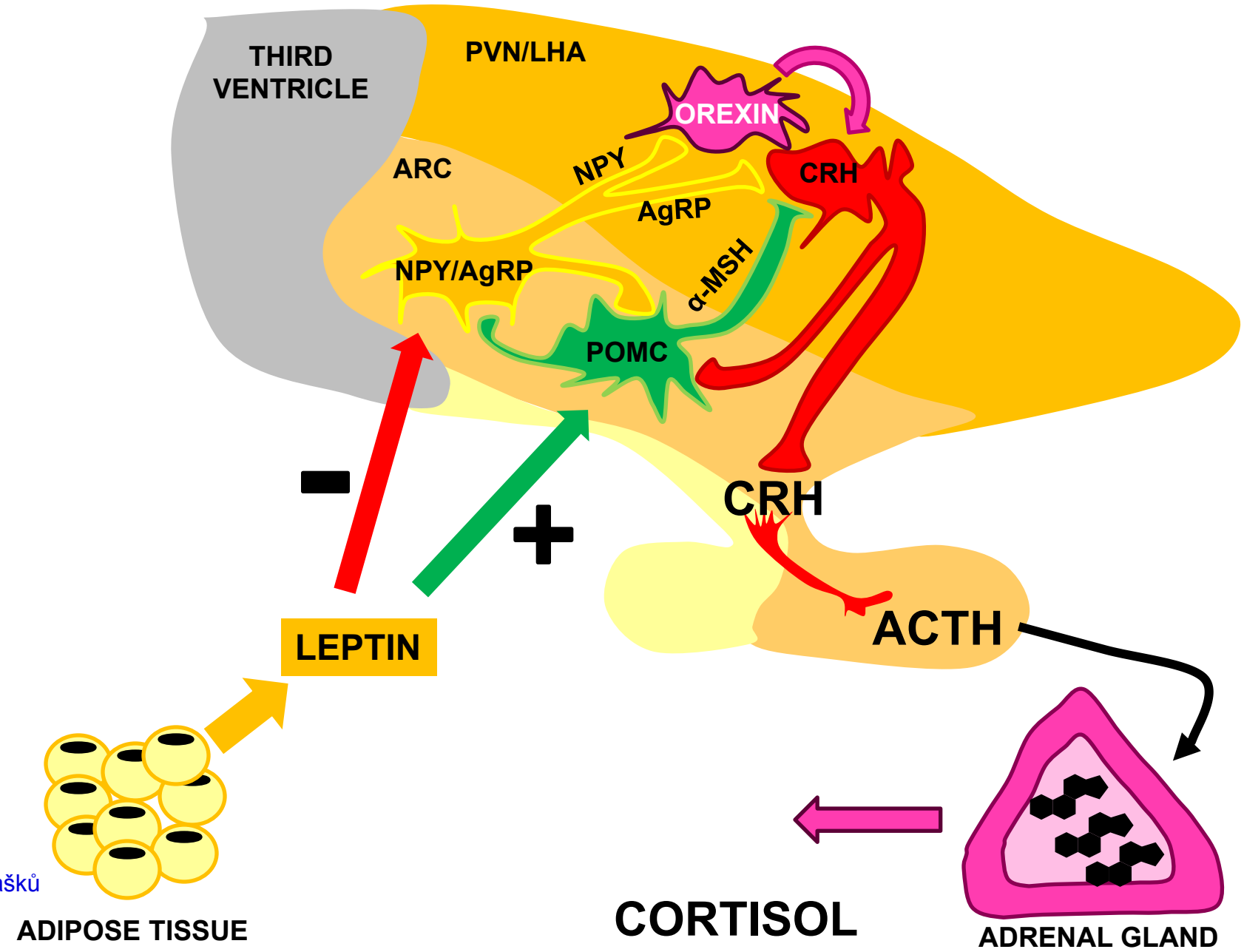
Gluconeogenesis



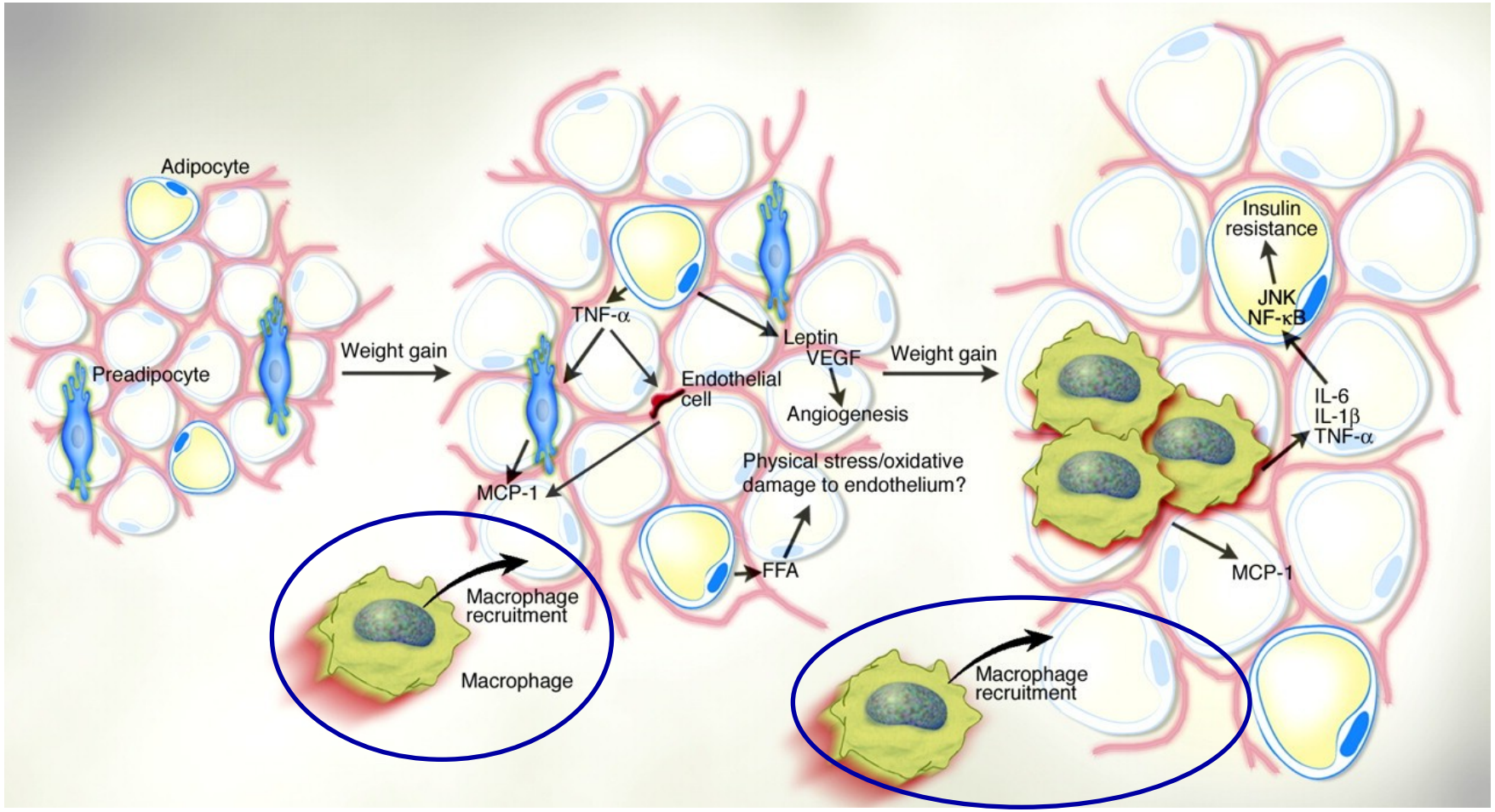
Major enzymes and substrates involved in the regulation of gluconeogenesis. Red arrows and text represent the major enzymes and pathways involved in the regulation of gluconeogenesis. Direct glucose release from glycogen via the debranching enzyme accounts for <10% of the total glucose made via gluconeogenesis.

AAT, alanine aminotransferase;
fruc-1,6-bisphosphatase, fructose-1,6-bisphosphatase;
glu-6-phosphatase, glucose-6-phosphatase;
glyceraldehyde-3-P, glyceraldehyde-3-phosphate;
glycerol-3-P, glycerol-3-phosphate;
LDH, lactate dehydrogenase;
OAA, oxaloacetate;
PC, pyruvate carboxylase;
PDH, pyruvate dehydrogenase
phosphoenolpyruvate carboxykinase (PEPCK)

RELATIONS TO GLUCOCORTICOIDS

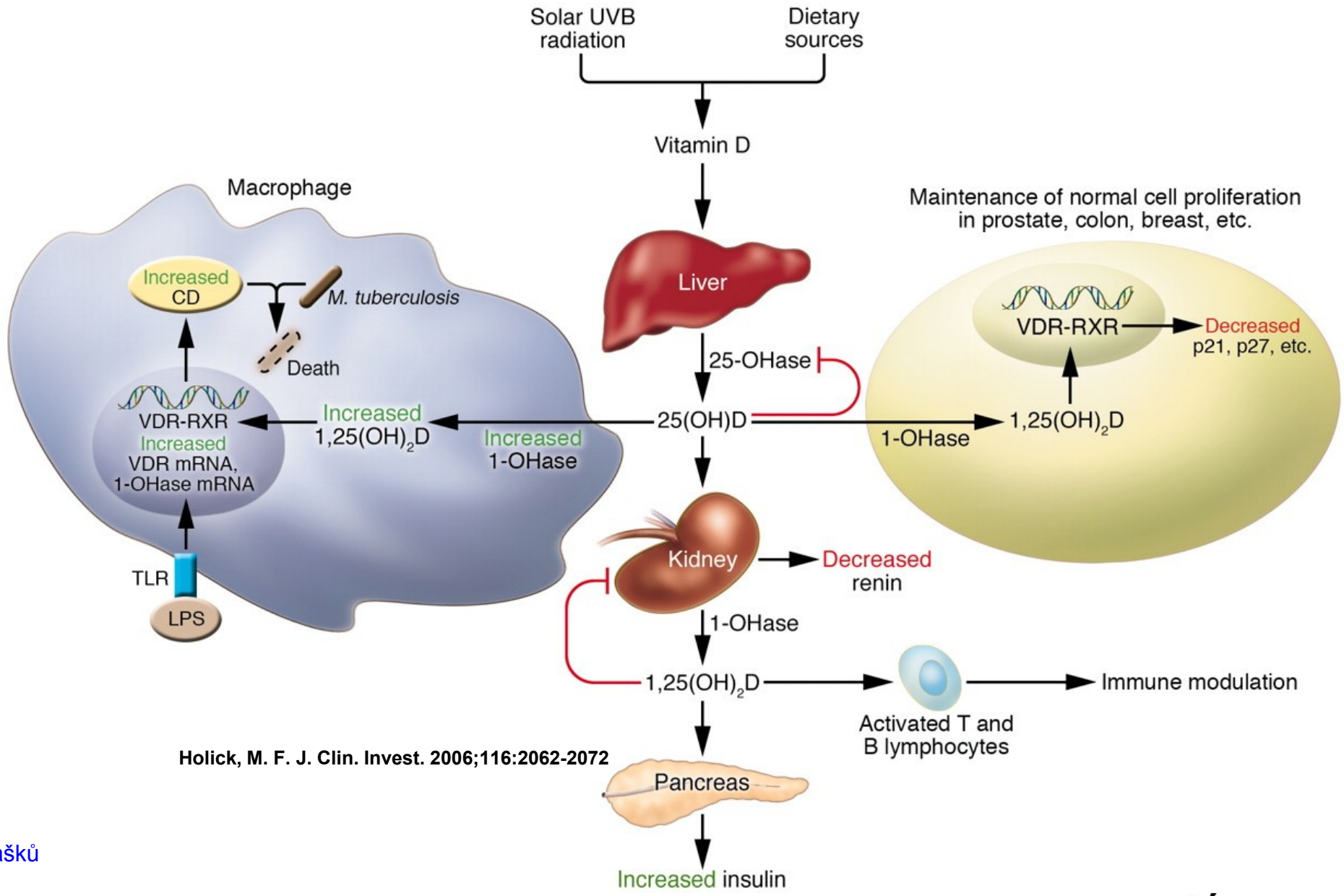


Obesity is associated with local inflammatory response in FAT



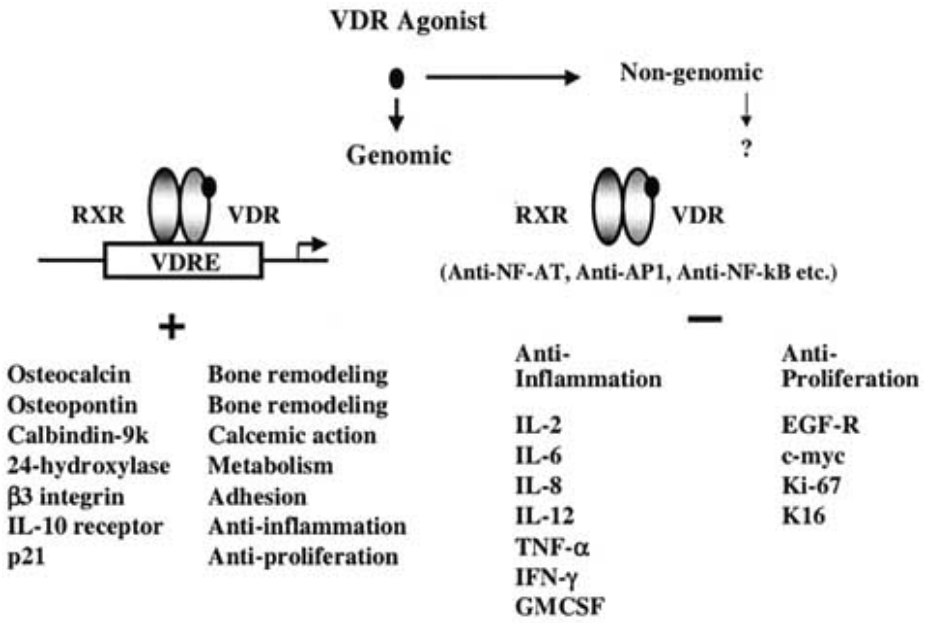
Vitamins soluble in lipids

- Vitamins A, D and K directly modify state of the bone.
- Their levels are dependent on composition of food (sufficient amount of fat is necessary for their absorption)
- State of the bone is related fo functional state of insulin and leptin (insulin and leptin sensitivity and rezistance)



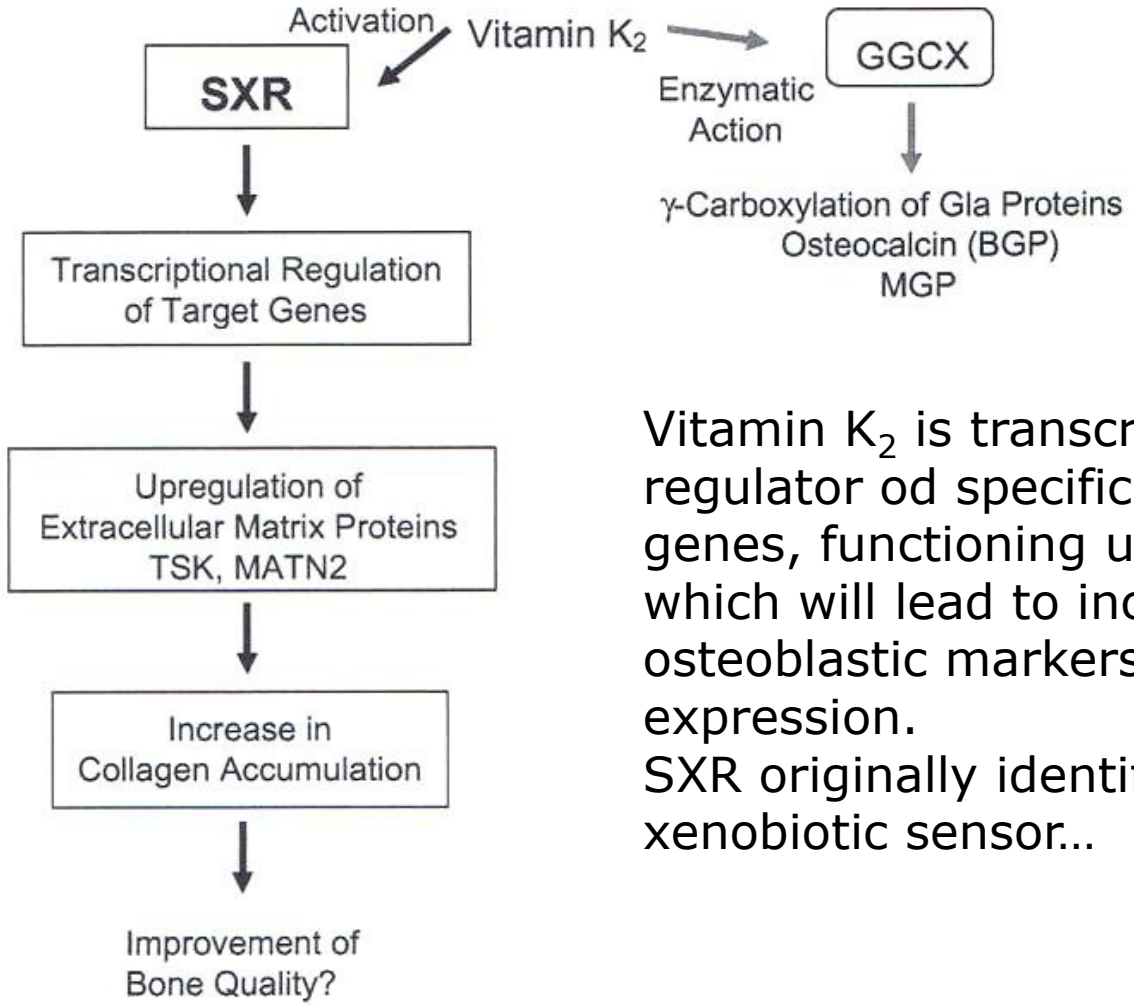
Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

Regulation of gene expresssion by VDR



Vitamin K and bones

- Vitamin K_2 is substantial cofactor for γ-carboxylase, enzyme which catalyses conversion of specific residuals of glutamic acid to Gla residuals
- Vitamin K_2 is necessary for γ-carboxylation of proteins of bone matrix which contain Gla as MGP (= matrix Gla protein) a osteokalcin.
- Uncompleted γ-carboxylation of osteocalcin and MGP during vitamin K decrease lead to osteoporosis and high risk of fractures. Vitamin K_2 stimulates synthesis of osteoblastic markers and bone deposition.
- Vitamin K_2 decreases bone reabsorbtion by inhibition of osteclasts formation and by decrease of their resorbtion activity.
- Vitamin K_2 treatment induces osteoclast apoptosis, but inhibits osteoblasts apoptosis which is leading to increased bone formation.
- Vitamin K_2 supports osteocalcin expression (increases its mRNA) which can be further modulated by 1, 25-$(OH)_2$ vitamin D_3.



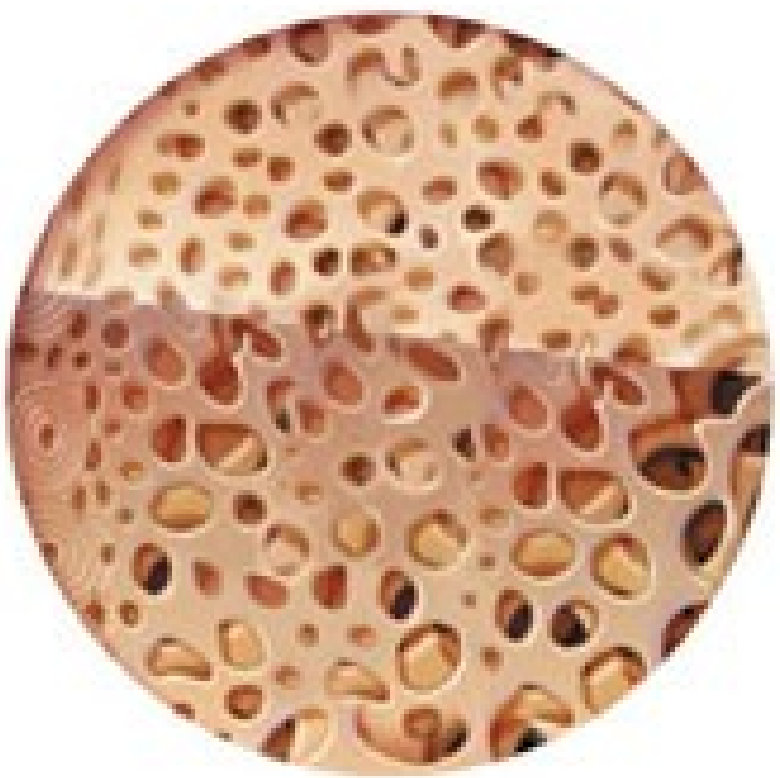
Vitamin K_2 is transcription regulator od specific bone genes, functioning using SXR which will lead to increase of osteoblastic markers expression.
SXR originally identifies as xenobiotic sensor…

Fig. 3. SXR- and vitamin K_2-dependent regulatory mechanisms of bone metabolism in osteoblastic cells. SXR promotes collagen accumulation in osteoblastic cells by regulating the transcription of its target genes including those encode extracellular matrix proteins. Vitamin K_2 plays a role in the posttranslational modification of Gla proteins by functioning as a coenzyme of γ-glutamyl carboxylase (GGCX) and also acts as a potent SXR ligand in bone metabolism

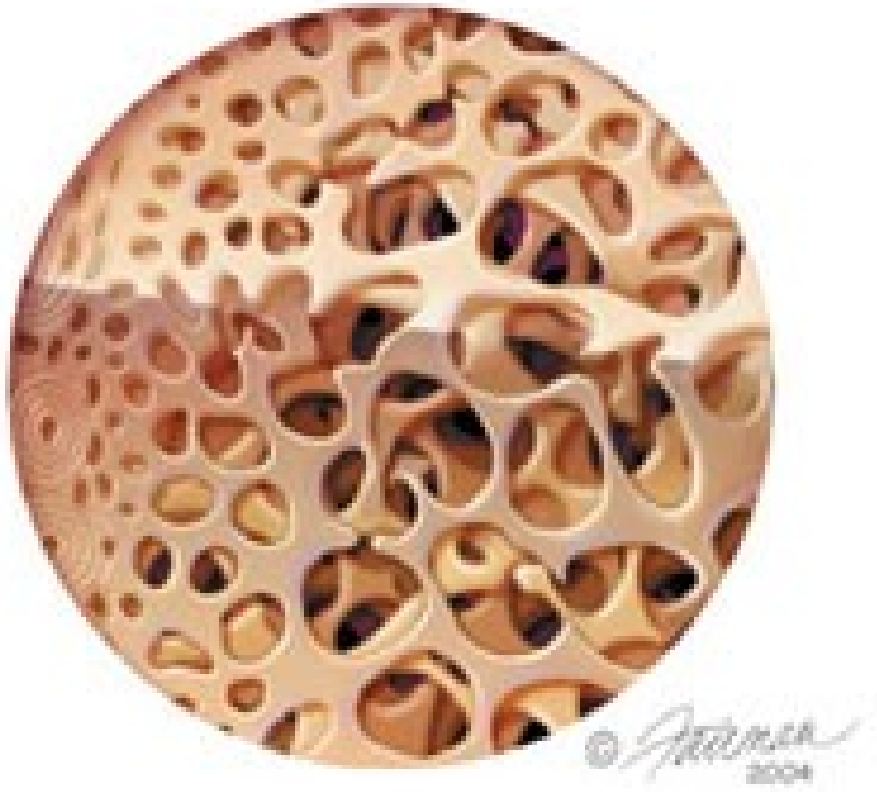
Osteoporosis

- is a skeletal disease characterised by low bone mass and microarchitectural deterioration with a resulting increase in bone fragility and hence susceptibility to fracture.
- It is an important public health issue because of the potentially devastating results and high cumulative rate of fractures; in white populations, about 50% of women and 20% of men older than 50 years will have a fragility fracture in their remaining lifetime.

Osteoporosis



Normal



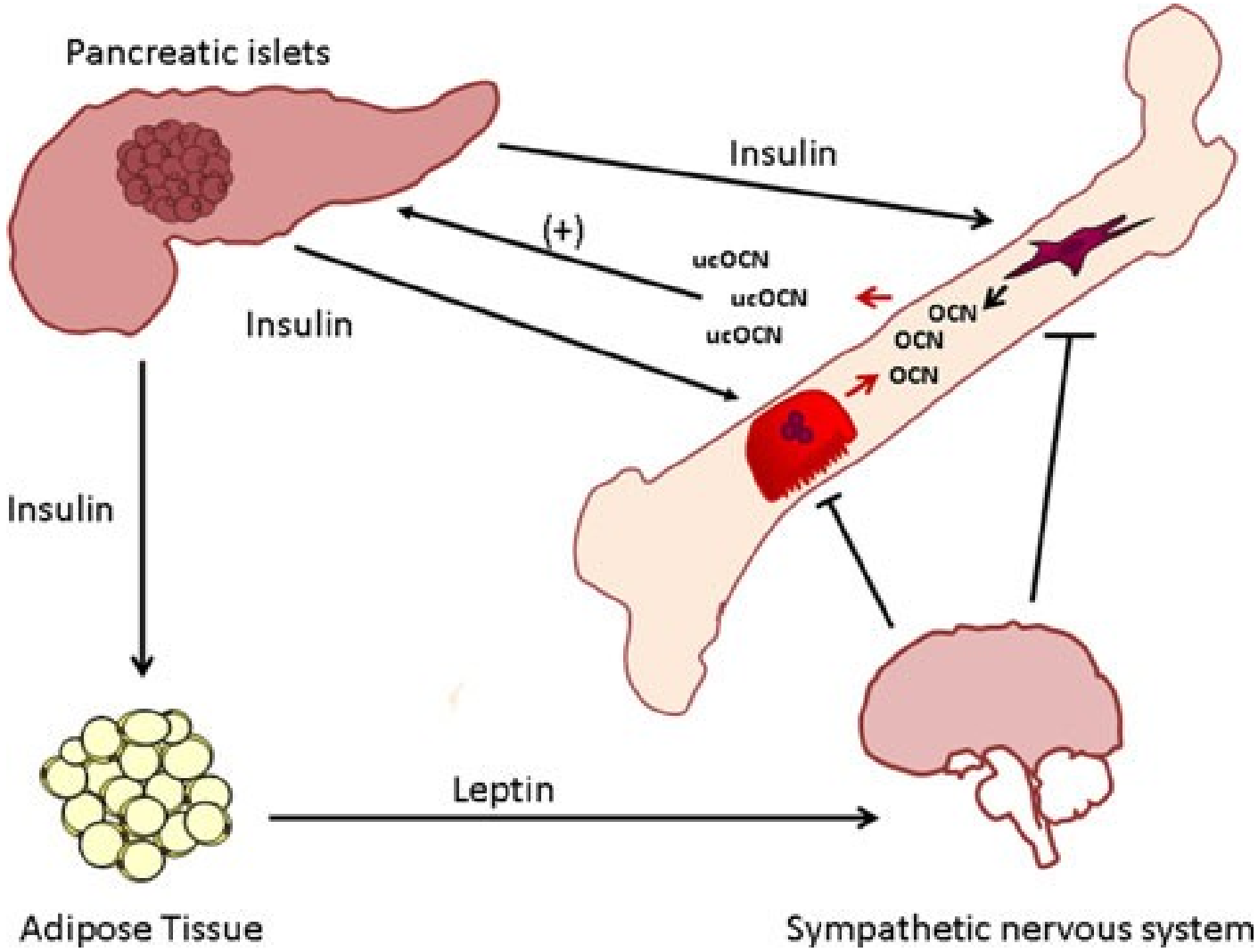
Osteoporotic bone

Osteoporosis

- Oestrogen has a central role in normal physiological remodelling, and oestrogen deficiency after the menopause results in a remodelling imbalance with a substantial increase in bone turnover.
- This imbalance leads to a progressive loss of trabecular bone, partly because of increased osteoclastogenesis.
- Enhanced formation of functional osteoclasts seems to be the result of increased elaboration of osteoclastogenic proinflammatory cytokines such as interleukin-1 and tumour necrosis factor, which are negatively regulated by oestrogen.
- A direct effect of oestrogen in accelerating osteoclast apoptosis has also been attributed to increased production of transforming growth factor β.

Osteoporosis - causes

- Glucocorticoids excess
- Estrogene deficiency
- Vitamin K2 deficiency?

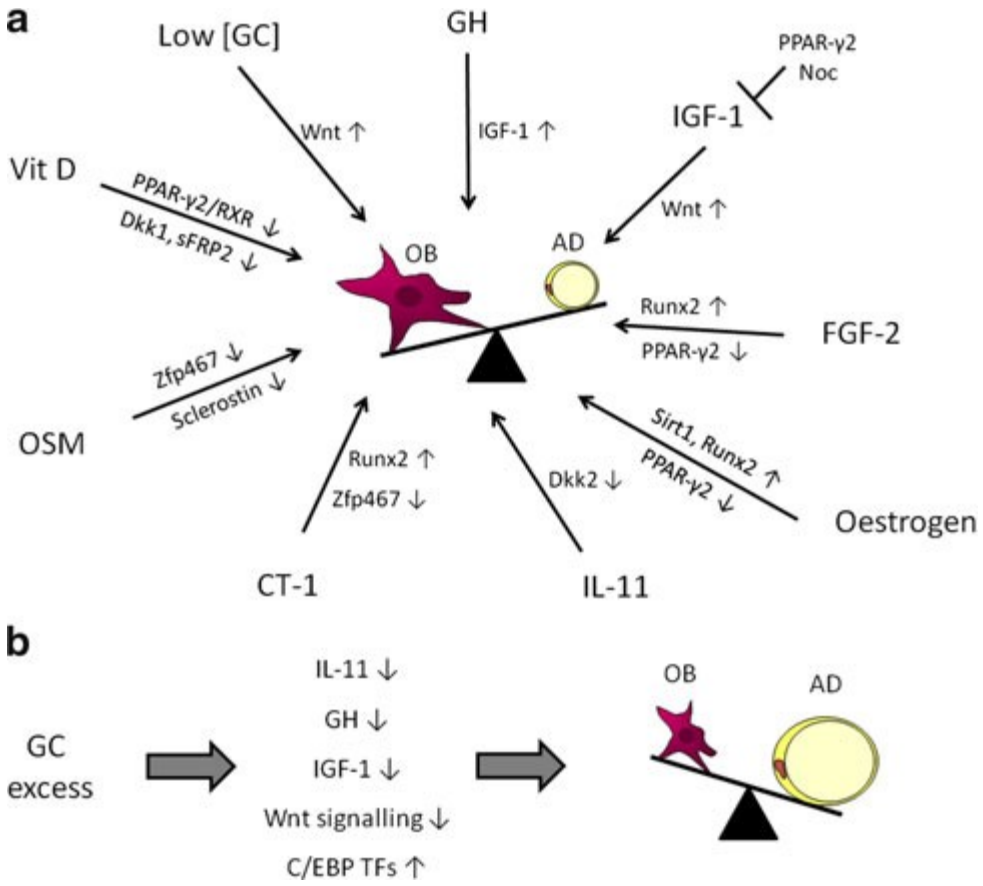


Cortisol generally antagonizes insulin …

Equilibrium between osteoblastogenesis (OB) and adipogenesis (AD)

a) Several endogenic factors support osteoblastogenesis against adipogenesis.
b) High levels of cortisol prefer adipogenesis to osteoblastogenesis

Low [GC] low (physiological) concentrations of glucocorticoids, GH- growth hormone, IGF-1 insulin-like
growth factor-1, FGF-2 fibroblast growth factor-2, IL-11 interleukin-
11, CT-1 cardiotrophin-1, OSM oncostatin M, OB osteoblast, AD-adipocyte



Common adverse effects of glucocorticoid therapy

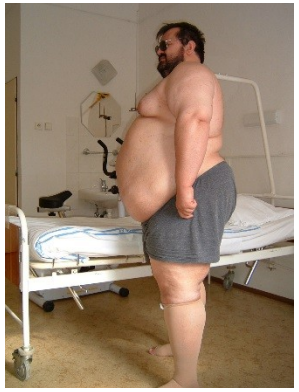
- There is substantial and accelerated decreases in bone mineral density (BMD) with oral glucocorticoid therapy, most pronounced in the first year, with trabecular bone more quickly affected than cortical bone.
- Even after only 2 months of high-dose glucocorticoids, studies show markedly decreased BMD at the lumbar spine, femoral neck and whole body, with the greatest loss in the trabecular lumbar vertebrae.
- In light of the high incidence of glucocorticoid-induced osteoporosis and associated fractures, screening and treatment rates for glucocorticoid-induced osteoporosis has come under substantial scrutiny.
- Less than 50% of patients receiving long-term glucocorticoids have been evaluated for osteoporosis, and less than 25% have been treated. There is great variability among clinicians in both the awareness of glucocorticoid-induced osteoporosis and the importance of prevention and treatment as the standard of care.
- The use of antiosteoporotic medication was observed to be most common among postmenopausal women, where it approached 50%.

Common adverse effects of glucocorticoid therapy-

glucocorticoid-induced osteoporosis

- Glucocorticoid-induced osteoporosis is the most common type of iatrogenic osteoporosis and a frequent cause of secondary osteoporosis.
- An estimated 50% of patients taking glucocorticoids for longer than 6 months will develop secondary osteoporosis .
- The absolute risk for glucocorticoid-induced osteoporosis is higher in patients aged 65 years or older given their baseline age-related fracture risk, although the relative risk of fracture related to glucocorticoid use may be even higher in patients under 65 .

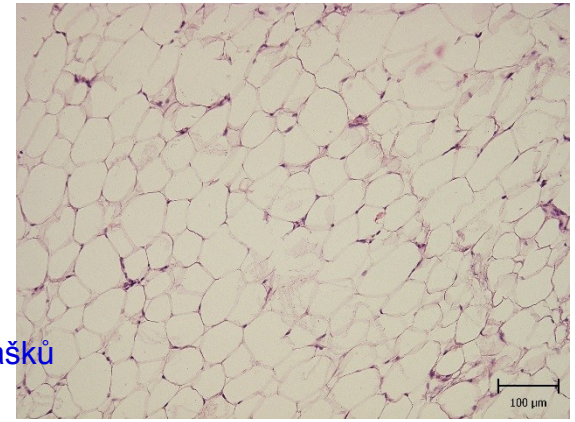
Size and endocrine profil of adipocytes is correlated with the whole adiposity

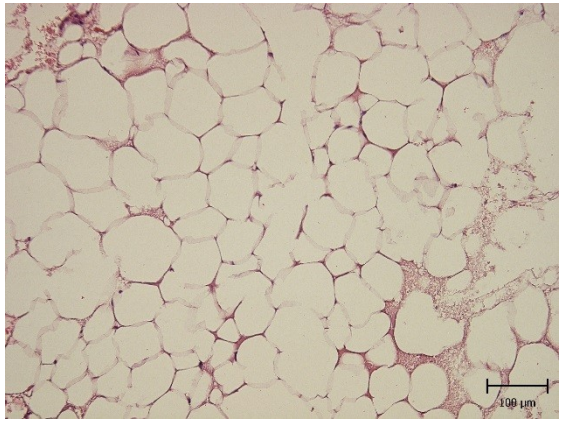


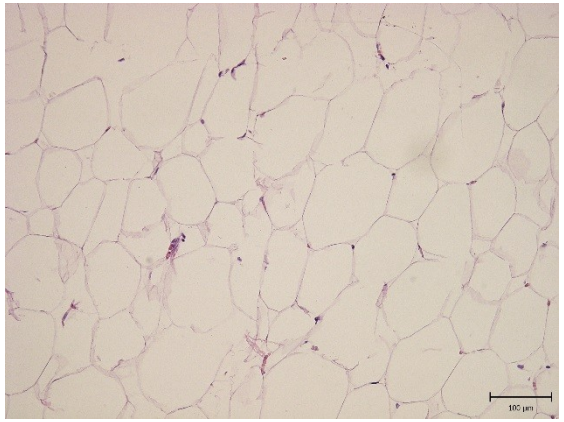
Malnutrition
(Anorexia nervosa)

Normal state (slight overweight))

Obesity







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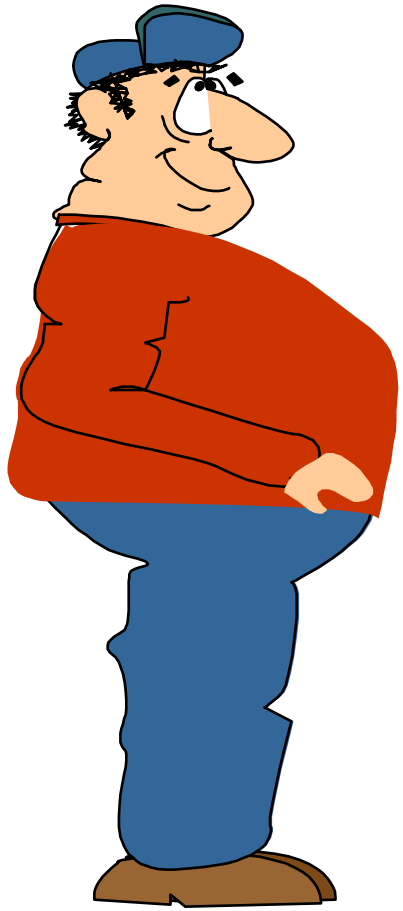
Diagnostic criteria of obesity (BMI)

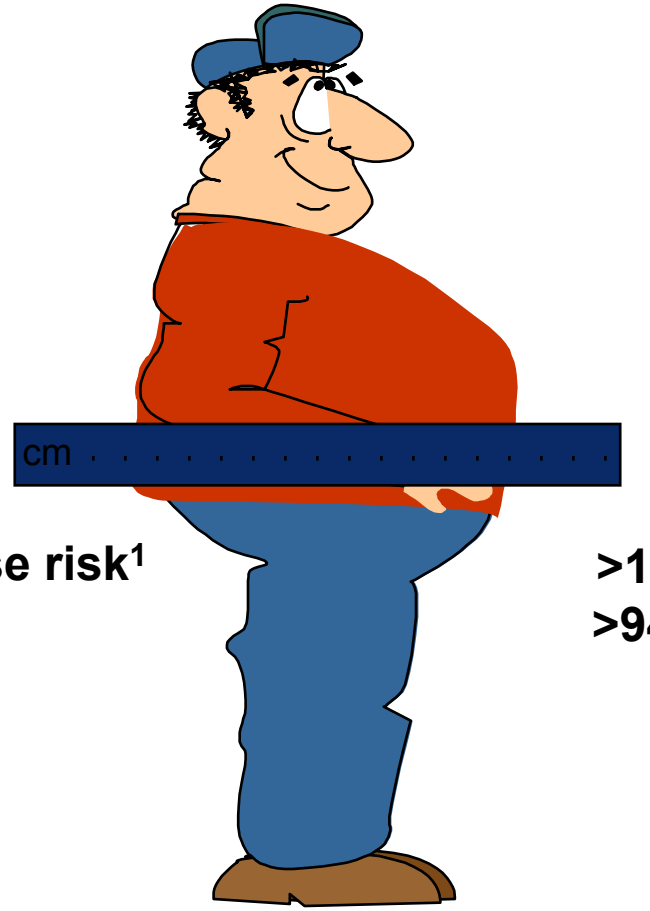


$$BMI = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$$

Classification	BMI (kg/m^2)	metabolic rate
Normal body weight	18.5–24.9	average
Overweight	25–29.9	increased
Obesity I	30.0–34.9	middle
Obesity II	35.0–39.9	high
Obesity III	≥40.0	very high

WHO, 1998

waist size seems to be the best indicator of visceral obesity



Women

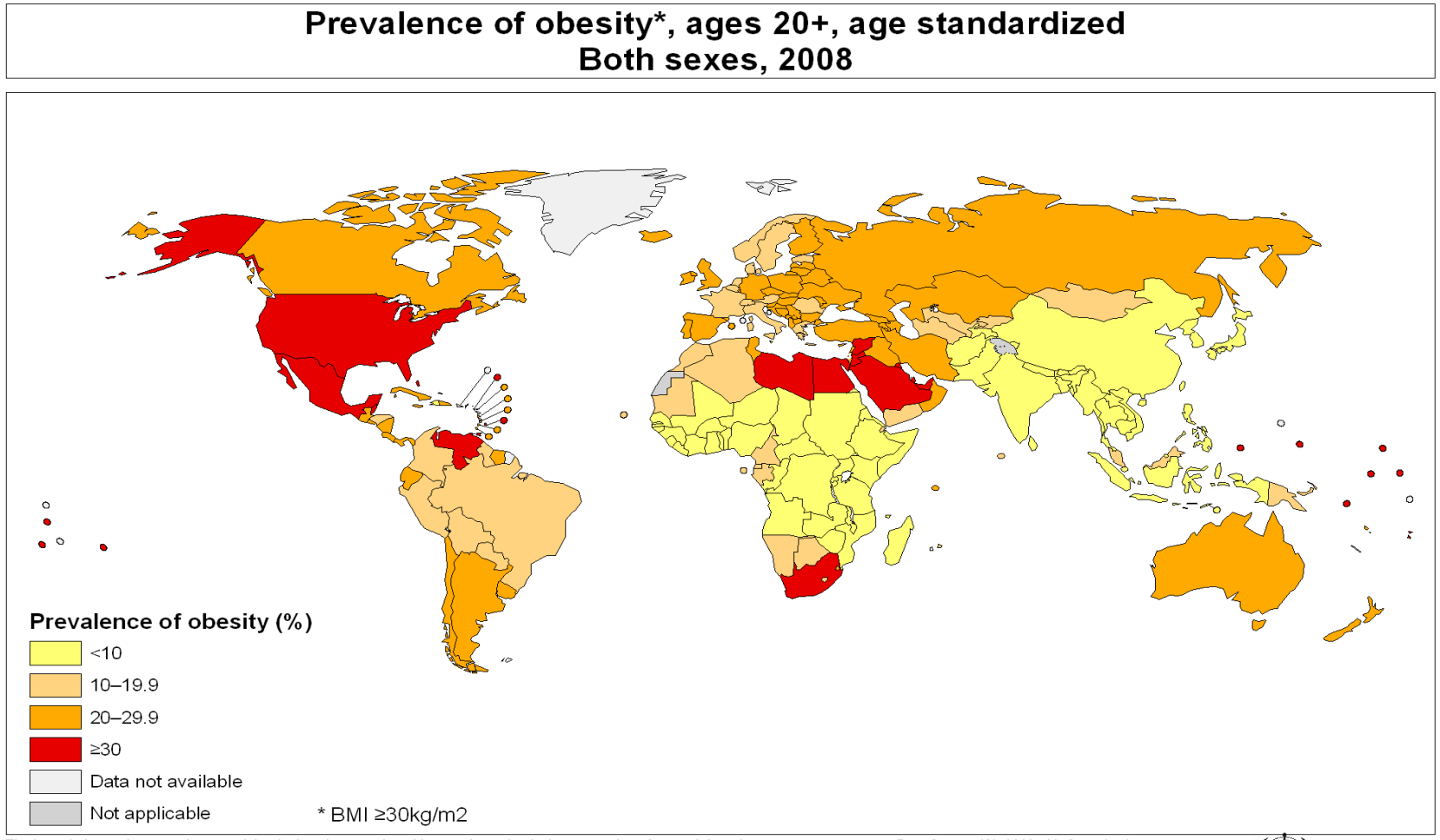
>88 cm = highly increase risk[1]
>80 cm = higher risk[1]

Men

>102 cm = highly increased risk[1]
>94 cm = higher risk[1]

[1]Lean MEJ, et al. Lancet;1998:351:853–6

STANDARDISED PREVALENCE OF OBESITY 2008



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

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OBESITY

Has obesity genetic background?

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- Argumenst why yes:
  - …nce in

HERITABILITy of OBESITY

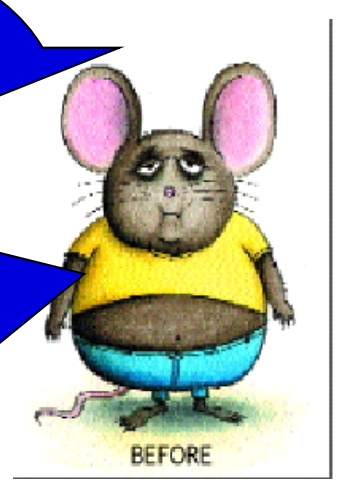
Family studies	**30-50%**
Adoption studies	**10-30%**
Twin studies	**50-90%**

GENETICS OF OBESITY – ARGUMENTS WHY NOT

IS OBESITY DONE BY
CULTURAL EATING HABITS?

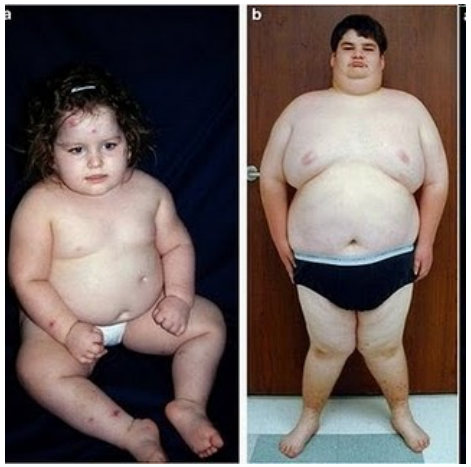
CLASSIFICATION OF OBESITY SYNDROMES

- pleiotropic syndromes with obesity
- „monogenic“ syndromes with obesity
- polygenic (complex) syndromes



PLEIOTROPIC SYNDROMES WITH OBESITY

About 30 syndromes, in which obesity represents constant component



MONOGENIC SYNDROMES WITH OBESITY

Genes Implicated in Monogenic Obesity and the Traits Found To Be Associated with Them in Genome-Wide Association Studies (GWAS)

Gene symbol	Gene name	Phenotype	Associated traits
BDNF	Brain-derived neurotrophic factor	Wilms tumor, aniridia, genitourinary anomalies, mental retardation, and obesity (WAGRO) syndrome	Obesity, BMI, weight
CART	Cocaine- and amphetamine-regulated transcript	Severe obesity	
LEP	Leptin	Morbid obesity due to leptin deficiency	
LEPR	Leptin receptor	Severe obesity due to leptin receptor deficiency	Serum level of C-reactive protein, serum level of leptin receptor
MC4R	Melanocortin-4 receptor	Early-onset severe obesity	Obesity, BMI, waist circumference, height, serum level of HDL cholesterol
NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	Early-onset severe obesity, hyperphagia, developmental delay	
PCSK1	Proprotein convertase subtilisin/kexin type 1 gene, or prohormone convertase 1	Early-onset severe obesity	BMI, serum proinsulin level, fasting serum glucose level (interaction with BMI)
POMC	Proopiomelanocortin	Early-onset severe obesity, adrenal insufficiency, red hair	Obesity, height
PPARG	Peroxisome proliferator-activated receptor gamma	Severe obesity, insulin resistance, lipodystrophy	Type 2 diabetes, fasting serum insulin level (interaction with BMI), plasma level of plasminogen activator inhibitor type 1
SIM1	Single-minded homolog 1 (Drosophila)	Early-onset severe obesity, Prader-Willi syndrome	

Note. BMI, body mass index; HDL, high-density lipoprotein.

N C Med J. 2013; 74(6):530-533

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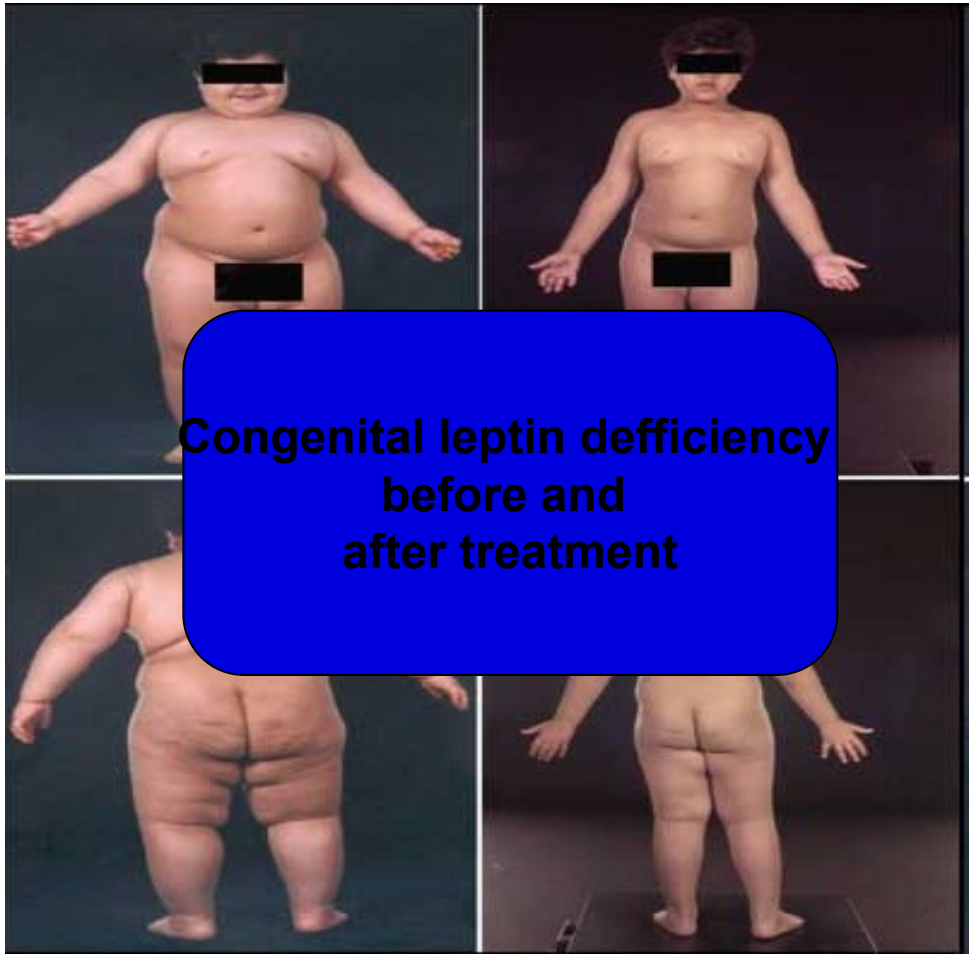
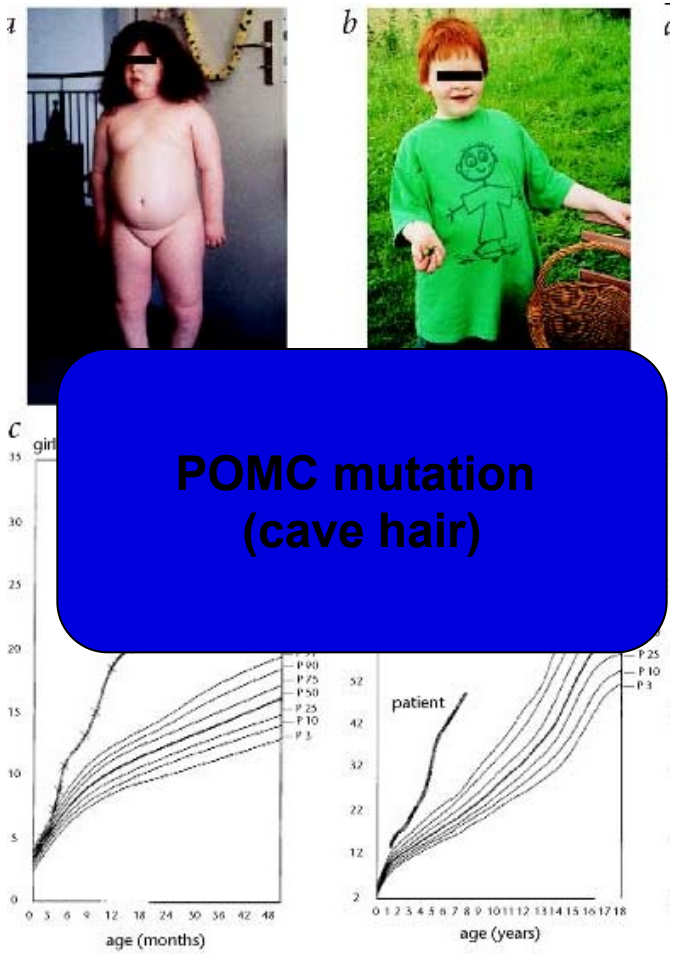
MONOGENIC OBESITY SYNDROMES



Congenital leptin defficiency before and after treatment

Prof.Stephen O'Rahilly, MD and I. Sadaf Farooqi, MD



POMC mutation (cave hair)

Heiko Krude, Heike Biebermann, Werner Luck, Rüdiger Horn, Georg Brabant & Annette Grüters

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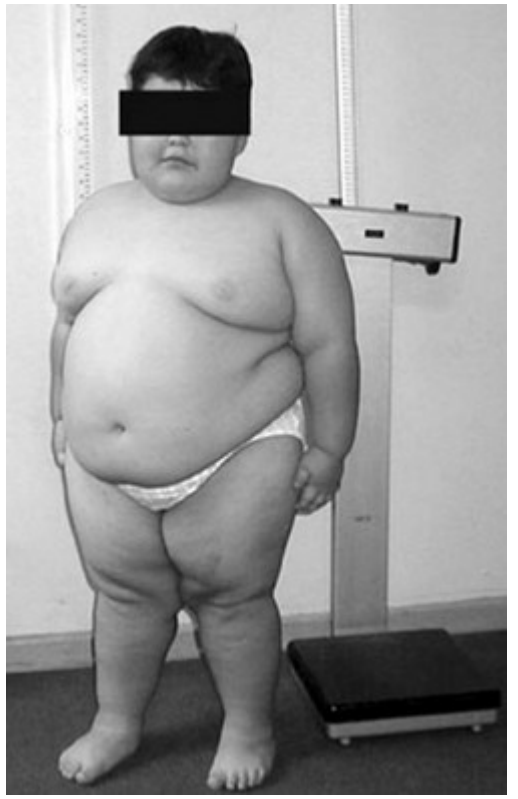
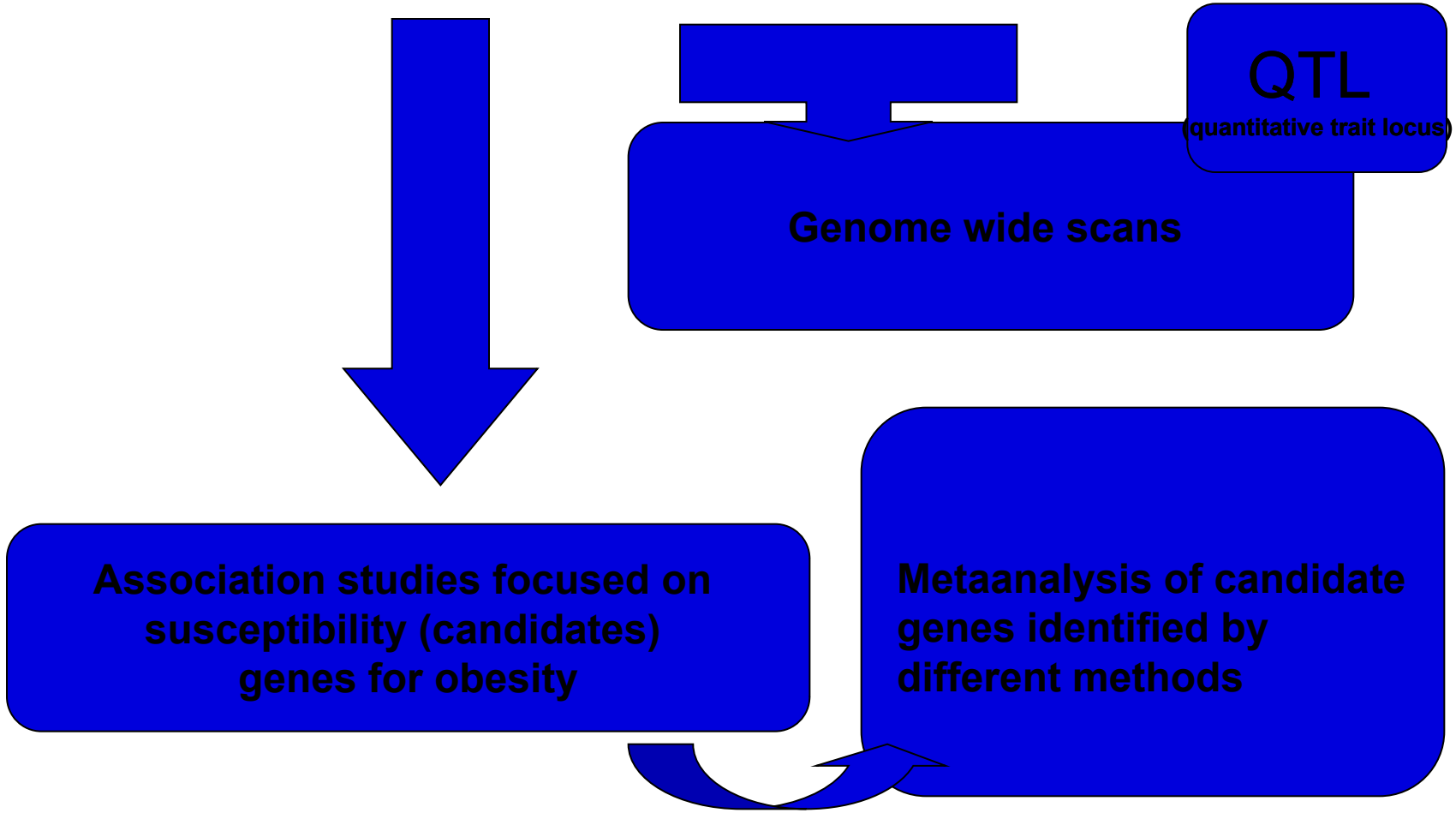
Sy Prader- Willi as a clinical example

- Hypotonic children, mental retardation, small figure, behavioral complacations (hyperphagy as a result of incontrolled appetite – one of the most common causes of children obesity)
- Loss of expression of paternally imprinted genes at15q11.2-q13 chromosome as a result of microdeletion in the region.



OBESITY AS A COMMON (COMPLEX) DISEASE

- Susceptibility genes



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Future

- BMC Med. 2017; 15: 50.
- Published online 2017 Mar 7. doi: 10.1186/s12916-017-0800-1
- PMCID: PMC5340003
- **Developmental pathways to adiposity begin before birth and are influenced by genotype, prenatal environment and epigenome**
- Xinyi Lin,[#1] Ives Yubin Lim,[#1,2] Yonghui Wu,[1] Ai Ling Teh,[1] Li Chen,[1] Izzuddin M. Aris,[1] Shu E. Soh,[1,3] Mya Thway Tint,[2,3] Julia L. MacIsaac,[4] Alexander M. Morin,[4] Fabian Yap,[5] Kok Hian Tan,[5] Seang Mei Saw,[6,7,8] Michael S. Kobor,[4] Michael J. Meaney,[1,9] Keith M. Godfrey,[10] Yap Seng Chong,[1,2] Joanna D. Holbrook,[1] Yung Seng Lee,[1,3,11] Peter D. Gluckman,[1,12] Neerja Karnani,[1,13] and on behalf of the GUSTO study group

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Obesity as a complex disease

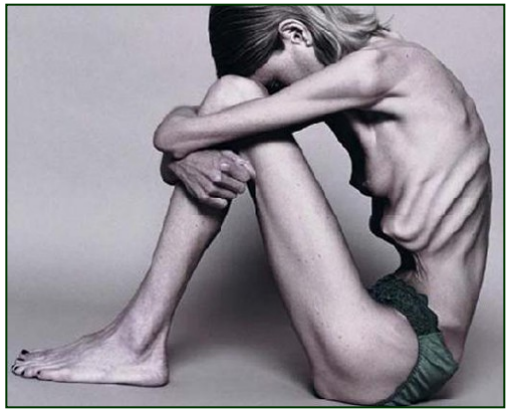
- Genetic, epigenetic and prenatal environmental factors are linked to offspring size and adiposity at birth and in early childhood.
- Individual prenatal environmental influences on birth weight was identified; some of these prenatal environment variables [maternal ppBMI, GWG („Gestational Weight Gain“) and glucose levels] continued to associate with offspring size and adiposity in early childhood.

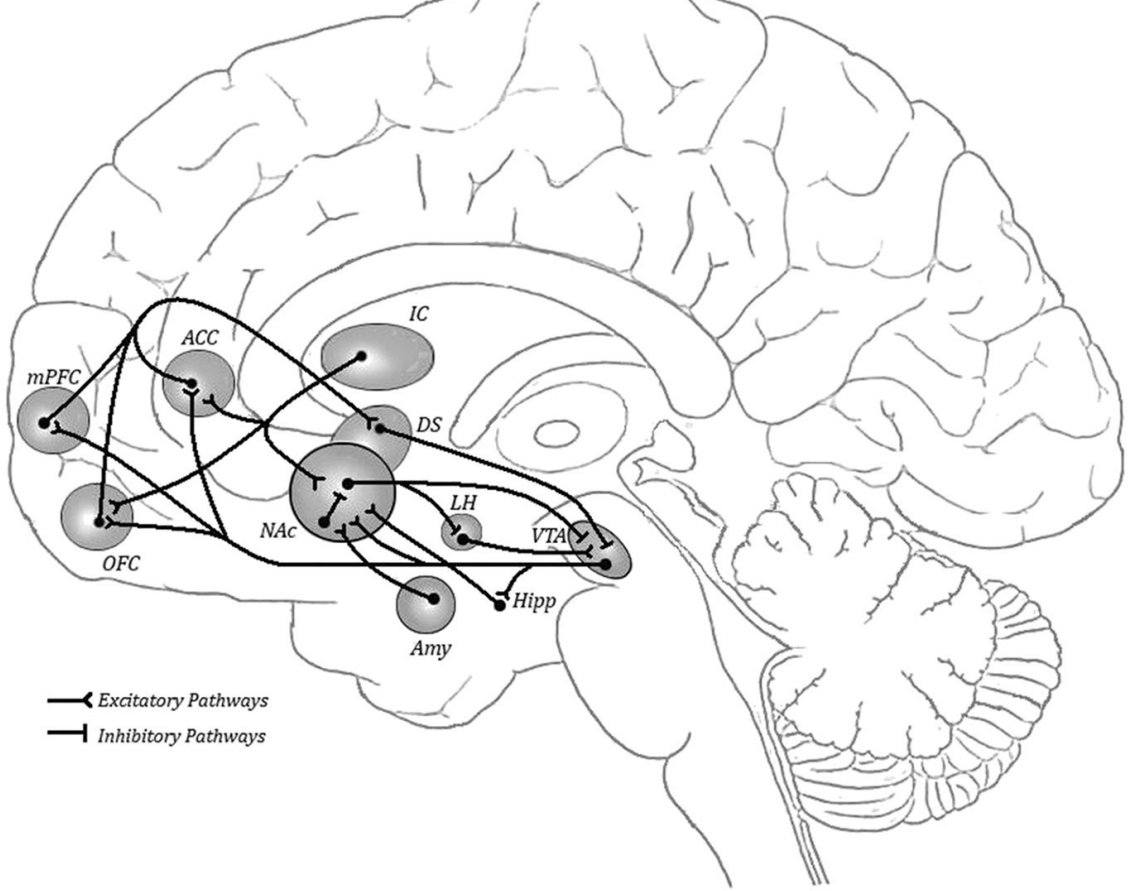
Obesity as a complex disease

- Genetic variation, as captured by PRS („Polygenic Risk Score“) , not only influenced birth weight, but also child size and adiposity up to 48 months of age, independent of birth weight.
- The PRS was constructed using adiposity-linked genetic risk variants previously reported in an adult population. The association of adult adiposity risk score with size and adiposity in pediatric population indicates that the effects of genetic risk variants can be detected as early as birth.

Anorexia nervosa (AN) and bulimia nervosa (BN)

- are complex psychiatric disorders of great importance for public health policies, as they are associated with a high burden of morbidity and mortality due to their severe medical and psychological consequences. Etiopathogenesis of these eating disorders (EDs) continues to remain elusive, with the result that their treatment is often unsuccessful.
- AN is a severe psychiatric disorder leading to life-threatening weight and fat loss. This illness could be characterized by irrational fear of becoming fat, abnormal eating behavior, hyperactivity, GIT complications and wide variety alterations of hormonal and metabolic systems.
- The exact etiopathogenesis is unknown and the way of treatment remain limited.





Schematic representation of brain reward circuits.
ACC anterior cingulated cortex; Amy amygdala; DS dorsal striatum; Hipp hippocampus; IC insular cortex; LH lateral hypothalamus; mPFC medial prefrontal cortex; NAc nucleus accumbens; OFC orbitofrontal cortex; VTA ventral tegmental area.

The brain reward system integrates basic and emotional stimuli, such as hunger, satiety, desire, pleasure and fear, with higher order cognitive processes aimed at modulating further actions or representation of the general experience. These high order processes involve anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (PFC), which are necessary for identification of rewarding stimuli, inhibition of emotional responses, and promote behavioral outcomes (Haber and Knutson, 2010; Wittman *et al.*, 2010 ; Sripada *et al.*, 2011). Overall, the PFC provides inhibitory influences on motivation and reward-directed behavior, integrating sensory inputs, memories, goals, and physiological states with the aim to provide an adequate performance (Miller and Cohen, 2001). ACC and dorsolateral prefrontal cortex (DLPFC) may also serve to monitor potential conflict situations induced by reward stimuli (Walton *et al.*, 2003 ; Vogt *et al.*, 2005). Therefore, they have a *gating role* in action selection following reward cues (Goldstein and Volkow, 2011). Indeed, by a top-down effect, both OFC and ACC provide a negative feedback to mesolimbic areas regulating reward-seeking motivation (Goldstein and Volkow, 2011).

Anorexia nervosa (AN) and bulimia nervosa (BN)

- Functional magnetic resonance imaging (fMRI) techniques have been employed to investigate the brain's processing of reward elicited by both food-related and non-food-related stimuli in AN and BN (O'Hara et al., 2015).
- It has been shown that, compared to healthy controls, AN patients exhibit abnormal activation of different brain areas, including the parietal, the orbito-frontal, the dorso-lateral prefrontal, the anterior cingulate and the medial prefrontal cortex (Frank, 2015a ; Frank, 2015b) after exposure to visual food cues, especially for highly palatable foods.
- Similarly, altered insula, striatum or orbitofrontal responses to sweet stimuli have been found in recovered or symptomatic AN and BN patients.
- These findings suggest a dysregulation of brain mechanisms involved in the processing of food-related rewarding stimuli in the pathophysiology of EDs.

Pathophysiology of AN

- An integral pathophysiological scenario that fits to the natural history of AN with the following steps an be porposed:
- (1) enhanced vulnerability to stress (genetic, epigenetic, or environmental factors);
- (2) major stressing events activating the stress-axis, increased intestinal permeability, and increased virulence of the microbiota;
- (3) bacterial proteins (e.g., ClpB) challenge the immune response and due to molecular mimicry, cause increased production of Igs cross-reactive with neuropeptides (e.g., α-MSH);
- (4) this results in altered food intake, anxiety, gastrointestinal discomfort and other consequences of altered central and peripheral melanocortin signaling;
- (5) global malnutrition and some specific macro- and micro-nutrient deficiencies contribute to the perpetuation of gut barrier and immune dysfunction as well as behavioral symptoms.

Front Neurosci. 2016; 10: 256

Orexigenic neuropeptides

- Orexigenic neuropeptides including ghrelin, orexins and 26RFa are up-regulated in AN and it is thought that this orexigenic profile reflects an adaptive mechanism of the organism to promote food intake and thus to counteract undernutrition. However, this adaptive mechanism is ineffective in increasing food consumption leading to the concept of a global resistance of AN patients to orexigenic signals.
- We can speculate that a chronic increase of the activity of LHA orexigenic neurons expressing orexins, MCH, or 26RFa could reinforce dopamine-induced anxiety in the reward system of AN patients and thus the aversion to ingest food.

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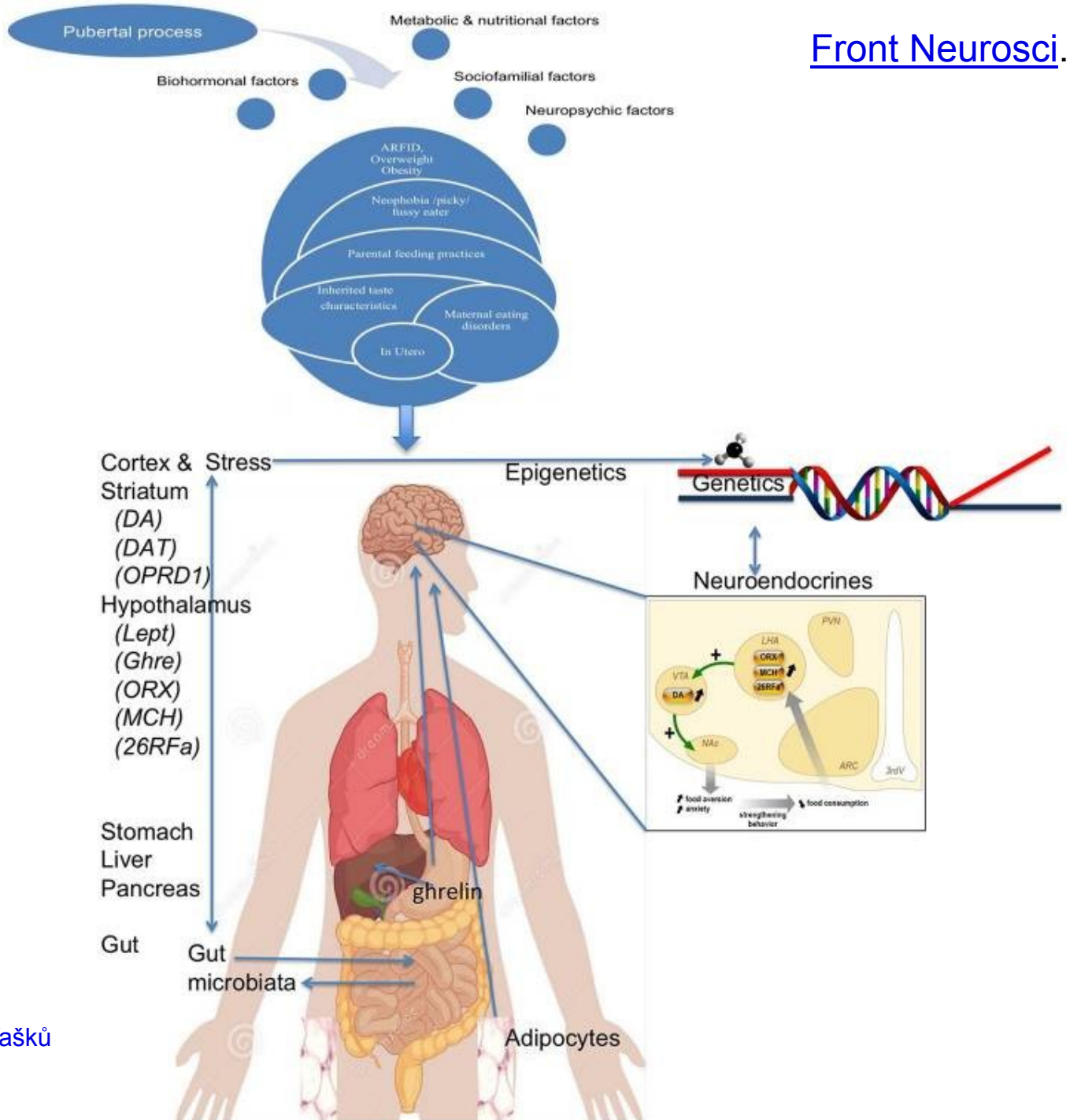

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Loss od adipose tissue is supposed to be the main factor contributing to the body weight loss

	Normal Weight (n = 50)	AN (n = 30)
Weight (kg)	62.2 ± 1.54	45.8 ± 1.89*
Lean mass (kg)	39.1 ± 0.76	37.8 ± 1.01
BMI (kg/m^2)	21.2 ± 0.42	15.7 ± 0.47*
Body fat content (%)	24.3 ± 0.79	7.1 ± 0.88*
Total fat skinfold (mm)	120.5 ± 12.17	42.1 ± 4.78*
Abdominal skinfold (mm)	12.5 ± 2.13	4.8 1.59*
Insulin (pmol/l)	28.3 ± 4.53	14.2 ± 3.67*
Glucose (mmol/l)	4.7 ± 0.08	4.1 ± 0.11
Menstruation	Yes - regular cycle	Secondary amenorrhea

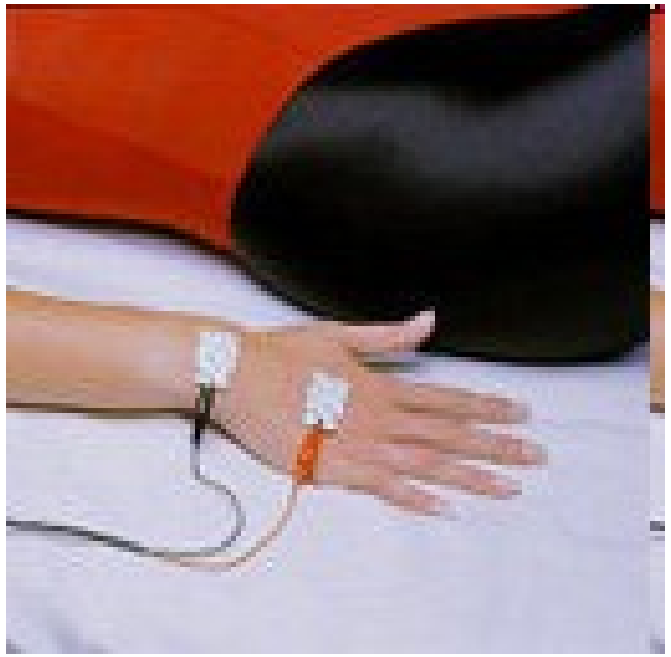
Means ± SEM

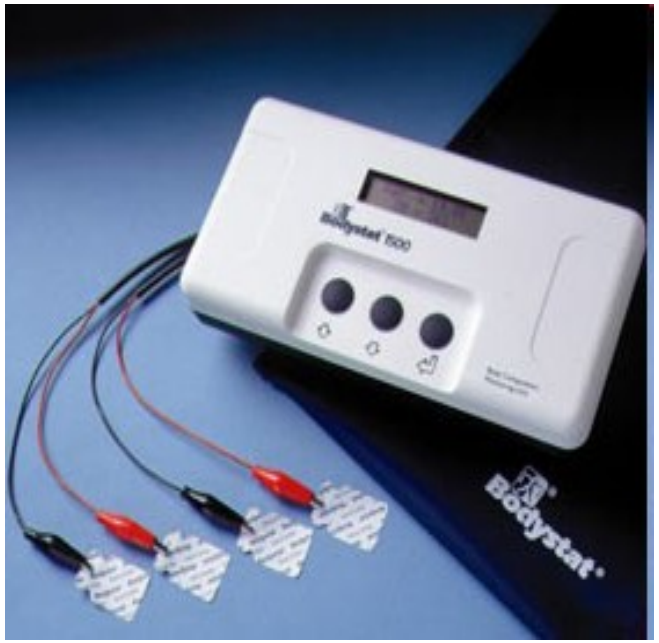
GENETIC ASSOCIATIONS???

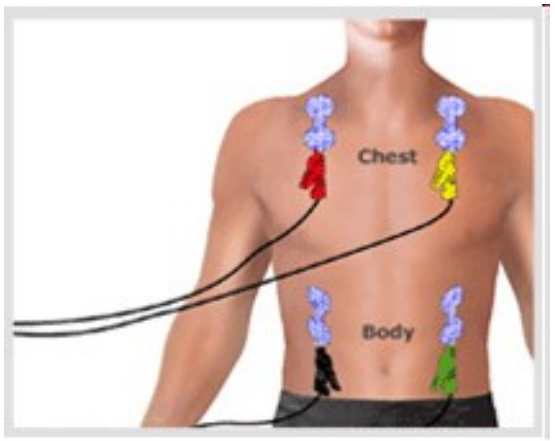
- AN is 11x more frequent in relatives of probands compared to physiological population.
- BN is 4-5x more frequent in relative women.
- ~15% risk of eating disorders in relatives of AN and BN vs. 4% risk in healthy population.

Strober et al. Am J Psychiatry 2000; 157:393

BODYSTAT







Děkuji vám za pozornost

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