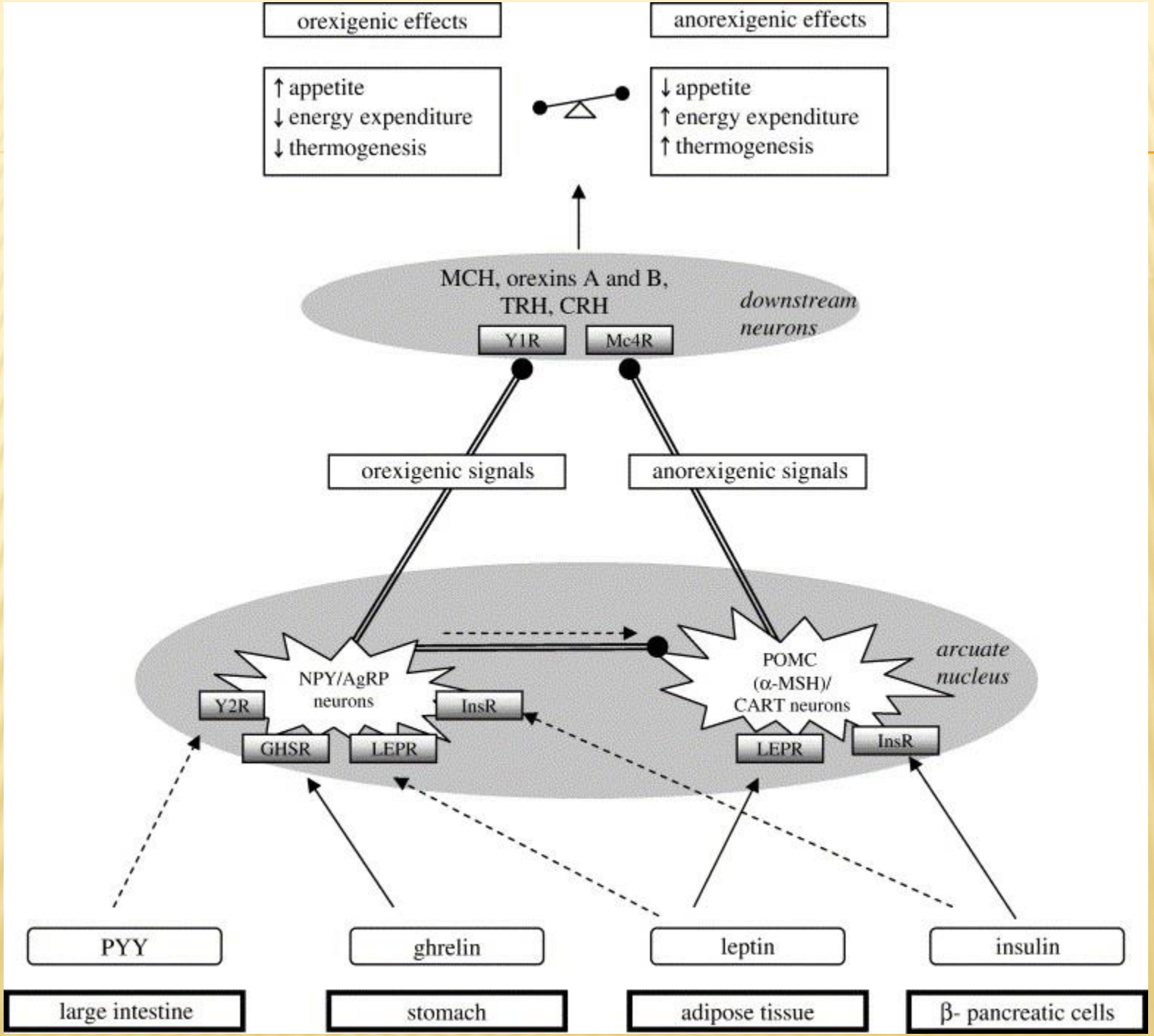
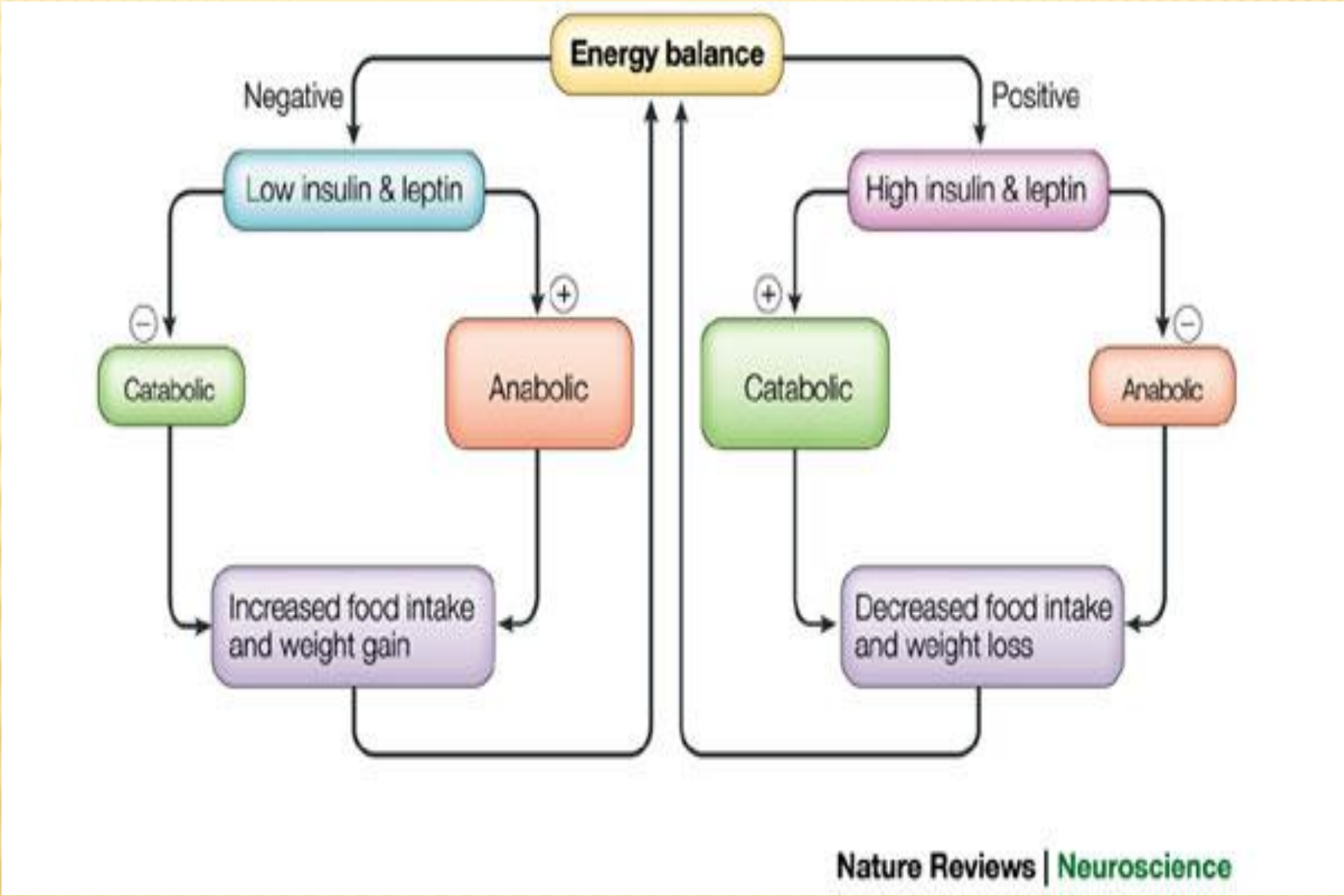
EATING DISORDERS

VLA 21. 3. 2017

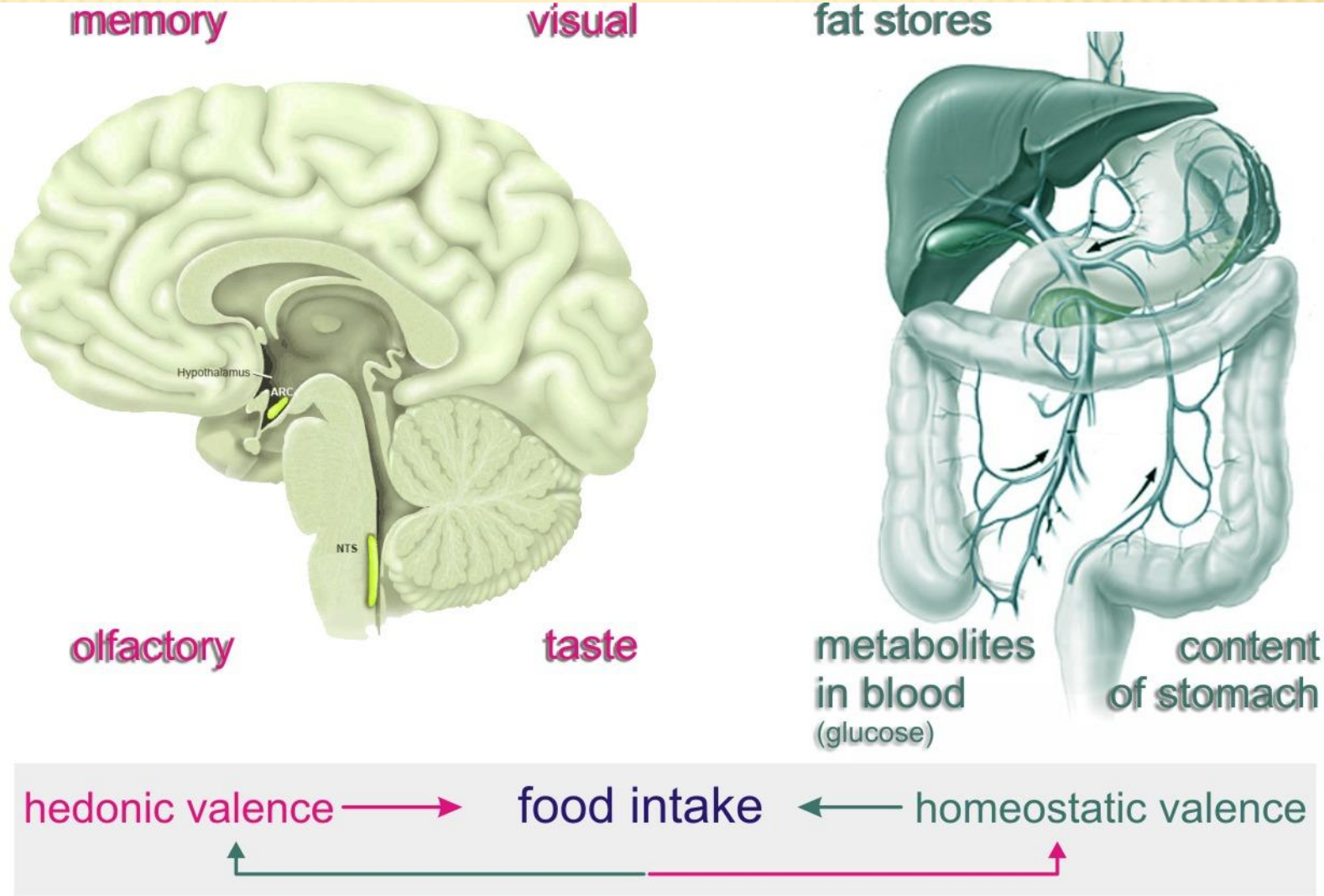

orexigenic effects
anorexigenic effects
↑ appetite
↓ energy expenditure
↓ thermogenesis
↓ appetite
↑ energy expenditure
↑ thermogenesis
MCH, orexins A and B,
TRH, CRH
downstream neurons
Y1R
Mc4R
orexigenic signals
anorexigenic signals
NPY/AgRP neurons
Y2R
GHSR
LEPR
InsR
POMC (α-MSH)/ CART neurons
LEPR
InsR
arcuate nucleus
PYY
ghrelin
leptin
insulin
large intestine
stomach
adipose tissue
β- pancreatic cells

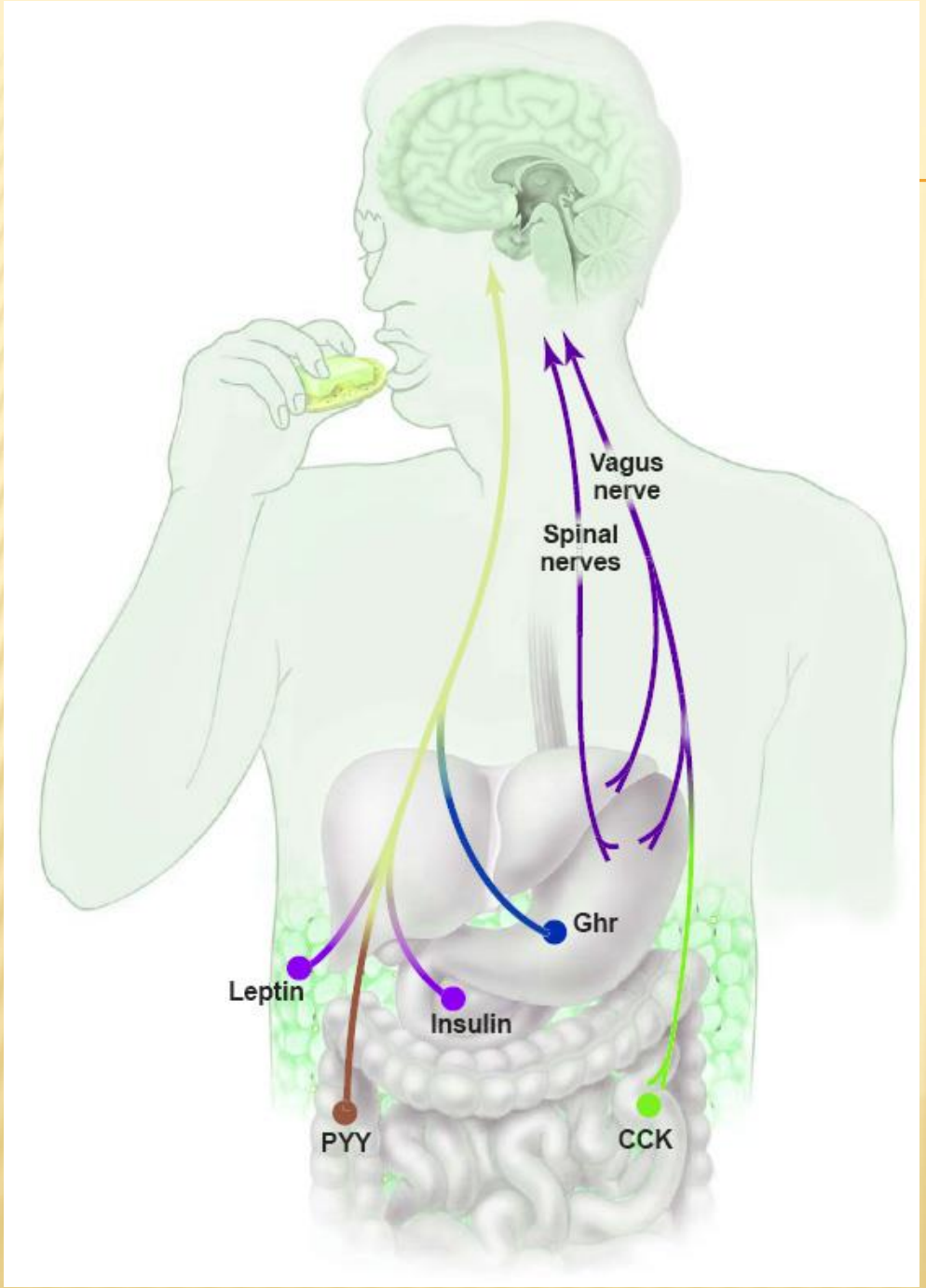

Energy balance
Negative
Positive
Low insulin & leptin
High insulin & leptin
Catabolic
Anabolic
Catabolic
Anabolic
Increased food intake and weight gain
Decreased food intake and weight loss
Nature Reviews | Neuroscience

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

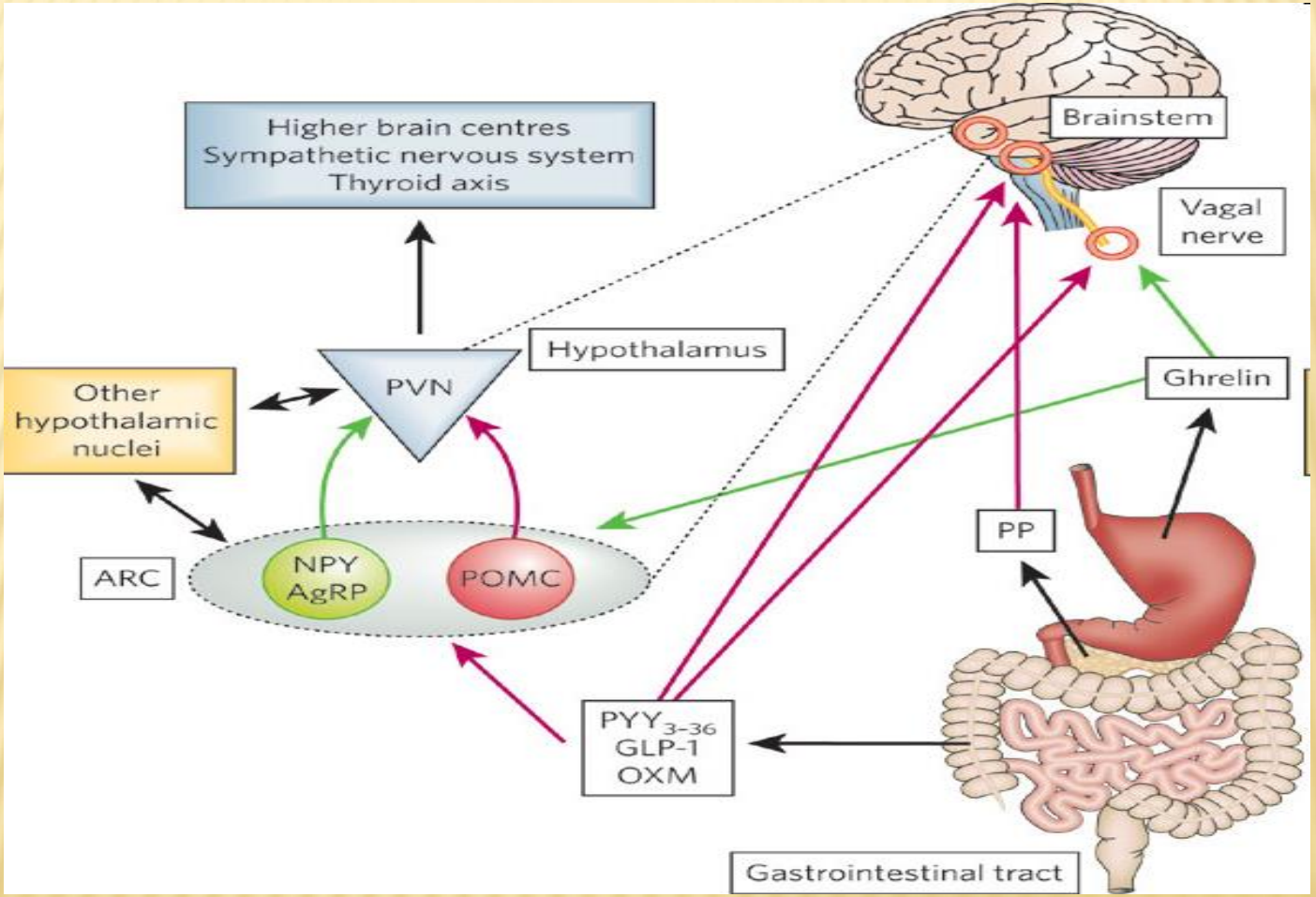




SIMPLIFIED SCHEME OF HOMEOSTATIC REGULATIONS OF FOOD INTAKE.

SUBSTANTIAL SIGNALS ORIGINATE FROM GIT (GHRELIN, CCK, PYY), ADIPOSE TISSUE (LEPTIN, OTHER ADIPOKINES) AND PANKREAS (INSULIN, GLUKAGON)

CENTRAL AND PERIPHERAL CIRCUITS IN REGULATION OF FOOD INTAKE

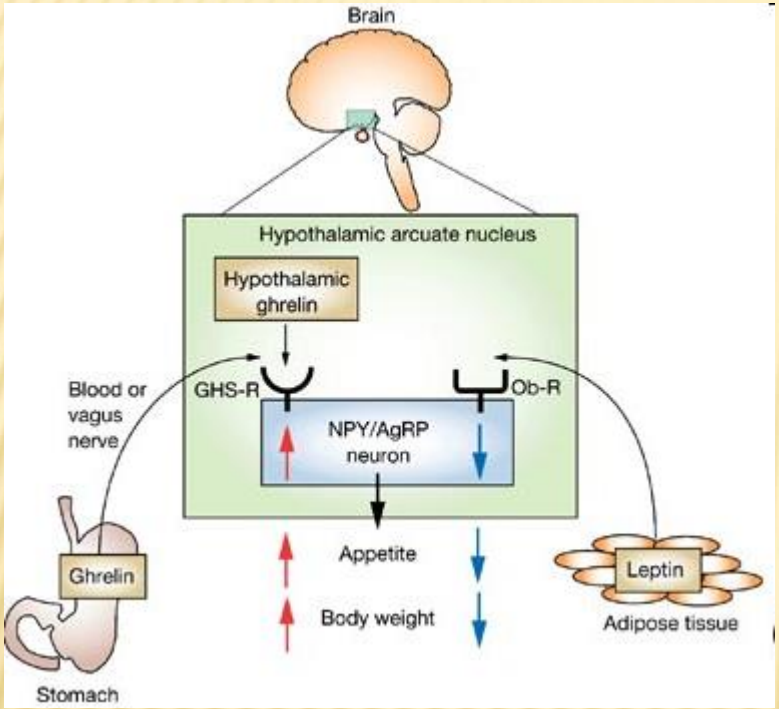


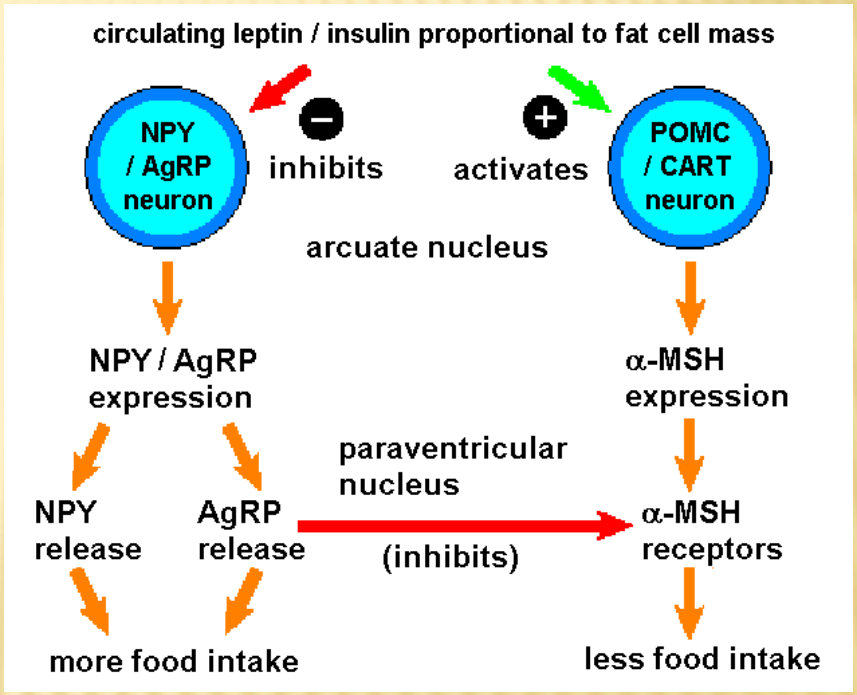
Gut hormones and the regulation of energy homeostasis
Kevin G. Murphy and Stephen R. Bloom
Nature 444, 854-859(14 December 2006)

PYY

- Peptide YY is related to the pancreatic peptide family by having 18 of its 36 amino acids located in the same positions as pancreatic peptide. The two major forms of peptide YY are PYY_{1-36} and PYY_{3-36}, which have PP fold structural motifs. However, the most common form of circulating PYY immunoreactivity is PYY_{3-36}, which binds to the Y2 receptor (Y2R) of the Y family of receptors. Peptide YY_{3-36} (PYY) is a linear polypeptide consisting of 36 amino acids with structural homology to NPY and pancreatic polypeptide.
- PYY is found in L cells in the mucosa of gastrointestinal tract, especially in ileum and colon. Also, a small amount of PYY, about 1-10%, is found in the esophagus, stomach, duodenum and jejunum. PYY concentration in the circulation increases postprandially (after food ingestion) and decreases by fasting. In addition, PYY is produced by a discrete population of neurons in the brainstem, specifically localized to the gigantocellular reticular nucleus of the medulla oblongata.
- PYY exerts its action through NPY receptors; it inhibits gastric motility and increases water and electrolyte absorption in the colon. PYY may also suppress pancreatic secretion. It is secreted by the neuroendocrine cells in the ileum and colon in response to a meal, and has been shown to reduce appetite. PYY works by slowing the gastric emptying; hence, it increases efficiency of digestion and nutrient absorption after a meal.

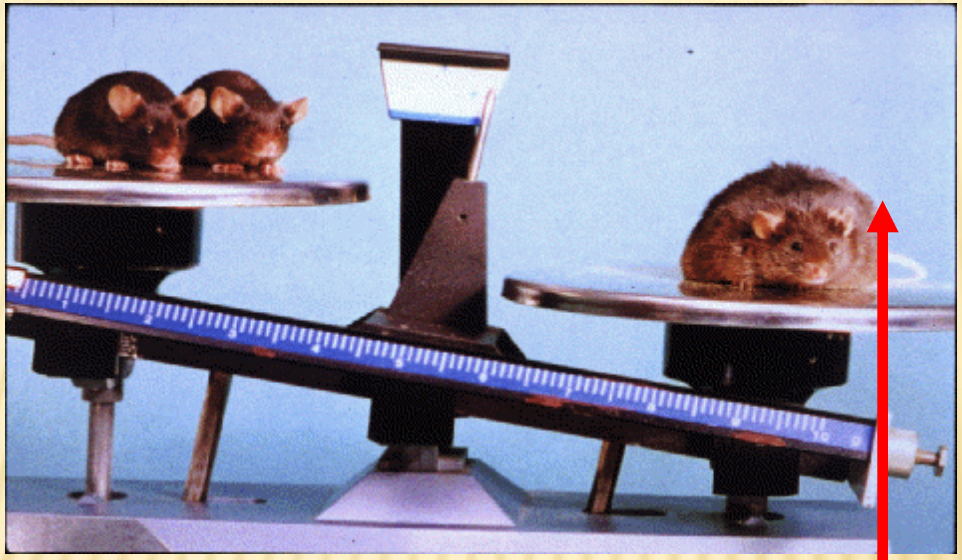
REGULATION OF FOOD INTAKE





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

1994 – ADIPOSE TISSUE IS ABLE TO PRODUCE HORMONS ITSELF – LEPTIN DISCOVERY



Mutation of *ob* gene coding for leptin is leading to significant obesity in mouse

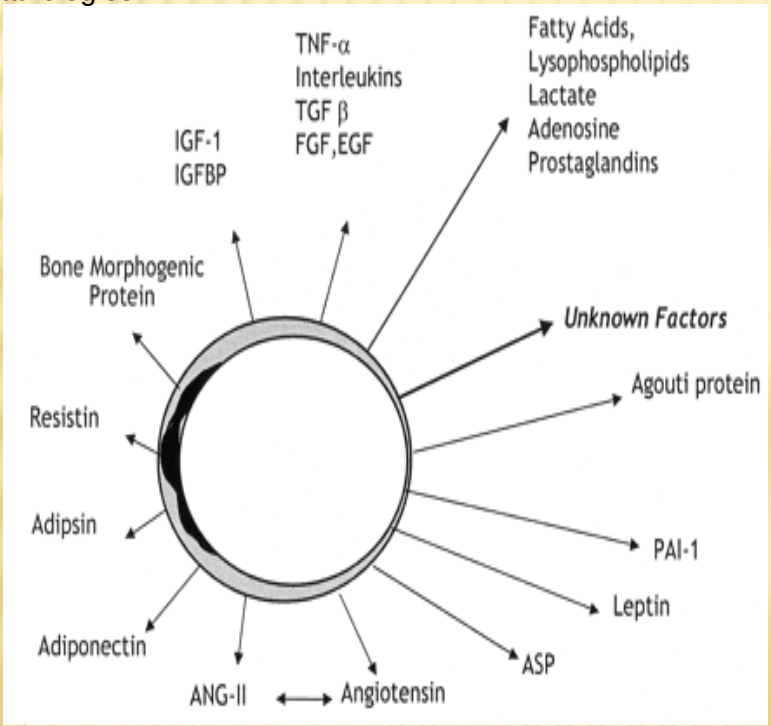
Leptin therapy led to normalized body weight and/or fertility of these mutated mice

Zhang et al, Nature, 1994.

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.



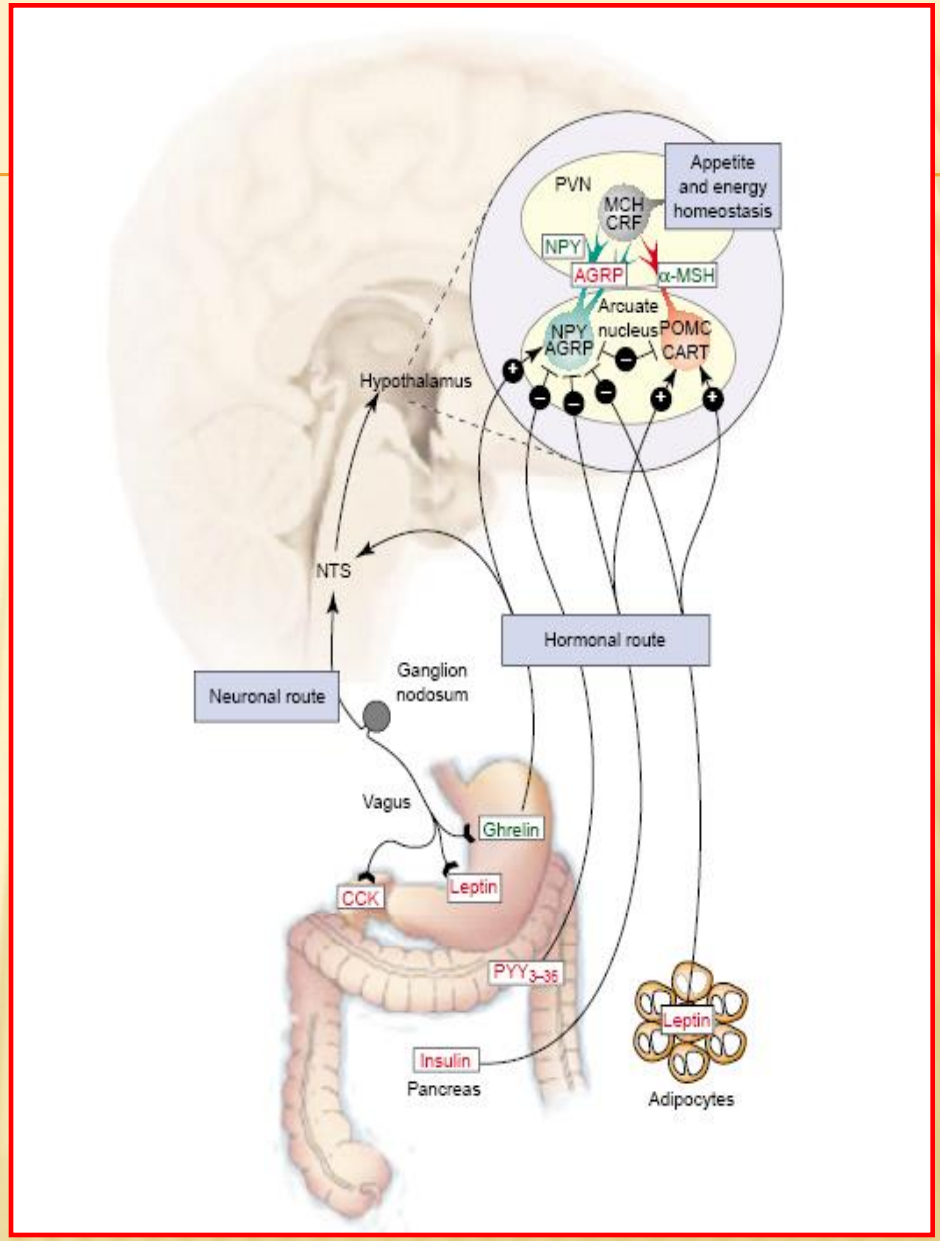
They are usually:

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

They are very important in metabolic regulations

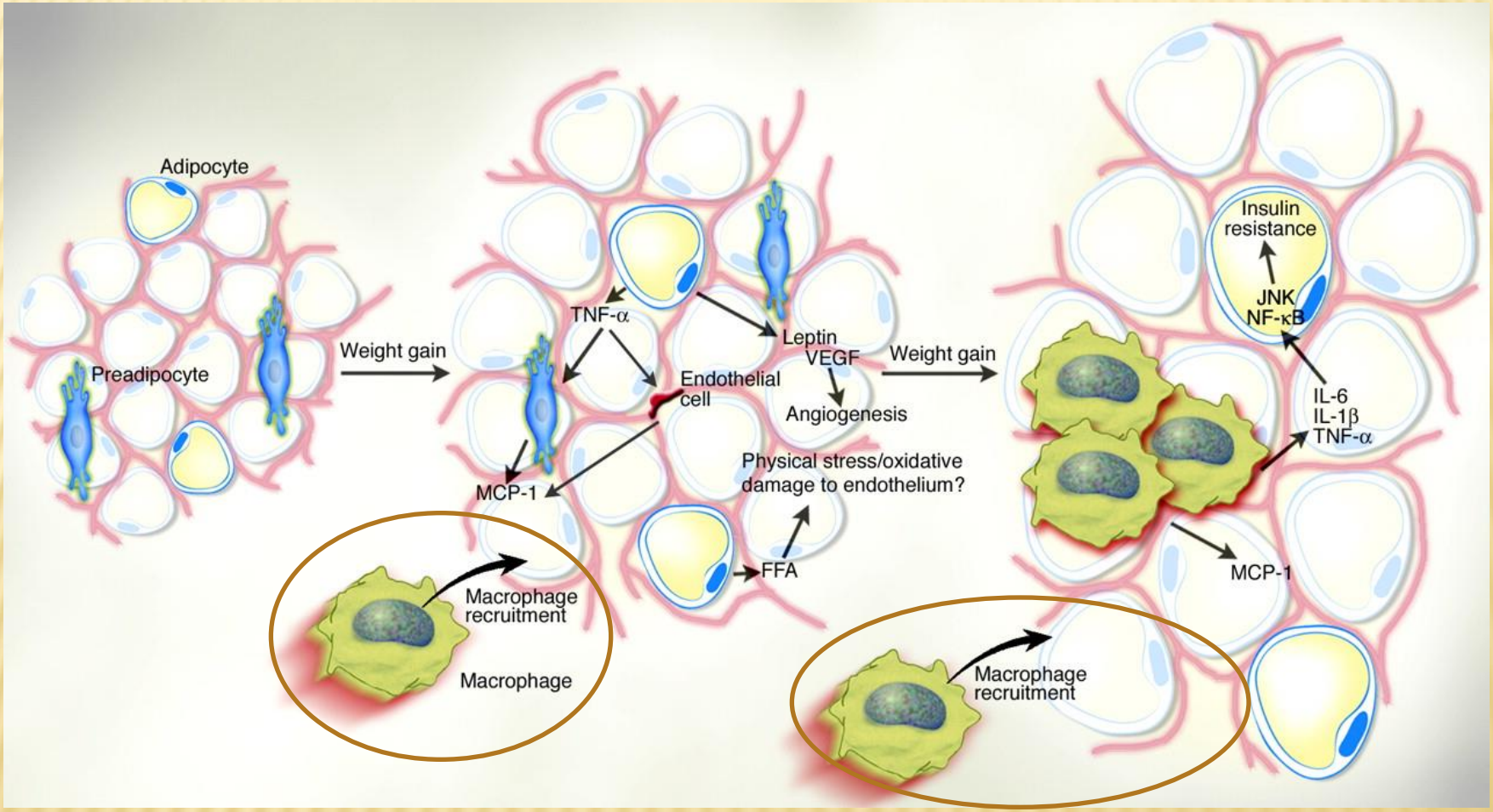
Food Intake and GIT…

In food intake and especially in postprandial supression of appetite, many substances produced in GIT play substantial roles.



Holst B, Schwartz TW. 2004

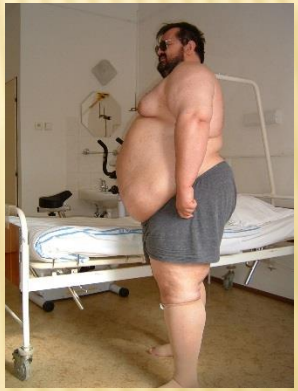
OBESITY IS ASSOCIATED WITH LOCAL INFLAMMATORY RESPONSE IN FAT



PATHWAYS OF TRANSCRIPTION FACTORS PARTICIPATING IN NUTRITION BASED INTERACTIONS

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

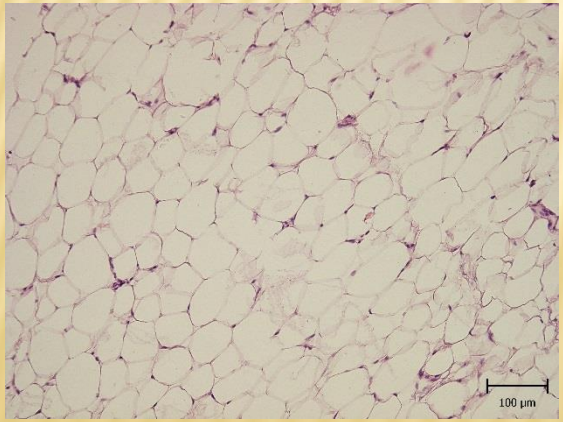
SIZE AND ENDOCRINE PROFIL OF ADIPOCYTES IS CORRELATED WITH THE WHOLE ADIPOSITY

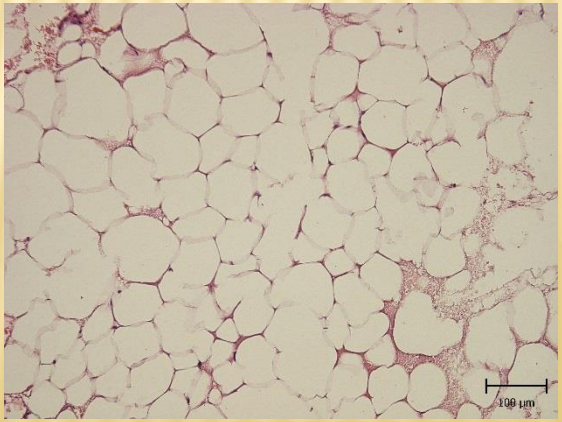


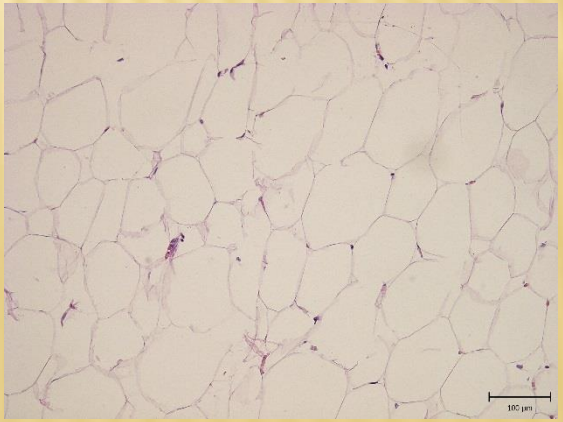
Malnutrition
(Anorexia nervosa)

Normal state (slight overweight))

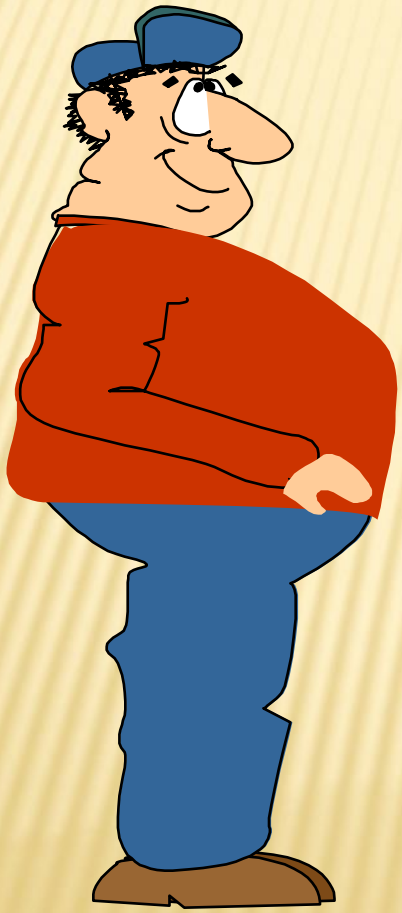
Obesity







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

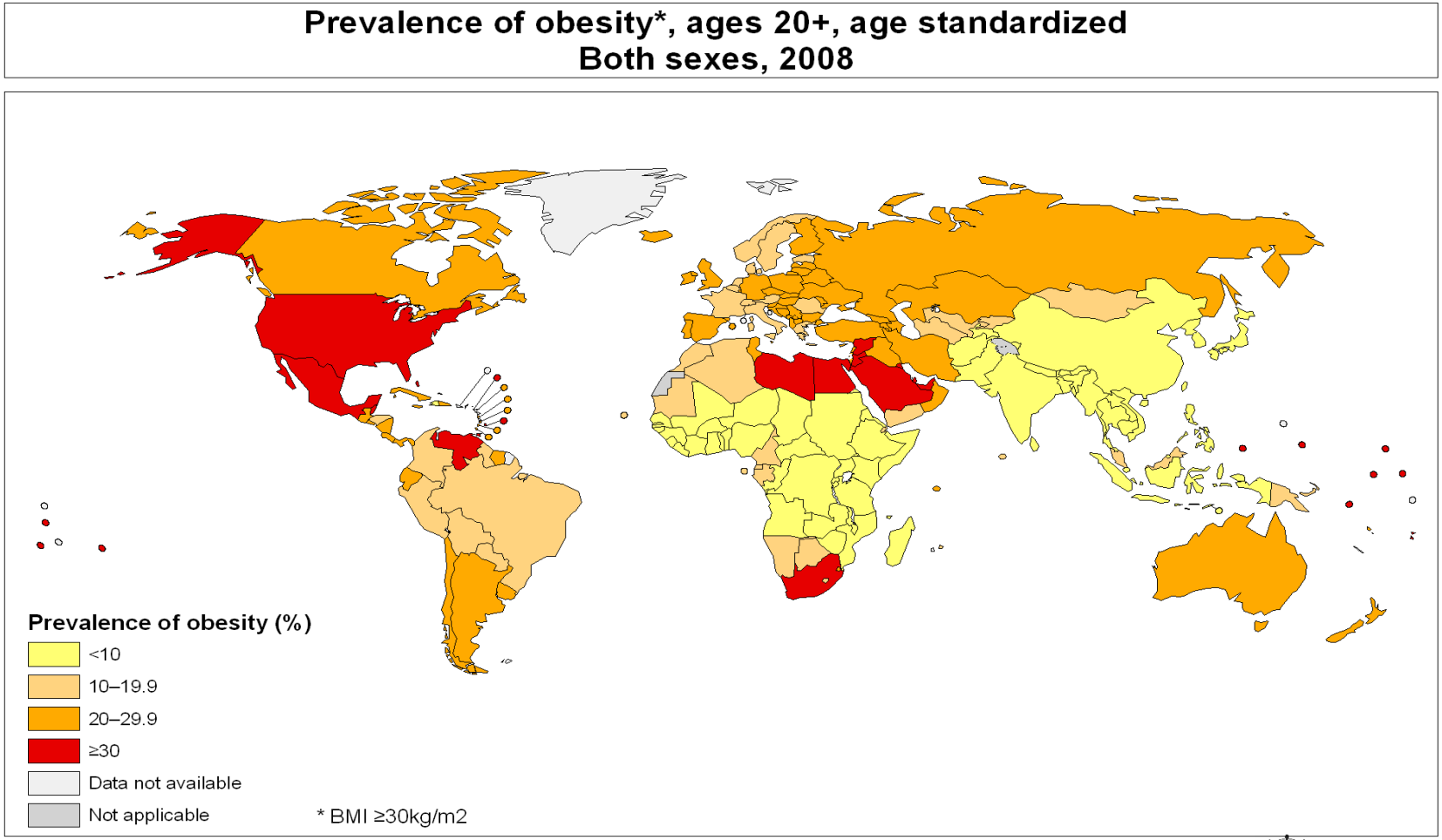
>88 cm = highly increase risk[1]
>80 cm = higher risk[1]

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



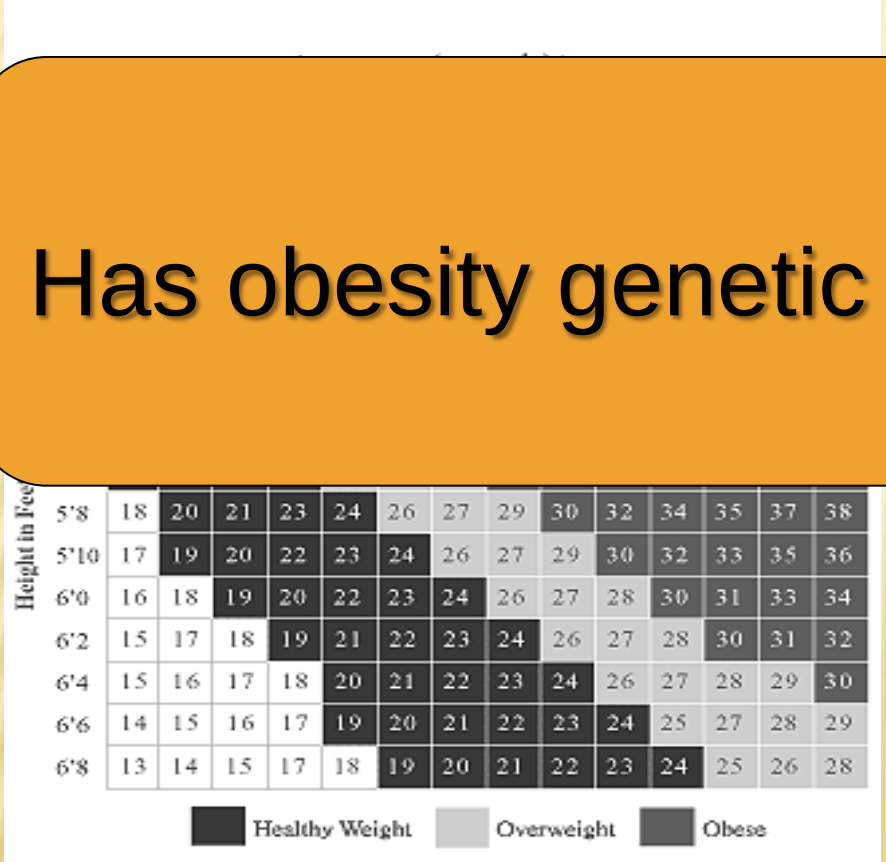
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers 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

OBESITY

Has obesity genetic background?



GENETICS OF OBESITY

- Argumenst why yes:
  - Familial aggregation
  - Twin studies (MZ twins more concordance compared to DZ twins)
  - + Large family studies

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

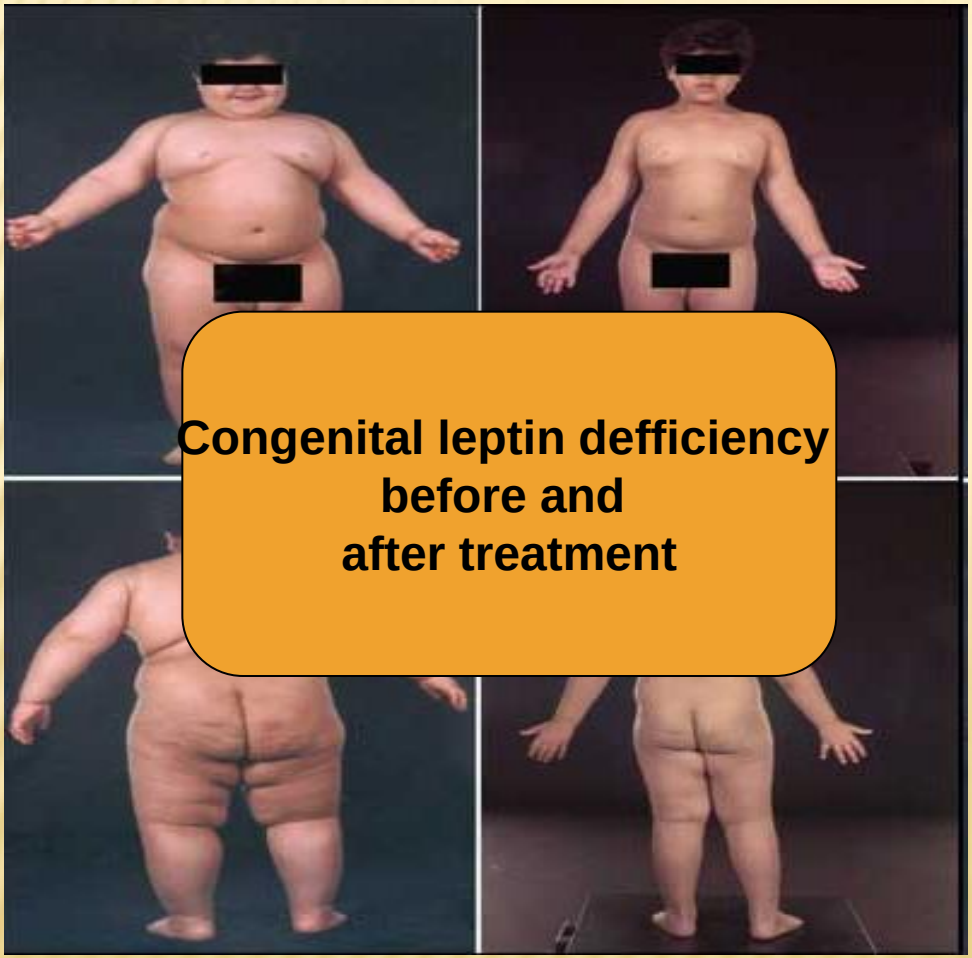
Genes Implicated in Monogenic Obesity and the Traits Found To Be Associated with Them in Genome-Wide Association Studies (GWAS)

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.

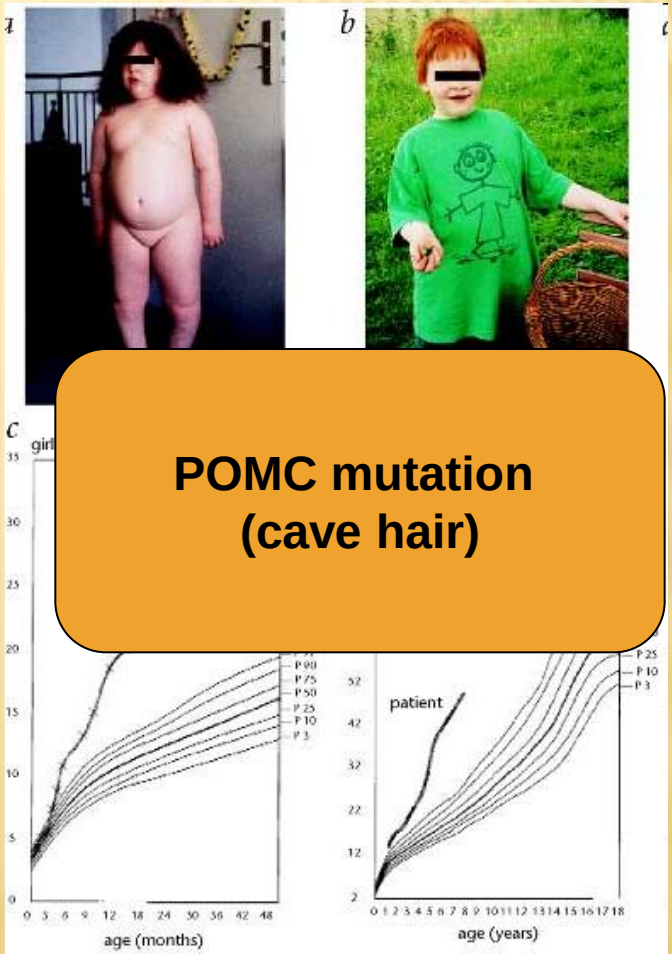
N C Med J. 2013; 74(6):530-533

MONOGENIC OBESITY SYNDROMES



Congenital leptin defficiency before and after treatment

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

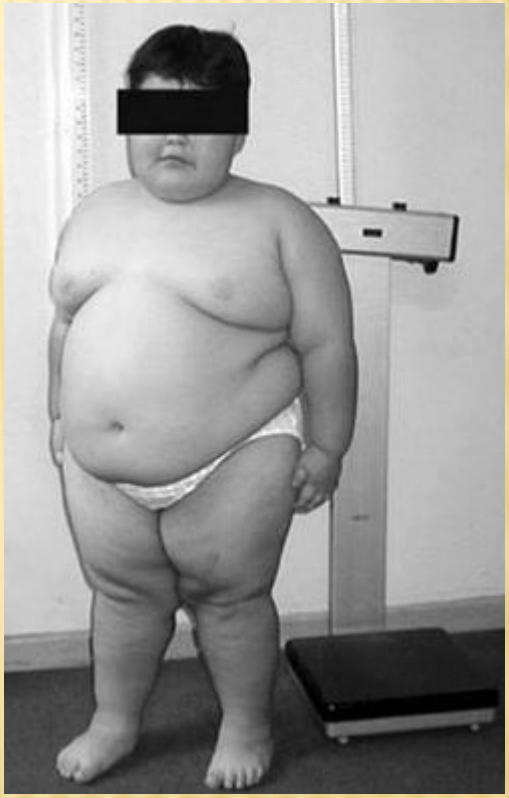


POMC mutation (cave hair)

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

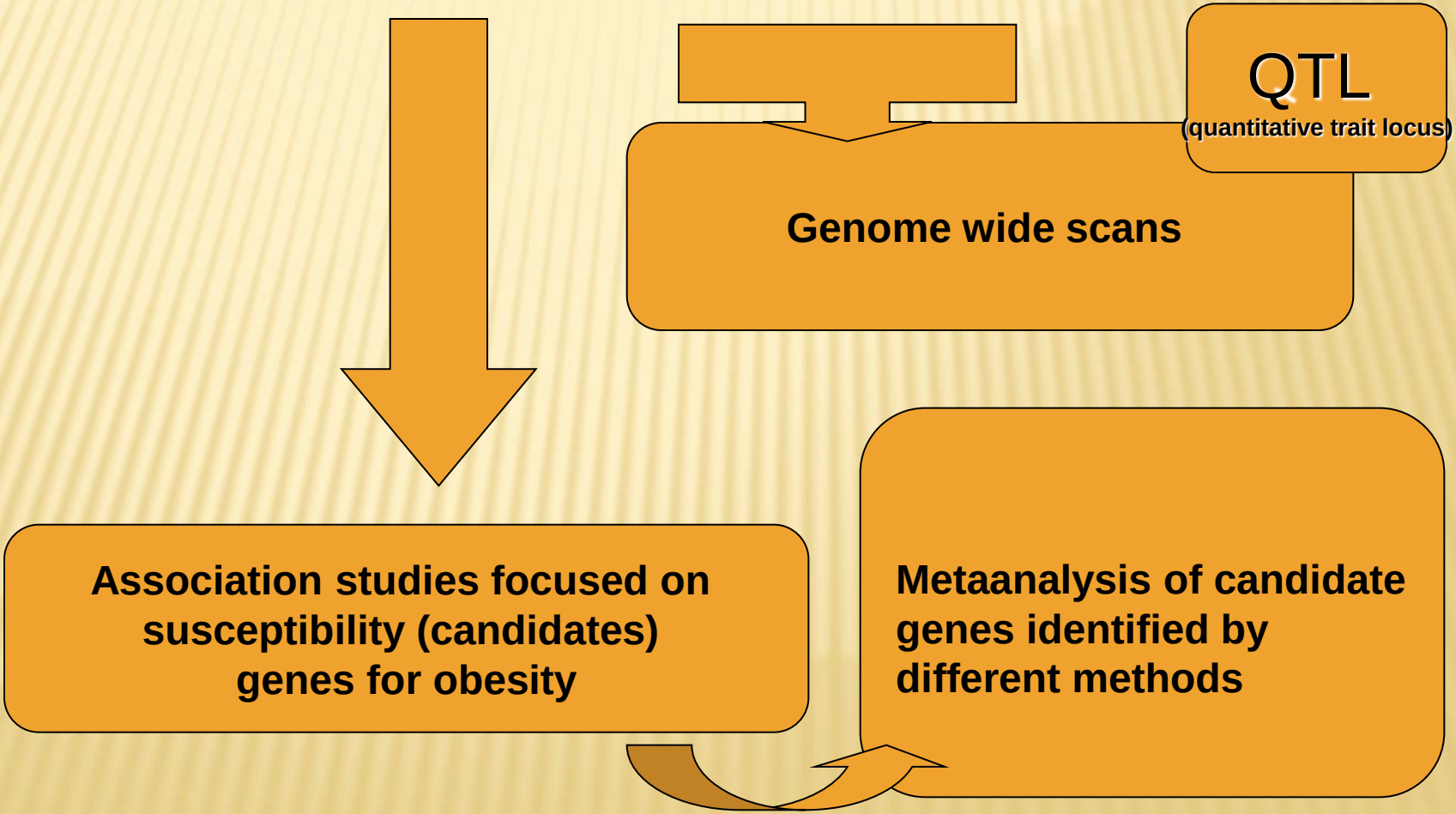
SY PRADER- WILLI AS A CLINICAL EXAMPLE

- 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



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

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

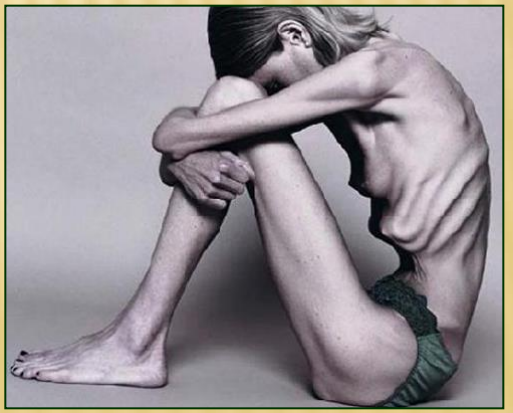
- Genetic variation, as captured by PRS („Polygenic Risk Score“) , not only influenced birth weight, but also child size and adiposity up to 48 months of age, independent of birth weight.
- The PRS was constructed using adiposity-linked genetic risk variants previously reported in an adult population.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

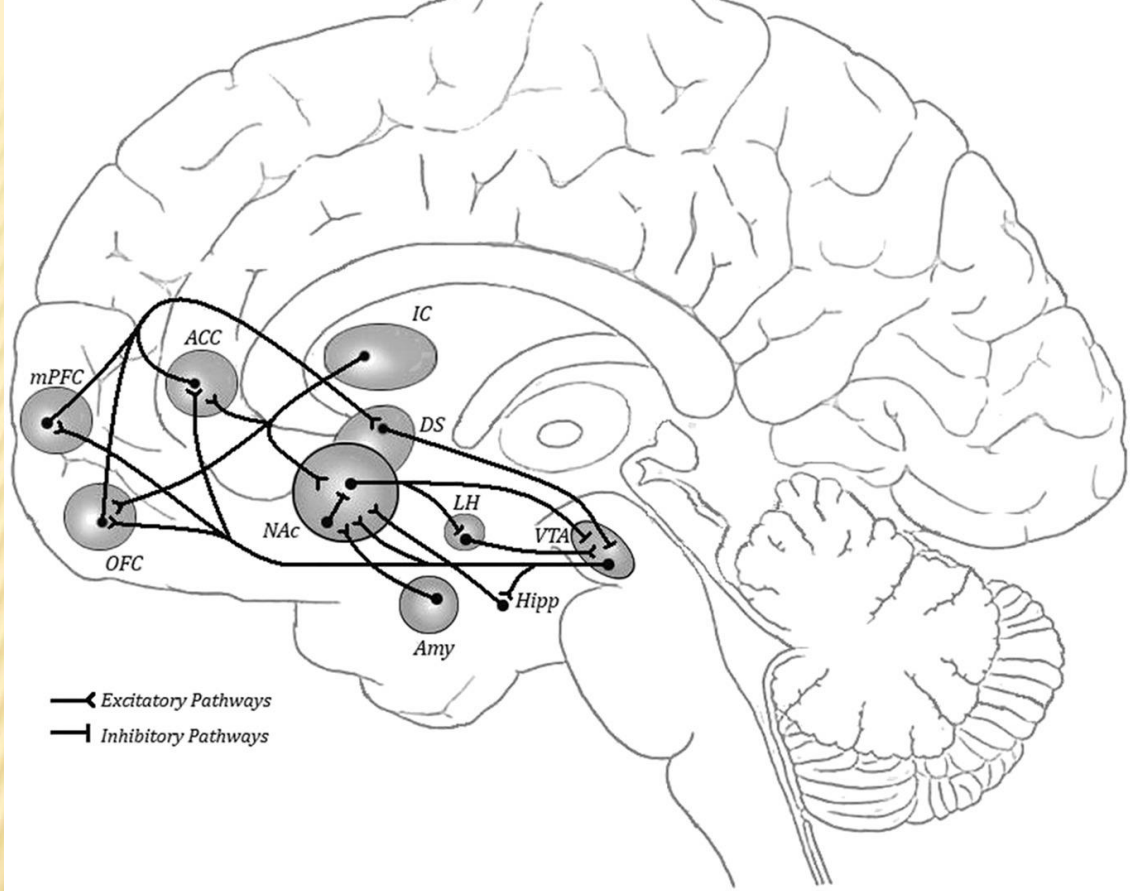
OBESITY AS A COMPLEX DISEASE (BMC MED. 2017; 15: 50)

- **Neonatal methylation levels at seven loci were associated with birth weight.** At six of the seven loci, there was suggestive evidence that the associations continued to persist up to 48 months of age. Among them, two of the loci (*CDKN2B/P4HA3*) also showed suggestive association with child BMI at 48 months. Even though the associations in early childhood did not survive multiple testing corrections, these CpGs still hold potential as biomarkers of adverse metabolic trajectory as the prevalence of obesity increases with age and might become more apparent later in the life-course. Lastly, methylation levels at three of seven loci associated with birth weight (*IGDCC4*, *MIRLET7BHG*, *CACNA1G*) also showed significant associations with the prenatal environment; however, similar analyses with childhood weight and adiposity measures showed suggestive associations.
- Birth weight seems to be influenced by **both genetic and prenatal environment factors, possibly acting through different mechanisms, either by altering the epigenome (evidenced by CpGs that were associated with prenatal environment and/or SNPs) or independently of the epigenome (e.g. the PRS).**

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.

ANOREXIA NERVOSA (AN) AND BULIMIA NERVOSA (BN)

- Compared to healthy women, symptomatic patients with AN and BN showed different patterns of brain area activation in response to pleasant and aversive basic taste stimuli with response activation by the pleasant sweet stimulus prevailing over that induced by the aversive bitter taste.
- Symptomatic AN patients showed a decreased response to the aversive bitter stimulus in the right amygdala and left anterior cingulate cortex while symptomatic BN individuals showed a reduced activation of right amygdala and left insula by the aversive bitter stimulus, which suggests an impairment of their physiological aversion to unpleasant bitter tastants. No quantitative differences emerged in brain responses to the pleasant sweet taste. These results may shed more light on the processing of rewarding and aversive food-related stimuli in patients with EDs, which may be relevant for understanding the pathophysiology of AN and BN.

LOSS OD ADIPOSE TISSUE IS SUPPOSED TO BE THE MAIN FACTOR CONTRIBUTING TO THE BODY WEIGHT LOSS

	NW (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

DĚKUJI VÁM ZA POZORNOST